NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

FOR

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

Contents

Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
BID	Twice Daily
BNF	British National Formulary
BSC	Best Supportive Care
CEA	Cost Effectiveness Analyses
CI	Confidence Interval
CR	Complete Response
CT	Computed Tomography
CTC	Common Toxicity Criteria
DOC	Docetaxel (Taxotere®)
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
Gem/carbo	Gemcitabine and carboplatin combination
Gem/cis	Gemcitabine and cisplatin combination
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IC	Incremental Cost
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention-To-Treat
IV	Intravenous
K-M	Kaplan-Meier
LYG	Life-Years Gained
MRI	Magnetic Resonance Imaging
N or n	Number of patients in the treatment arm
N/A	Not Applicable
NI	Non-inferiority
NICE	National Institute for Health and Clinical Excellence
NR	Not Reported
NS	Not (statistically) Significant
NSCLC	Non-Small Cell Lung Cancer
NSCLC-NOS	Non-Small Cell Lung Cancer Not Otherwise Specified
Pem/cis	Pemetrexed and cisplatin combination
PFS	Progression Free Survival

PR	Partial Response
PS 0/1	WHO Performance Status 0 or 1
QALY	Quality-Adjusted Life-Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RR	Response Rate
RT	Randomised and Treated (Population)
SCLC	Small-cell lung cancer
SD	Stable Disease
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
VAS	Visual Analogue Scale

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).

Alimta® (pemetrexed disodium) in combination with cisplatin was approved by the European Commission for the first-line treatment of NSCLC (other than predominantly squamous cell histology) on 8th April 2008.

Pemetrexed was originally approved for malignant pleural mesothelioma (MPM) and previously treated NSCLC, 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

Pemetrexed in combination with cisplatin (pem/cis) 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.

Maintenance in NSCLC : a licence for use following 4 cycles of platinum based chemotherapy is anticipated Q3 2009.

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 has been commercially available in the UK since November 2004 and licensed for use in the first-line setting since April 2008. Use in the first-line setting is minimal (<1%) according to Lilly market research data although there is use in private healthcare settings.

Ongoing trials

There are currently two Lilly sponsored clinical trials underway in the UK: S124 and JMIK and there is also one Investigator-Initiated trial: UK NCRN, ET trial.

S124: Multicentred phase III trial across the EU in which patients receive four cycles of pem/cis and are then randomised to pemetrexed and best supportive care (BSC) in the maintenance phase, in patients with non-squamous histology. The primary outcome is progression-free survival. This trial is ongoing.

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, pem/cis is given for four cycles and then continued as maintenance therapy for patients with non-squamous histology. Recruitment is expected to complete by Q4 09 and results expected at ASCO 2010.

ET trial: this is a phase III RCT with two trial arms: pemetrexed/cisplatin or pemetrexed/paclitaxel. The aim of this trial is to investigate whether NSCLC patients with high ERCC would benefit from a non-platinum combination. Results for this trial are expected in 2012.

Lilly is not aware of any other ongoing studies in the UK using pemetrexed in this indication.

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

Pemetrexed has been approved for use in approximately 100 countries, including the European Union, the US, Australia, Canada and Japan.

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 for the first-line treatment of NSCLC (other than predominantly squamous cell histology) is currently under consideration by the SMC, decision expected January 2009.

Completed assessments

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 (Aug 2007). However, this recommendation is for a patient population that is now, in part, out of licence.

Pemetrexed in combination with cisplatin has been recommended by NICE as a treatment option for malignant pleural mesothelioma (MPM) (Jan 2008, TA135) and 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 Cisplatin 75mg/m^2, iv infusion 30 minutes after pemetrexed on Day 1
Dosing Frequency	Every 21 days
Length of course	Four cycles*
Frequency of Repeat Courses	None

* based on mean number of cycles in the pemetrexed registration trial, JMDB, UK clinical practice

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 and cisplatin are both intravenous infusions, it will most likely 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?

Administration

Pemetrexed is a 10 minute IV infusion.

Concomitant Medication Regimen

Platinum

In the first-line setting pemetrexed is licensed for use with cisplatin (75mg/m^2) on Day 1 of the 21-Day cycle. Cisplatin requires hydration and anti-emetic support.

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. Corticosteroids are commonly used with cisplatin.

Monitoring

The level of monitoring for pemetrexed is similar to that expected with most other chemotherapies.

Investigations needed for selection: Histological Diagnosis

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

To identify this population a more specific histological diagnosis is needed than is required to differentiate between small cell and non-small cell lung cancer, the level of specificity currently mandated. However, current best practice in cytology and/or biopsy sample analysis, including basic immunohistochemistry, is sufficient to make the diagnosis. Other new therapies require the same level of histological diagnosis in order to prevent adverse events (eg bevacizumab) or to identify appropriate patients (eg erlotinib).

Pemetrexed would therefore, not require any additional investigations but would require best practice to become routine in line with other new treatment requirements. If a clear histological diagnosis is not made the option is to repeat the histology diagnosis or to treat with a different chemotherapy.

2. Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC other than predominantly squamous cell histology who are unsuitable for surgery.	Patients who are chemotherapy naïve with locally advanced or metastatic NSCLC other than predominately squamous cell histology, who are unsuitable for surgery. The target population in this submission is patients with adenocarcinoma or large cell carcinoma.
Intervention	Pemetrexed in combination with cisplatin	Pemetrexed (500mg/m^2 iv infusion) in combination with cisplatin (75mg/m^2 iv infusion) on Day 1 of a 21-day cycle, repeated for a maximum of four cycles.
Comparator(s)	Platinum-based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine	Primary comparator: gemcitabine/cisplatin Secondary comparators: gemcitabine/carboplatin and docetaxel/cisplatin
Outcomes	The outcome measures to be considered include: ▪ Overall survival ▪ Progression free survival ▪ Response rates ▪ Adverse effects of treatment ▪ Health-related quality of life	The outcome measures to be considered include: ▪ Overall survival ▪ Progression-free survival ▪ Tumour response rate ▪ Adverse effects of treatment ▪ Health-related quality of life

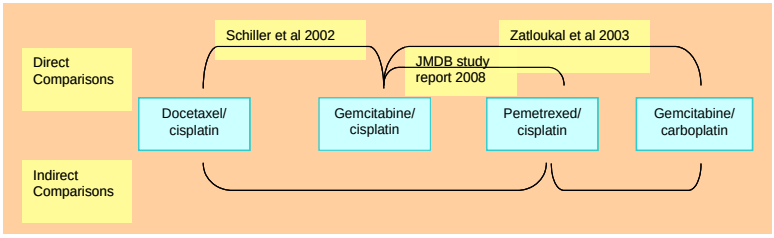
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	Cost-effectiveness analysis results expressed as incremental cost per QALY gained. A cost per Life Year (cost per LY) gained analysis was also conducted as this type of analysis is relevant in disease areas where extended survival is a key outcome of treatment.
	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.	Time horizon will be 6 years (a lifetime model).
	Costs will be considered from an NHS and Personal Social Services perspective.	Costs will be considered from an NHS and Personal Social Services perspective.
		A continuation rule is also modelled to reflect clinical practice of discontinuing treatment in patients who do not respond after three cycles of chemotherapy.
Subgroups to be considered	If evidence allows subgroups of patient populations in whom the technology is clinically effective and cost effective should be considered. These may be related to histology	This submission will be based on the licensed population: patients with NSCLC other than predominantly squamous cell histology. The evidence in the submission also supports the use of pem/cis in the target population – adenocarcinoma and large cell carcinoma patients.
Special considerations, including issues related to equity or equality		

Section B

3. Executive summary

Disease Background	Patients diagnosed with lung cancer have a generally poor prognosis. The disease is often undetected until it has passed the curative stage. Treatment for advanced lung cancer is concerned with extending the life of terminally ill patients and reducing symptoms. Therapy has to be well tolerated in this sick patient group. Developments in chemotherapy are gradually extending survival duration and rates. Potentially, chemotherapy may be tailored to individual patients in order to produce improvements in outcomes, including overall survival. Recently, histological diagnosis has emerged as a variable that may help tailor therapies to individuals.
Approved name **Brand name**	Pemetrexed disodium Alimta ®
Pharmacological mechanism of action	Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.
Indication and marketing status	Alimta® (pemetrexed disodium) in combination with cisplatin was approved for the first-line treatment of NSCLC (other than predominantly squamous cell histology) on 8th April 2008. Pemetrexed was originally approved, for malignant pleural mesothelioma (MPM), and previously treated NSCLC, in 2004.
Formulation(s) **Strength (price)** **Pack size(s)**	Powder for concentrate for solution for infusion 100mg (£160) or 500mg (£800) glass vial 1 vial (single use)
Proposed course of treatment	Pemetrexed 500mg/ m^2 10-minute iv infusion on Day 1, cisplatin 75mg/ m^2 iv infusion 30 minutes after pemetrexed on Day 1 of a 21 day cycle. The duration of treatment in England and Wales is expected to be a maximum of 4 cycles.
Comparators	In the UK, gemcitabine in combination with carboplatin (gem/carbo) or cisplatin (gem/cis) is the standard treatment, accounting for over 80% market share in this patient group (UK Market Research Data, 2008). The licence for gemcitabine is in combination with cisplatin (rather than carboplatin) and the licensed combination is more widely used globally. Use in the UK is split between cisplatin and carboplatin, with use of carboplatin preferred due to a shorter administration time. The two platinums were considered interchangeable in terms of efficacy (and cost) until a recent meta-analyses demonstrated superior outcomes in cisplatin (e.g. Jiang et al 2007). Therefore gem/cis is the primary comparator to pem/cis in this submission and gem/carbo is the secondary comparator. Remaining platinum doublets account for ≤15% market share. Docetaxel plus cisplatin, was assessed in comparison with pem/cis as an example of an alternative first-line platinum doublet that does not have Day 8 administration.

Histological diagnosis and current treatment	Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers diagnosed. Small cell lung cancers (SCLC) make up the remaining 20%. There are four main histological classifications of NSCLC: squamous cell carcinoma (33%), adenocarcinoma (25%) and large cell carcinoma (4%), with the remaining 36% being NSCLC 'not-otherwise specified' (LUCADA, 2007). Histological diagnosis is based on biopsy and/or cytology samples and immunohistochemistry. Current lung cancer diagnosis distinguishes between NSCLC and SCLC as treatment options differ depending on this. It is possible to diagnose to a more specific histological level using the same techniques. The National Cancer Audit (2007), recommends routine clinical practice should aim for an optimum histological and/or cytological diagnosis of around 80-85% of all lung cancers. A number of newer oncolytics require the more specific histotyping for either safety reasons (eg bevacizumab) or efficacy reasons (pemetrexed). In the case of pemetrexed, histological diagnosis would identify the patient population most likely to benefit from treatment.
Clinical Results of Pemetrexed in first-line NSCLC	Pemetrexed is the first platinum doublet to demonstrate survival outcomes by histotype, offering the possibility of tailoring treatment to patients most likely to benefit. Data from a large phase III RCT in advanced NSCLC demonstrated improved tolerability in all patients and a survival advantage in patients with adenocarcinoma or large cell carcinoma (Scagliotti et al.2008): **Median overall survival** ▪ *Adenocarcinoma* - pem/cis (12.6 months) vs. gem/cis (10.9 months) (HR 0.84, 95% CI 0.71-0.99). ▪ *Large cell carcinoma*- pem/cis (10.4 months) vs. gem/cis (6.7 months) (HR 0.67, 95% CI 0.48-0.96). ▪ JMDB is the first trial of platinum doublets in NSCLC to demonstrate median Overall Survival >12 months, in adenocarcinoma patients. **Improved tolerability** ▪ Incidence of grade 3/4 haematological toxicities was significantly lower in the pem/cis group compared with the gem/cis group. ▪ Fewer transfusions (all patients) pem/cis (16.4%) vs. gem/cis (28.9%, p<0.001). ▪ Alopecia (hair-loss), a side effect which has a detrimental impact upon a patient's quality of life, was also significantly reduced from 21% to 12% (p<0.001) in pem/cis vs. gem/cis

Source of clinical evidence for economic evaluation	The evidence for the primary comparison between pem/cis and gem/cis comes from the direct head-to-head phase III RCT registration study, JMDB (Scagliotti et al,. 2008). There were no head-to-head trials comparing pem/cis to gem/carbo or doc/cis therefore an adjusted indirect analysis was carried out for the secondary comparators. The literature review produced two references that enabled the comparison of pem/cis with gem/carbo (Zatloukal et al 2003) and doc/cis (Schiller et al 2002) using gem/cis as the intermediary therapy: 
Results of the economic evaluation	A Markov model followed a cohort of 500 advanced NSCLC patients through treatment and disease progression, over a six-year time horizon. Overall survival and progression-free survival - by responder and non-responder - drove transition through the health states: response, stable disease, progression, and death. Adverse events were also modelled. A continuation rule was applied so patients not responding to therapy after three cycles discontinued therapy. The incremental cost-effectiveness ratio of pem/cis compared to gem/cis in the non-squamous population, without a continuation rule is £35,188. With the continuation rule applied the ICER is £26,985. For the target population with a continuation rule applied the ICER is £18,370 for adenocarcinoma and £8,035 for large cell carcinoma.
Place of pemetrexed in the treatment of first-line NSCLC	Pem/cis is a platinum doublet licensed for the treatment of patients with locally advanced or metastatic NSCLC 'other than predominantly squamous cell histology'. As such it is targeted towards a smaller population than, for example, gemcitabine, which is used in all NSCLC histology types. The evidence in the submission demonstrates that targeting adenocarcinoma and large cell carcinoma patients for pem/cis treatment in the first-line setting offers the most clinically and cost-effective option over other routinely used first-line therapies.
Estimated Budget impact	Budget impact is estimated to range from £68,868 (a 3% share of eligible patients in 2008) to £2,047,554 (a 75% share of eligible patients in 2012).
Summary	Pem/cis is the first tailored chemotherapy to demonstrate survival gain in by histology in NSCLC and a median overall survival of >12 months in NSCLC. Pem/cis offers survival advantages over gem/cis in the first-line setting in patients with adenocarcinoma and large cell carcinoma, with 1 year survival rates of 49.4% and 41.9% respectively, Pem/cis has a better safety and tolerability profile compared to gem/cis. Pemetrexed has a simpler administration schedule and shorter infusion time when compared to gemcitabine, with a single administration per cycle compared to a two administrations per cycle with gemcitabine.

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 leading cause of death worldwide (Rosell et al 2004). 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%) and large cell carcinoma (4%), with the remaining 36% being NSCLC 'not-otherwise specified' (NOS) (LUCADA, 2007).

Over 38,000 people in the England and Wales were diagnosed with lung cancer in 2005 see Table 1, making it the second most commonly diagnosed cancer, after breast cancer, equivalent to more than 100 people per day being diagnosed with lung cancer. The link between smoking and lung cancer is well established: approximately 90% of lung cancer is the result of tobacco smoke. The link between smoking and poverty has also been proven; making lung cancer a disease that disproportionately affects people in the lowest socio-economic groups (Cancer Research UK, 2008, LUCADA 2007).

Survival from lung cancer is poor. It was responsible for approximately 34,000 deaths in 2006 and is the most common cause of cancer death in the UK, accounting for more than one-in-five. Only 7% of lung cancer patients survive over five years after diagnosis.

Table 1: **Lung cancer statistics in the UK (Cancer Research UK, 2008)**

Lung cancer - UK	Males	Females	Persons
Number of new cases (UK 2005)	22,259	16,339	38,598
Rate per 100,000 population*	61.3	36.8	47.4
Number of deaths (UK 2006)	19,600	14,550	34,150
Rate per 100,000 population*	52.3	31.3	40.4
One-year survival rate (for patients diagnosed 2000-2001**, England & Wales)	25%	26%	-
Five-year survival rate (for patients diagnosed 2000-2001**, England & Wales)	7%	7%	-

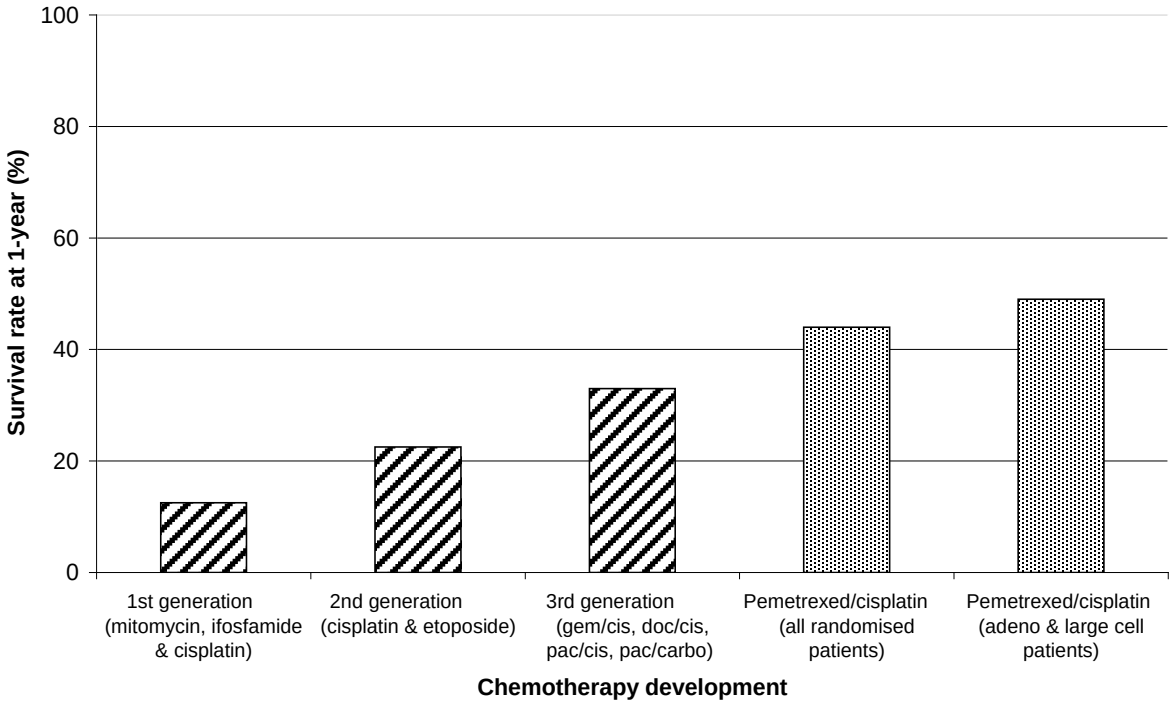
One reason for this poor prognosis is the late identification of the disease. Lung cancer is asymptomatic in the early stages - about two-thirds of patients are not diagnosed until it has reached advanced stages of the disease and is not amenable to curative treatment. Another reason, which explains the UK's relatively poor performance in comparison with other developed countries, is low active anti-cancer treatment rates.

Chemotherapy and Lung Cancer

The National Lung Cancer Audit states only 25% of first-line NSCLC patients in England and Wales received chemotherapy in 2006, which is low by international standards (LUCADA 2007). The report recommends an increase in rate of chemotherapy treatment and an increase in speed with which patients move through the treatment system, accessing diagnosis (CT scans) and treatment. Other policy documents, such as the Cancer Reform Strategy (2007), set out a programme of action to improve outcomes for cancer patients and have called for patients to have faster access to high quality treatments for cancer.

A link between developments in chemotherapy and improved survival outcomes over time has been observed (Figure 1). Current third-generation regimens (e.g. gemcitabine/cisplatin 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).

Figure 1: **Incremental improvement in lung cancer survival and associated chemotherapy development, US data (Schiller et al.2002; Scagliotti et al.2008)*.**



The adoption of every advance in chemotherapy has incrementally increased quantity and quality of life for patients with newer treatments offering improved tolerability and ease of administration. Despite the improvements made with chemotherapy, there remains an unmet need for new treatments to improve survival outcomes. For the first time in advanced NSCLC, data for pem/cis suggest that survival rates of 50% at one year might be achieved in patients with adenocarcinoma.

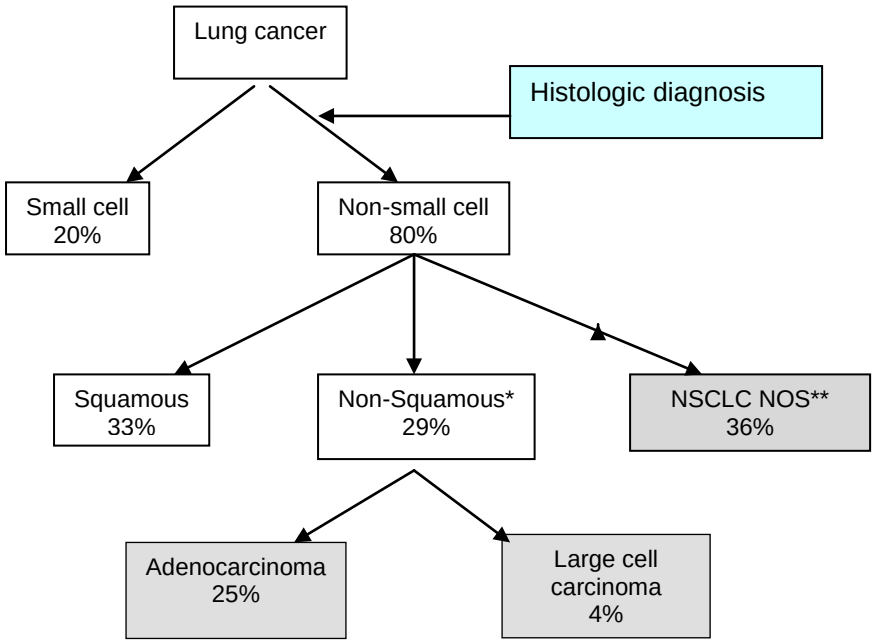
Histological diagnosis and treatment options

Histological diagnosis is emerging as a potential variable that may help tailor therapies to individuals. Whether a patient has squamous, adenocarcinoma or large cell histology influences their survival outcomes. For example patients with large cell carcinoma tend to have the poorest prognosis (García-Yuste et al.2008; Moro-Sibilot 2008).

Current lung cancer diagnosis distinguishes between small cell and non-small cell cancers, as treatment differs depending on this. However, it is possible to diagnose to a more specific histological level as part of this NSCLC diagnosis without significant cost or resource impact. Histological diagnosis is not an additional step but is performed at the same time as the identification of NSCLC or SCLC. Figure 2 shows the level of diagnostic specificity possible, based on the World Health Organisation Classification (Travis et al., 2004).

* Data for 1st, 2nd and 3rd generation therapies' one-year survival rates from Schiller *et al*., 2002. The average % is calculated based on the range reported. Data for pem/cis one-year survival rates from Scagliotti *et al*., 2008.

Figure 2: **Different histological classifications of lung cancer (Travis et al 2004)**



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

Diagnosis is based on biopsy and/or cytology samples and immunohistochemistry. Samples are classified by morphology (e.g. what shape are the cells: square or not? Are intracellular bridges observed?) and immunohistochemistry (is there a TTF1 positive result?). Depending on the results of these investigations, it is possible to classify the specific histologic types of NSCLC shown in Figure 2.

Diagnostic practice varies across the country and there is variation in the certainty surrounding different diagnosis. Squamous cell carcinomas are generally easier to identify with 87% certainty reported. Adenocarcinoma was identified 80% of the time while a large cell carcinoma diagnosis was more uncertain at 50% (Edwards et al. 2000). NSCLC-NOS is the diagnosis received if squamous cell carcinoma, adenocarcinoma or large cell carcinoma are not certain diagnoses.

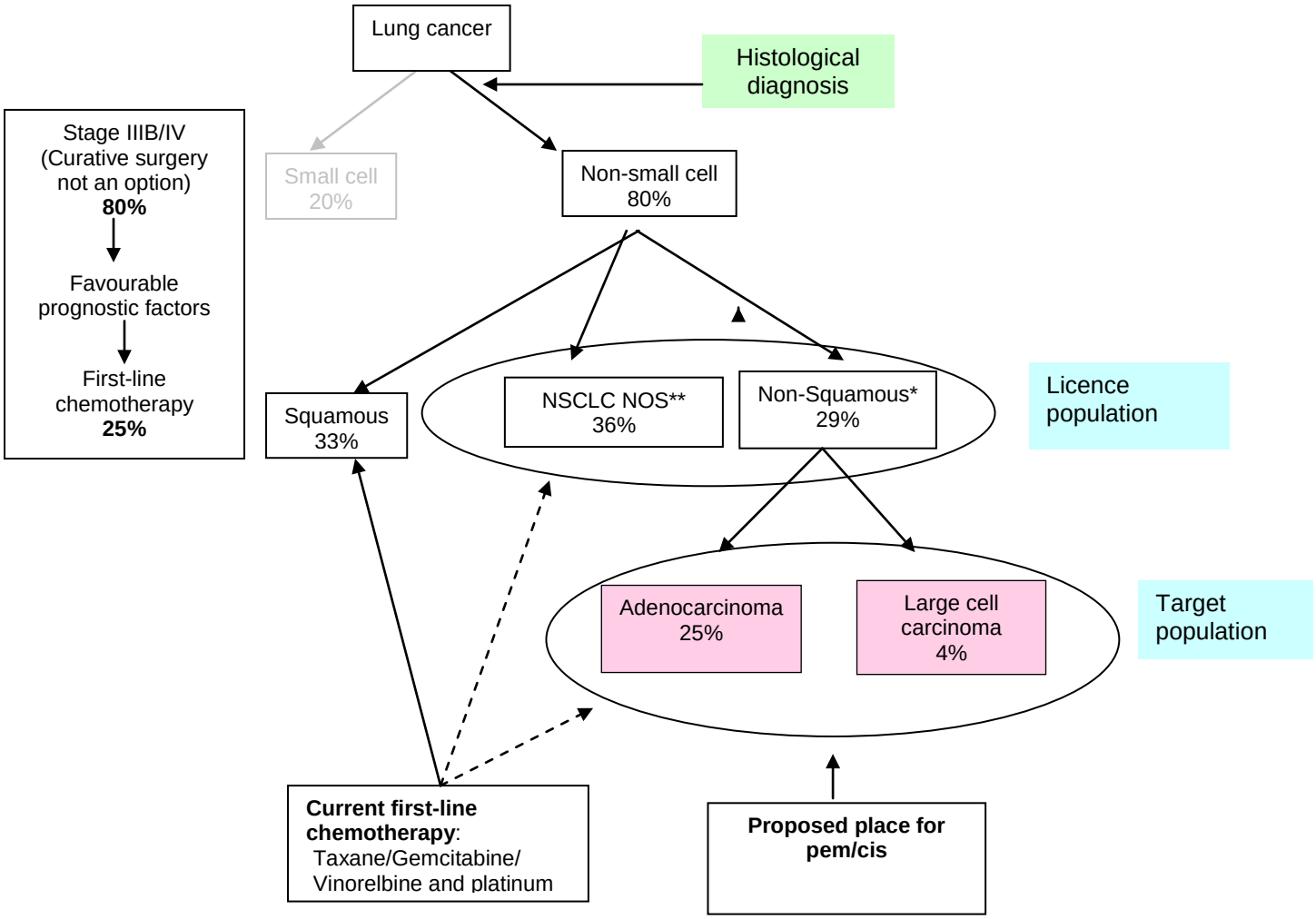
If there is uncertainty surrounding a histology diagnosis and a consideration of pemetrexed therapy, the diagnosis could be repeated, which depends on the individual patient's performance status, or an alternative chemotherapy could be prescribed.

Treatment options for patients with lung cancer in England and Wales

Figure 3 summarises the current treatment pathway and proposed place for pem/cis in the treatment pathway, for patients with lung cancer. A patient who presents with symptoms of lung cancer has a number of investigations (including chest X-rays, CT scans, biopsy and cytology samples taken to (1) assess the stage of disease and (2) differentiate between SCLC and NSCLC (NICE, 2005). The stage and type of lung cancer directs the treatment pathway. A minority of patients with NSCLC are identified at an early stage when curative surgery can be considered. The majority present with advanced disease (80%) which means treatment focuses on symptom alleviation and extending life.

NICE recommend that patients with advanced NSCLC (stage IIIB or IV) and good performance status should be offered a platinum doublet (docetaxel, gemcitabine, paclitaxel or vinorelbine with carboplatin or cisplatin). Approximately 50% of patients who receive first-line chemotherapy may also receive second-line treatment. In England and Wales second-line treatment is limited to docetaxel or erlotinib.

Figure 3: **Treatment pathway for NSCLC patients in England and Wales**



*The remaining 2% at squamous/non-squamous level are bronchio-alveolar carcinoma and cancer *in situ.*

**NOS = Not otherwise specified

Twenty-five percent of NSCLC patients receive first-line chemotherapy in the UK, although rates vary by treatment centre. Pem/cis can be used in all patients for whom squamous cell histology has been ruled out. As such, it is targeted towards a smaller population than the other platinum doublets, which are used in all NSCLC histology types.

This submission demonstrates that targeting adenocarcinoma and large cell carcinoma patients for pem/cis treatment in the first-line setting offers the greatest survival gains over currently available treatment options.

Patients with squamous NSCLC (and NSCLC NOS) would continue to receive gemcitabine doublets or the physicians' chosen alternative as treatment by histology data is not available for other chemotherapies.

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

Pemetrexed was developed as an oncolytic that would have similar efficacy to currently available therapies but with an improved tolerability/toxicity and administration profile.

Preclinical data led to the hypothesis that pemetrexed may have enhanced antitumor activity compared with other antifolates. Pemetrexed has been tested in chemotherapy-naive patients, as a single agent (Rusthoven et al. 1999; Clarke et al. 2002) or in combination with cisplatin (Manegold et al. 2000; Shepherd 2001). The efficacy results compare favourably with those of other drugs (such as gemcitabine, vinorelbine, and taxanes). In pem/cis phase II trials in NSCLC, tumour response rates were 38.9% and 44.8% and median survival times were 10.9 months and 8.9 months. Pemetrexed/cisplatin was found to be an effective treatment for malignant pleural mesothelioma (Vogelzang et. al. 2005) and for the treatment of 2nd-line NSCLC (Hanna et. al, 2004). Initial toxicity concerns were satisfactorily addressed by vitamin supplementation and now pemetrexed is considered one of the most tolerable chemotherapy agents. Additionally the administration schedule of pemetrexed is more convenient compared to gemcitabine (pemetrexed is a single infusion of 10 minutes on the first day of a 21-day cycle compared to gemcitabine which is given as a 30 minute infusion on day 1 and day 8 of a 21-day cycle). These findings led to a general conclusion that pem/cis could exhibit similar efficacy to gem/cis, may show a better safety profile, and could offer a more convenient treatment option. This was the rationale for designing a non-inferiority phase III trial (JMDB) comparing pem/cis to gem/cis.

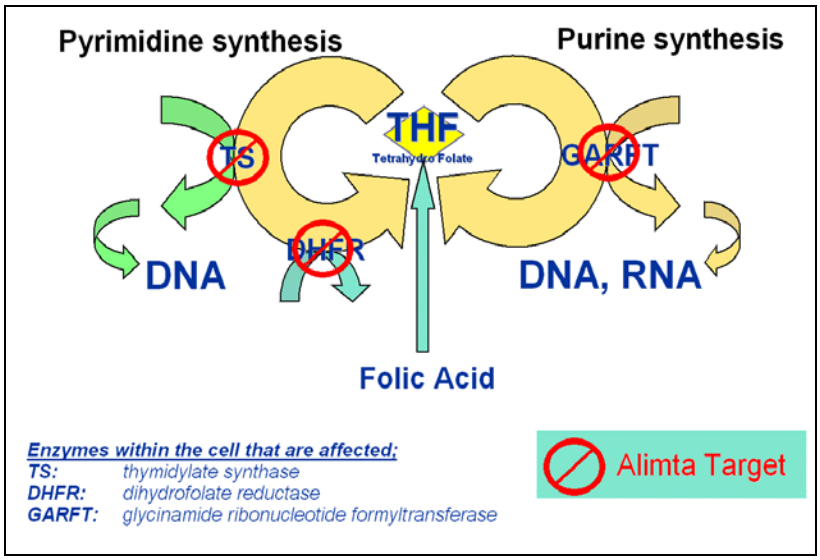
Retrospective analyses of the Hanna et al (2004) trial (in previously treated patients with advanced NSCLC) showed a statistically significant treatment-by-histology interaction, suggesting that pemetrexed produced better survival in non-squamous histologies, compared with docetaxel. Further data observed higher thymidylate synthase (TS) expression levels in squamous cell carcinoma compared with adenocarcinoma (Ceppi et al, 2006). Preclinical data correlated overexpression of TS with reduced sensitivity to pemetrexed in antifolate-resistant cell lines (Sigmond et al.2003, Giovannetti et al.2005) and these results together suggested a plausible biological hypothesis for the clinically observed treatment-by-histology interaction. Therefore, pre-specified histology analyses were included in the statistical analysis plan for the JMDB trial, prior to the trial datalock.

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.

Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells, see Figure 4 for a diagram of pemetrexed mechanism of action.

Figure 4: **Diagram of pemetrexed mode of action**



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

See Figure 3 and accompanying text for the positioning of pem/cis.

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

Comparators

Gemcitabine in the first-line setting is administered with either cisplatin or carboplatin. There is variation between oncologists as to which platinum is preferred. The hydration needed for cisplatin, which requires more hospital time than carboplatin, deters some clinicians from using it. The licensed indication for gemcitabine is in combination with cisplatin. Although in previous years, the majority of use was in combination with carboplatin, the platinum combination agents are now used more equally since publication of a meta-analysis suggesting superior efficacy associated with cisplatin (Jiang et al 2007; Ardizzoni et al 2007).

Histologic diagnosis

There is variation across England and Wales in current practice with respect to histological diagnosis of NSCLC. LUCADA reports 67% of patients had a histological diagnosis in 2006, an optimum rate of 80 – 85%, 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 and the proportion of tumours classified as NOS will decrease.

Treatment cycles

According to clinical experts, four cycles of platinum chemotherapy is standard practice in England and Wales. Data from a large observational pan-European trial in NSCLC demonstrated that the median duration of first-line therapy for gemcitabine plus platinum combination was 12.3 weeks which, based on a 3 week cycle, would equate to 4.1 cycles (Data on File_SELECTTION_cycles, 2008). Ongoing and

published clinical trials involving platinum combinations, approved by regulatory authorities, are based upon 4 cycles of therapy as the accepted reference standard for UK/EU clinical practice.

4.6 Provide details of any relevant guidelines or protocols.

NICE Clinical Guideline No. 24: The diagnosis and treatment of lung cancer

The current NICE guideline recommends that chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status to improve survival, disease control and quality of life. This should consist of a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking into account their toxicities, efficacy and convenience. Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation agent.

SIGN 80: Management of patients with lung cancer

The current SIGN guideline states that chemotherapy with a platinum-based combination doublet regimen should be considered in all stage IIIB and IV NSCLC patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive chemotherapy. It further states that in these patients, the number of chemotherapy cycles given should not exceed four. No particular chemotherapy doublet or platinum agent is recommended in the guideline.

ESMO guidelines

The European Society for Medical Oncology (ESMO) has published clinical recommendations for diagnosis, treatment and follow-up of NSCLC. The recommendation for the treatment of stage IV disease states that "*Platinum-based combination chemotherapy prolongs survival, improves quality of life, and controls symptoms" (ESMO 2001).*

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)?

There is a clear and positive associated between smoking and increasing levels of deprivation as shown by deprivation index finding of the LUCADA database (2007). Lung cancer tends to affect people in lower socio-economic groups.

How has the analysis addressed these issues?

Issues relating to equity and equality were not directly addressed in this submission, as per discussions at the NICE decision problem meeting. However it is important to draw attention to the impact of social disadvantage in making resource allocation decisions.

6. Clinical evidence

A review of the published literature aimed to identify the relevant evidence base for first-line treatments of NSCLC.

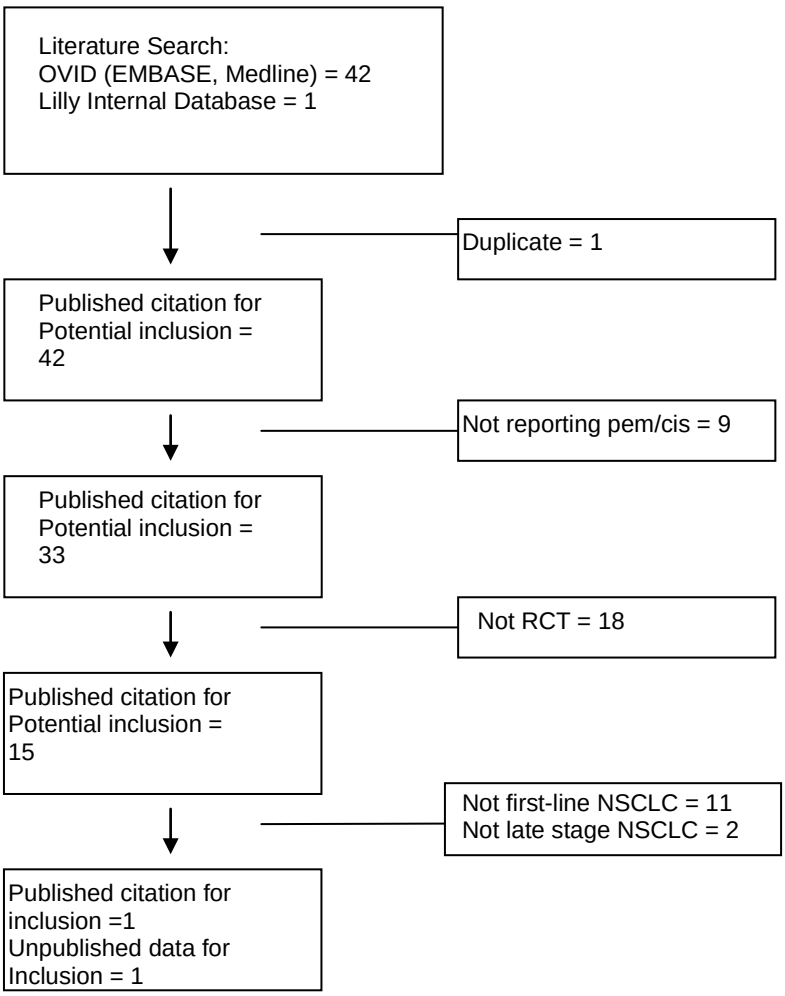
The search strategy is presented in Appendix 10.2.

6.1 Identification of studies

A range of sources was reviewed to identify the pivotal published Phase III randomised controlled trials for each of the main treatment comparators. Phase III randomised controlled trials were sought from the published literature and unpublished data held by Lilly. Full references were also checked for any additional studies that may have provided useful and relevant clinical data.

The literature review looked for any therapies compared with the intervention (pem/cis) in the first-line NSCLC setting. It was then refined to consider only those therapies identified in the decision problem. A protocol was prepared for the literature search, detailing inclusion and exclusion criteria and search terms, search dates and data span searched. Details of these are given in Appendix 10.2.

6.2.1 List of relevant RCTs



In first-line NSCLC, pem/cis has been compared directly to gem/cis in one head-to-head, phase III trial: Scagliotti et al (2008): Scagliotti GV, Parikh P, von Pawel J, et al A randomized phase III trial comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small cell lung cancer J Clin Oncol 2008; 26: 3543-3551.

This paper reports the main findings from the JMDB registration trial for pem/cis in the first-line setting, sponsored by Lilly. Relevant sections of the pem/cis Clinical Study Report (CSR) are used in addition to Scagliotti et al (2008) to support this submission as not all data required for the clinical and economic submission were reported in Scagliotti et al.

Author	Date	Title	Reference
Scagliotti	*2008*	A randomized phase III trial comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small cell lung cancer	*J Clin Oncol* 2008; 26: 3543-3551.
Scagliotti	*16 July 2007*	Clinical Study Report: A Randomized Phase 3 Trial of ALIMTA® and Cisplatin versus GEMZAR® and Cisplatin in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer	

6.2.2 List of relevant non-randomised controlled trials

No non-randomised controlled trials have been included in this submission.

6.2.3 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

Details of ongoing studies are provided in response to question 1.4. There are no additional data from these studies likely to be available in the next 12 months in this indication.

6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

Study design

JMDB was an international, open-label, randomised, phase III, non-inferiority trial comparing overall survival in the experimental arm (pem/cis) to the control arm (gem/cis) as first-line therapy for advanced NSCLC on an intent-to-treat basis. Further analyses of overall survival (OS) based on baseline patient and disease characteristics were pre-specified and performed prospectively. Histological type was included in these characteristics. See Figure 5 for a summary of the trial protocol.

From July 2004 to December 2005 a total of 1725 patients were enrolled into the trial. This was the largest trial in this patient population at the time of publication.

Study sites

This was a multi-centre study that entered 1833 patients at 177 sites in 26 countries. Of these patients, 1725 (94.1%) were randomly assigned (enrolled) to receive either pem/cis or gem/cis. Appendix 10.9 reports the distribution of patients by country and the number of investigational sites in each country.

Study objectives

The primary objective was to demonstrate the non-inferiority of pem/cis to gem/cis for OS in previously untreated patients with locally advanced stage IIIB (not amenable to curative treatment) or stage IV metastatic NSCLC. OS was measured from the date of randomisation to the date of death from any cause; patients that had not died by data lock were censored at the date of last contact.

Secondary endpoints included comparison between the treatment arms for time-to-event efficacy variables:

- progression-free survival time (PFS);
- objective tumour response rates;
- toxicities

Pre-specified histology analyses were included in the statistical analysis plan for the JMDB trial, prior to the trial datalock. The pre-specified analysis of treatment-by-histology was based on the earlier clinical data showing better pemetrexed efficacy in non-squamous histotypes.

Analysis of efficacy by histological group was not in the trial protocol as differential efficacy by histotypes only emerged after the trial protocol had been finalised. However, the statistical analysis was prospective, (planned prior to data lock) and the size of the trial was sufficiently powered.

Interventions

Experimental arm (pem/cis): Pemetrexed 500 mg/m^2 iv infusion over 10 minutes on Day 1 plus cisplatin 75 mg/ m^2 iv infusion administered as per local practice 30 minutes after pemetrexed on Day 1, every 21 days.

Control arm (gem/cis): Gemcitabine 1250 mg/ m^2 iv infusion over 30-60 minutes on Day 1 and Day 8 plus cisplatin 75 mg/m^2 iv infusion administered as per local practice 30 minutes after gemcitabine on Day 1, every 21 days.

Concomitant medications

Both experimental and control arms received prior and concomitant medication with folic acid, vitamin B_{12}, and dexamethasone as recommended in the pemetrexed Summary of Product Characteristics (SPC; see Appendix 10.1).

Concomitant supportive therapies, such as erythropoietic agents or granulocyte colony-stimulating factors were allowed according to the American Society of Clinical Oncology guidelines.

Randomisation

The study randomly assigned patients to receive treatment with pem/cis or gem/cis. The patient and the physician did not know the patient's treatment until the patient was randomly assigned to a treatment arm. A computerised, interactive, voice-activated response system (IVRS) at a central location controlled random assignment.

Investigational sites involved in the trial were also invited to participate in an optional companion biomarker research protocol.

The central randomisation system assigned patients to treatment arms according to a two-step process. First, there was an overall stratification based on whether the investigative centre was participating in the

companion biomarker study (yes versus no). Second, within each of the two overall strata, randomisation occurred independently, according to the method of Pocock and Simon (Pocock and Simon 1975). In each stratum, a given patient was assigned with probability 0.75 to the treatment arm that minimized imbalances among the following equally weighted prognostic factors:

- disease stage (IIIB versus IV)
- ECOG performance status (0 versus 1)
- history of brain metastases (yes versus no)
- sex (male versus female)
- basis for initial pathological diagnosis (histopathological versus cytological)
- investigative centre

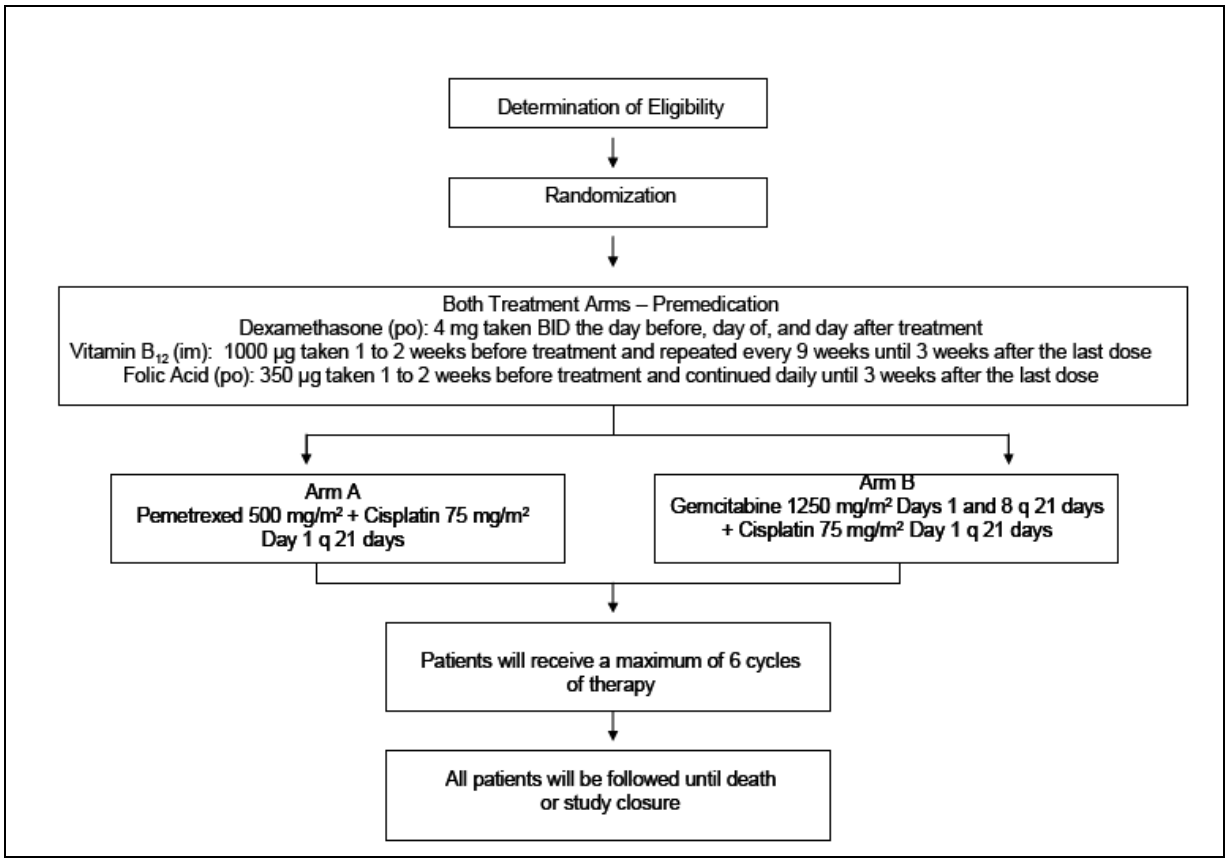
These stratification factors were independent of the pre-specified histology analyses, referred to above.

Blinding

This study was not blinded. This was an open-label study therefore, each patient was aware of his or her own assigned treatment group. At each investigative site, all staff involved in treating and caring for study patients had full knowledge of treatment assignments for those patients under their care. Blinding was not feasible due to different administration schedules, a consideration common to iv cytotoxic trials.

For the accumulated aggregate database, Lilly prospectively scrambled data on treatment assignments and laboratory results. During the trial, scrambling was further expanded to include study drug dose dates. Therefore, Lilly and all investigative sites remained blinded to treatment group assignments for the aggregate database until the final analysis.

Figure 5: **Summary of JMDB study design**



Abbreviations: BID – twice daily, IM,- intramuscular, po - 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 of the following criteria:

- histologic or cytologic diagnosis of NSCLC Stage IIIB (not amenable to curative treatment) or IV American Joint Committee on Cancer Staging Criteria for NSCLC
- no prior systemic chemotherapy for lung cancer
- at least 1 uni dimensionally measurable lesion meeting RECIST criteria
- performance status of 0 or 1 on the ECOG Scale
- at least 18 years of age
- adequate organ function, including the following:
    - Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) ≥1.5 × 109/L, platelets ≥100 × 109/L, and haemoglobin ≥9 g/dL
    - Hepatic: bilirubin ≤1.5 times the upper limit of normal (× ULN), alkaline phosphatase (AP), aspartate transaminase (AST), and alanine transaminase (ALT) ≤3.0 × ULN (AP, AST, and ALT ≤5 × ULN is acceptable if the liver has tumour involvement.)

    - Renal: calculated creatinine clearance (CrCl) ≥45 mL/minute 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 on file
- male and female patients with reproductive potential must have been using an approved contraceptive method, if appropriate (for example, intrauterine device [IUD], birth control pills, or barrier device) during and for 3 months after the study. Female patients with childbearing potential must have had a negative serum pregnancy test within 7 days prior to study enrolment
- estimated life expectancy of ≥12 weeks
- patient compliance and geographic proximity that allowed for adequate follow-up.

Exclusion criteria

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

- 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
- peripheral neuropathy of ≥CTC Grade 1
- inability to comply with protocol or study procedures
- a serious concomitant systemic disorder that, in the opinion of the investigator, would have compromised the patient's ability to complete the study
- 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
- second primary malignancy that was clinically detectable at the time of consideration for study enrolment
- documented brain metastases, unless the patient had completed successful local therapy for central nervous system (CNS) metastases and had been off of corticosteroids for at least 4 weeks before enrolment
- brain imaging was required in symptomatic patients to rule out brain metastases, but was not required in asymptomatic patients.
- presence of clinically detectable (by physical exam) third-space fluid collections; for example, ascites or pleural effusions that could not be controlled by drainage or other procedures prior to study entry
- significant weight loss (that is, ≥10%) over the previous 6 weeks before study entry
- concurrent administration of any other antitumour therapy
- inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents for a 5-day period (8-day period for long-acting agents, such as piroxicam)
- inability or unwillingness to take folic acid or vitamin B_{12} supplementation
- inability to take corticosteroids
- pregnant or breast-feeding.

Table 2: **Baseline patient characteristics**

Characteristic	Pem/cis (n = 862) No of patients	%	Gem/cis (n = 863) No of patients	%
Age, years				
Median (range)	61.1 (29 - 83)		61 (26 - 79)	
Age < 65 years	541	62.8	577	66.9
Age ≥ 65 years	321	37.2	286	33.1
Sex				
Female	257	29.8	258	29.9
Male	605	70.2	605	70.1
Smoking status				
Former/current smoker	629	73	637	73.8
Never-smoker	128	14.8	122	14.1
Unknown	105	12.2	104	12.1
Stage of disease				
Stage IIIB, dry	138	16	159	18.4
Stage IIIB, wet	67	7.8	51	5.9
Stage IV	657	76.2	653	75.7
ECOG performance status				
0	305	35.4	307	35.6
1	556	64.5	554	64.2
Unknown	1	0.1	2	0.2
Pathologic diagnosis				
Histologic	573	66.5	575	66.6
Cytologic	289	33.5	288	33.4
Race				
African descent	18	2.1	18	2.1
White	669	77.6	680	78.8
East/South East Asian	116	13.5	104	12.1
Other	59	6.8	61	7.1
Histologic type*				
Adenocarcinoma	436	50.6	411	47.6
Large-cell carcinoma	76	8.8	77	8.9
Squamous cell carcinoma	244	28.3	229	26.5
Other: NSCLC, NOS	106	12.3	146	16.9

ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; NOS = not otherwise specified.

*Histologic type was reported by the investigative site. Investigators were asked to provide histology by usual practice. Typically, investigators provide the most specific information that has been provided on a pathology report. The only other information that they were asked to provide is whether it was based on cytological or histological basis.

Summary point on patient characteristics

The baseline patient demographic characteristics, disease characteristics and prognostic factors were well balanced between the treatment arms. Among all randomized patients the median age was 61 years in both arms. The majority of patients were Caucasian (78% in the pem/cis arm and 79% in the gem/cis arm), most were male, (70% in both arms), and reported ever using tobacco (73% pem/cis and 74% gem/cis).

Similarly, most patients had stage IV disease (76% both arms) and ECOG performance status of 1 (65% in the pem/cis arm and 64% in the gem/cis arm). In both arms adenocarcinoma was the predominant

histological type (51% pem/cis and 48% gem/cis), followed by squamous cell carcinoma (28% pem/cis and 27% gem/cis).

The trial characteristics were mapped onto the patient characteristics from the LUCADA database. The LUCADA database represented 57% of all cases of lung cancer in England and Wales for 2006-07. Comparing the two populations, patients in the trial were younger, median age for LUCADA patients was 71 years. Patients in LUCADA had poorer performance status: in the trial 100% had PS 0-1, in LUCADA only 43% had PS 0-1, however, the LUCADA database refers to all patients, including those not treated with chemotherapy.

More than 60% of LUCADA patients had a histological diagnosis, but the distribution was quite different, as shown in Table 3.

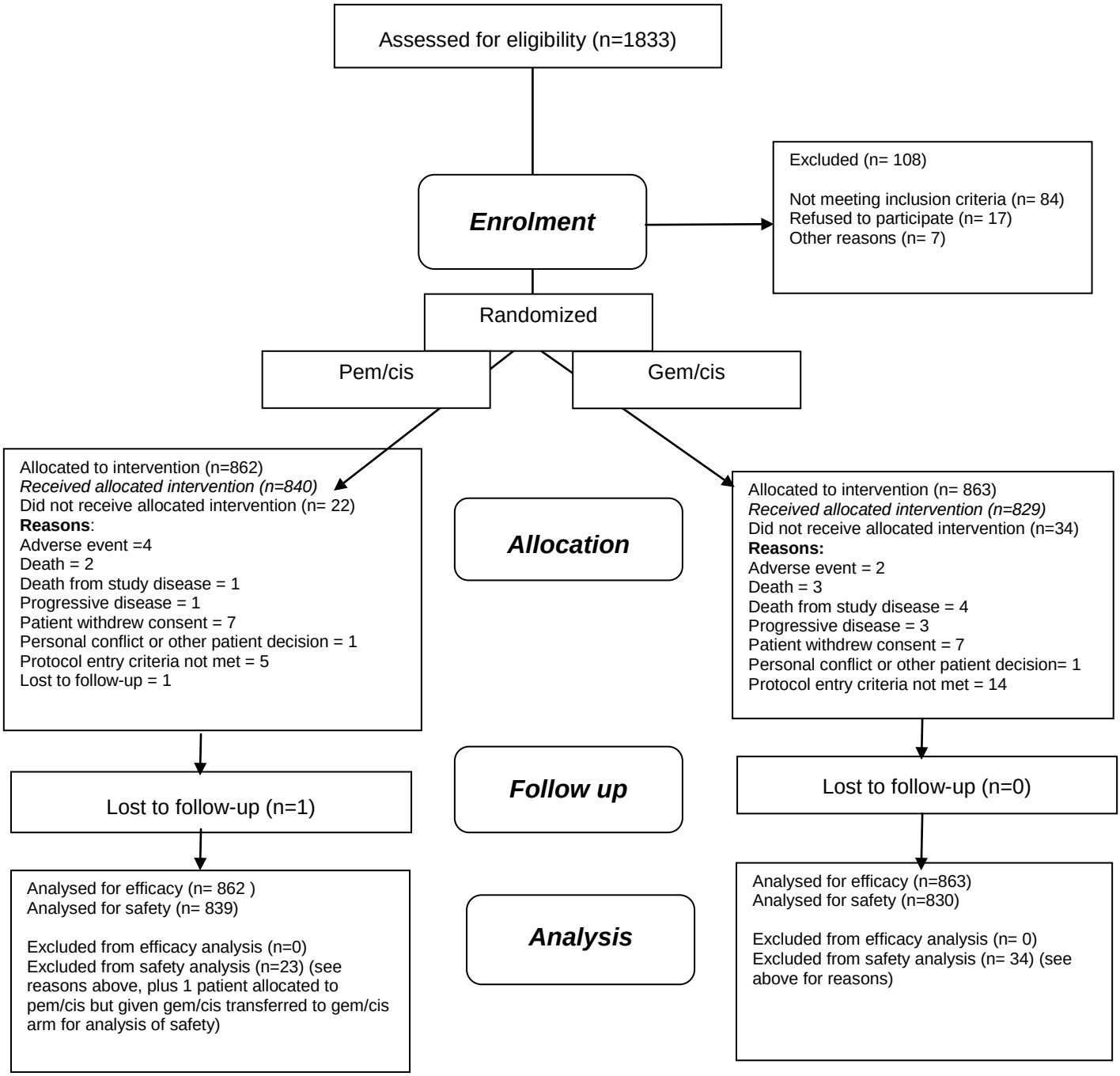
Table 3: **Variation in histotype between England and Wales audit data (LUCADA 2007) and the JMDB trial (Scagliotti et al 2008)**

	Squamous cell carcinoma	Adenocarcinoma	Large-cell carcinoma	NSCLC – NOS*
LUCADA 2007	33%	25%	4%	36%
Scagliotti *et al* 2008	27%	49%	9%	15%

The main differences are in the adenocarcinoma and NSCLC-NOS groups. Scagliotti et al (2008), reports a larger proportion of adenocarcinoma but fewer NSCLC-NOS than LUCADA. This is in part due to the changing proportion of European patients in whom adenocarcinoma is is identified over time due to changes in gender and smoking patterns across Europe.

6.3.3 Patient numbers (from www.Consortstatment.org)

CONSORT diagram of the study. A total of 1,669 patients (96.8%) received study treatment consisting of at least one dose of pem/cis; n = 839 or gem/cis; n = 830. One patient was assigned to the pem/cis arm but received gem/cis treatment. This patient was included in the gem/cis arm for the safety evaluation.



Following randomisation, each patient underwent a treatment period and a follow-up period. The treatment period consisted of up to 6 treatment cycles, each 21 days long. The follow-up period began when the treatment period ended. Patients were to be followed up with periodic tumour response evaluation [every 6 weeks] until disease progression. All patients were followed until death or study closure.

The length of the study was two years and six months. The first patient was enrolled on 6 July 2004. The final analyses for this study were planned after 1190 patients randomized to treatment were known to have died. After 1190 death events were confirmed by Lilly, the database was locked on 09 March 2007. At the time of final data-lock, the total number of deaths was 1270.

Datasets analysed

Of the 1833 idenitifed patients, 1725 (94.1%) were enrolled (randomised), the remainder did not meet the inclusion criteria. All 1725 randomised patients (pem/cis n=862; gem/cis n=863) were included in the primary analysis of overall survival (OS) and the secondary time-to-event analyses (PFS, TtPD, and TtTF), which are the intent-to-treat analyses as described in the study protocol.

All patients (n=1669) who received at least one dose of pemetrexed, gemcitabine, or cisplatin were evaluated for safety.

- 839 received at least one dose of pemetrexed or cisplatin
- 830 received at least one dose of gemcitabine or cisplatin

Median overall survival was also tested by histological sub-group, patient numbers reported in the table below.

Table 4: **Number of patients by group**

Population	Numbers analysed
All randomised patients (intent-to-treat)	(N=1725)
Patients with squamous histology	(N=473)
Patients with non-squamous histology	(N=1252)
Target population (adeno & large cell carcinoma)	(N=1000)
Patients with adenocarcinoma	(N=847)
Patients with large cell carcinoma	(N=153)
Patients with NSCLC - NOS	(N=252)

6.3.4 Outcomes

Efficacy evaluations

Within two weeks of enrolment, a physical examination was performed for the measurement of palpable tumour lesions. Tumour response in patients was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) (Appendix 10.4). Within four weeks before the first dose of study drug, baseline tumour measurement(s) were performed on each patient and the study protocol specified that the same method used at baseline must be used consistently for tumour assessment and will be repeated every two cycles except in the event of a response.

The efficacy measure (OS, PFS, TTP, duration of response) was censored for that analysis at the date of last prior contact.

Quality of life data were not collected in JMDB.

Table 5: **Outcome measures, definitions and follow-up**

Outcome	Definition	Measure	Follow-up (median)
Primary outcomes			
Overall survival	Duration is measured from the date of randomisation to the date of death from any cause	Death	N/A
Secondary outcomes			
Progression-free survival	Duration is 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	Every two cycles except in the event of a response. The study protocol specified that the same method used at baseline must be used consistently for tumour assessment
Clinical Progression	Defined as other evidence of progression that was not based on RECIST and hence not based on tumor measurements	Investigator assessment of patient symptoms	Every two cycles except in the event of a response
Objective Progression	Defined as progression based on RECIST using tumor measurements	RECIST – based on computed tomography (CT), including spiral CT, scans and magnetic resonance imaging (MRI), or in some cases chest X-rays	Every two cycles except in the event of a response. The study protocol specified that the same method used at baseline must be used consistently for tumor assessment
Time to progressive disease	Measured from the date of randomisation to the first date of progression of disease	RECIST – based on computed tomography (CT), including spiral CT, scans and magnetic resonance imaging (MRI), or in some cases chest X-rays	Every two cycles except in the event of a response. The study protocol specified that the same method used at baseline must be used consistently for tumor assessment
Safety	Adverse events were reported using the Medical Dictionary for Regulatory Activities (MedDRA), Version: 10.0.	Investigators assessed the causality of any adverse event experienced by a patient and graded it using the Common Toxicity Criteria (CTC) rating scale (v2.0, NCI 1998).	N/A

6.3.5 Statistical analysis and definition of study groups

Using a non-inferiority design, this study compared overall survival between the two treatment arms using a fixed margin method. Assuming a hazard ratio (HR) of 1.0 and including all randomly assigned patients, when at least 1,190 deaths occurred, the analysis provided 80% power to reject the null hypothesis (H0). The H0 assumed that gem/cis would provide a 15% reduction in the risk of death over pem/cis,

corresponding to a fixed margin of 1.176. Using the Cox proportional hazards model (with pre-planned stratification factors - sex, diagnosis [histologic v cytologic], disease stage, and performance status) and two-tailed 95% CIs for the HR, rejection of the H0 occurred when the upper bound of the HR's 95% CI was less than 1.176.

Cox proportional hazard models were also used to compare the other time-to-event end points between the treatment arms and to test for treatment-by-histology interaction; the Kaplan-Meier method was used to estimate the medians for time-to-event parameters. Tests were conducted as follows: non-inferiority tests at one-sided $\alpha = .025$ level; superiority tests at two-sided $\alpha = .05$ level; and two-sided CIs at 95%. Tumour response was compared using the normal approximation test for superiority. The incidences of toxicities, hospitalizations, and supportive care were analysed using Fisher's exact test and analysis of variance (as appropriate). Prespecified analyses of overall survival by random assignment factors and additional factors included age group, race, smoking status, and histology. All HRs are reported as adjusted, unless otherwise specified. P values were not adjusted for multiple comparisons.

6.3.6 Critical appraisal of relevant RCTs

NICE evaluative criteria	Scagliotti trial
How was allocation concealed?	Allocation was not concealed as this was an open-label trial due to differing administration schedules for each arm.
What randomisation technique was used?	A computerised, interactive, voice-activated response system (IVRS) at a central location controlled random assignment.
Was a justification of the sample size provided?	Sample size justification is provided in section 6.4.5. Of note, this is the largest study in this patient population to date.
Was follow-up adequate?	Yes. Each patient underwent a treatment period and a follow-up period. The treatment period consisted of 21-day treatment cycles. Patients received up to 6 cycles of assigned treatment. The follow-up period began when the treatment period was completed. Patients were to be followed up with periodic tumour response evaluation until disease progression. All patients were followed until death or study closure (length of the study 30 months). Of the 1725 (ITT) patients that entered the trial, 1270 deaths had occurred at the time the database was locked.
Were the individuals undertaking the outcomes assessment aware of allocation?	Yes, this was an open-label trial
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	The trial design was parallel-group. Subsequent therapy was at investigator discretion, so some crossover did occur. The rate of crossover was low and unlikely to affect the comparison of survival between treatment arms. Overall, fewer patients on the pem/cis arm received post study systemic anticancer treatment (chemotherapy, targeted therapy, or immunotherapy) than patients on the gem/cis arm (52.6% versus 56.1%), and significantly fewer patients on the pem/cis arm received chemotherapy agents post study (41.5% versus 47.3%, p=0.018). Details of post study chemotherapy are provided in appendix 10.8.
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?	This was a multi-centre trial in 26 countries with majority of the patients coming from Western Europe. Approximately 3% of patients were from the UK. Germany recorded the highest number of patients enrolled in the trial (11%). The study was closely monitored to identify and evaluate any violations of good clinical practice (GCP) and clinically important protocol violations (defined as those deviations from the protocol that could have potentially affected patient safety, data integrity, or the conclusions drawn from the study). Overall, the number of protocol violations in this study was balanced between treatment arms and low in incidence, such that they were not likely to have affected the analyses or conclusions of this trial.

NICE evaluative criteria	Scagliotti trial
How do the included in the RCT participants 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.	The baseline patient, disease characteristics, and prognostic factors were well balanced between treatment arms. Patients in JMDB were generally fitter (PS0-1), younger compared to average lung cancer patients in the UK (LUCADA, 2007). This can be expected for a clinical trial in which the inclusion criteria restrict patients entered in order to limit confounding factors. More patients have adenocarcinoma and fewer have NSCLC-NOS than seen in LUCADA. This is likely to be a result of changing histology distributions that show adenocarcinoma increasing as the proportion of men to women with lung cancer decreases as the effect of more women smoking and static male smoking rates present themselves in the lung cancer incidence statistics.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	See section 6.4.1 for dosage regimens. These are in line with the SPC
Were the study groups comparable?	Yes, the treatment arms were well balanced with respect to demographic characteristics.
Were the statistical analyses used appropriate?	See section 6.4.5 above for statistical analyses
Was an intention-to-treat analysis undertaken?	Yes. ITT was undertaken for efficacy evaluations, but randomised and treated (patients who received at least one dose of pem/cis or gem/cis) were analysed for safety.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	There are no confounding factors.

6.4 Results of the relevant comparative RCTs

The results below are presented for the overall ITT population then each of the histological populations:

- squamous cell carcinoma
- large cell carcinoma
- adenocarcinoma
- NSCLC NOS

The pemetrexed licence is based on all three latter populations, known as the non-squamous population. The target population for the submission is the adenocarcinoma and large cell populations.

Scagliotti et al (2008) clinical paper is based on study JMDB. The authors report results for the adenocarcinoma and large cell population but refer this group as the 'non squamous' population although in this submission this is referred to as the target population. Technically the non-squamous population is the licence population and should include large cell, adenocarcinoma and NSCLC-NOS, as explained above.

Table 6: **Explanation of the Histological population for JMBD**

Pemetrexed Licence	Scagliotti et al 2008	Submission
Other than predominantly squamous = large cell, adeno and NSCLC NOS	Non-squamous = adeno and large cell carcinoma	Target population= adeno and large cell carcinoma

Outcomes

The mean number of treatment cycles administered in the trial was just over four, on both arms, with a median of five (Table 7). Dose adjustments (delays, reductions and omissions) were less frequent in patients treated with pem/cis compared with those treated with gem/cis.

Table 7: **Dose adjustments, reductions, omissions and delays in intent-to-treat population (Scagliotti et al. 2008)**

Cycle and dose adjustment	Pem/cis (n=839)	Gem/cis (n=830)
No of cycles per patient		
Median (range)	5.0 (1-7*)	5.0 (1-8**)
Total number of cycles administered (mean)	3,648 (4.4)	3,626 (4.4)
Dose adjustment on Day 1		
Pemetrexed (Number [%])	54 [1.5%]	-
Gemcitabine (Number [%])	-	362 [10%]
Cisplatin (Number [%])	64 [1.8%]	154 [4.2%]
Doses omitted on Day 8		
Gemcitabine (Number [%])	Not applicable	339 [9.3%]

*One patient on the cisplatin/pemetrexed arm received more than six cycles.

**Four patients on the cisplatin/gemcitabine arm received more than six cycles.

Efficacy Results

Primary Efficacy Outcome - Overall survival

The study met its primary endpoint of non-inferiority for pem/cis compared to gem/cis for OS in all randomised patients (ITT). Median survival was 10.3 vs.10.3 months for both arms (HR 0.94, 95% CI 0.84-1.05) with the upper CI for the HR well below the 1.176 non-inferiority margin (Table 8).

The pre-planned analyses evaluating the differences in OS showed a differential effect on survival according to histology subtype (classified as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and “other”). OS was statistically significantly better for pem/cis patients with adenocarcinoma and large cell carcinoma than for gem/cis patients with these histologies, according to Cox-adjusted and Kaplan-Meier analyses. In patients with adenocarcinoma, median survival exceeded 12 months, a first in advanced NSCLC with a doublet. The Kaplan-Meier OS curves for all patients (ITT), non-squamous group (pemetrexed licence population) and each of the histologic groups that make up the non-squamous group are shown below.

Table 8: **Analysis of median OS (Scagliotti et al. 2008; Data on file_JMDB_OS data, 2008; Data on file_JMDB_OS significance testing, 2008)**

Patient Group	Median OS (months) (95% CI)		Adjusted HR (95% CI)	p-value (superiority)
	Pem/cis	Gem/cis		
All randomised patients (N=1725)	10.3 (9.8-11.2)	10.3 (9.6-10.9)	0.94 (0.84-1.05)	p<0.001** p=0.259*
Patients with squamous histology (N=473)	9.4 (8.4-10.2)	10.8 (9.5-12.2)	1.23 (1.00-1.51)	p=0.050*
Patients with non-squamous histology (N=1252)	11.0 (10.1-12.5)	10.1 (9.3-10.9)	0.84 (0.74-0.96)	P=0.011*
Target patients: adeno & large cell carcinoma (N=1000)	11.8 (10.4-13.2)	10.4 (9.6-11.2)	0.81 (0.70-0.94)	p=0.005*
Patients with adenocarcinoma (N=847)	12.6 (10.7-13.4)*	10.9 (10.1-11.9)*	0.84 (0.71-0.99)	p=0.033*
Patients with large cell carcinoma (N=153)	10.4 (8.6–14.1)*	6.7 (5.5-9.0)*	0.67 (0.48-0.96)	p=0.027*
Patients with NSCLC - NOS (N=252)	8.6 (6.8-10.2)	9.2 (8.1-10.6)	1.08 (0.81-1.45)	p=0.586*

* Data on file; ** non-inferiority NOS – not otherwise specified

These results demonstrate that pem/cis is non-inferior to gem/cis in all NSCLC patients for overall survival and that pem/cis has superior OS compared to gem/cis in the target population (adeno & large cell carcinoma).

Based on the evidence from this study, pem/cis has been granted a licence for the non-squamous population (i.e adenocarcinoma, large cell carcinoma and not otherwise specified NSCLC). In this combined group, the survival gain of pem/cis over gem/cis was also statistically significant.

Figure 6: **Kaplan-Meier overall survival curves for all patients randomised/ ITT, N=1725**

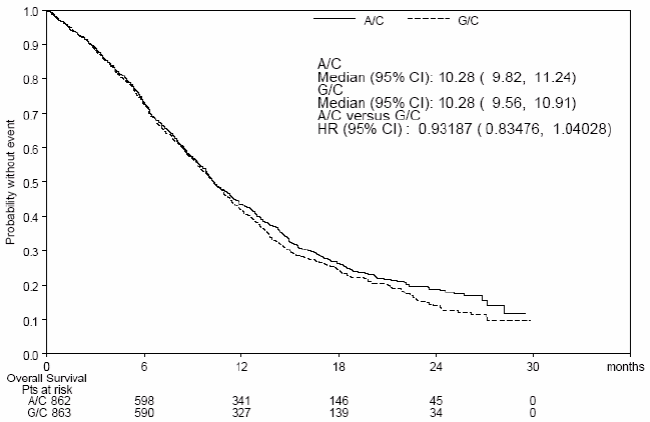


Figure 7: **Kaplan-Meier overall survival curves for non-squamous (licensed) population N=1252**

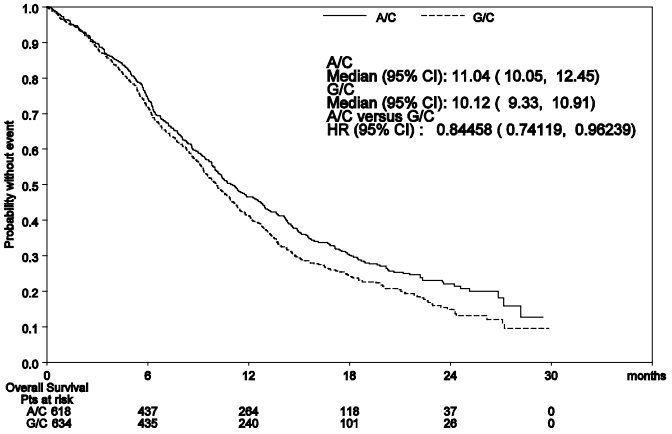


Figure 8: **Kaplan-Meier overall survival curves for all patients with large cell histology, N=153**

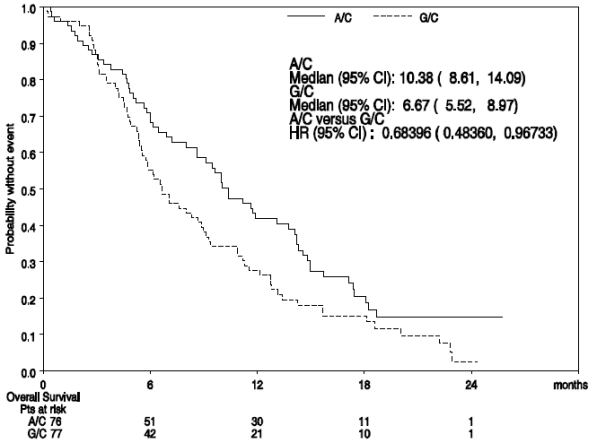


Figure 9: **Kaplan-Meier overall survival curves for all patients with adenocarcinoma histology, N=847**

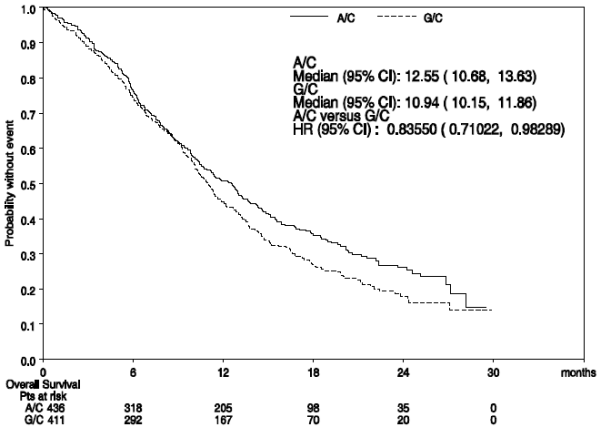
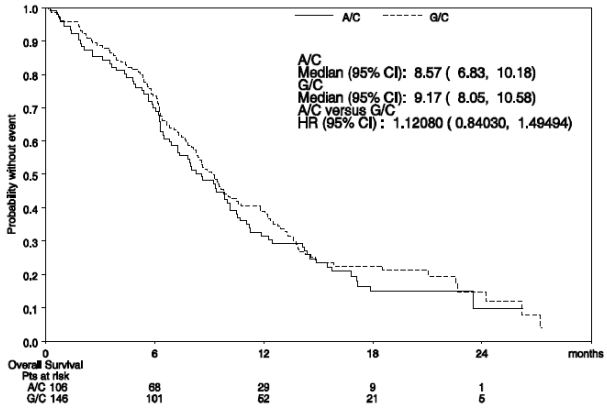


Figure 10: **Kaplan-Meier overall survival curves for all patients with 'not otherwise specified' histology, N=252**



Survival Rates

Survival rates at 12 months and 24 months were also reported. For the ITT population, 12 month survival was 44% for pem/cis and 42% for gem/cis and 24 month survival was 18.9% for pem/cis and 14.0% for gem/cis. In the non-squamous population, the 12 month survival was 44% and 41% (pem/cis vs. gem/cis) and 24 month survival was 22% and 13% (pem/cis vs. gem/cis).

In the target population (adeno & large cell carcinoma), 12 month survival was 49% and 42% (pem/cis vs. gem/cis) and 24 month survival was 24% and 15% (pem/cis vs. gem/cis).

Secondary Efficacy Outcomes

Progression-Free Survival

Progression-free survival was also non-inferior for all patient groups (Table 9).

Table 9: **Median progression free survival (Scagliotti et al.2008; Data on file_JMDB_PFS data 2008)**

Patient Group	Median progression-free survival (months) (95% CI)		Adjusted HR (95% CI)
	Pem/cis	Gem/cis	
All randomised patients (N=1725)	4.8 (4.6 - 5.3)	5.1 (4.6 - 5.5)	1.04 (0.94 - 1.15)
Patients with non-squamous histology (N=1252)	5.3 (4.7-5.5)	5.0 (4.6-5.4)	0.95 (0.84 – 1.06
Target patients: adeno & large cell carcinoma (N=1000)	5.3 (4.8-5.7)	4.7 (4.4-5.4)	0.90 (0.79-1.02)
Patients with adenocarcinoma (N=847)	5.5 (4.9-5.7)	5.0 (4.5-5.5)	0.90 (0.78-1.03)
Patients with large cell carcinoma (N=153)	4.4 (3.0-5.8)	4.2 (3.5-4.7)	0.89 (0.65-1.24)
Patients with NSCLC - NOS (N=252)	4.5 (4.0-5.5)	5.6 (4.7-5.9)	1.28 (0.99-1.67)

*Data on file

Tumour response rates

The publication by Scagliotti et al, 2008 reports objective tumour response data for the 'tumour response-qualified patients' which is defined as all randomised patients who had eligible disease, did not take prohibited anticancer therapy prior to study treatment discontinuation, had a baseline scan and at least one follow-up scan, and received at least one dose of study treatment. The population eligible was pem/cis N=762 and gem/cis N=755. Therefore the tumour response rates reported in Scagliotti (2008) are calculated as follows:

Pem/cis: 234/762 = 30.6% compared to gem/cis: 213/755 = 28.2% (*p*=0.243)

The data presented below are based on the ITT population and have been reported for the purpose of supporting the economic evaluation and significance test results are not available for all comparisons.

Table 10: **Tumour response rates based on ITT population (Data on file_JMDB_Response Rates, 2008)**

	Pem/cis	Gem/cis
ITT population	**n=862**	**n=863**
Response rate	27.15%	24.68%
Non-squamous histology	**n=618**	**n=634**
Response rate	28.64%	22.24%
Adenocarcinoma	**n=436**	**n=411**
Response rate	28.90%	21.65%
Large cell carcinoma	**n=76**	**n=77**
Response rate	27.63%	27.27%

* There is no data for the proportion of gem/carbo or doc/cis patients responding by cycle 3, so response rates are assumed to be that of gem/cis

6.5 Meta-analysis

Data for the primary comparison of pem/cis vs gem/cis were available from the head-to-head trial, JMDB. For the secondary comparisons, data for gem/carbo and doc/cis were available from a simple indirect analysis described below.

6.6 Indirect/mixed treatment comparisons

An indirect comparison was carried out in order to be able to compare data for the secondary comparators (gem/carbo and doc/cis) with pem/cis. The decision to use the indirect analysis method was made after the literature review produced only two references that met the inclusion criteria that would allow comparison of pem/cis with gem/carbo and doc/cis using gem/cis as the intermediary therapy. While this method reduces the volume of data available it also reduces the uncertainty associated with the adjusted indirect analysis.

The populations in the studies were similar enough that adjustment for baseline charactertistics was not needed. Adjustment for histotype was part of the analysis.

Choice of comparator

Gemcitabine with a platinum accounts for over 80% market share in this patient group (UK Market Research Data, 2008). The licence for gemcitabine is in combination with cisplatin (rather than carboplatin) and gem/cis is more widely used globally. Therefore gem/cis is the primary comparator in this submission. A secondary comparison between pem/cis and gemcitabine/carboplatin (gem/carbo) has also been conducted.

In addition, docetaxel plus cisplatin (doc/cis) has been assessed in comparison with pem/cis as an example of these alternative first-line platinum doublet combinations that do not require a Day 8 administration, as agreed at the Decision Problem meeting.

Other regimens used in England and Wales in the first-line advanced NSCLC setting include vinorelbine plus cisplatin or carboplatin, and paclitaxel or docetaxel plus cisplatin or carboplatin. The total market share of these combinations is only approximately 15% of the first-line NSCLC market.

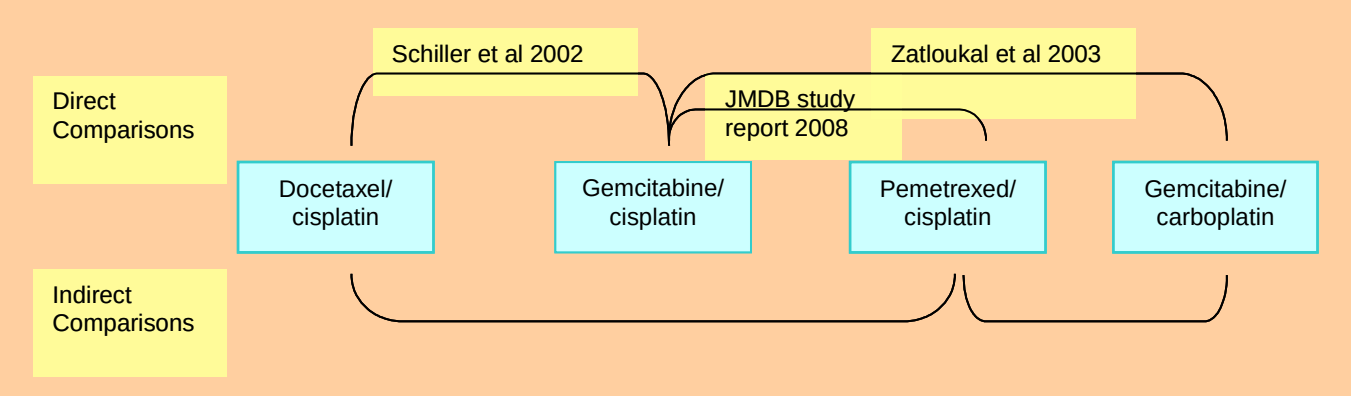
No head-to-head trial data exist comparing pem/cis to doc/cis or gem/carbo. For the comparison of pem/cis to these therapies, an indirect comparison was carried out using gem/cis (the comparator in the JMDB trial) as the link. The data in the indirect analysis were collected from a systematic literature review, described in Appendix 10.2.

For gem/carbo, only one head-to-head trial phase III trial was identified that met all the inclusion criteria, comparing gem/carbo with gem/cis (Zatloukal et al. 2003). Similarly, for doc/cis, only one phase III trial made the relevant comparison against gem/cis (Schiller et al. 2002). Summary details of each trial are provided in Tables 11 and 12. Additional details, including methodology are provided in Appendix 10.6.

Method for indirect analysis

In order to compare gem/carbo and doc/cis with pem/cis, a hazard ratio for each (gem/carbo and doc/cis) versus gem/cis was calculated. The hazard ratio was based on median overall survival (OS).

Figure 11: **Indirect comparison**



To do this, hazard rates for both gem/cis and gem/carbo were calculated based on the median OS data reported in Zatloukal et al (2003). The formula for calculating a hazard rate is given below with a worked example.

Formula	Worked example
Hazard rate = LN(2)/median OS	LN(2)/37.91 = 0.0183 LN(2)/34.53 = 0.0201

The values used in the table: 37.91 and 34.53 are the median overall survival, in weeks, for gem/cis and gem/carbo respectively, as reported in the Zatloukal paper. They were converted into weeks from 8.7 months (gem/cis) and 8.0 months (gem/carbo).

The two hazard rates are then divided to get a hazard ratio for gem/cis vs gem/carbo:

1.

Hazard ratio = 0.0201/0.0183

Hazard ratio = 1.098

This hazard ratio was then applied to the hazard rate of the gem/cis arm in the JMDB trial - to get an adjusted hazard rate for gem/carbo. The hazard rate for the gem/cis arm of the JMDB trial is calculated in the same way as the hazard rate for the gem/cis and gem/carbo in the Zatloukal trial:

2.

LN (2) / 47.41 = 0.01462

(47.41 is the median OS in weeks, for adenocarcinoma patients treated with gem/cis from the JMDB study, or 10.9 months)

Therefore, applying the gem/cis hazard rate from JMDB (0.01462) to the hazard ratio for gem/cis:gem/carbo (1.098) gives the hazard rate for gem/carbo adjusted for the JMDB population for the indirect analysis:

3.

0.01462*1.098 = 0.01605

By inputting this value into the formula we started with, the median OS in weeks for gem/carbo, adjusted for the JMDB population can be calculated:

4.

LN(2)/0.01605 = 43.19

43.19 weeks is the median overall survival estimate for gem/carbo in the adenocarcinoma population.

The same method was used to calculate the adjusted OS estimates for doc/cis, except that the hazard ratio for gem/cis vs doc/cis had already been calculated in the le Chevalier paper (Le Chevalier 2005), so the calculations started at step 3.

Adjustment for histology in the indirect analysis

Zatloukal and Schiller do not report OS by histology group. However, the hazard ratios for gem/carbo and doc/cis are multiplied by the gem/cis hazard rate from the JMDB study. There is a gem/cis hazard rate for each histology group in the JMDB study. In that way, the estimates for gem/carbo and doc/cis are adjusted for each histology group.

It is important to note that step 2 above, adjusts gem/carbo and doc/cis data by histotype. The assumption made is the gem/carbo and doc/cis behave in the same way as gem/cis and do not demonstrate by-histotype differences in outcomes, any variation in outcome is due to variation in population sizes or natural variation in the population (Hirsch et al 2008).

These studies were relatively homogenous in terms of patient population and when compared to the JMDB trial. There were some slight discrepancies in doses, discussed further below, insufficient to suggest these studies could not be used in an indirect analysis. Only the JMDB trial (Scagliotti et al.2008), presents results by histological type (Einhorn 2008). The data for gem/carbo vs. gem/cis and doc/cis vs. gem/cis are for all NSCLC patients. We have assumed therefore, that gem/carbo and doc/cis will behave in the same way as gem/cis, with no differential efficacy by histotype observed, although prognosis differs across groups.

Table 11: **Summary details of Zatloukal et al. and Schiller et al. clinical trials**

	Trial design	Patient Population	Dosage regimes	Primary endpoint	Secondary endpoint
Zatloukal et al. (2003)	Randomised, multicentre, phase III trial conducted between December 1999 and December 2001. Nine centres participated.	Chemotherapy naive patients with NSCLC classified as stage III, stage IV or recurrent with a Karnofsky performance status of at least 70 (this equates to an ECOG performance status of 0-1)	Gemcitabine 1200mg/m^2 + cisplatin 80mg/m^2 Gemcitabine 1200mg/m^2 + carboplatin AUC 5 Maximum of six cycles allowed	Tolerability	Tumour response, duration of response, time to progressive disease and survival
Schiller et al. (2002)	Randomised, multicentre phase III trial conducted between October 1996 and May 1999.	Chemotherapy naive patients with NSCLC classified as stage III or stage IV with an ECOG performance status of 0,1,or 2	Paclitaxel 135mg/m^2 + cisplatin 75mg/m^2 Gemcitabine 1000mg/m^2 + cisplatin 100mg/m^2 Docetaxel 75mg/m^2 + cisplatin 75mg/m^2 Paclitaxel 225mg/m^2 + carboplatin AUC6 No maximum number of cycles specified	Survival	Tumour response, time to progressive disease and toxicity

Table 12: **Summary eligibility criteria**

Study	Eligibility criteria
Zatloukal et al. (2003)	Inclusion criteria ▪ Chemonaive patients with histologic or cytologic diagnosis of NSCLC who were not eligible for curative surgery or radiotherapy. ▪ Patients between ages of 18 and 75 years, with bi-dimensionally measurable lesions at least 1 cm by 1 cm (or 2 cm by 2 cm by physical examination) ▪ Prior radiation therapy was permitted as long as the irradiated area was not the only source of measurable disease. ▪ No other form of therapy was allowed for at least 3 weeks before entering the study. ▪ Patients with an estimated life expectancy of at least 12 weeks and adequate bone marrow reserve Exclusion criteria ▪ Patients with active infection, symptomatic central nervous system metastases, pregnancy, second primary malignancy, or serious concomitant systemic disorders incompatible with the study ▪ Patients with inadequate liver function or inadequate renal function
Schiller et al. (2002)	Inclusion criteria. ▪ Confirmed disease, measurable or not measurable; an age of at least 18 years; and adequate haematological, hepatic and renal function ▪ Prior radiation therapy at symptomatic sites was permitted provided that the indicator had not been irradiated and that the radiation therapy had been completed before chemotherapy was initiated. ▪ Patients with stable brain metastases Exclusion criteria Patients who had received prior chemotherapy

The indirect analysis also adjusted adverse events rates to ensure they were standardised to the gem/cis arm in the JMDB trial.

Table 13: **Baseline patient and disease characteristics**

Study	Scagliotti et al.(2008) – JMDB Trial		Zatloukal et al. (2003)		Schiller et al. (2002)	
Treatment	pem/cis (n=862)	gem/cis (n=863)	gem/cis (n=87)	gem/carbo (n=89)	gem/cis (n=301)	doc/cis n=304)
Demographics	Male: 70.2% Female: 29.8% Median age: 61.1years (Range: 29-83 years)	Male: 70.1% Female: 29.9% Median age: 61 years (Range:26-79 years)	Male: 77% Female: 23% Median age: 63 years (Range: 39-75 years)	Male: 76% Female: 24% Median age: 62 years (Range: 46-76 years)	Male: 62% Female: 38% Median age: 64 years (Range: 32-87 years)	Male: 63% Female: 37% Median age: 63 years (Range: 34-84 years)
ECOG Performance Status	0: 35.4% 1: 64.5%	0: 35.6% 1: 64.2%	Karnofsky >80: 69%* " >70 <80: 31%*	Karnofsky>80: 67%* " >70 <80: 33%*	0: 33% 1: 62% 2: 5%	0: 32% 1: 62% 2: 6%
Stage of disease	IIIB, dry: 16% IIIB, wet: 7.8% IV: 76.2%	IIIB, dry: 18.4% IIIB, wet: 5.9% IV: 75.7%	IIIB: 41% IV: 59%	IIIB: 38% IV: 62%	IIIB: 14% IV or recurrent disease: 86%	IIIB: 14% IV or recurrent disease: 86%
Histologic type	Squamous: 28.3% Adenocarcinoma: 50.6% Large cell: 8.8% Others: 12.3%	Squamous: 26.5% Adenocarcinoma:47.6% Large cell: 8.9% Others: 16.9%	Squamous: 56% Adenocarcinoma: 26% Large cell: 7% Others: 10%	Squamous: 46% Adenocarcinoma: 33% Large cell: 7% Others: 15%	Not reported	
Number of cycles	Patients received a median number of 5 cycles (range 1-8)		Patients received a median number of 4 cycles (range 0-6).		Not reported	

*It is assumed for the pupose of this submission that a Karnofsky score > 70 is equivalent to a PS ≤2

Results

Patient Baseline Characteristics

In both studies, the patient characteristics were well balanced between the treatment groups and comparable to those of the JMDB trial (Table 13).

Efficacy results

There median overall survival results were comparable among the treatment groups in either of the studies (Table 14). These results compare with those observed in the JMDB trial

Table 14: **Median OS (months)**

Study	Treatments	Median overall survival (months)
Zatloukal et al. 2003	Gem/cis vs. Gem/carbo	8.75 vs. 8.00
Schiller et al. 2002	Gem/cis vs. Doc/cis	8.1 vs. 7.4
Scagliotti et. al. 2008	Pem/cis vs. Gem/cis	10.3 vs. 10.3 (all randomised patients)
		11.0 vs 10.1 (non-squamous patients)
		11.8 vs. 10.4 (target population: adeno & large cell carcinoma)
		12.6 vs. 10.9 (adenocarcinoma patients)
		10.4 vs. 6.7 (large cell carcinoma patients)

The outcomes reported in the three studies were adjusted in the indirect comparison, so the data are directly comparable. Results for OS and PFS are reported in Table 15, the calculations used to derive these values are reported in Appendix 10.7.

Table 15: **Overall survival and progression-free survival, results from the indirect analysis for licensed and target population**

	pem/cis	gem/cis	Gem/carbo	doc/cis
non-squamous histology	**(n=618)**	**(n=638)**	**(n=89)**	**(n=289)**
Median overall survival (months) (95% CI)	11.0	10.1	9.2	9.5
Median PFS (months)	5.26	4.96	4.01	4.32
Target population: adeno & large cell carcinoma	**(n=512)**	**(n=488)**	**(n=89)**	**(n=289)**
Median overall survival (months) (95% CI)	11.8 (10.4-13.2)	10.4 (9.6-11.2)	9.5 (8.10-13.38**)**	9.8 (8.61-11.48)
Median PFS (months)	5.32	4.67	3.77	4.06

Table 16: **Response rates for the intent-to-treat population (Data on file_JMDB_Response Rates, 2008, Data on file_JMDB_Response by cycle 3, 2008)**

	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
ITT population	**n=862**	**n=863**	**n=89**	**n=289**
Response rate	27.15%	24.68%	17.42%	19.52%
% of responding patients who respond during the first three cycles of treatment*	58.97%	65.26%	*65.26%*	*65.26%*
Non-squamous histology	**n=618**	**n=634**	**n=89**	**n=289**
Response rate	28.64%	22.24%	15.70%	17.59%
% of responding patients who respond during the first three cycles of treatment*	60.45%	64.54%	*64.54%*	*64.54%*
Adenocarcinoma	**n=436**	**n=411**	**n=89**	**n=289**
Response rate	28.90%	21.65%	15.29%	17.13%
% of responding patients who respond during the first three cycles of treatment*	57.14%	61.80%	*61.80%*	*61.80%*
Large cell carcinoma	**n=76**	**n=77**	**n=89**	**n=289**
Response rate	27.63%	27.27%	19.25%	21.57%
% of responding patients who respond during the first three cycles of treatment*	85.71%	76.19%	*76.19%*	*76.19%*

* There is no data for the proportion of gem/carbo or doc/cis patients responding by cycle 3, so response rates are assumed to be that of gem/cis

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.

JMDB trial

All patients who received at least one dose of pemetrexed, gemcitabine, or cisplatin were evaluated for safety.

- 839 received at least one dose of pemetrexed or cisplatin
- 830 received at least one dose of gemcitabine or cisplatin

For all patients, key haematologic grade 3/4 drug-related common toxicity criteria (CTC) were significantly lower ($p \leq 0.001$) for pem/cis compared with gem/cis:

- Neutropenia, 15.1% vs. 26.7% ($p<0.001$),
- Anaemia, haemoglobin 5.6% vs. 9.9% ($p=0.001$),
- Thrombocytopenia, platelets 4.1% vs. 12.7% ($p<0.001$)

For pem/cis vs. gem/cis, drug-related grade 3/4 febrile neutropenia and all grade alopecia were also significantly lower. Drug-related grade 3/4 nausea was higher for pem/cis (Table 17).

The analysis of safety by histology groups was consistent with the safety profile observed in the total population (Scagliotti et al, 2008, Pimentel et al. 2008). No clinically significant safety trends were identified suggesting that no one histology subgroup experienced a different toxicity in the pem/cis arm when compared to another subgroup or to the overall treated population.

Table 17: **Percentage of patients with CTC grade 3/4 drug related toxicities (all patients that received study drug; Scagliotti et al. 2008)**

Toxicity	Pem/cis(%) (n=839)	Gem/cis (%) (n=830)	p-value
Any CTC laboratory toxicity*	22.6	39.9	<0.001
Neutropenia	15.1	26.7	<0.001
Anaemia, haemoglobin	5.6	9.9	0.001
Thrombocytopenia,platelets	4.1	12.7	<0.001
Febrile neutropenia	1.3	3.7	0.002
Alopecia, any grade	11.9	21.4	<0.001
Nausea	7.2	3.9	0.004
Vomiting	6.1	6.1	1.000

Patients in the pem/cis arm received significantly fewer transfusions compared with those on gem/cis including red blood cell transfusions (Table 18). In addition the administration of erythropoietic and granulocyte colony-stimulating factors was significantly lower in favour of pem/cis. The lower use of haematopoietic-stimulating agents and transfusions for patients

receiving pem/cis is consistent with the lower incidence of haematologic toxicities observed in the patients.

Table 18: **Concomitant Medications and transfusions for all randomised patients (Scagliotti et al. 2008)**

Concomitant Medications/Transfusions	Pem/cis (%)	Gem/cis (%)	p-value
Erythropoietin or darbepoetin	10.4	18.1	<0.001
Granulocyte colony-stimulating factors	3.1	6.1	0.004
Any transfusion	16.4	28.9	<0.001
Red blood cells	16.1	27.3	<0.001
Platelets	1.8	4.5	0.002

Indirect analysis

Safety vs. gem/carbo and doc/cis

- Gem/cis vs. gem/carbo (Zatloukal et al. 2003)

In the head to head study of gem/cis vs. gem/carbo the main adverse events were due to haematologic toxicity. The major toxicities in both arms were anaemia, leukopenia, neutropenia and thrombocytopenia. The incidence of thrombocytopenia was significantly lower in the gem/cis treatment arm (p=0.014).

Non-haematologic toxicities were comparable between the two treatment groups although higher incidence of alopecia and nausea/vomiting was observed in the gem/cis group compared with gem/carbo group (p=0.52 and p=0.013 respectively).

In conclusion, the authors stated that while having less non-haematologic toxicity in terms of nausea and vomiting gem/carbo is more haematoxic in terms of an increased incidence of thrombocytopenia.

- Gem/cis vs. doc/cis (Schiller et al. 2002)

In this head-to-head study the adverse event profile was comparable between the two treatment arms with no statistically significant differences observed.

The data resulting from the indirect comparison for adverse events are reported in Table 20. Not all adverse events are reported in all studies, in the economic evaluation gaps in the data are addressed by assuming the same rate as gem/cis.

Table 19: **Summary safety results and conclusions for pem/cis**

Study **Comparators**	**Scaglotti et al. 2008** **Pem/cis vs. Gem/cis**	**Zatloukal et al. 2003** **Gem/cis vs Gem/carbo**	**Schiller et al. 2002** **Gem/cis vs. Doc/cis**
Summary safety results	For pem/cis vs gem/cis ▪ Key haematologic grade 3 or 4 drug-related toxicities (neutropenia, anaemia and thrombocytopenia) were significantly lower (p≤0.001) for pem/cis compared with gem/cis: ▪ Febrile Neutropenia and alopecia were also significantly lower, ▪ Drug-related grade 3 or 4 nausea was higher	For gem/cis vs gem/carbo ▪ Drug-related grade 3 or 4 thrombocytopenia was lower (p=0.014) ▪ Drug-related grade 3 or 4 nausea/ vomiting and any grade alopecia were higher (p=0.52 and p=0.013 respectively)	No statistically significant difference between the two adverse event profiles

Table 20: **Adverse event rate data by therapy for Grade 3&4 CTC drug-related toxicities for the target population (adeno & large cell carcinoma) - results from indirect analysis**

	pem/cis[†] **(n=512)**	**gem/cis**[†] **(n=488)**	**gem/carbo* (n=89)**	**doc/cis**[‡] **(n=289)**
Febrile Neutropenia	1.17%	3.28%	-	9.02%
Neutropenia	15.04%	23.77%	-	26.03%
Nausea/ Vomiting	13.28%	9.22%	2.92%	5.53%
Fatigue	6.45%	3.89%	-	3.60%
Diarrhoea	0.98%	1.84%	-	6.15%
Anaemia	3.91%	9.63%	-	1.16%
Thrombocytopenia	2.93%	10.45%	-	-

[†] Data on file_Adverse Events, 2008, * Based on data in Zatloukal et al, 2003, [‡]Based on data in Schiller et al, 2002

6.8 Non-RCT evidence

No non-RCT data are reported in the submission.

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.

Relevance of evidence base to decision problem

The evidence base reported in this submission, from the JMDB trial and the indirect analysis, is highly relevant to the decision problem.

Comparators

The comparators, as agreed at the decision problem meeting, are reported: gem/cis, gem/carbo, doc/cis. Evidence for the primary comparison of efficacy and tolerability of pem/cis vs gem/cis comes directly from the JMDB/Scagliotti et al (2008) trial. The efficacy and tolerability of gem/carbo and doc/cis compared with pem/cis is assessed through an adjusted indirect comparison.

Population

There are some differences in the trial population compared with the usual NSCLC population in England and Wales. The proportion of adenocarcinoma was higher and NSCLC-NOS was lower in the trial. Two important differences in the population concern age and performance status. The trial participants are slightly younger than would be seen in routine clinical practice in England and Wales, which may or may not be related to performance status. The trial excluded patients with performance status two or more (only PS 0-1 were included), there were more PS 2 patients reported in LUCADA as not all patients were chemotherapy treated.

Outcomes

The outcomes described in the decision problem were all reported in the clinical trial with the exception of quality of life (QoL) data. No QoL data were collected in the trial. Utility in the economic evaluation is modelled with data from a separate survey that attempted to collect societal valuations of health states. The outcomes in the trial are relevant to the decision problem and relevant to clinical benefits experienced by patients in practice.

Cycles & continuation rule

Although the trial protocol allowed for a maximum of six cycles of chemotherapy, in England and Wales many cancer centres limit the maximum number of cycles to four according to treatment guidelines based upon publications that have discussed limited or no benefit of extending treatment beyond 4 cycles (Smith 2001, von Plessen 2006). In the trial patients continued on treatment until disease progression. In usual clinical practice there is some variation, but many clinicians would not continue to administer chemotherapy if no response

to therapy had been observed by the end of the second or third treatment cycle. We model this 'continuation rule' (stopping treatment if patients don't respond) in the economic section.

Relevance of outcomes to clinical benefits for patients

Patients diagnosed with lung cancer have a generally poor prognosis. The disease is often undetected until it has passed the curative stage. Treatment for advanced lung cancer is concerned with extending the life of terminally ill patients and reducing symptoms. Developments in chemotherapy are gradually extending survival duration and rates. Potentially, chemotherapy may be tailored to individual patients in order to produce improvements in outcomes, including overall survival. Histological diagnosis is emerging as a potential variable that may help tailor therapies to individuals. Whether a patient has squamous, adenocarcinoma or large cell histology influences their survival outcomes. For example, patients with large cell carcinoma tend to have the worst prognosis[*] (García-Yuste et al.2008; Moro-Sibilot 2008).

Therefore, the two major aims of oncology therapy are to increase survival and to reduce symptoms and have a good tolerability profile. The response rates from JMDB are comparable to other oncology trials and response rates have been shown to correspond to symptom palliation. Results from JMDB demonstrate that pem/cis meets both of these aims for survival and tolerability with the following benefits over gem/cis (Scagliotti et al.2008):

- Improved survival
    - 11.0 vs 10.1 months – the non-squamous group
    - 11.8 vs. 10.4 months – the target population (adeno & large cell carcinoma)
    - 12.6 vs. 10.9 months - the adenocarcinoma group
    - 10.4 vs. 6.7 months - the large cell carcinoma group

- Tolerability
    - Comparative safety with significantly fewer grade 3/4 laboratory toxicities (22.6% vs. 39.9%, p<0.001)
    - A reduction in need for transfusions (16.4% pem/cis vs. 28.9% gem/cis) and supportive care therapies

Indirect Comparison

In the absence of head-to-head trials, data from JMDB (pem/cis vs. gem/cis) were compared to the other two trials – Zatloukal et al.(2003) and Schiller et al.(2002) – via adjusted indirect comparison, using gem/cis to determine the efficacy of:

- Pem/cis compared with gem/carbo (via gem/cis)
- Pem/cis compared with doc/cis (via gem/cis)

[*] Large cell neuroendocrine carcinoma and large cell basaloid carcinoma have poor prognosis. The other variants of large cell NSCLC under WHO classification are very rare.

The indirect analysis suggests pem/cis also has advantages over gem/carbo and doc/cis in terms of improved overall survival and reduced rates of adverse events.

Pem/cis potentially offers efficacy and safety advantages over currently available therapies, particularly for patients with adenocarcinoma or large cell carcinoma.

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?

Trial Design

The open label-design is a potential limitation as patients and clinicians had full knowledge of the treatment assignments; though this type of design is not unusual in oncology trials.

Treatment cycles

The mean number of cycles in the JMDB trial is just over four, which is slightly higher than standard clinical practice. In the trial, treatment continued until disease progression or until the maximum number of cycles had been received. This is different to routine clinical practice in which treatment might be stopped if a patient does not respond to therapy by the second or third cycle. The influence this has on routine clinical practice is tested in the economic model.

Choice of Eligible Patient: Histological Diagnosis

All patients with NSCLC received pem/cis in the trial, whereas in routine clinical practice only those with adenocarcinoma or large cell carcinoma are more likely to receive pem/cis.

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, if it is not possible to make a confident diagnosis it is suggested that patients should be treated with an alternative therapy, probably gemcitabine.

Doses

The doses within the trial protocol for the JMDB clinical trial are the same as those contained in the pemetrexed SPC. The doses used within the trial for gem/carbo vs gem/cis (Zatloukal 2003) are also in line with each agent's SPC. The carboplatin dose would be calculated on the AUC basis and it is likely that a lower dose than 400mg/ m^2 would be given to patients with late stage NSCLC. There is some difference in doses of gem/cis reported in the Schiller et al study (2002) compared with the SPC, the doses in Schiller are those used in the past.

7. Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

The literature review to support the economic evaluation has a number of requirements: to identify efficacy, cost and utility data and also to identify other cost-effectiveness models to inform the structure and development of the model and cost-effectiveness studies including the comparators being evaluated

The clinical efficacy data come from the literature review reported in the clinical section of this submission, which resulted in three published papers and the JMDB registration study report being identified, see Table 21 for clinical efficacy literature

Table 21: **Clinical efficacy literature**

Scagliotti GV, Parikh P, von Pawel J, et al	A randomized phase III trial comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small cell lung cancer	J Clin Oncol 2008; 26: 3543-3551
Scagliotti et al	Clinical Study Report: A Randomized Phase 3 Trial of ALIMTA® and Cisplatin versus GEMZAR® and Cisplatinin Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer	Lilly Data on File 16 July 2007
Schiller JH, Harrington D, Belani CP et al.	Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.	N Engl J Med 2002; 346:92–98.
Zatloukal P, Petruzelka L, Zemanova M et al.	Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: A phase III randomized trial.	Lung Cancer 2003;41:321–331.

Having recently carried out an extensive literature review for the submission of pemetrexed in the second-line setting for NSCLC, we address the remaining points by updating that search. The review of published literature (TA124) had aimed to both identify all relevant published economic evaluations of chemotherapy in NSCLC and to identify the important parameters needed to inform the design of the economic model.

The full search strategy is reported in Appendix 10.3

7.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

We have included the papers identified in the previous search and supplemented them with an additional search. The majority of reasons for not including the papers are: not economic model articles (instead critiques, comments, letters or reviews or papers about chemotherapy and NSCLC but not an economic paper) and not focussing on chemotherapy, instead considering scanning techniques. A range of other reasons for exclusion were being papers about staging the disease, papers about earlier stage disease. The papers below are those that informed the construction of the economic model and fed into the section on valuing health/quality of life.

Economic evaluations

Study	**Holmes et al., (2004). A cost-effectiveness analysis of docetaxel in the second-line treatment of non-small cell lung cancer.**
Aims	To develop a model to assess the economics of second-line treatment of non-small cell lung cancer (NSCLC) from the perspective of the UK NHS, based on the resources and outcomes from a clinical trial comparing docetaxel 75mg/m^2 with best supportive care (BSC).
Methods	The area under the survival curve for each treatment was analysed and the difference in mean survival between the docetaxel group and the BSC group was calculated as 3.82 months. Measurable incremental costs for the docetaxel group were largely driven by drug acquisition and administration. These cost drivers, as well as toxicity treatment costs and cost offsets, were varied in the sensitivity analysis.
Results	The base case cost-effectiveness analysis (mean values) reported a cost per life-year gained of £13, 863 for docetaxel 75mg/m^2 (year 2000/2001 values). Sensitivity analysis showed that the number of treatment cycles per patient, which affected total treatment cost, had most influence on the cost per life-year gained in the base case scenario. Using the 95% confidence intervals around the mean number of treatment cycles, the base case cost per life-gained varied from £10,985 to £16,738. Using the 95% confidence intervals around the mean difference in survival, to represent the best and worst case scenarios, the cost per life year saved ranged from £10,020 to £32,781. The study concluded that docetaxel 75mg/m^2 in 3-weekly cycles is a cost-effective second-line treatment for pre-treated NSCLC in terms of survival gains made for a reasonable increase in costs.
Relevance to decision-making in England and Wales	The cost perspective was that of the NHS as this was the economic evaluation on which the NICE decision regarding docetaxel for 2nd line NSCLC treatment was based. It is not relevant to the first-line setting.

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

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

Study	**Maniadakis et al (2007). Economic evaluation of Docetaxel/gemcitabine versus Docetaxel as frontline treatment of patients with advanced metastatic non-small cell lung cancer in Greece**
Aims	To assess the cost-effectiveness of doc/gem compared to doc monotherapy as part of a phase III trial in chemonaive patients.
Methods	Resource use, unit cost and survival data were collected as part of the phase III trial. A simple decision analytic model was used with stochastic analysis used to construct a cost-effectiveness acceptability curve.
Results	Median survival rates were reported. The incremental cost per LYG for doc/gem vs gem was €9,538, with 97% probability of the treatment being cost effective at a threshold of €35,000.
Relevance to decision-making in England and Wales	Prescribing of doc/gem or doc monotherapy as first-line treatment is not common in the UK, therefore while it is interesting to read from a modelling perspective, to which not much is added by this paper, it follows a very standard format, the results are not relevant.

Studies of Resource Use and Cost

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

costs. Two cost analyses involving pemetrexed are reported first and then the remaining results of the literature search.

Table 22: **Pemetrexed cost studies**

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

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

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

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

Studies of Quality of Life

A larger body of literature exists on patients' quality of life and utility with non-small cell lung cancer, however, a number of these are methodological papers, ie, mapping of different valuation tools. We only include studies with utility values that we could potentially incorporate into the model. The study by Earle et al., (2000) acted as a useful source that synthesised all of the available utility estimates. The study by Nafees et al (2008) which was Lilly sponsored, is the most applicable as reporting more of the adverse events of interest. Although initially commissioned to support the submission for pemetrexed in second-line treatment for NSCLC, this study was based on health state vignettes valued by 100 members of the general public. The vignettes were developed with the help of clinical experts, but do not mention either cancer or lung cancer, but try and describe the symptoms without using these words in order not to bias results, therefore, the results can be as reliably utilised in first-line as second-line NSCLC.

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

Dancey et al., (2004)	Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial.	To investigate quality of life in NSCLC patients treated with either second-line docetaxel or best supportive care.	Patients were assessed with the Lung Cancer Symptom Scale (LCSS) and/or QLQ-C30 (with LC13 module) every 3 weeks.
Fallowfield & Harper (2005)	Health-related quality of life in patients undergoing drug therapy for advanced non-small cell lung cancer	A review article describing the validated tools for assessing lung-cancer-specific symptoms and HRQoL, and RCTs with HRQoL evaluations in patients with advanced NSCLC.	1st and 2nd line treatment. A literature search of PubMed was used.
Brown et al., (2005)	Assessment of quality of life in the supportive lung setting of the Big Lung Trial in non-small cell lung cancer.	To evaluate the quality of life implications of primary treatment (i.e. surgery, radical radiotherapy) or supportive care in non-small cell lung cancer patients.	1st line treatment.
Paesmans (2002)	Benefits of chemotherapy for quality of life in patients with advanced non small cell lung cancer.	To analyse the quality of life results reported in the published randomized clinical trials that compare chemotherapy with best supportive care and integrate quality of life as a trial's endpoint.	1st and 2nd line treatment
A. Brown., et al (2004)	Pemetrexed versus docetaxel in second-line treatment of advanced non-small cell lung caner: Evaluating patient preference	Evaluating patient preference in second-line treatment of advanced non-small cell lung cancer.	Discrete choice conjoint analysis methodology was used to quantify patient treatment preference and willingness to pay. Review of data, along with expert opinion, identified clinically meaningful toxicities that were statistically significantly different between treatment arms. Logistic regression analysis was applied to the stated scenario preferences against the individual attribute levels.
Lloyd et al., (2005) (see also section 3.2.6.2)	Health state utility scores in Lung Cancer: a community survey	The study was designed to elicit UK based societal utility scores for non-treatment specific health states in NSCLC.	Health states were developed using an iterative process of interviews and focus groups. Preferences were elicited using Standard Gamble with 78 members of the general public.
Nafees et al 2008	This study is described in detail below		

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

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

7.2.1.1 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 in combination with cisplatin (pem/cis) 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 (500mg/m^2) plus cisplatin (75 mg/m^2) is administered on day one of a 21-day cycle. In line with UK standard practice, the maximum number of cycles administered is four.

Concomitant medications required are (Summary of Product Characteristics, 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.

7.2.1.2 Continuation rule

Following consultation with clinical experts a continuation rule was incorporated into model. The continuation rule is based on the separation of patients into those who respond and those who do not respond to chemotherapy. Essentially, those who respond to chemotherapy receive the maximum of four cycles of treatment. Those who do not respond, in this model, receive only three cycles of therapy.

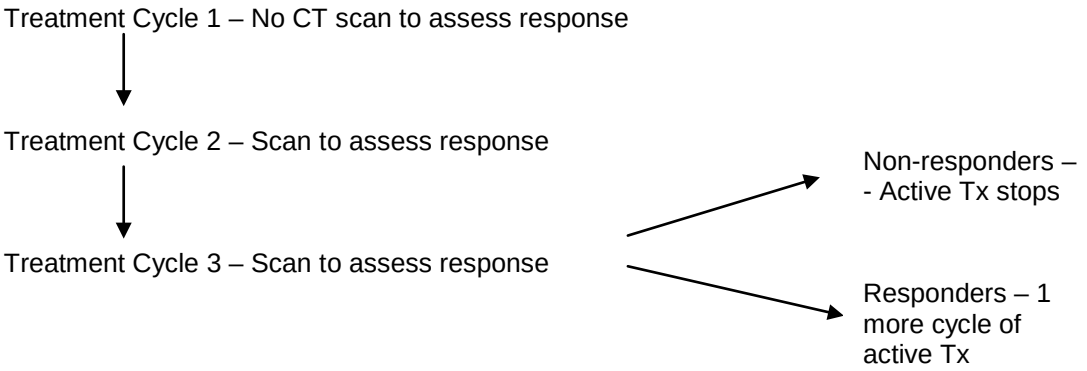
The rule is based on the idea that chemotherapy is challenging for patients and it is not appropriate to continue to challenge a patient with advanced NSCLC if they are not benefiting from treatment. Many clinical oncologists implement a continuation rule in routine clinical practice – although the practical details differ by clinician and available resources. Practice may differ with regard to two crucial factors: how response is measured and the cycle after which treatment ceases – either cycle two or three.

There are two ways of measuring response. The first is objectively, based on RECIST, see Appendix 10.4, in which there is measurable tumour shrinkage of at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. A CT or MRI scanner is needed to measure response in this way. Alternatively, tumour response can be assessed subjectively by the clinician. Response here might be interpreted as symptom relief, disease stabilisation or improvement in patient's general well-being. Subjective measurement of response does not require a CT scanner and is likely to capture more patients than an objective measure of response.

The other aspect of the continuation rule that differs between clinicians is the cycle after which treatment stops. Some clinicians stop after the second cycle (first sceening for tumour shrinkage) and some stop after the third (second screening for tumour shrinkage). In this economic model, non-responders discontinue after the third cycle (second screening) see Figure 12 below and responders after the fourth cycle.

In this model, the continuation rule uses the objective, RECIST, measure of tumour response and discontinues treatment after cycle three (second screening). This differs from the trial protocol in which patients continue until progression. The continuation rule implemented in the model prevents patients from responding in cycles 4 onwards, so under-reporting response rates compared with the trial. This is a reasonable assumption that reflects clinical practice but it under-reports efficacy as 39% of pemetrexed and 35% of gemcitabine patients who achieved tumour response responded from stable or post-treatment stable states after the first three cycles of treatment in the JMDB trial.

Figure 12: **Schedule for assessment of response**



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

The continuation rule does not demand any additional resources and in many places is already practised. Patients are routinely assessed so no additional monitoring is required. Response is a plausible endpoint that is easily defined and measured – as already discussed the availability of a CT or MRI scanner affects which measure of response is used. The time at which the response is measured in the model is less restrictive than might happen in clinical practice as we did not want to under report efficacy and to balance the more restrictive definition of response used in the model. The continuation rule has no equity issues associated with it.

7.2.2 Patients

7.2.2.1 Which patients are included in the economic evaluation?

Patients included in the economic evaluation are those with NSCLC that is not amenable to surgical resection. The licensed population, those with non-squamous histology, are assessed, as is the target population: those with adenocarcinoma and large cell carcinoma. Because the model is based on the trial data there is an assumption of good performance status, an ECOG PS of 0 or 1 which is consistent with UK clinical guidelines. These are the fitter, ambulatory, patients who likely to be to derive more benefit from therapy. They are chemo-naïve. The model is based on a patient with an average body surface area (BSA) of $1.8m^2$ which is varied in the sensitivity analysis, based on the mean BSA reported in the ACTION observational study (Piemental et al 2005) and EU patients within the clinical trial. Maximum dose allowed in the trial according to the protocol was 500 mg/m^2 up to a maximum of 1000 mgs per patient. In the UK patient population, no patient over 2.0 m^2 received more than 1000mg (ie, 2x500mg vials) of pemetrexed.

7.2.2.2 Patient subgroups

Analysis was carried out on patients with adenocarcinoma and large cell carcinoma, two subgroups of non-squamous NSCLC. These subgroups report different relative treatment effects to each other and to the intent-to-treat population. This is the first time that differential treatment efficacy has been demonstrated by histology (Einhorn 2008). The histological classification is based on the World Health Organisation's classification of lung cancer

tumours (Travis 2004) and so is biologically plausible. Adenocarcinoma and large cell carcinoma can be identified by analysis of cell morphology from cytology and biopsy tissue samples with some immunohistochemistry (TTF1 testing, which is widely available already).

Analysis of efficacy by histological sub-group was pre-planned. Analysis of efficacy of by histological group was not in the trial protocol as differential efficacy by histotype only emerged after the trial protocol had been finalised. However, the statistical analysis was prospective, (finalised prior to data lock) and the size of the trial provided sufficient power. The JMDB clinical study report presented results by histology type separately.

7.2.2.3 Excluded subgroups?

No obvious subgroups were excluded. We report the licensed population, which is composed of patients with the histological diagnoses: adenocarcinoma, large cell carcinoma and those with NSCLC 'not-otherwise-specified' (NOS). We then report for the target population, adenocarcinoma and large cell carcinoma. The data for these two groups are presented separately. We don't present the data for the NOS group separately because the OS data for this population in isolation is not as good as for the adenocarcinoma or large cell carcinoma population. One possible explanation for the efficacy results for the NOS group is the heterogeneous nature of this population.

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 evaluation when they receive their first cycle of chemotherapy and exit the evaluation at death. This is a lifetime model and as such all patients in the model die. These points do not differ between treatment regimens. A half cycle correction is reported in the sensitivity analysis.

7.2.3 Comparator technology

The primary comparator is gemcitabine/cisplatin. Gemcitabine in combination with a platinum is the market leader in the UK with a market share of 83% (Data on file, Market Research Data, 2008). As such it is the therapy most likely to be replaced by pemetrexed/cisplatin, although pemetrexed is licensed for a more restricted population than gemcitabine: 'other than predominantly squamous cell histology' NSCLC compared with all NSCLC patients (Pemetrexed SPC, 2008, Appendix 10.1; Gemcitabine SPC 2008).

Gemcitabine/carboplatin (gem/carbo) is a secondary comparator. Carboplatin is often used in the UK in place of cisplatin as it has simpler administration and lower administration costs. Carboplatin is not in the licence for gemcitabine or pemetrexed. We report the results for pem/cis compared with docetaxel/cisplatin (doc/cis), which we have included as an example of the other chemotherapy platinum doublets available for first-line treatment of NSCLC that do not require a Day 8 administration.

- Pemetrexed 500mg/m^2 with cisplatin 75mg/m^2
- Gemcitabine 1250mg/m^2 with cisplatin 75mg/m^2
- Gemcitabine 1250mg/m^2 with carboplatin 500mg (for target AUC of 5mg/ml*min)
- Docetaxel 75mg/m^2 with cisplatin 75mg/m^2

Gemcitabine treatment regimens require gemcitabine infusions on days 1 and 8 of a 21-day treatment cycle.

7.2.4 Study perspective

The perspective adopted is that of the NICE reference case: the NHS and Personal Social Services (PSS). Direct costs associated with provision of treatment incurred by both agencies are reported. We have attempted to exclude costs incurred by other agencies, charitably funded hospices or nursing staff, however, because treatment for NSCLC patients is multi-agency it is difficult to disaggregate costs to enable the exclusion of non-tax funded services. Direct, indirect and intangible costs incurred by patients and their relatives, for example, productivity losses or out-of-pocket expenses incurred attending hospital appointments are not included.

7.2.5 Time horizon

This is a lifetime model. The time, in whole years, in which all patients in the model will have died is six years, which is the reason for this time horizon being used. The majority of patients have died by the end of the fourth year, with a small percentage of survivors continuing past that time. We report four- and two-year time horizons in the sensitivity analysis.

7.2.6 Framework

a) Model-based evaluations

In the following section questions 7.2.6.1-7.2.6.8 are answered. The model structure is described, including a schematic. The model type and structure and how it represents NSCLC and disease progression is justified. The model's cycle length is described, including a comment on a half-cycle correction. All variables and assumptions used in the model are reported, as are the sources of information used to populate the model. The method of extrapolation is described.

Model structure

A Markov structure was used to model the costs and outcomes associated with pem/cis and gem/cis, with gem/carbo and doc/cis as secondary comparators. All clinically important events are modelled as transition probabilities. The passage of time is divided into three-weekly cycles, which corresponds with the length of a chemotherapy treatment cycle. During each cycle, each member of the cohort may remain in the same health state or move to another state. The exception is death, the all absorbing state. The transition probabilities are calculated based on the JMDB trial data or adjusted for gem/carbo and doc/cis. A detailed explanation of the calculation of transition probabilities is given in section 7.2.12.

Models in this disease area are necessarily complex in order to capture the movement of patients through treatment pathways, although we made the decision to develop as simple a model as possible. Figure 13 presents a simplified schematic. The model has three main health states, which replicate those in the JMDB study:

- Response
- Stable Disease
- Progression

Each health state has a utility increment attached to it per cycle. States during the treatment phase also have a treatment cost attached per cycle. In the post-treatment phase progression also has a best supportive care cost attached per cycle. Stable or responding in the post-treatment phase have utility values attached per cycle but no costs, as it is assumed the extra costs associated with best supportive care are only required once the disease has progressed.

Seven adverse event (AE) states are also built into the model as separate states that can be added to the stable or response health states.

- Neutropenia
- Nausea and vomiting
- Fatigue
- Diarrhoea
- Anaemia
- Thrombocytopenia
- Febrile neutropenia

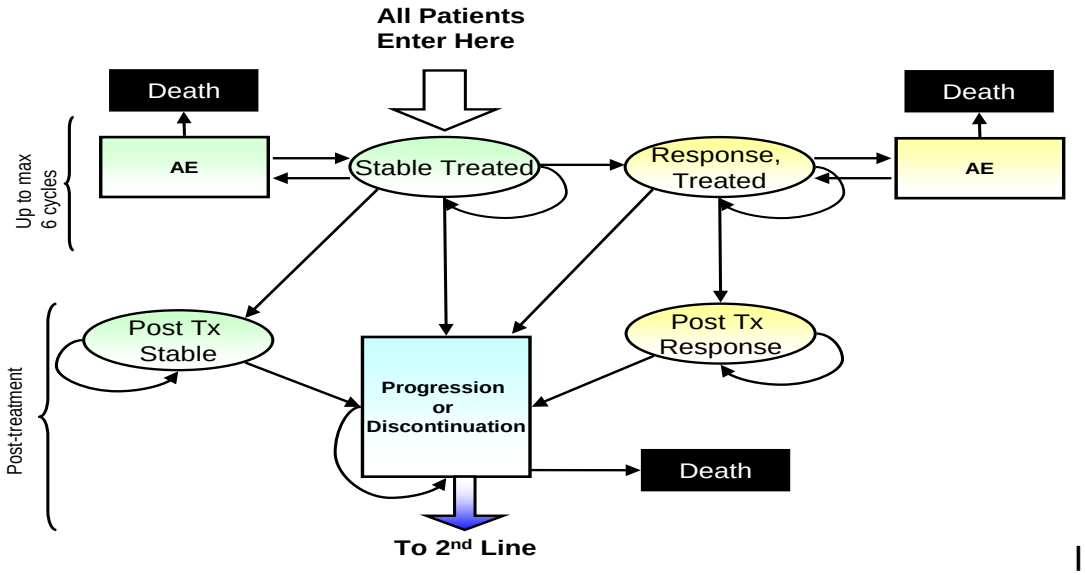
Adverse events have associated disutilities, costs and, for febrile neutropenia, risk of death. Death is the all absorbing state in the model and can only be entered from the progression state or following febrile neutropenia, which has a risk of death of 3.9% per incident of febrile neutropenia (Paul et al. 2006).

Sequencing of health states

First-line treatment

All patients enter the model in a baseline 'stable' state i.e., neither in response nor progression following diagnosis. From here patients can stay in the stable state or move to response or progression. It is assumed that patients who move into response remain in that state until they enter progression. Patients in progression, entering from either stable or response, move either into second-line treatment or death.

Figure 13: **Simplified model schematic of first line treatment and post treatment states**



Patients can be stable or responding while on active treatment or after treatment has ended. The model captures this latter option, after treatment has ended, in the two health states post-treatment stable and post-treatment response. Patients can also discontinue treatment, through their choice, physician choice or following an AE. These patients are included in the progression state as it is assumed that treatment discontinuation leads directly to disease progression.

Second-line treatment

Second-line therapy is received by approximately 53% (pem/cis) and 56% (gem/cis) patients based on JMDB trial data. In the model, second-line treatment is a single state in which costs are incurred as a lump sum as the patients enter the state. No additional benefit is accrued and no utility value is attached, as agreed in the Scoping Workshop.

It is not possible to disaggregate the effect of first-line therapy from second-line therapy in the overall efficacy results. Therefore, the simplifying assumption was made, that all second-line therapies have equivalent efficacy, safety and duration. Costs associated with docetaxel and erlotinib are assumed to be equal in the light of the FAD for erlotinib which recommends erlotinib based on the premise that it has equivalent efficacy, and should therefore have equivalent cost, to docetaxel.

Cycle length

Each cycle in the Markov model is 21 days which corresponds with a chemotherapy treatment cycle of 3 weeks. There are two phases treatment and post-treatment, see Figure 13.

The treatment phase is a maximum of four cycles (Markov cycles 1-4), corresponding to usual clinical practice in England and Wales. This is different to the clinical trial protocol which allowed a maximum of six treatment cycles. However, the mean number of cycles received during the trial was 4.35 (pem/cis) and 4.36 (gem/cis), which is similar to UK clinical practice. The mean values from the trial were based the less restrictive trial protocol, that allowed patients to continue treatment until disease progression. In standard UK clinical practice treatment would be more likely to stop earlier, if no response was observed, rather than

allowing treatment to continue until progression was observed. The maximum number of cycles was tested in the sensitivity analysis.

The post-treatment phase was a maximum of 102 cycles, which accounts for the remaining time until the six-year model limit.

We include a half-cycle correction in the sensitivity analysis although it is not expected to have much impact due to the short cycle duration, the fact all patients enter the trial at the same point, and because it is a lifetime model in which all patients die (Sonnenberg & Beck 1993).

Transition through the model

Transition through the model is driven by response rates and progression free survival. These data are from the JMDB trial (pem/cis and gem/cis), Zatloukal et al.(2003; gem/carbo) and Schiller et al (2002; doc/cis). Results for gem/carbo and doc/cis are assumed to be equivalent to gem/cis where no data were available.

Progression free survival is separated for two groups of patients: responders and non-responders. This is to allow the different times spent in response and progression for the two groups to be evaluated. Non-responders move directly from stable disease to progression. Responders move from stable disease to response, and then on to progression.

Adverse events

Grade 3/4 adverse events (AEs) were included if there was a statistically significant difference between study arms in the JMDB trial or an incidence rate of at least 4% in the pem/cis arm. The exceptions were febrile neutropenia (FN), which was included with lower incidence rates because of the mortality risk and diarrhoea which is associated with patient discomfort and need for hydrational fluids. Leukopenia was considered redundant with neutropenia. The Common Toxicity Criteria (CTC) grade 3/4 drug-related AEs were:

- Neutropenia
- Nausea and Vomiting
- Fatigue
- Diarrhoea
- Anaemia
- Thrombocytopenia
- Febrile neutropenia

Where data for gem/carbo or doc/cis were not available they were assumed to be the same as gem/cis.

Each AE is mutually exclusive and is bounded within a cycle (i.e. starts and finishes within the same cycle). The exception is neutopenia which is assumed to last for the duration of treatment. Patients can experience more than one AE as they move through the model, but can only experience one AE at a time. This is a simplification of trial data made in the model: if 15 people in the trial experienced 30 AE, in the model this is represented by 30 people each experiencing one AE. A per-cycle risk of experiencing each adverse event was calculated and then applied across all treatment cycles.

Alopecia was not included in the model as it is not classified as a 'severe or life-threatening adverse event', does not have an impact on resource use and would increase the complexity of the model. However, it has a detrimental impact on patients' quality of life which needs to be considered alongside the findings of the economic evaluation.

Extrapolation of trial data

The model time horizon is six years while the trial data cover 30 months, therefore the trial data were extrapolated out to the six year time horizon. The median values for overall survival observed in the JMDB trial were converted into a per cycle risk of death (transition probability) assuming the data fit an exponential function. This per-cycle risk of death was then used to extrapolate the data out to six years.

The same assumptions and methods for data extrapolation were applied to all comparators.

Data Inputs

The primary comparison in the economic evaluation, pem/cis vs. gem/cis was based on data from the JMDB randomised controlled trial comparing these chemotherapies in the first-line setting for NSCLC (Scagliotti et al., 2008). 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 (NICE, 2008) for head-to-head RCT data.

The methodology guide also states the RCT should be carried out in the appropriate patient population, which the JMDB does as closely as is possible while meeting the requirements of a clinical trial with the requirements it has to test the hypothesis under investigation without confounding variables, for that reason the patient population is slightly younger and healthier than would be expected in clinical practice, as is usual in transferring clinical trial data to the real world.

We also evaluated gem/carbo and doc/cis. There were no head-to-head data for these comparators vs. pem/cis so an adjusted indirect analysis was carried out to adjust the data from the Zatloukal et al (2003) trial and the Schiller et al (2002) trial to the JMDB population. Details for the indirect analysis are given in section 6.7.

Efficacy differs by histology type for patients treated with pem/cis. As yet, there is no evidence that efficacy differs by histology for the other chemotherapies (Einhorn 2008). The data for gem/carbo and doc/cis report data for all NSCLC patients, equivalent to the ITT population in the JMDB study. The indirect analysis adjusts the gem/carbo and doc/cis data by histology group by assuming these two chemotherapies behave in the same way that gem/cis behaves. The hazard rate for each of the histology types for gem/cis is applied to the transformed gem/carbo and doc/cis data to get efficacy estimates for each histology type for all chemotherapies.

The evaluation used survival curves based on the modelled data. The modelled curve assumes a constant hazard ratio for an exponential curve, based on hazard ratio reported in the trial. The 'tail end' of the model is a more uncertain because it relies on censored trial data. Approximately 27.6% of the non-squamous population in the trial were censored for overall survival (Data on file_JMDB_censoring rates, 2008). The mean estimates from the trial data are calculated by assuming that all censored points at time of data lock have overall survival equivalent to their duration in the trial.

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

Efficacy data

The data in this section are needed to drive the model, as they are the basis for the probabilities by which patients move between the states: response, stable disease, progression and death. The data reported includes:

- Tumour response rates
- Overall survival (OS)
- Progression-free survival (PFS)
- Adverse events
- Extra data required for model
    - PFS for responders
    - PFS for non-responders

Response rates

Response was defined according to RECIST and includes complete and partial responders. In the model, response rates are broken down into overall response rates and response rates after the third cycle as this is important information when considering a continuation rule.

Table 23: **Response rates – ITT population (Data on file_JMDB_Response Rates, 2008, Data on file_JMDB_Response by cycle 3, 2008)**

	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Non-squamous histology	**n=618**	**n=634**	**n=89**	**n=289**
Response rate	28.64%	22.24%	15.70%	17.59%
% of responding patients who respond during the first three cycles of treatment*	60.45%	64.54%	*64.54%*	*64.54%*
Adenocarcinoma	**n=436**	**n=411**	**n=89**	**n=289**
Response rate	28.90%	21.65%	15.29%	17.13%
% of responding patients who respond during the first three cycles of treatment*	57.14%	61.80%	*61.80%*	*61.80%*
Large cell carcinoma	**n=76**	**n=77**	**n=89**	**n=289**
Response rate	27.63%	27.27%	19.25%	21.57%
% of responding patients who respond during the first three cycles of treatment*	85.71%	76.19%	*76.19%*	*76.19%*

* There is no data for the proportion of gem/carbo or doc/cis patients responding by cycle 3, so response rates are assumed to be that of gem/cis

These data are used to calculate the proportion of responders that would be expected in the first 3 cycles of treatment, so allowing the continuation rule to function.

Overall survival and progression free survival

An estimate for risk of death for patients in the progression state was calculated. Death can only be entered from the progression state or following febrile neutropenia. Risk of death in progression was based on median overall survival and median progression-free survival. By

subtracting median PFS from median OS an estimate for median time in progression was produced, from this a per cycle risk was calculated.

Table 24: **Overall survival model inputs (Data on file JMDB_OS_data, 2008, Scagliotti et al.2008)**

Patient Group	Median OS (months) (95% CI)		Adjusted HR (95% CI)*
	Pem/cis	Gem/cis	
Patients with non-squamous histology n=1252	11.0 (10.1-12.5)	10.1 (9.3-10.9)	0.84 (0.74-0.96)
Patients with adenocarcinoma N=847	12.6 (10.7-13.4)*	10.9 (10.1-11.9)*	0.84 (0.71-0.99)
Patients with large cell carcinoma N=153	10.4 (8.6–14.1)*	6.7 (5.5-9.0)*	0.67 (0.48-0.96)

* Data on file_JMDB_OS (2008)

Table 25: **Overall survival model inputs for the non-squamous, adenocarcinoma and large cell populations using the indirect comparison (Scagliotti et al. 2008; Data on File_JMDB_OS, 2008; Data on File_JMDB_PFS, 2008)**

	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Non-squamous	**n=618**	**n=634**	**n=89**	**n=289**
Median overall survival (months) (95% CI)	11.0 (10.1-12.5)	10.1 (9.3-10.9)	9.2 (6.7-17.2)	9.5 (8.0-11.5)
Overall Survival Hazard Ratio (95% CI) relative to gem/cis*	0.84 (0.74-0.96)		1.1 (1.52-0.59)	1.06 (0.88-1.27)
Adenocarcinoma	**n=436**	**n=411**	**n=89**	**n=289**
Median overall survival (months) (95% CI)	12.6 (10.7-13.4)*	10.9 (10.1-11.9)*	10.0 (7.2-18.6)	10.3 (8.7-12.5)
Overall Survival Hazard Ratio (95% CI) relative to gem/cis*	0.84 (0.71-0.99)		1.1 (1.52-0.59)	1.06 (0.88-1.27)
Large cell carcinoma	**n=76**	**n=77**	**n=89**	**n=289**
Median overall survival (months) (95% CI)	10.4 (8.6–14.1)*	6.7 (5.5-9.0)*	6.1 (4.4-11.4)	6.3 (5.3-7.6)
Overall Survival Hazard Ratio (95% CI) relative to gem/cis*	0.67 (0.48-0.96)		1.1 (1.52-0.59)	1.06 (0.88-1.27)

*All comparisons to gem/cis.

Table 26: **Progression-free survival model inputs (Data on File_JMDB_PFS, 2008)**

Patient Group	Median PFS (months) (95% CI)		Adjusted HR 95% CI)
	Pem/cis	Gem/cis	
Patients with non-squamous histology n=1252	5.3 (4.7-5.5)	5.0 (4.6-5.4)	0.95 (0.84 – 1.06
Patients with adenocarcinoma n=847	5.5 (4.9-5.7)	5.0 (4.5-5.5)	0.90 (0.78-1.03)
Patients with large cell carcinoma n=153	4.4 (3.0-5.8)	4.2 (3.5-4.7)	0.89 (0.65-1.24)

Table 27: **PFS for the non-squamous, adenocarcinoma and large cell populations using the indirect comparison (Scagliotti et al. 2008; Data on File_JMDB_OS, 2008; Data on File_JMDB_PFS, 2008)**

	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Non-squamous	**n=618**	**n=634**	**n=89**	**n=289**
Median PFS (time to progression) (months)	5.3 (4.7-5.5)	5.0 (4.6-5.4)	4.0 (3.0-6.5)	4.3 (3.6-5.2)
PFS Hazard Ratio (95% CI) relative to gem/cis*	0.95 (0.84 - 1.06)	-	1.24 (0.77-1.68)	1.15 (0.96-1.37)
Adenocarcinoma	**n=436**	**n=411**	**n=89**	**n=289**
Median PFS (time to progression) (months)	5.5 (4.9-5.7)	5.0 (4.5-5.5)	4.0 (3.0-6.5)	4.3 (3.6-5.2)
PFS Hazard Ratio (95% CI) relative to gem/cis*	0.90 (0.78-1.03)	-	1.24 (0.77-1.68)	1.15 (0.96-1.37)
Large cell carcinoma	**n=76**	**n=77**	**n=89**	**n=289**
Median PFS (time to progression) (months)	4.4 (3.0-5.8)	4.2 (3.5-4.7)	3.4 (2.5-5.5)	3.7 (3.1-4.4)
PFS Hazard Ratio (95% CI) relative to gem/cis*	0.89 (0.65-1.24)	-	1.24 (0.77-1.68)	1.15 (0.96-1.37)

Data were split by responder and non-responder in order to account for the different time spent in progression for the two groups: responders and non-responders. The data in table 28 below are used to calculate transition probabilities for the responding patients, ie, the transition probability for moving from the response state to the progression state. The data in table 29, are used to calculated the transition probabilities for the non-responders: moving from stable state to progression.

Table 28: **PFS for responders (Data on file_JMDB_TtP Responders, 2008 and indirect comparison)**

	Pem/cis	Gem/cis	Gem/ carbo	Doc/cis
Non-squamous	**n=177**	**n=141**	**n=26**	**n=50**
Responders – Median time to Progression (TtP) (months)	4.8	4.2	3.4	3.6
Adenocarcinoma	**n=126**	**n=89**	**n=26**	**n=50**
Responders – Median time to Progression (TtP) (months)	5.1	5.1	4.1	4.4
Large cell carcinoma	**n=21**	**n=21**	**n=26**	**n=50**
Responders – Median time to Progression (TtP) (months)	5.0	5.0	4.0	4.3

Table 29: **PFS for non-responders data (Data on file_JMDB_TtP Non-Responders, 2008 and indirect comparison)**

	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Non-squamous	**n=441**	**n=493**	**n=63**	**n=239**
Non-Responders – Median time to Progression (TtP) (months)	3.9	4.2	3.4	3.6
Adenocarcinoma	**n=310**	**n=322**	**n=63**	**n=239**
Non-Responders – Median time to Progression (TtP) (months)	4.2	4.2	3.4	3.7
Large cell carcinoma	**n=55**	**n=56**	**n=63**	**n=239**
Non-Responders – Median time to Progression (TtP) (months)	2.9	3.4	2.7	2.9

Adverse event data

The adverse event data were modelled based upon data in the JMDB trial. They are reported below for the non-squamous population. Data were reported separately for the adenocarcinoma and the large cell carcinoma group but we report only the non-squamous population for simplicity as there were no significant differences across histological groups. Zatloukal (2003) and Schiller (2002) are assumed to be equivalent to gem/cis where data were not available. The imputed data are highlighted in italic font in Table 30 below.

Table 30: **Adverse event rate data by therapy for Grade 3&4 CTC drug-related toxicities for the non-squamous population (JMDB data on file) – for ITT population***

	Pem/Cis (n=618)	Gem/Cis (n=634)	Gem/Carbo (n=89)	Doc/Cis (n=289)
Neutropenia	14.90%	25.62%	*25.62%*	28.06%
Nausea/ Vomiting	14.24%	10.34%	3.27%	6.21%
Fatigue	6.62%	4.43%	*4.43%*	4.17%
Diarrhoea	1.16%	1.48%	*1.48%*	4.93%
Anaemia	4.97%	10.18%	*10.18%*	5.45%
Thrombocytopenia	3.64%	10.84%	*10.84%*	*10.84%*
FN – Cycle 1	0.12%	1.80%	*1.80%*	4.95%
FN – Cycle 2	0.24%	0.42%	*0.42%*	1.17%
FN – Cycle 3+	0.96%	1.06%	*1.06%*	2.91%

FN = Febrile neutropenia

There is a risk of death associated with febrile neutropenia (FN). A meta-analysis of 23 studies involving 4,938 patients by Paul et al. (2006) reported a risk of death of 3.9% per incident. For pem/cis the risk of experiencing an incident of febrile neutropenia across all cycles of treatment was 1.17% for gem/cis it was 3.28%. The risk associated with gem/carbo was assumed to be the same as gem/cis. The risk of FN associated with doc/cis was reported by Schiller et al (2002) to be 3.7% for doc/cis and 1.3% for gem/cis. Preserving this relationship of an approximate hazard ratio of 2.7 the rate of FN across the first three cycles was estimated to 9.0%

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.

* For the economic model all analysis was assumed to be carried out on the ITT population. The safety evaluable population was the population that received at least one dose of either pemetrexed, cisplatin or gemcitabine. The count of AEs recorded in the safety evaluable population was applied to the ITT population to produce an estimate for AEs in the ITT population.

Table 31: **Methodological/structural Assumptions**

Assumptions	Assumption Description	Justification
Structural assumptions		
Sequencing of health states	It was assumed that patients who move into the 'response' health state remain there until they progress or discontinue, at which point they move to the 'progressive' health state.	Endorsed by expert clinical opinion.
	Patients could only enter death from the progressive state or following febrile neutropenia (FN). It was implicit that other than FN, patients would only die due to progression.	The model applies the logic that a patient will die from non-small cell lung cancer after their disease has progressed (and not before), except if they experience febrile neutropenia. A risk of death following this adverse event was determined based on Paul et al (2006).
Sequencing of health states	Patients in progression (who are also patients who have discontinued due to AEs or patient choice) will either enter second-line treatment, remain in progression receiving BSC or move to death.	This assumption is based on previous models developed for metastatic breast cancer (Cooper et al., 2003) that assumes that patients in the progressive state will not achieve a response from their existing chemotherapy treatments.
Discontinuation is equivalent to progression	Referring to patients who stop chemotherapy because of AEs or patient choice it is assumed discontinuation leads directly to disease progression.	This is a conservative assumption as patients who discontinue may have stable disease.
Best supportive care	All patients receive BSC at every cycle once disease has progressed.	BSC has palliative benefits to deal with symptoms and disease progression. Most cancer patients in the UK receive significant best supportive and palliative care (NICE 2005)
Scheduling of best supportive care	BSC was received once disease progressed BSC was not received during active chemotherapy BSC was not received post-treatment before progression	BSC is intended to moderate the symptoms of progressive disease. Active chemotherapy should control symptoms and in the post-treatment stable phase symptoms should be minimal – assuming that symptom exacerbation corresponds with progressive disease.
Body Surface Area (BSA)	BSA is assumed to be 1.8 m^2.	This is based on ACTION, a pan-European observational study of 196 NSCLC patients from the UK who reported average BSA of 1.8m^2 and European patients in the JMDB trial. This is tested in the sensitivity analysis (Pimentel et al 2005).

Number of treatment cycles	The maximum number of treatment cycles in the base case was four.	UK standard practice is four cycles of chemotherapy. Literature recommends a maximum of 4 cycles (Smith 2001, von Plessen 2006), as do clinical guidelines (SIGN). The mean number of cycles in the trial was just over four (the protocol allowed for a maximum of six cycles). The number of treatment cycles is varied in the sensitivity analysis
Continuation rule	Patients discontinued treatment if no response was observed after the 3rd treatment cycle. Only responsive patients continued to receive treatment, up to a maximum of 4 cycles.	In line with UK clinical practice and endorsed by expert clinical opinion
Continuation rule consequence	Beyond cycle 3, patients in the stable state were considered to have the same utility decrement as progressive patients.	Beyond cycle 3, patients in the stable phase did not receive treatment. It is possible that some patients in that health state may deteriorate enough to match the HRQoL state of a patient in progression. This assumes all patients who stop treatment after cycle 3 will immediately have the same utility as a patient in progression.
Continuation rule consequence	Patients who discontinue incur the disutility of being progression but don't move through the model any quicker.	Only utility and costs are adjusted, the transition probability remains the same for patients who discontinue as part of the continuation rule. There is no plausible evidence to base any change in transition rate through the model on.
Continuation rule consequence	Patients in the stable state do not have a risk of mortality, even beyond cycle 3, but continue to move to progression at the same rate.	Mortality rate for the stable health state was not adjusted to that of progression with the continuation rule applied.
Outcomes and adverse events		
Response evaluation	Patients can only be classified as 'responsive' after the delivery of the second treatment cycle infusion.	Screening only takes place after receiving second cycle of treatment therefore it is not possible to identify a response before then.
Risk of death in the progressive state	Risk of death in the progressive state was calculated by subtracting median PFS, split by responder and non-responder, from median OS to produce a median time in progressive disease. From this, a risk of death per cycle was calculated.	This was based on analysis of the JMDB trial data and assumes an exponential curve form.

Study of adverse events	It was decided to include only grade 3/4 toxicities	Grades 1/2 AEs have a less impact on patients' quality of life than grade 3/4 and have relatively low treatment costs. Endorsed by expert clinical opinion.
AEs in the indirect analysis	Where data were missing in the indirect analysis for gem/carbo or doc/cis the same AE rates as gem/cis were assumed	This was considered appropriate for gem/carbo as both therapies are gemcitabine-based, and for doc/cis (as very little data were missing for doc/cis). This was endorsed by clinical experts who suggested this was a conservative assumption as doc/cis and gem/carbo are more toxic combinations than gem/cis
Incidence of adverse events	It is assumed in the model that adverse events are mutually exclusive of one another.	For simplicity it was assumed that adverse events were mutually exclusive but the Incidence reflected that in the trial i.e. if 15 patients had 2 AEs each, 30 AEs are included in the model. Endorsed by expert clinical opinion.
Frequency of adverse events by health state	The model makes no distinction between the frequency of adverse events by health state. Therefore AE rates were applied equally for stable and responding patients. It was assumed that patients will not experience any adverse events once they progress.	There is no evidence to suggest that stable or responding patients experience differential rates of adverse events.
Utility decrement associated with AEs	The utility decrements associated with AEs are additive	To enable AEs to be picked up in either the stable or the response state, a mixed model was used to produce the utility values, which means they can be added to a health state utility to produce a single utility value for being in that health state with that AE.
Utility decrement associated with AEs	Utility values associated with AEs were taken from a large utility study of 100 members of the general public (Nafees et al 2008). It was assumed that utility values relating to second-line NSCLC would be applicable to the first-line NSCLC setting. The sensitivity analysis varied utility values used to investigate impact on findings.	Based on the NICE reference case.
Differences in clinical outcome based on the incidence of adverse events	No attempt was made to model potential differences in clinical outcomes (i.e. survival, response, progression) based on the adverse events with the exception of febrile neutropenia where a probability of death is determined	The effect of adverse events on outcome is incorporated by introducing discontinuation rates into the model based on adverse events.

Risk of experiencing AEs	A constant risk per cycle was assumed for all the grade 3/4 AEs per cycle with the exception of FN	The risk of the AE is based on the relevant clinical trial data for the appropriate arm. However the assumption of the risk being constant is based on detailed data from the JMDB trial.
Risk of death following FN	Based on the analysis by Paul et al (2006) a risk of death of 3.9% per incident was assumed.	The risk of death was taken from a meta analysis of 23 studies involving 4,938 patients by Paul et al., (2006). It was based on a general cohort of patients making no distinction between those that had been hospitalised and those that had not.
Treatment for FN	Because of the associated mortality risk, all patients with FN would be hospitalised	Endorsed by clinical opinion
AE duration	Adverse events last for the duration of one treatment cycle, with the exception of neutropenia which lasted throughout treatment.	Analysis of duration of adverse event from JMDB trial showed average duration to be under 21 days (1 cycle). Neutropenia is likely to recur as long as treatment is administered.
AE drop-out	Patients who drop out due to AEs will go to Progression.	This was a conservative assumption underestimating the extended benefit of treatment; patients will immediately move to progression rather than remaining in response or stable.
Response rates by cycles	Response rates differ during the first three treatment cycles	This is based on examinatiaon of the JMDB trial data
Response rates by cycles – indirect analysis	There was no data available for response rate by cycle in the indirect analysis so the same response rates as gem/cis were assumed for gem/carbo and doc/cis	Endorsed by expert clinical opinion
Costs and resources		
Choice of inflation indices	The unit costs for febrile neutropenia and terminal care were inflated to present values (2006-2007).	Inflation indices were taken from the Unit Costs of Health and Social Care Publication (2008), University of Kent and the ONS RPI (2008) to increase the validity of the model to reflect the current economic case.
Palliative care resource utilisation	All patients receive the equivalent of three months of palliative care before death	Most patients in the UK receive comprehensive palliative care (NICE 2004).
Cost of concomitant medications	The cost of concomitant medication, folic acid, vitamin B_{12} and steroids are assumed to be incorporated in the HRGs	

Histological differentiation		
Histological differentiation	Only pemetrexed has differential efficacy by histotype: gemcitabine and docetaxel do not demonstrate histological differentiation	There is no evidence that there is differential efficacy for gemcitabine or docetaxel (Einhorn 2008; Hirsch et al 2008)
Histological differentiation for gem/carbo and doc/cis	We assume different histotypes respond to gem/carbo and doc/cis in the same way as gem/cis. Therefore, as part of the indirect analysis each comparator is assumed to have the same hazard rate as gem/cis for each different histology group.	In the absence of any data to the contrary this seemed the most appropriate thing to do. Endorsed by clinical experts. There is no evidence that gem/cis, gem/carbo or doc/cis have differential efficacy by histotype therefore we adjust according to gem/cis JMDB data.
Therapies/doses		
Doses used in model correspond to licensed dose	With the exception of carboplatin and high dose pemetrexed, explained below, we assume that the doses of chemotherapy used are the same as the licensed dose.	We apply the same rule to all therapies in the absence of consistent evidence about deviations from the license.
Maximum dose for pemetrexed is 1000mg	Larger patients, those with BSA>2m^2, do not receive more than 1000mg of pemetrexed.	Based on an examination of the trial data for UK patients, even larger patients do not receive more than a maximum of 1000mg.
AUC=5 for carboplatin equivalent to 500mg/cycle	Based on the literature we have assumed that an AUC=5 is essentially equivalent to 500mg/cycle or 278mg/m^2	Zinner at al (2005) report AUC=6 corresponds to mean/median dose of 550mg per cycle and Scagliotti et al., (2005) reports AUC=6 corresponds to mean 600mg and median 560mg per cycle. Based on Rudd et al (2005) we estimated AUC=5, corresponds to a per cycle dose of 500mg.
Second line treatment	It is assumed that docetaxel and erlotinib in the second line have equal efficacy and equal cost in the second-line setting in the model	Based on the most up to date publicly available information, NICE assumed erlotinib to have equal efficacy with docetaxel. Price negotiation with the Department of Health therefore fixed the cost at the same as docetaxel.
Second line treatment	It is assumed that the rate of second-treatment received in the trial 53% for pem/cis and 56% for gem/cis, is standard for the UK	Based on JMDB trial data.

All key drivers of cost, utility or survival are included in the model. Not every possible scenario has been modelled, for example adverse events that occurred in fewer than 4% of patient were excluded unless they had a risk of mortality attached (febrile neutropenia). However, none of the adverse events excluded were viewed to be a major cost driver.

b) Non-model-based economic evaluations

Not applicable – the economic submission is model based

7.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

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

The treatment strategy that represents the baseline is gem/cis chemotherapy. The experimental strategy, pem/cis, is tested against in the baseline in the economic evaluation, resulting in the incremental cost-effectiveness ratio.

The baseline risk for disease progression was based on the clinical data reported in the JMDB trial and the indirect analysis. The efficacy results from the JMDB trial are reported in section 6.4, the efficacy results from the indirect analysis are reported in section 6.6, for adverse event data for both the JMDB study and the indirect analysis see section 6.7. The baseline risk of disease progression was based on the clinical trial data and converted into a risk per cycle – details of how these values are converted into per cycle are reported below in section 7.2.12 under statistical analysis.

The values for the clinical parameters used in the model are reported in section 7.2.6 under Efficacy Inputs.

7.2.7.2 How were the relative risks of disease progression estimated?

The relative risk of disease progression was again estimated based on the data in the JMDB clinical trial and the indirect analysis. These data can be seen in section 7.2.6,

7.2.7.3 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?

Overall survival was the primary outcome of the clinical trial. Utility data were gathered from the survey by Nafees et al 2008 and multiplied by the life years gained data to get QALY estimates.

7.2.7.4 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 adverse events included in the model are reported above. Only adverse events that occurred in at least 4% of cases or were significantly different between the pem/cis and gem/cis arms in the JMDB trial were included. Therefore, any adverse events that might increase or decrease the estimated cost effectiveness have been included.

7.2.7.5 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?

The continuation rule was devised with the help of clinical experts. All other clinical parameters were based on clinical trial data. Treatment algorithms for AEs were also developed in consultation with clinical experts.

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

All assumptions described above.

7.2.8 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.

7.2.8.1 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. We also report life years gained as this was the primary outcome in the JMDB trial and survival is a clinically meaningful outcome in oncology.

7.2.8.2 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.

Overall survival, PFS, response rates, and adverse events were measured, utility values are applied, as described below. In the model, the stable and responding states can also have an AE applied to them with the corresponding utility decrement and AE treatment costs. QoL data were not collected as part of the trial so utility values from an external source were required.

7.2.8.3 How were health effects measured and valued?

Quality of life data were not collected as part of the JMDB study, or reported by Schiller et al. (2002) or Zatloukal et al. (2003). Therefore, external sources for utility data were needed. We carried out a review of the utility data in advanced NSCLC and identified a number of sources, see Table 33. None of the identified studies met all the requirements of the model, generally not adequately reporting adverse events, the most appropriate was deemed to be the recent Lilly-sponsored study (Nafees et al., 2008) which although commissioned for second-line NSCLC was considered applicable to the first-line setting.

The aim of the study was to produce societal valuations of utility for the main health states, symptoms and adverse events associated with NSCLC. The first part of the study was concerned with the identification and description of the most significant health states though a brief literature review and exploratory interviews with clinical oncologists (n=4) and lung cancer specialist nurses (n=4). Experts were asked to draw on their clinical experience to identify how functioning and health related quality of life is affected in the different health states and stages of NSCLC and by different adverse events. Based on these findings, seventeen health state vignettes were devised which were tested on 100 members of the general public, who were recruited through a local London newspaper and each paid £25 for their time. The health states described progressive disease, stable disease and responding disease and the impact of toxicities: neutropenia, febrile neutropenia, nausea/vomiting, diarrhoea, rash and fatigue.

The visual analogue scale (VAS) and standard gamble (SG) interview were used to elicit societal valuations in the members of the general public. The health state valuations from the SG interview were analysed using a mixed model analysis with random effects on the participant level to determine the change in utility score associated with moving between stages of disease and from no toxicity to one of the toxicities included. The raw data were transformed using a logistic transformation (transformed utility= log ((1-utility)/utility)).

Table 32 shows the estimates and utility decrements for all disease states and toxicities. All disease states and toxicities were independent significant predictors of utility ($p<0.001$). All toxicities were associated with a significant decline in utility compared to stable disease with no toxicity, ranging from -0.03248 (rash) ($p=0.007$) to -0.09002 (febrile neutropenia) ($p=0.0001$).

The base health state (stable disease with no toxicity) had a utility value of 0.653. SG utility scores ranged from 0.673 (responding disease with no toxicity) to 0.473 for progressive disease. Moving from stable disease to progressive disease was associated with a significant decline in utility (-0.1798, $p=0.0001$). The mixed model allows a utility value for any combination of disease states and toxicities to be calculated.

Table 32: **Utility values for health states and adverse events in the model**

Health State	Assigned Utility Value/Disutility
Stable	0.65
Response	0.67
Progression	0.47

Adverse Event	Assigned Utility Value/Disutility
Febrile Neutropenia	-0.090
Neutropenia	-0.089
Fatigue	-0.073
Diarrhoea	-0.047
Nausea/Vomiting	-0.048
Anaemia	*-0.073 (Considered same disutility as fatigue)*
Thrombocytopenia	*-0.089 (Considered same disutility as neutropenia)*

To calculate the utility of someone with fatigue who is in the stable disease state, the utilities of the two states are summed, for example -0.073+0.65 = 0.577.

The values obtained in this study were consistent with other published utility estimates in this disease areas but add further detail on the impact of toxicity on NSCLC patients' lives (see Table 33 below).

Table 33: **Utility values for advanced NSCLC based on reported literature - Alternative published utility values in NSCLC**

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

The JMDB trial identified two adverse events occurring in more than 4% of patients or being significantly different in both arms of the trial not captured in the Nafees et al., (2008): thrombocytopenia and anaemia. Data were therefore imputed. Thrombocytopenia, as a haematological disorder, was considered equivalent to neutropenia. Anaemia was considered equivalent to fatigue, as they tend to require the same treatment and fatigue is often a consequence of anaemia.

Although this study was conducted with health state vignettes in the context of second-line therapy, it was deemed acceptable for the first-line setting. The vignettes did not identify lung cancer in an attempt to reduce bias in the societal valuation. Reviews of the available

literature revealed very few sources of utility weights for NSCLC and none distinguished between first- and second-line therapies.

7.2.8.4 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 method for valuing health was used.

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

Alopecia was not included in the model as it is not classified as a 'severe or life-threatening adverse event', does not have an impact on resource use and would increase the complexity of the model. However, it has a detrimental impact on patients' quality of life which needs to be considered alongside the findings of the economic evaluation. Alopecia rates were lower in pemetrexed than in gemcitabine patients so this is a conservative decision.

7.2.9 Resource identification, measurement and valuation

The following questions are amalgamated to present the data as clearly as possible.

- What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)
- How were the resources measured?
- What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

Resource utilisation and unit costs

Resource use and unit costs for the following were identified:

- Medication
  - Chemotherapy acquisition
  - Platinum acquisition
  - Concomitant medication (assumed to be incorporated into the NHS HRGs used, however we report the values to show they are relatively inexpensive)
- Administration
  - Chemotherapy administration (NHS HRGs were used which include concomitant medications)
- Adverse events
  - Febrile neutropenia
  - Neutropenia
  - Nausea and Vomiting
  - Fatigue
  - Diarrhoea
  - Anaemia
  - Thrombocytopenia
- Best supportive care
- Palliative care

Only minimal resource utilisation rate data were collected as part of the JMDB trial. This included data on rates of transfusions and rates of adverse events, but not information on any wider resources used to treat adverse events or information on length of hospital stay or alternative treatment setting data, so not enough to comprehensive model resource use. No resource use data were reported in Schiller et al (2002) or Zatloukal et al (2003). Chemotherapy acquisition costs and administration dose data are taken from the trial and the therapies' SPCs and national UK prices are applied from the BNF (BNF 55, 2008). Similarly, national HRGs are used to estimate a standard price for chemotherapy administration, based on license treatment protocol. We considered using the HRGs for both procurement and delivery based on the OPCS Classification (NHS, 2008) however, because of uncertainty regarding the accuracy of cisplatin based codes and gemcitabine outpatient procurement costs codes, it was decided to use these data in the sensitivity analysis. A discussion of the HRGs for procurement and delivery is given in Appendix 10.10

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).

The unit costs for the model are based on the most up to date UK NHS reference costs (DH, 2008) which report data for 2006-07, the BSC/palliative care costs were inflated to 2006-7 rates, the most up to date available.

Chemotherapy

The doses upon which the unit costs are based are from the JMDB trial, for pem/cis and gem/cis and from the SPCs for gem/carbo and doc/cis. There were doses reported in both Zatloukal et al (2003) and Schiller et al (2002), however, in the case of the Schiller study these represented doses that are no longer routinely used, Zatloukal differs only very slightly from the licensed dose, 50mg/m^2 less for gemcitabine and 5 mg/m^2 more for cisplatin, the same dose for carboplatin (AUC=5) is used. In the model we have applied cost data based on the licensed doses of all the medication.

Chemotherapy list prices from the BNF are used for all therapies and concomitant medications. Prices were based on BNF 55 (2008) and are estimated on a body surface area of 1.8m^2. Costs per vial (wastage) are reported in the base case with costs per mg (no wastage) tested in the sensitivity analysis, as are HRG chemotherapy procurement costs.

Table 34: **Chemotherapy unit costs (BNF 55, 2008), based on BSA of 1.8m2**

	Unit cost per vial	Calculated cost per mg	DOSE	Cost per dose
Chemotherapy				
Pemetrexed (100mg vial)	£160.00	£1.60		
Pemetrexed (500mg vial)	£800.00	£1.60	500mg/m^2	£1440.00
Gemcitabine (200mg vial)	£32.55	£0.16	1250mg/m^2	£390.62
Gemcitabine (1000mg vial)	£162.76	£0.16		
Docetaxel (20mg vial)	£162.75	£8.14	75mg/m^2	£1023.00
Docetaxel (80mg vial)	£534.75	£6.68		
Platinum				
Cisplatin (50mg vial)	£25.37	£0.51	75mg/m^2	£75.59
Cisplatin (100mg vial)	£50.22	£0.50		
Carboplatin (50mg vial)	£22.04	£0.44	AUC=5 (500mg per cycle)	£190.89
Carboplatin (150mg vial)	£56.29	£0.38		
Carboplatin (450mg vial)	£168.85	£0.38		
Carboplatin (600mg vial)	£260.00	£0.43		

	Mean cost per patient per cycle	Mean number of cycles per patient**	Mean total cost per patient
Pem/cis	£1440 + £75.59	3.80	£5,759.24
Gem/cis	(£390.62 x 2*) + £75.59	3.81	£3,264.52
Gem/carbo	(£390.62 x 2*) + £190.89	3.75	£3,645.49
Doc/cis	£1023 + £75.59	3.79	£4,163.66

*Day 1 and Day 8 gemcitabine administration

** mean number of cycles for non-squamous population without the continuation rule applied.

The dose for carboplatin is AUC=5. From the literature AUC=6 corresponds to mean/median dose of 550mg per cycle (Zinner at al 2005) and AUC=6 corresponding to mean 600mg, median 560mg per cycle (Scagliotti et al., 2005). Therefore we estimated that an AUC=5, as reported in Rudd et al., (2005), corresponds to a per cycle dose of 500mg.

The total cost per cycle for chemotherapy is derived from the dose for each patient multiplied by the number of cycles they received in the economic model. Gemcitabine is administered on Day 1 and Day 8, but only in combination with cisplatin on Day 1.

Concomitant medication

Premedication including anti-emetics, folic acid, vitamin B_{12}, antihistamines and paracetamol are used with these chemotherapy regimens. 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 33 and therefore inclusion or exclusion would not affect the results.

Table 35: **Chemotherapy concomitant medication unit costs (BNF 55, 2008)**

Concomitant therapy	Unit cost
Premedication	
Dexamethasone	£2.39
Folic Acid	£1.65
Vitamin B_{12}	£2.46
Piriton	£1.62
Paracetamol	£1.59
Pharmaceutical Products	
Lomotil	£1.63
Domperidone	£2.35

Administration

Resource use associated with chemotherapy administration is assumed to be standard, as captured within the appropriate HRGs (DH 2008). It is assumed that on Day 1 of every treatment a chemotherapy platinum doublet is administered. For patients receiving gemcitabine, a Day 8 gemcitabine monotherapy administration is also included.

HRG costs for chemotherapy administration are from the NHS Reference Cost database 2006-7 prices (DH, 2008). Gem/cis and gem/carbo both have additional administration costs for the day 8 visit, '*Deliver subsequent elements of a chemotherapy cycle',* which is given in an outpatient setting. It is important to note that it is the platinum component of the chemotherapy that drives the type of administration required. So, while pemetrexed is only a 10 minute i.v. infusion and as a monotherapy would be classed as SB12Z, 'simple parenteral chemotherapy at first attendance', cisplatin has hydration requirements that mean patients are either brought in over night the day before chemotherapy or need a long day case making the pem/cis combination SB14Z, '…complex chemotherapy including prolonged infusional treatment at first attendance.'

In the base case we assume inpatient administration and in the sensitivity analysis we test the effect of outpatient administration.

Table 36: **National schedule of reference costs 2006-07 NHS Trusts, Chemotherapy inpatients and outpatients (DH, 2008)**

HRG Code	HRG Label	Unit cost	
		Outpatients	***Inpatients***
SB12Z	Deliver simple parenteral chemotherapy at first attendance	£170	£309
SB13Z	Deliver more complex parenteral chemotherapy at first attendance	£104	£298
SB14Z	Deliver complex chemotherapy including prolonged infusional treatment at first attendance.	£179	£430
SB15Z	Deliver subsequent elements of a chemotherapy cycle	£189	£255

Table 37: **Unit costs associated with the delivery of each chemotherapy regimen**

	Resource utilisation	Unit cost	Total per cycle
Pem/cis	1 x SB14Z (*inpatient*)	£430	£430
Gem/cis	1 x SB14Z (*inpatient*)	£430	£619
	1 x SB15Z (*outpatient*)	£189	
Gem/carbo	1 x SB14Z (*outpatient*)	£179	£368
	1 x SB15Z (*outpatient*)	£189	
Doc/cis	1 x SB14Z (*inpatient*)	£430	£430

Adverse Events

Adverse event rates were collected as part of the JMDB trial and are reported in both Schiller et al (2002) and Zatloukal et al (2003). However, detailed resource use data were not collected as part of the JMDB trial and are not reported in Schiller et al., (2002) or Zatloukal et al., (2003).

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 each AE included in the model. The clinicians were asked to describe the resource use associated with treating the grade 3/4 AEs. The duration of the AEs was derived from data from Hanna et al.(2004), the registration trial for single-agent pemetrexed in second-line treatment of NSCLC or based on clinical opinion where it was considered to differ from the clinical trial. It was assumed that all patients experiencing febrile neutropenia would be hospitalised. This was considered reasonable by clinical experts.

The proportion of the AE unit cost driven by inpatient care is the result of the duration of hospitalisation multiplied by the cost of a non-elective inpatient stay (£400). It is assumed that medication is incorporated into the HRG for the non-elective stay.

Table 38: **Adverse event Hospital resource utilisation (Duran et al.2008)**

Average Inpatient LOS	LOS (days)
Neutropenia	1.7
Nausea & Vomiting	3.0
Fatigue	0.0
Diarrhoea	3.5
Anaemia	1.7
Thrombocytopenia	2.0

Table 39: **The daily cost of a non-elective inpatient stay (DH, 2008)**

General	Unit cost
Non-elective Inpatient HRG	£400.00

To calculate outpatient and day care unit costs for treating each adverse event, the cost of medication and interventions needed was estimated. A *per AE unit cost* was calculated by

calculating the proportion of treatment by setting, i.e., inpatient%, outpatient% and day case% (calculation in Appendix 10.5).

Table 40: **Calculated unit costs of treating AEs**

Adverse Event	Unit cost
Neutropenia	£330.93
Nausea and Vomiting	£700.79
Fatigue	£38.90
Diarrhoea	£867.12
Anaemia	£615.04
Thrombocytopenia	£314.69

Febrile neutropenia

As already mentioned there is a 3.9% risk of death due to febrile neutropenia per incident. We have assumed 100% rate of hospitalisation associated with treatment, and an average length of stay of 4.3 days.

Table 41: **Cost and resource use associated with febrile neutropenia**

Hospitalisation due to FN	100%
Days per hospitalisation (LOS)	4.30
Cost per day	£400
Cost per episode of FN	**£1,720**

The above cost for treating FN is based on the study by Duran et al. (2008). Holmes et al. (2004) report a unit cost for the treatment of FN of £3582 in 2004 prices, this cost, inflated for 2006/7 prices (£3884), is tested in the sensitivity analysis.

Best Supportive Care & Terminal Care Costs

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 £3,581, based on an inflation index of 1.107 (ONS, 2008) to get a cost of care over 12 months. We assumed that the majority of this cost would be incurred in the later stages of the disease. For this reason we apply a one-off cost of £2,686 to each patient in the last three months of life, this is equivalent to 75% of the yearly cost. The remaining 25% of the costs were distributed equally over the remaining nine months and cut to get a per cycle cost of £68.86 which is applied to every cycle to all patients in progression.

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

Resources were not measured using the same sources of evidence as the baseline and relative risks for disease progression. Resource use data on chemotherapy administration and acquisition were based on the clinical trial protocol and SPCs, and it is straightforward to apply national unit costs for administration and acquisition to doses. Identifying resource use and unit costs for adverse events and BSC/terminal care is more problematic. Even if data

had been collected as part of the trial it would have not have been appropriate to use any non-UK data as resource use is likely to be highly variable between countries depending on the available resources within the health systems.

7.2.9.4 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. Following the initial treatment period, stable patients are assumed not to receive any treatment with significant resource implications. Once they enter the progression state patients are assigned a per cycle cost for BSC, which is described above. All patients receive the equivalent of three months of terminal care in the cycles before death.

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

The sources of information are described above, and tabulated below:

Table 42: **Sources of resource utilisation rate and unit cost data**

Resource	Resource utilisation rates	Source of unit cost
Medication	Clinical trial data, SPC	BNF 55, 2008
Administration	Clinical trial protocol, UK standard practice, SPCs	HRGs (DH, 2008)
Adverse events	Survey of clinical experts	Duran et al (2008)
Febrile neutropenia	Published literature	Paul et al (2006) – inflated to 2006-07 using PSSRU
Best supportive care	Survey of clinical experts	Duran et al (2008)
Terminal/palliative care	University of Sheffield/NICE research	NICE 2005b – inflated for 2007 costs using ONS RPI inflation index

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

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.

7.2.9.7 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 already. All that needs to happen is for skills in this area to improve as the necessity for histological diagnosis increases. Additional immunohistochemistry tests could be carried out but are not necessary.

7.2.9.8 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 the base case and the alternative cases.

7.2.9.9 Were resource values indexed to the current price year?

Cost estimates for FN and terminal care were indexed to 2007, the latest date available (PSSRU, 2008; ONS, 2008) using the most recent inflation indices. Other costs reported are for the most recent years and so did not require inflating: administration HRGs and medication.

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

Nothing additional to report from that in the assumptions table or discussed above.

7.2.10 Time preferences

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

Both costs and benefits were discounted at a rate of 3.5% per year.

7.2.11 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.

7.2.11.1 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.

Structural assumptions have been investigated in the one-way sensitivity analysis.

- Model parameters
    - Mean body surface area
    - Discount rates
    - Time horizon

The numbers of treatment cycles received are varied in a separate 'scenario analysis' and the continuation rule is tested.

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

One-Way Sensitivity Analysis

- Costs
    - All costs +/- 25%
    - Chemotherapy costs +/- 25%
    - All costs (excluding chemotherapy drugs) +/- 25%
    - Per mg costing
    - Outpatient costs applied
    - All DH, HRG procurement and delivery costs applied
    - Chemotherapy administration costs – decreased by 50%
    - BSC at 75% (increased to £267 from £178 per cycle)
    - Cost of FN increased to £3884 (from £1720)
    - GEM drug acquisition cost discount of 20%
    - Second-line costs excluded
- Resource use
    - Hospital days for AEs +/- 50%
- Utility
    - Disutility assigned to AEs +/- 50%
    - Assume no disutility assigned to AEs (so only have a cost impact in model)
    - Utility weights assigned to health states all lower and upper of 95% confidence interval
- Efficacy
    - Upper and lower 95% limit for PEM survival
    - Upper and lower 95% limit for GEM survival
- Patient population
    - Mean body surface area (BSA) $1.6m^2$- $2.0m^2$

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.

The numbers of treatment cycles received are varied in a separate 'scenario analysis'.

7.2.11.3 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'.

Probabilistic Sensitivity Analysis (PSA)

The model can be tested deterministically and stochastically. Setting the model to stochastic, 500 replications were carried out to assess the robustness of the analysis and to construct a cost-effectiveness acceptability curve for the non-squamous, adenocarcinoma and large cell carcinoma populations.

Model parameters with second-order uncertainty, were fitted with an appropriate distribution and then varied according to randomly generated probabilities between 0 and 1. The variables were:

- Response rates were assumed to have a Poisson distribution, which predicts the probability of an event (response) over a time. In this model, the mechanics of the beta distribution was used instead of the mechanics of the Poisson distribution, which is considerably more complicated and has higher data requirements, in order to keep the model simple and functional.
- Time-to-event data (e.g., time to progression, overall survival) were assumed to have an exponential distribution.
- The cost of febrile neutropenia was given a gamma distribution.
- All other parameters were assumed to have a beta distribution.

- A complete list of all the parameters varied in the PSA is provided in Appendix 10.9
- Uncertainty in the parameter values was tested simultaneously by randomly re-sampling (500 replications) mean/median values from a series of assigned distributions, based on point estimates and standard errors for each parameter.

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

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

SE of the exponential median = SD / SQRT (N)

where; SD = SQRT (Variance)

Variance = 1 / (Lambda)^2

Lambda = ln(2) / median OR 1 / mean

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

For rate parameters such as response rate, the Poisson distribution is appropriate for predicting events over time. The Poisson distribution is described as having the following relationship:

SE of the Poisson mean = SD/SQRT(Sample Size)

Where SD = SQRT(Variance)

Variance = Mean * (1- Mean)*SampleSize/(SampleSize-1)

However, MS Excel does not contain an inverse Poisson function to allow for a simple use of this distribution.

The beta distribution is constructed out of two parameters, alpha and beta.

Alpha and beta are derived by:

Alpha = mean*(((mean*(1-mean))/(variance))-1)

Beta = (1-mean)*(((mean*(1-mean))/(variance))-1)

Where variance = SD^2

The gamma distribution is also defined by two parameters, alpha and beta.

Alpha and beta have the following relationship:

SD = SQRT(alpha)*beta

Beta = mean/alpha

Alpha and beta can be derived given the mean and the SD.

For beta and gamma distributions a random probability and the distribution parameters alpha and beta were used to independently resample values for each iteration.

7.2.12 Statistical analysis

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

Response rates were converted into transition probabilities by taking the response rate over a certain number of cycles, x, and assuming response was equally distributed over those cycles. (To account for different rates of response over time, this was done in separate sections for cycle 1, cycles 2-3 and the remaining cycles). For instance, if there was y%

response over x cycles, then the probability of not responding over two cycles is 1-y%. The per cycle probability of not responding is (1-y%)^(1/x). The per cycle probability of responding can then be calculated as 1-EXP(-(-LN(1-y%)/x)).

OS and PFS were converted into transition probabilities by using the hazard rates and assuming a constant hazard to fit an exponential distribution. Since median values were expressed in weeks, the following equation gives the probability of death/progression within a cycle. Cycle length should also be expressed in weeks.

1-EXP(-(hazard)*(cycle length))

Transition probabilities for AEs were calculated in a similar manner to response, and the number of cycles over which the events occurred were assumed to be equal to the approximate average number of cycles given, rather than the maximum number of cycles.

7.2.12.2 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.

There is evidence that response rate varies over time. This was included in the evaluation by calculating different rates of response for cycle 1, cycles 2-3, and the remaining cycles (more details above). No other probabilities were assumed to vary over time.

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

Model validity

In order to see how closely the modelled data followed the clinical trial results we compared trial medians and means with the means produced in the model see Table 62 in validation section. We would expect some slight variation but consistent direction of trends and degree of incremental benefit. The economic data are based on means that have to be extrapolated from clinical trial data that are censored. For overall survival in the known non-squamous population (adeno+large cell carcinoma) the censoring rate was 28% which affects the estimation of mean values from the trial data.

Table 43: **Censoring rates for participants in the JMDB trial (Data on file_JMDB_OS, 2008; Data on file_JMDB_PFS, 2008).**

Known non-squamous population	**Pem/cis n=512**	**Gem/cis n=488**
% censoring in OS	32.2%	24.8%
% censoring in PFS	7.4%	6.4%

7.3 Results

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.

7.3.1 Base-case analysis

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

Results

The baseline deterministic analysis is run over a six year time horizon, with a cohort size set to 500, (but reported on a per patient basis for simplicity). Results are reported both with and without a continuation rule. The maximum number of cycles is four. Cost calculations are on a per vial basis. BSC is assumed to be given at disease progression. Costs for second-line treatment are included. It is assumed all first-line therapies are followed by docetaxel/erlotinib in second-line, except for doc/cis which is followed by erlotinib. Based on the recent agreement with NICE/DH we have assumed that docetaxel and erlotinib have equivalent efficacy and equivalent cost.

Results from the head to head trial are presented for the licensed population: non-squamous histology.

Costs

The costs associated with alternative therapy options and incremental costs of pem/cis versus gem/cis are reported in Tables 44, 45 and 47.

Table 44: **Costs associated with different therapy options (non-squamous population)**

Costs	pem/cis	gem/cis	gem/carbo	doc/cis
First line chemotherapy acquisition	£4,889	£2,763	£3,022	£3,457
First line chemotherapy administration	£1,387	£1,996	£1,144	£1,353
Second line chemotherapy	£1,701	£1,814	£1,817	£1,814
BSC	£845	£759	£767	£765
Terminal care	£2,621	£2,629	£2,636	£2,634
Adverse events	£232	£350	£299	£269
TOTAL COST	**£11,674**	**£10,310**	**£9,686**	**£10,291**

Table 45: **Costs associated with different therapy options with continuation rule applied (non-squamous population)**

Costs	pem/cis	gem/cis	gem/carbo	doc/cis
First line chemotherapy acquisition	£4,237	£2,364	£2,559	£2,931
First line chemotherapy administration	£1,202	£1,708	£969	£1,147
Second line chemotherapy	£1,701	£1,814	£1,818	£1,813
BSC	£845	£759	£768	£765
Terminal care	£2,621	£2,629	£2,636	£2,634
Adverse events	£193	£292	£244	£346
TOTAL COST	**£10,798**	**£9,566**	**£8,993**	**£9,636**

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).

Table 46: **Mean number of cycles of chemotherapy for known non-squamous population.**

	pem/cis	gem/cis	gem/carbo	doc/cis
Mean number of treatment cycles	3.23	3.22	3.11	3.15
Mean number of treatment cycles (with continuation rule applied)	2.88	2.76	2.63	2.67

Table 47: **The incremental cost of pem/cis compared with gem/cis**

	Pem/cis vs gem/cis	Pem/cis vs gem/carbo	Pem/cis vs doc/cis
Incremental cost	£1,364	£1,988	£1,383
Incremental cost (with continuation rule applied)	£1,232	£1,805	£1,162

Because there are higher response rates associated with pem/cis the mean number of cycles is higher than with the other therapies, which leads to higher costs hence, the greater the incremental cost difference between pem/cis and comparators when the continuation rule is applied.

Health outcomes

LYGs and QALYs gained

The health benefits associated with pemetrexed/cisplatin and comparators are reported below.

Table 48: **Indirect comparison –non-squamous patients**

Mean benefits	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Quality Adjusted Life Years (QALYs)	0.60	0.57	0.51	0.53
Life Years Gained (LYG)	1.13	1.05	0.97	1.00
Quality Adjusted Life Years (QALYs) – with continuation rule	0.58	0.53	0.49	0.50
Life Years Gained (LYG) – with continuation rule	1.13	1.05	0.97	1.00

Table 49: **Incremental benefit of pem/cis compared to comparators for the licensed population**

Incremental benefit of pem/cis	Incr. Benefit - QALY	Incr. Benefit – LYG
Pem/cis vs gem/cis	0.039	0.08
Pem/cis vs gem/carbo	0.089	0.15
Pem/cis vs doc/cis	0.072	0.13
Pem/cis vs gem/cis	0.046	0.08
Pem/cis vs gem/carbo	0.091	0.16
Pem/cis vs doc/cis	0.078	0.13

Modelled Overall Survival curves

The model fitted the data from the JMDB trial for the non-squamous population with an exponential distribution in order to parameterise the survival function. The overall survival curve from the model is superimposed on the survival curve from the JMDB trial to demonstrate how closely the model approximated the trial data Figure 14 and 15. There are two figures, the first for three years is closer to the trial duration and the second, for six years, corresponds to the duration of the lifetime model.

Figure 14: **Three year time horizon: Survival curve for modelled and trial data for pem/cis and gem/cis for non-squamous population**

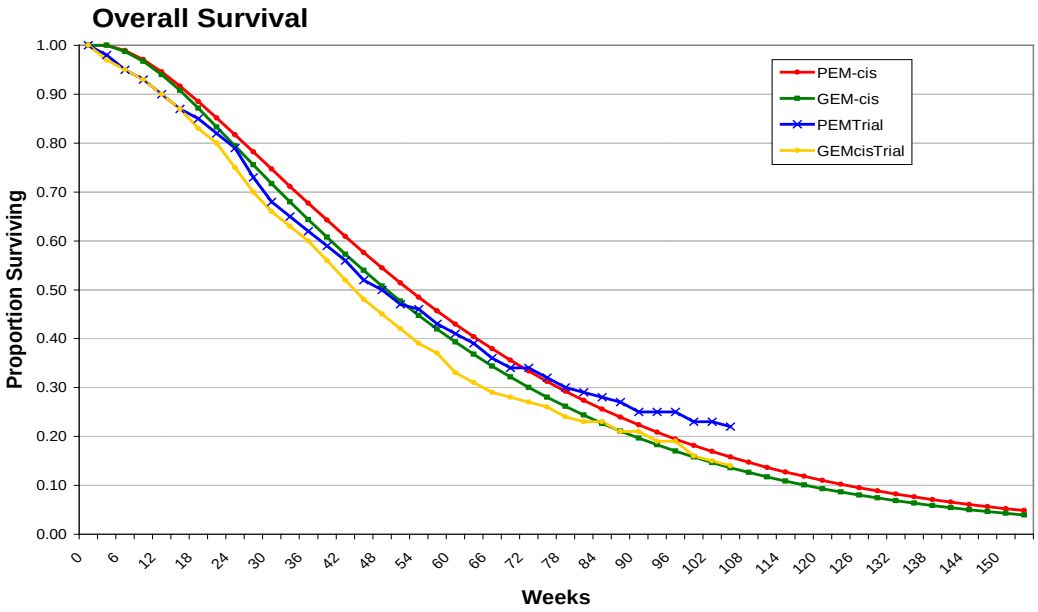
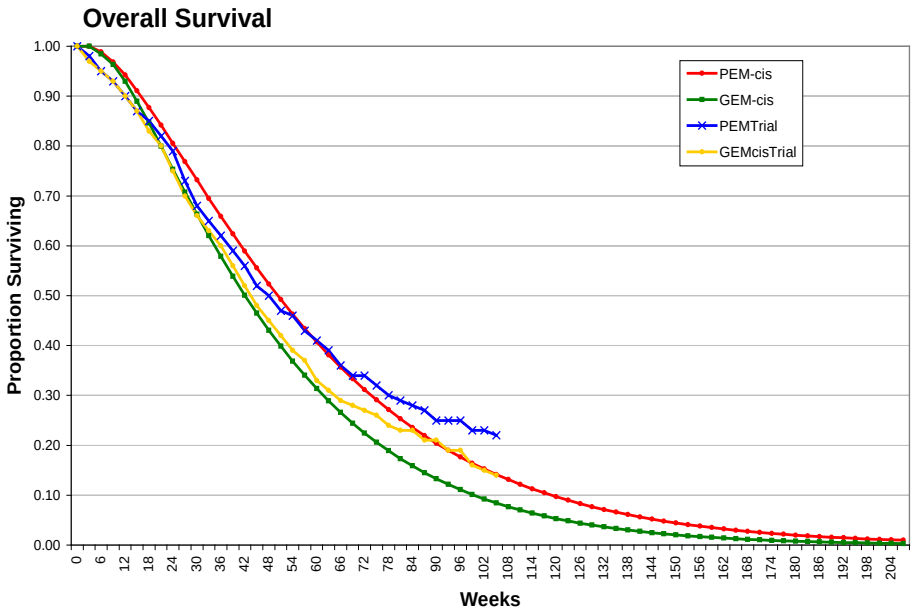


Figure 15: **Six year time horizon: Survival curves for modelled and trial data for pem/cis and gem/cis for non-squamous population**



From the survival curves above it can be seen that the model over-estimates survival for the first year, but underestimates it for the second and subsequent years. We can further validate the model by comparing survival rates at one and two years from trial data and modelled data. Again, we see the model slightly over-estimates survival in the first year and underestimates survival in the second year.

Table 50: **Modelled and trial survival rates at one and two years for the non-squamous population**

	Pem/cis		Gem/cis	
	Model	**JMDB**	**Model**	**JMDB**
1 year survival	50%	47%	45%	41%
2 year survival	16%	22%	12%	15%
3 year survival	4%		3%	
4 year survival	1%		1%	
5 year survival *	0%		0%	
6 year survival*	0%		0%	

** Please note these are rounded values. Although in the overall non-squamous population all patients were dead by year 5, 1% of pemetrexed patients were alive in the adenocarcinoma patient group at year 6, hence the 6 year time horizon.*

Incremental Cost Effectiveness Ratio

The incremental cost-effectiveness ratio for pem/cis compared to gem/cis is: £35,188 in the non-squamous population without the continuation rule applied, and £26,985 with the continuation rule applied.

Table 51: **Costs per Additional LYG and QALY gained for non-squamous population.**

	ICER of pem/cis	**ICER**	**Incr. Cost per LYG**
Without continuation rule	*vs gem/cis*	£35,188	£17,935
	vs gem/carbo	£22,233	£13,131
	vs doc/cis	£19,130	£10,821
With continuation rule	*vs gem/cis*	£26,985	£15,423
	vs gem/carbo	£19,939	£11,629
	vs doc/cis	£14,972	£8,804

7.3.2 Subgroup analysis

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

Results

The baseline deterministic analysis is run over a six year time horizon, with a cohort size set to 500, (but reported on a per patient basis for simplicity). It is assumed that the stopping rule is applied: treatment is stopped if the patient has not responded following the third cycle. The maximum number of cycles is four. Cost calculations are on a per vial basis. BSC is given

once disease has progressed. Costs for second-line treatment are included. It is assumed all first-line therapies are followed by docetaxel/erlotinib in second-line. Docetaxel and erlotinib are assumed to have equivalent efficacy and cost as per the agreement with the DH/NICE.

Results from the head to head trial are presented for the adenocarcinoma and large cell groups separately. There are important differences between the adenocarcinoma and large cell histology group in terms of the distribution of survival and the sample size: The large cell carcinoma group is much smaller (152 patients compared with 857 adenocarcinoma patients), the survival profile is quite different (large cell patients have poorer overall survival compared with adenocarcinoma however, the incremental difference for pem/cis vs gem/cis is much larger for large cell compared with adenocarcinoma). This leads to a greater uncertainty surrounding the results for large cell carcinoma.

Costs

The costs associated with alternative therapy options and incremental costs of pem/cis versus gem/cis are reported in Tables 52, 53 and 55.

Table 52: **Costs associated with different therapy options - Adenocarcinoma**

Costs	pem/cis	Gem/cis	gem/carbo	doc/cis
First line chemotherapy acquisition	£4,264	£2,369	£2,566	£2,938
First line chemotherapy administration	£1,210	£1,712	£971	£1,150
Second line chemotherapy	£1,699	£1,812	£1,817	£1,812
BSC	£1,022	£866	£866	£866
Terminal care	£2,601	£2,617	£2,626	£2,623
Adverse events	£180	£271	£231	£338
TOTAL COST	**£10,976**	**£9,648**	**£9,077**	**£9,728**

Table 53: **Costs associated with different therapy options – large cell carcinoma**

Costs	pem/cis	Gem/cis	gem/carbo	doc/cis
First line chemotherapy acquisition	£4,162	£2,388	£2,578	£2,969
First line chemotherapy administration	£1,181	£1,725	£976	£1,162
Second line chemotherapy	£1,703	£1,816	£1,819	£1,817
BSC	£867	£385	£415	£406
Terminal care	£2,624	£2,658	£2,664	£2,662
Adverse events	£187	£315	£256	£349
TOTAL COST	**£10,723**	**£9,287**	**£8,707**	**£9,365**

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).

Table 54: **Mean number of cycles of chemotherapy for *known* non-squamous population.**

Mean number of treatment cycles	Pem/cis	gem/cis	gem/carbo	Doc/cis
Adenocarcinoma	2.81	2.77	2.64	2.67
Large cell carcinoma	2.75	2.79	2.65	2.70

Table 55: **The incremental cost of pem/cis compared with gem/cis**

Incremental cost	**Pem/cis vs gem/cis**	**Pem/cis vs gem/carbo**	**Pem/cis vs doc/cis**
Adenocarcinoma	£1,328	£1,899	£1,248
Large cell carcinoma	£1,436	£2,016	£1,358

Health outcomes

LYGs and QALYs gained

The health benefits associated with pemetrexed/cisplatin and comparators are reported below.

Incremental benefit of pem/cis compared to comparators for the target histology population. For results based on the JMDB head-to-head trial we report the results by each histological subgroup. For data based on the indirect comparison we report for adenocarcinoma and large cell together.

Table 56: **Summary of health-related outcomes by therapy and histology type**

Mean benefits	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Adenocarcinoma				
Quality Adjusted Life Years (QALYs)	0.66	0.59	0.53	0.55
Life Years Gained (LYG)	1.31	1.17	1.07	1.10
Large cell				
Quality Adjusted Life Years (QALYs)	0.56	0.38	0.34	0.36
Life Years Gained (LYG)	1.09	0.72	0.65	0.67

Table 57: **Incremental benefit of pem/cis compared to comparators for target population**

Incremental benefit of pem/cis vs.	Gem/cis	Gem/carbo	Doc/cis
Adenocarcinoma			
Incremental QALYs gained	0.07	0.13	0.11
Life Years Gained (LYG)	0.14	0.23	0.21
Large cell			
Quality Adjusted Life Years (QALYs)	0.18	0.22	0.21
Life Years Gained (LYG)	0.37	0.44	0.42

Modelled Overall Survival curves

The model fitted the data from the JMDB trial for the target population with an exponential distribution in order to parameterise the survival function. The overall survival curve from the model is superimposed on the survival curve from the JMDB trial to demonstrate how closed the model approximated the trial data Figure 16 and 17. There are two figures, the first for three years is closer to the trial duration and the second, for six years, corresponds to the duration of the lifetime model.

Figure 16: **Three year time horizon: Survival curve for modelled and trial data for pem/cis and gem/cis – adenocarcinoma plus large cell carcinoma**

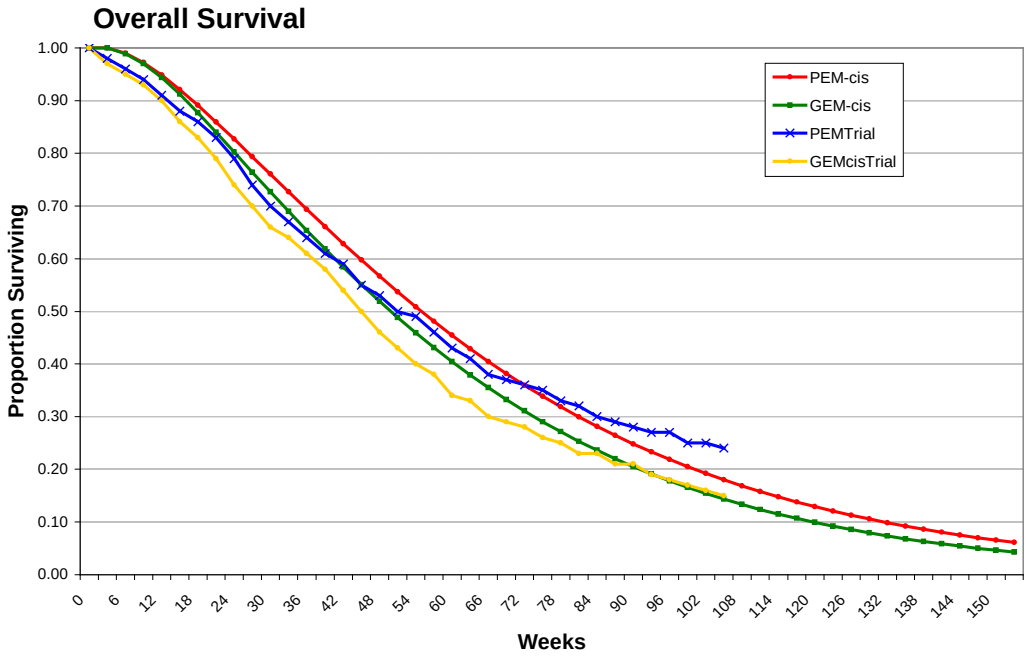
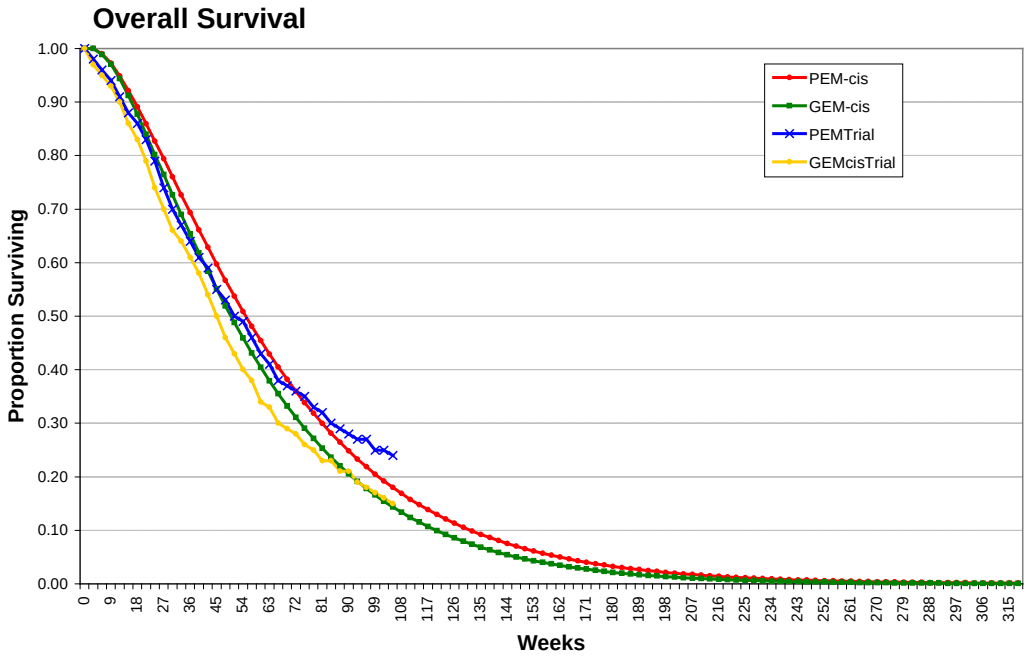


Figure 17: **Six year time horizon: Survival curves for modelled and trial data for pem/cis and gem/cis- adenocarcinoma plus large cell carcinoma population**



From the survival curves above it can be seen that the model over-estimates survival for the first year, but underestimates it for the second and subsequent years. We can further validate the model by comparing survival rates at one and two years from trial data and modelled

data. Again, we see the model slightly over-estimates survival in the first year and underestimates survival in the second year.

Table 58: **Modelled and trial survival rates at one and two years – Adenocarcinoma and large cell carcinoma patients**

	Pem/cis		Gem/cis	
	Model	**JMDB**	**Model**	**JMDB**
1 year survival	54%	49%	49%	42%
2 year survival	19%	24%	15%	15%
3 year survival	6%		4%	
4 year survival	2%		1%	
5 year survival	1%		0%	
6 year survival	0%		0%	

Incremental Cost Effectiveness Ratio

The incremental cost-effectiveness ratio for pem/cis compared to gem/cis is: £18,730 in the adenocarcinoma population and £8,035 in the large cell carcinoma population.

Table 59: **Costs per Additional LYG and QALY gained.**

ICER and Incr. cost per LYG of pem/cis vs.	**Gem/cis**	**Gem/carbo**	**Doc/cis**
Adenocarcinoma			
ICER	**£18,370**	**£14,917**	**£11,159**
Incr. cost per LYG	£9,407	£8,097	£6,042
Large cell carcinoma			
ICER	**£8,035**	**£9,132**	**£6,566**
Incr. cost per LYG	£3,839	£4,612	£3,264

The results of this economic evaluation suggest that for the target population (known non-squamous histology) pem/cis is a cost-effective option compared with gem/cis, gem/carbo and doc/cis. Both cost per QALY and cost per LYG suggest that pem/cis offers a viable treatment option in the right patient population.

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

Sensitivity Analysis

Results of the sensitivity analyses are presented below. The model is driven by two key clinical parameters: overall survival and progression free-survival.

One-way Sensitivity Analysis

The results of the one-way sensitivity analysis (SA) demonstrate that the model is robust as there is little variation in the ICER when structural variables are changed. From the model it is clear that the two drivers of incremental cost-effectiveness are efficacy, overall survival for both pem/cis and gem/cis, and chemotherapy acquisition costs. Using the Department of Health's HRG for chemotherapy procurement and delivery reference prices, pem/cis dominates gem/cis in every histotype.

The cost/QALY for the base case without the continuation rule ranges from around £27,000 to £40,000, outliers are using the HRG costs, in which pem dominates and using the lowest confidence interval for pem/cis survival in which gem dominates. Similarly for non-squamous with continuation rule applied the majority of variables lead to a cost/QALY within (+/-) £10,000 of the original ICER, for adenocarcinoma, the cost/QALY is again within (+/-) £7-10,000 of the original ICER. For large cell carcinoma the cost/QALY range is much tighter with most cost/QALYs (+/-) £2,000.

These results suggest that pem/cis is a cost-effective option compared to gem/cis in the target patient population.

Scenario analysis

A number of scenarios are considered and the impact on incremental cost, incremental benefit and incremental cost per QALY are reported:

Table 60: **Constant parameters in the scenario analysis:**

Parameter	Value
Population	Non-squamous, adenocarcinoma and large cell carcinoma populations
BSA	$1.8m^2$
Treatment pathway	Pem/cis → doc/erlotinib*
Chemotherapy costing	Per vial
BSC	At progression

* All second-line therapies are assumed to have equivalent efficacy therefore the second-line part of the treatment pathway only affects costs

Table 61: **Scenario analysis looking at the impact of number of treatment cycles on cost/QALY for adenocarcinoma and large cell carcinoma populations**

	ICER		
	Non-squamous NSCLC	**Adeno-carcinoma**	**Large cell carcinoma**
Scenario 1 – No continuation rule, maximum of four cycles (Equivalent to a mean of four cycles of therapy)	*£35,188*	*£21,044*	*£8,888*
Scenario 2 – Continuation rule on, maximum of four treatment cycles (Non-responders receive three cycles, responders receive four)	*£26,985*	*£18,370*	*£8,035*
Scenario 3 – No continuation rule, maximum of six cycles (Equivalent to a mean of four cycles of therapy)	*£47,663*	*£28,420*	*£10,431*
Scenario 4 –Continuation rule, maximum of six cycles (Equivalent to a mean of three cycles of therapy)	*£33,197*	*£22,764*	*£9,403*

This scenario analysis demonstrates that pem/cis is a cost-effective therapy compared to gem/cis only if a continuation rule is applied or used within the target population.

Base case	No continuation rule Non-squamous ICER = £35,188	Continuation rule Non-squamous ICER = £26,985	Continuation rule Adenocarcinoma ICER = £18,370	Continuation rule Large cell carcinoma ICER = £8,035
Costs				
All costs decreased by 25%	£27,049	£20,805	£14,393	£6,279
Chemotherapy costs decreased by 25%	£22,208	£17,349	£12,208	£5,713
Chemotherapy costs increased by 25%	£48,169	£36,621	£24,533	£10,357
All costs (excluding chemotherapy drugs) decreased by 25%	£40,030	£30,440	£20,566	£9,051
All costs (excluding chemotherapy drugs) increased by 25%	£30,100	£23,346	£16,072	£6,961
Per mg costing	£39,249	£29,929	£20,232	£8,798
HRG procurement and delivery costs applied	-£64,292	-£45,794	-£27,801	-£10,459
	PEM DOMINATES	PEM DOMINATES	PEM DOMINATES	PEM DOMINATES
Chemotherapy administration costs - Lower quartile from HRG (£210)	£43,198	£32,633	£21,910	£9,589
Chemotherapy administration costs - upper quartile from HRG (£795)	£27,335	£21,448	£14,901	£6,512
BSC/palliative care decreased by 25%	£35,237	£27,029	£18,426	£8,083
BSC/palliative care increased by 25%	£35,139	£26,942	£18,315	£7,988
Cost of FN increased to £3884 (from £1720)	£34,175	£26,095	£17,730	£7,916
GEM drug acquisition cost discount of 20%	£48,184	£36,427	£24,346	£10,472
PEM drug acquisition cost discount of 20%	£11,244	£9,351	£7,612	£3,611
Second-line costs excluded	£38,109	£29,468	£19, 934	£8,677
Half cycle correction included	£35,355	£27,093	£18,418	£8,039

Base case	No continuation rule Non-squamous ICER = £35,188	Continuation rule Non-squamous ICER = £26,985	Continuation rule Adenocarcinoma ICER = £18,370	Continuation rule Large cell carcinoma ICER = £8,035
Resource use				
Hospital days for AEs decreased by 50%	£35,775	£27,366	£18,567	£8,223
Hospital days for AEs increased by 50%	£34,191	£26,337	£18,036	£7,716
Utility				
Disutility assigned to AEs decreased by 50%	£35,859	£27,330	£18,492	£8,068
Disutility assigned to AEs increased by 50%	£34,542	£26,650	£18,250	£8,003
Assume no disutility assigned to AEs (so only have a cost impact in model)	£36,566	£27,683	£18,616	£8,101
Utility weights assigned to health states all lower of 95% confidence interval	£39,906	£29,783	£20,740	£9,218
Utility weights assigned to health states all upper of 95% confidence interval	£31,465	£24,688	£16,485	£7,116
Efficacy				
Lower 95% limit for PEM survival	GEM DOMINATES	GEM DOMINATES	GEM DOMINATES	£14,732
Upper 95% limit for PEM survival	£13,496	£11,633	£11,421	£5,023
Lower 95% limit for GEM survival	£17,947	£15,056	£12,676	£6,534
Upper 95% limit for GEM survival	GEM DOMINATES	GEM DOMINATES	£57,085	£22,275
Patient population				
Mean body surface area (BSA) 1.6m^2	£32,704	£25,056	£17,123	£7,608
Mean body surface area 2.0m^2	£43,087	£32,848	£22,107	£9,478

Base case	No continuation rule Non-Squamous ICER = £35,188	Continuation rule Non-squamous ICER = £26,985	Continuation rule Adenocarcinoma ICER = £18,370	Continuation rule Large cell carcinoma ICER = £8,035
Model parameters				
Time horizon 2 years	£47,833	£34,921	£25,619	£7,712
Time horizon 4 years	£35,998	£27,480	£18,946	£8,000
Discounting rates				
Discounting rates 0% for costs and benefits	£34,048	£26,212	£17,795	£8,030
Discounting rates 6% for costs and benefits	£35,986	£27,525	£18,775	£8,040

*The cost per QALY for the non-squamous population reflects pemetrexed's licensed population: adenocarcinoma, large cell carcinoma and the 'not otherwise specified' (NOS) patients. The statistically significant survival advantage of pem/cis compared with gem/cis observed in the adenocarcinoma and large cell group is not seen in the NOS group, which is why the cost per QALY increases.

The HRG costs for procurement and delivery are as follows
Pem/cis £1294; gem/cis £2020; gem/carbo £1523; doc/cis £1816

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted using 500 iterations, the results of which can be seen below comparing pem/cis with gem/cis for the non-squamous (with and without a continuation rule applied), adenocarcinoma and large cell populations.The majority of points for all populations fall within the north east quadrant, the percentage of points in the northeast quadrant increases for non-squamous with the continuation rule applied. The target population also shows a high degree of certainty that pem/cis is a cost-effective option in this population compared with gem/cis.

All of the figures below are for the primary comparator: pem/cis vs gem/cis. The first twofigures for the licensed non-squamous population are without the continuation rule applied, all the other figures, for the licensed population and the target population, adenocarcinoma and large cell carcinoma, have the continuation rule applied.

Figure 18: **Cost effectiveness plot for licensed (non-squamous) population - without continuation rule applied**

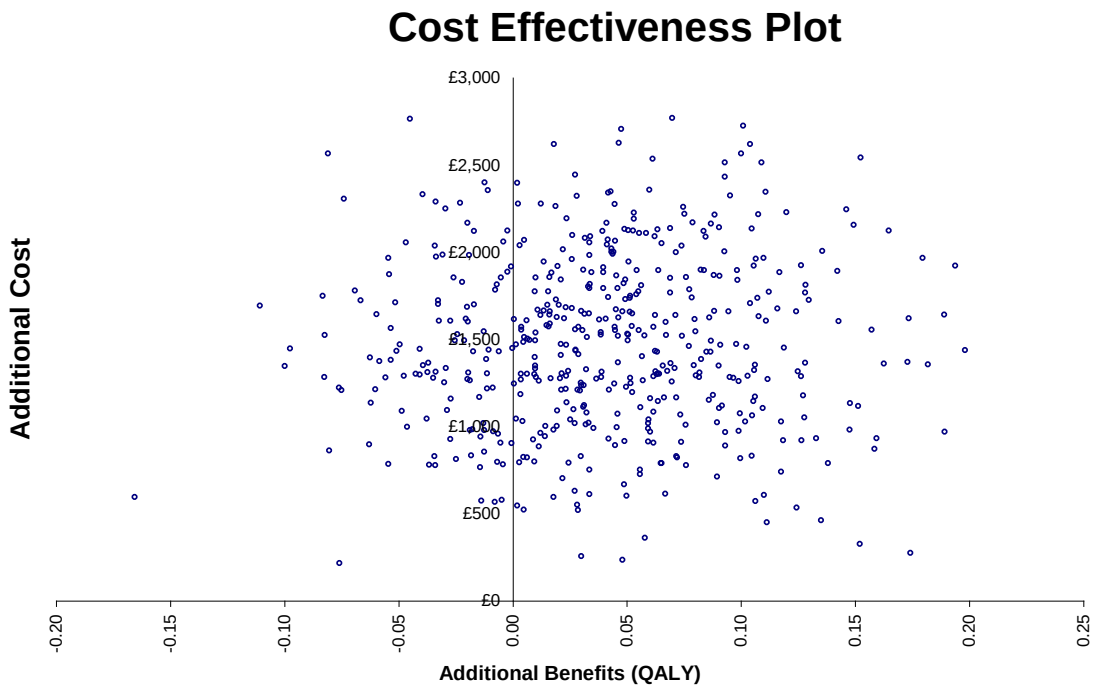


Figure 19: **Cost effectiveness acceptability curve, cost per QALY gain – for licensed (non-squamous) population - without continuation rule applied**

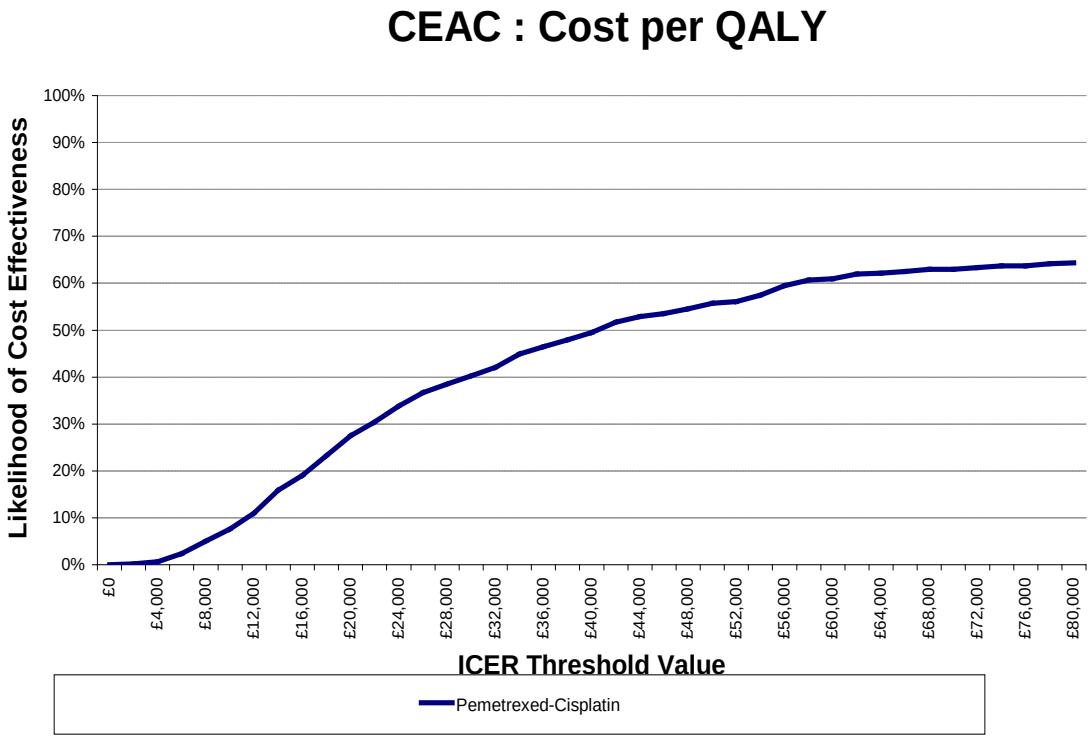


Figure 20: **Cost effectiveness plot for licensed (non-squamous) population - with continuation rule applied**

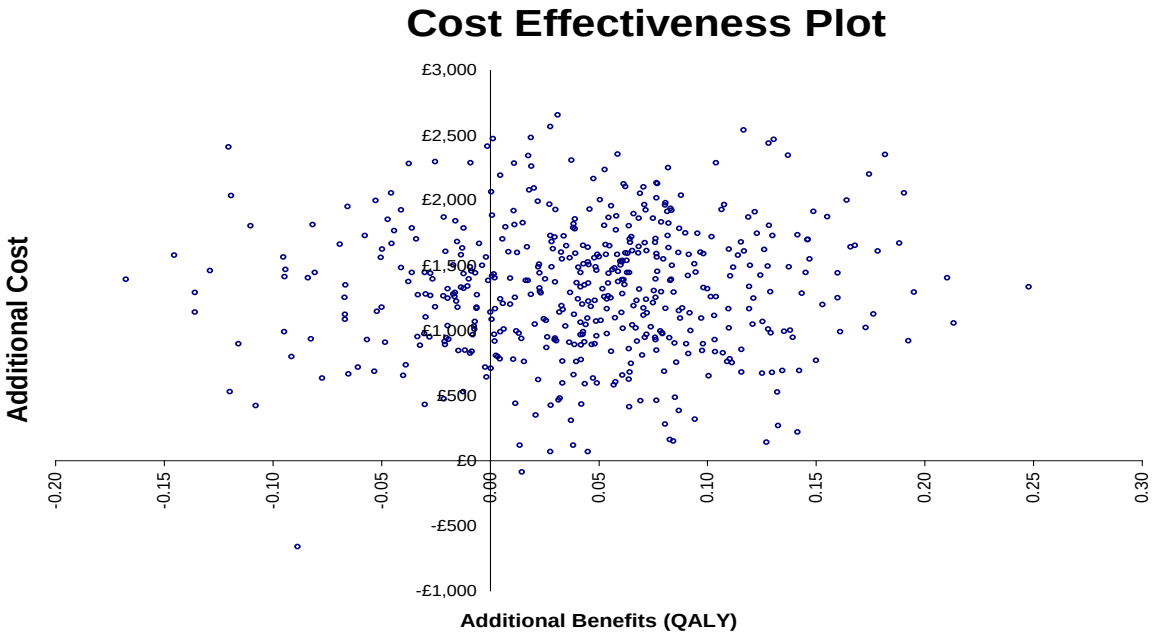


Figure 21: **Cost effectiveness acceptability curve, cost per QALY gain – for licensed (non-squamous) population – with continuation rule applied**

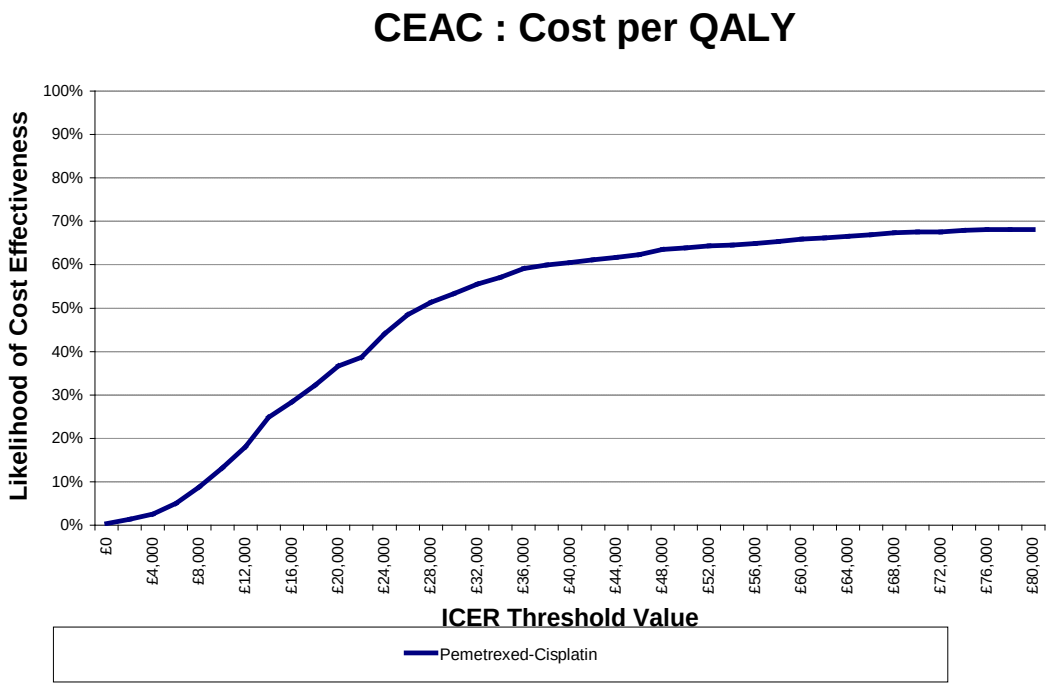


Figure 22: **Cost-effectiveness plot for adenocarcinoma population – with continuation rule applied**

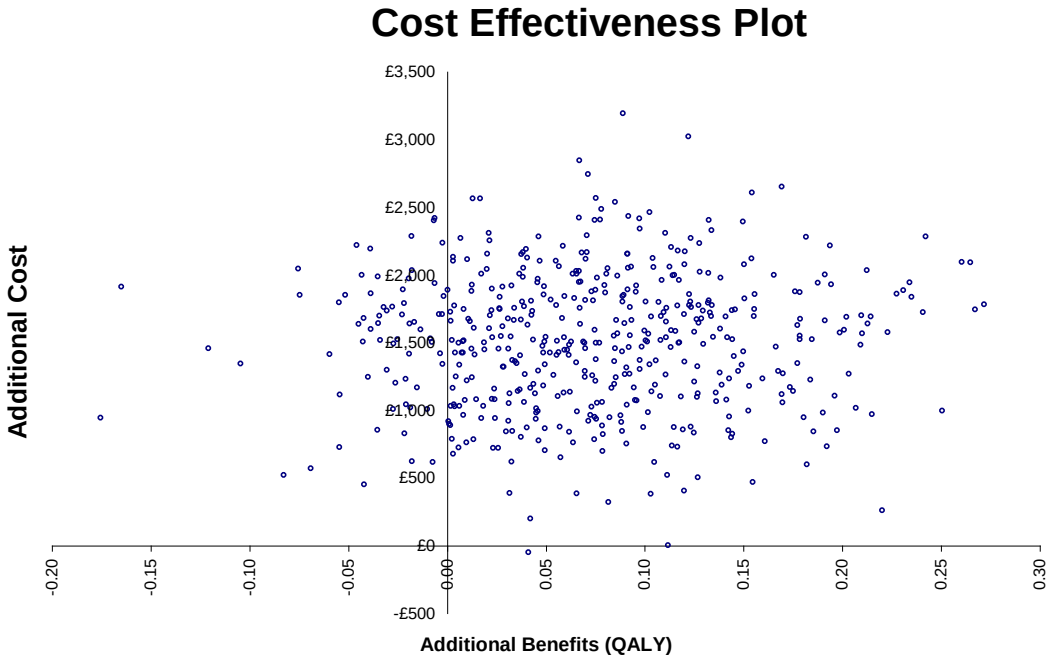


Figure 23: **Cost effectiveness acceptability curve, cost per QALY gain – for adenocarcinoma population – with continuation rule applied**

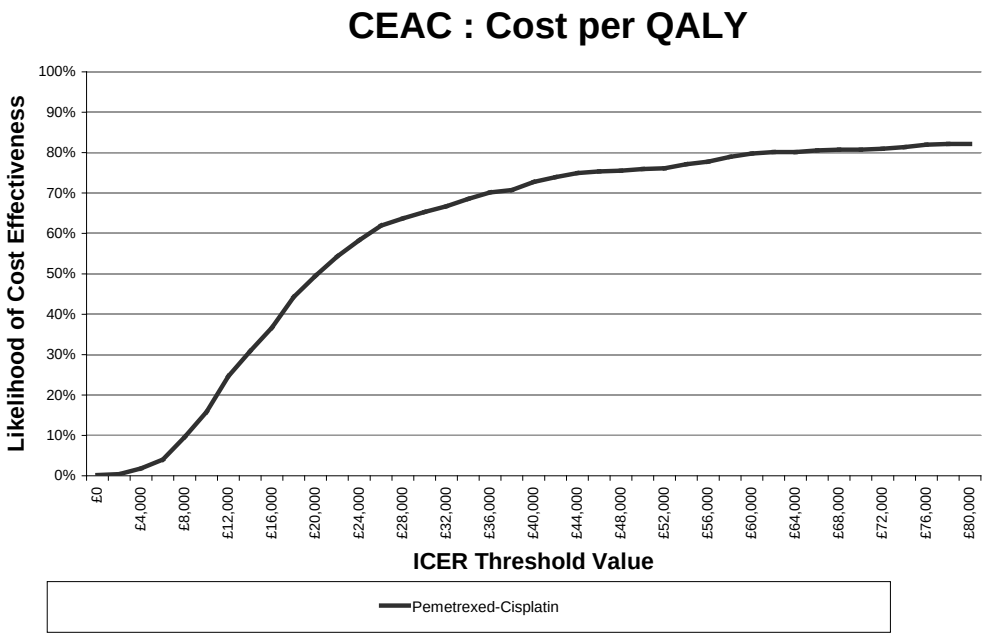


Figure 24: **Cost-effectiveness plot for large cell carcinoma population – with continuation rule applied**

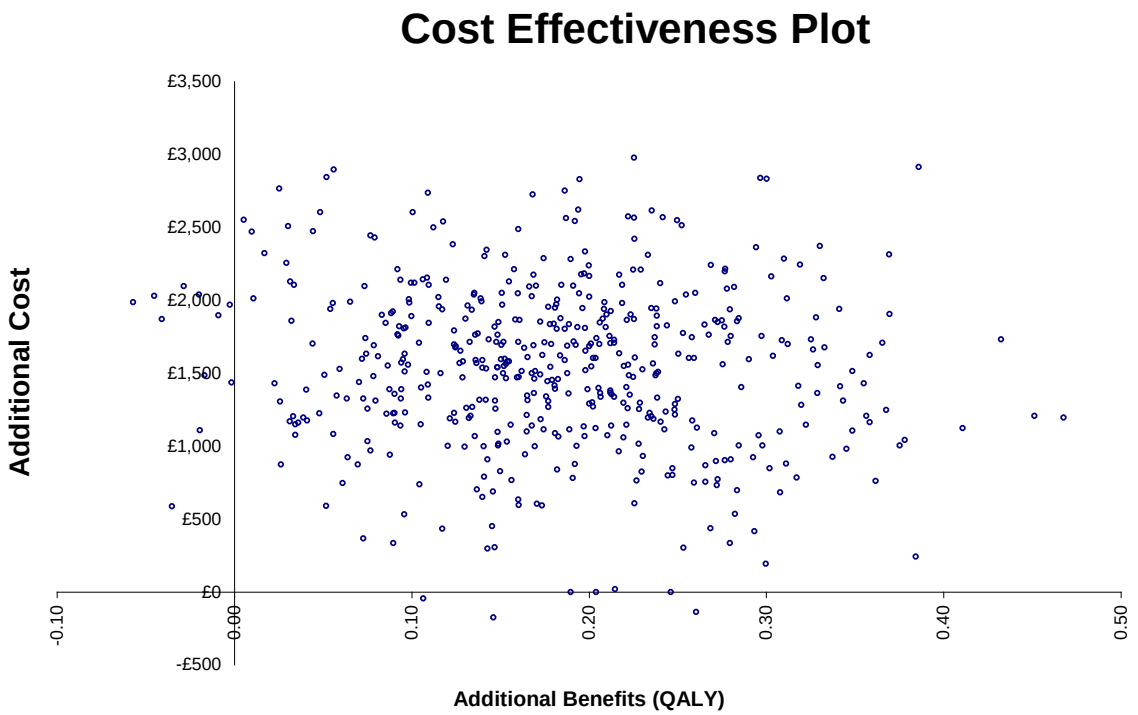
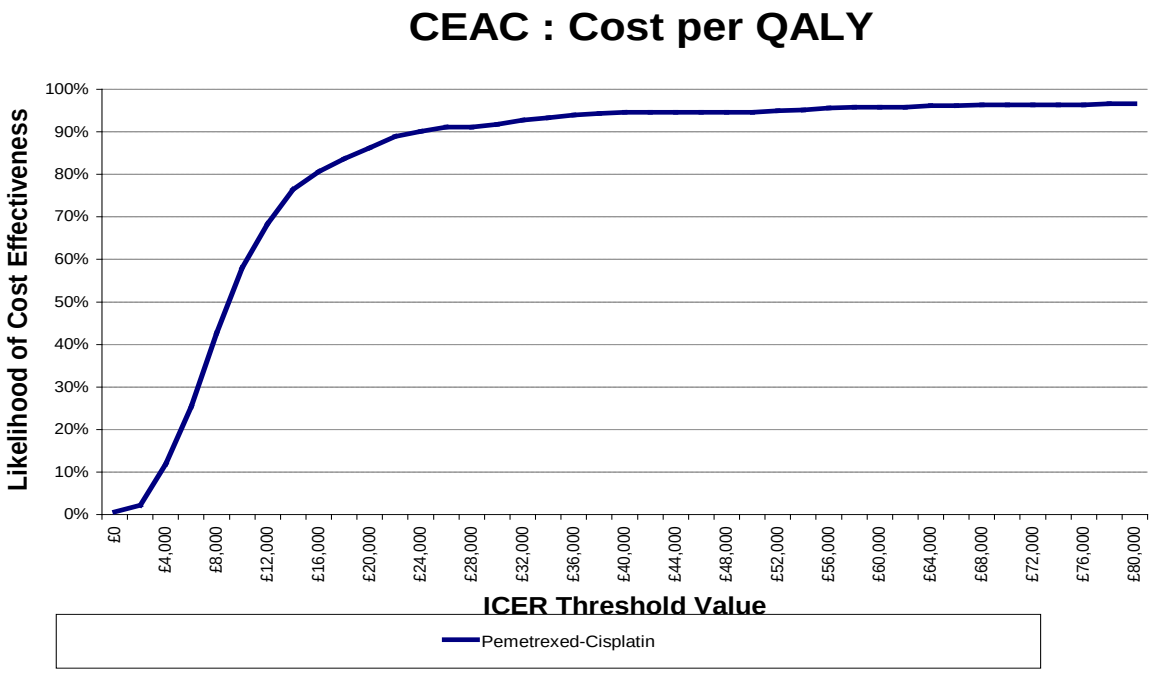


Figure 25: **Cost effectiveness acceptability curve, cost per QALY gain – for large cell carcinoma population – with continuation rule applied**



These Figures (18-24) suggest pem/cis will be a cost-effective option compared with gem/cis in the target adenocarcinoma and large cell carcinoma, and while there is more uncertainty in the non-squamous population the majority of points fall in the north-east quadrant of the scatter plot suggesting that the majority of the time pem/cis will be a cost-effective alternative to gem/cis when a continuation rule is applied.

Model Validity Modelled LYG versus Mean Survival

As a means of ensuring that the model is modelling survival in a reasonable manner a further comparison was carried out to check the life years gained output of the model against the mean survival output of the JMDB trial. The results are shown below.

The model returns comparable results against the results of the JMDB trial. There is a difference in mean output from the trial and modelled output for large cell carcinoma patients; this can be attributed to the difference in mean and median values reported for this group which result from a large confidence interval, a relatively small sample size and censored data. The trial means are calculated based on 28.7% censored data for overall survival in the target non-squamous population.

Table 62: **Means and median overall survival data from the trial compared with the modelled overall survival output**

	Mean from Trial (Yrs) (censored data)			Median from Trial (Yrs)			Output from Model (Yrs)		
	pem/cis	**gem/cis**	**Incre-mental**	**pem/cis**	**gem/cis**	**Incre-mental**	**pem/cis**	**gem/cis**	**Incre-mental**
All Patients	1.06	1.008	**0.052**	0.857	0.857	**0.00**	1.07	1.07	**0.00**
Licensed population	1.09	1.01	**0.08**	0.920	0.843	**0.08**	1.13	1.05	**0.08**
Target population	1.17	1.02	**0.15**	0.983	0.867	**0.12**	1.22	1.13	**0.10**
Adenocarcinoma	1.2	1.07	**0.13**	1.046	0.912	**0.13**	1.31	1.16	**0.14**
Large Cell Carcinoma	0.89	0.75	**0.14**	0.865	0.556	**0.31**	1.07	0.70	**0.36**

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

The key drivers of the cost-effectiveness results are the chemotherapy acquisition costs and overall survival data.

The results of the one-way sensitivity analysis (SA) demonstrate that the model is robust to change as there is little impact on the QALY outcomes for most of the parameters varied, Results are presented on a per patient basis for simplicity but were estimated using a cohort of 500 patients. The cost per QALY gained in the non-squamous population is generally in the range £27,000-£40,000, without continuation rule. For the adenocarcinoma group the

cost/QALY is generally in the range £16,000-£20,000 while in the large cell group the general range is £6,000 to £10,000.

The exceptions are for efficacy outcomes and chemotherapy costs, as would be expected. If the lower value of the 95% CI for OS for pem/cis is used, and/ or the upper for gem/cis, then gem.cis dominates. If the converse is done then pem/cis is highly cost-effective. If Department of Health HRG chemotherapy procurement and delivery prices are used, as recommended in the Decision Problem meeting, then pem/cis dominates.

7.3.4 Interpretation of economic evidence

7.3.4.1 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 evaluation to report the cost-effectiveness of pem/cis vs gem/cis and gem/carbo in the first-line NSCLC setting in England and Wales.

7.3.4.2 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. We have presented the 'target' population, of adenocarcinoma plus large cell carcinoma, the population that has the most potential to benefit from pem/cis in the first line setting with the current data available. We also present the data for the licensed population

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

One of the key strengths of this economic evaluation is that it is based on a direct head to head comparison of pem/cis to gem/cis in a large, phase III randomised clinical trial. Gemcitabine plus a platinum is the standard of care in the UK currently. The choice of platinum varies by centre which means that an additional comparison was made to gem/carbo. However, as this was based on an indirect comparison, the outcomes of this analysis are less certain than the results for gem/cis. Cisplatin and carboplatin have in general been considered to be interchangeable in terms of efficacy, with the differences being in the administration time required for delivery. A recent meta-analysis (Jiang 2007, Ardizzoni 2007) suggested that cisplatin delivers greater efficacy than carboplatin, and subsequently use of cisplatin has increased, but overall clinical practice in the UK is still split between the two platinums. The results for the incremental cost-effectiveness of gem/cis compared to pem/cis using a direct comparison are the most robust economic results; on the basis of similar efficacy for the platinums and slightly higher costs for carboplatin compared to cisplatin, the results for gem/cis can be expected to be similar but slightly higher ICERs than for gem/carbo. Therefore, the outcome of the direct comparison can be used to support and supplement the incremental cost-effectiveness estimates for pem/cis vs gem/carbo produced by the indirect comparison.

One of the most complex issues faced within this economic evaluation was the histology that is needed for the identification of the patient who is most likely to benefit. Up until the licensing for bevacizumab and pemetrexed, there was no requirement for histology to be more specific than non-small cell or small cell carcinoma. For pemetrexed, the differentiation

between squamous and non-squamous histology is important as gemcitabine performs better in squamous patients and pemetrexed better in non-squamous patients. The accuracy of histology is greatest for identification of squamous (87%), therefore excluding patients not appropriate. This is the basis for the licence. Within non-squamous, adenocarcinoma is the most readily and accurately identified using standard histological procedures (around 80% accuracy). Large cell carcinoma is more difficult to identify and the sample size within the trial is smaller. These factors need to be taken into consideration when interpreting the results of the economic analysis. If a pathologist is not certain of the patient's histology, the standard of care should be provided rather than pemetrexed. The implication of this is one of budget impact, not cost-effectiveness i.e. if there is uncertainty surrounding a definitive diagnosis of non-squamous NSCLC, then gem/platinum should be used, which reduces the number of patients receiving pemetrexed, but not the incremental cost-effectiveness of pem/cis vs gem/cis. It is anticipated that as the need for histology continues with the advent of new therapies, the number of patients in the 'NOS' /uncertain diagnosis group will be reduced.

The level of censorship of the survival data meant that survival had to be extrapolated from the end of the clinical trial to the time horizon of 6 years. An exponential form was used assuming constant hazard, and appeared to demonstrate a relatively good fit to the data. Validation tests of modelled output versus clinical trial output show consistency of the degree and direction of incremental benefits for pemetrexed.

There was no QoL data collected in the clinical trial so utilities had to be applied to the health states within the model. These utilities were from a study looking at second-line NSCLC but it was assumed that the values would be similar in first-line; the results are not sensitive to small changes in utility as survival is the main driver of cost-effectiveness in this case. The key limitation is that the utilities do not incorporate symptomatic benefits of chemotherapy or the benefit of avoiding an additional infusion per cycle on Day 8 for gemcitabine.

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

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 estimated annual budget impact for the NHS in England and Wales, in the first five years following the licensing of pemetrexed/cisplatin (pem/cis) ranges from £68,639 in 2008, or a 0.7% increase on the budget without pem/cis being available, to £2,040,756 in 2012, or a 30 % increase in the budget without pem/cis being available. The estimate for the budget impact in the five years post-launch is shown in Table 63 below. The estimate for 2012 assumes 75% market share of eligible patients.

Table 63: **Annual budget impact for pem/cis in England and Wales in the five years post-launch**

	2008	2009	2010	2011	2012
No. eligible patients	1179	1291	1402	1515	1626
Cost without pem/cis	£4,902,636	£5,368,365	£5,829,937	£6,299,825	£6,761,396
No. pem/cis patients	41	81	244	732	1219
Cost with pem/cis	£4,971,503	£5,504,421	£6,239,783	£7,529,365	£8,808,950
Net Impact	£68,868	£136,056	£9,847	£1,229,540	£2,047,554

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

The estimate for the total lung cancer population in 2008 is based on registered cancer diagnoses reported by the Office for National Statistics (England data) and the Welsh Cancer Intelligence and surveillance Unit (Welsh data). The most up to date, 2005, were used. This population is assumed to be constant over time (ONS 2008b; WCISU 2008).

The eligible patients were then identified based on information in the England and Wales Lung Cancer Audit Report for 2006 (LUCADA 2007). Table 64 reports patient numbers, Figure 26 describes how they were derived. It was assumed that the adenocarcinoma plus large population would increase by 2.75% each year, as the rate of adenocarcinoma increases and diagnosis of adenocarcinoma (and large cell) improves. There are alternative ways of estimating the eligible patient population however, we chose to base this estimate on the LUCADA data, considering it the most representative for an England and Wales population as it has internal validity, rather than amalgamating information from a range of different sources.

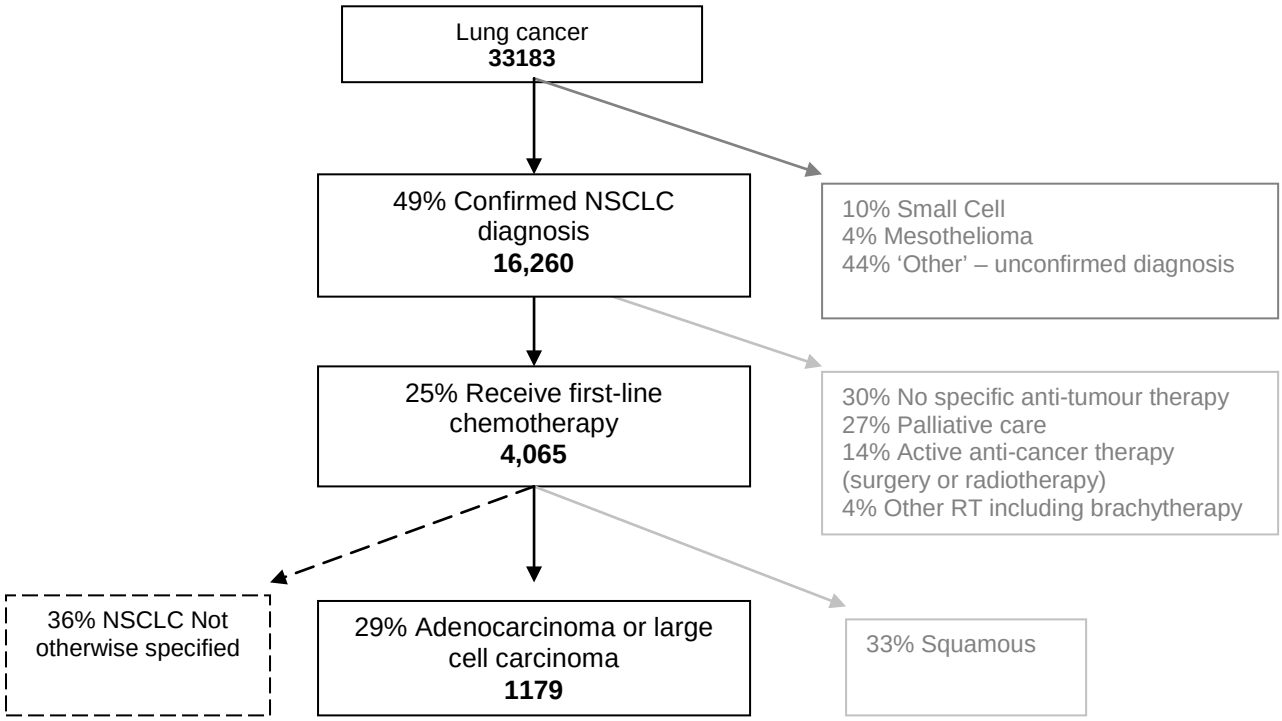
An important assumption is that all patients reported in LUCADA as receiving chemotherapy as their first active treatment given are equivalent to first-line patients who would be eligible for pem/cis, assuming the correct histological diagnosis. Built into this is the assumption that these patients are fit enough to receive chemotherapy, Second, it assumes these are patients with advanced disease, as these are patients who

can benefit from chemotherapy but have disease that is too advanced to be given surgical resection. Pem/cis is licensed for patients with locally advanced or metastatic NSCLC (Pemetrexed SPC 2008).

Table 64: **Eligible patient population – based on the confirmed NSCLC population**

Year	2008	2009	2010	2011	2012
Total lung cancer incidence 2005	33183	33183	33183	33183	33183
49% Confirmed NSCLC	16260	16260	16260	16260	16260
25% Receiving 1st line chemo	4065	4065	4065	4065	4065
% Adenocarcinoma or large cell diagnosis	*29%*	*32%*	*35%*	*37%*	*40%*
No. patients adenocarcinoma or large cell carcinoma (eligible patient population)	1179	1291	1402	1515	1626

Figure 26: **Algorithm for the identification of patients eligible for pem/cis in the first-line setting (LUCADA 2007).**



The LUCADA data represent 57% of all lung cancer patients diagnosed in one year. It is assumed that the data reported in LUCADA is representative of England and Wales as a whole, ie, the trusts for whom there is not data would not present widely different trends. One area of uncertainty was whether to base the calculations on cases with a confirmed NSCLC diagnosis (49% of all lung cancers) or those described as 'all lung cancers excluding confirmed small cell and mesothelioma' (86% of all lung cancers), this includes the 49% of confirmed NSCLC cases.

There is no breakdown by histology for the 'unconfirmed' NSCLC cases. However data for the percentage of these patients that receive chemotherapy as the first treatment are available. The effect of repeating the algorithm with this population using the reported 18% chemotherapy rate, rather than 25%, is reported in table 65. The final row reports the difference in the two estimates. For this population, the 'all lung cancers excluding confirmed small cell and mesothelioma', we have assumed the same distribution of adenocarcinoma and large cell carcinoma as in the confirmed NSCLC population.

Table 65: **Eligible patient population – based on the '*all lung cancers excluding confirmed small cell and mesothelioma*' population**

	2008	2009	2010	2011	2012
Total lung cancer incidence 2004	*33183*	*33183*	*33183*	*33183*	*33183*
86% unconfirmed NSCLC	28537	28537	28537	28537	28537
18% to get chemo	5137	5137	5137	5137	5137
Increase in % adenocarcinoma as diagnosis improves	29%	32%	35%	37%	40%
No. eligible patients with ad or large	1490	1631	1772	1914	2055
Difference in estimated patients	*311*	*340*	*370*	*399*	*429*

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

It was assumed that an increase in adenocarcinoma and a decrease in NSCLC-NOS will be observed over time with adenocarcinoma increasing from 29%, as reported in LUCADA (2008) to 40% over five years, an increase of 2.75% per year.

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

The increasing market share assumption is reported in table 66. This is based on the percentage of all NSCLC patients who receive first-line chemotherapy, so in table 64 above, it corresponds with 4065 patients.

Table 66: **Market share**

Year	2008	2009	2010	2011	2012
Market share of fit NSCLC pts receiving chemotherapy	1.0%	2.0%	6.0%	18.0%	30.0%
% of target pem/cis market	3.0%	6.0%	17.0%	48.0%	75.0%

This estimate is also translated into a market share for patients who are the 'target' patients population for pem/cis, i.e., those with adenocarcinoma or large cell carcinoma. It is hoped that targeting the therapy to those patients most likely to benefit from it could lead to this large market share.

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

Costs were calculated on a per vial basis (including wastage), assuming a BSA of $1.8m^2$ and an average of three treatment cycles. An estimate for best supportive care (BSC) and terminal/palliative care (the cost of the final month of care) is assumed for each patient to give a more accurate estimate for the budget impact. An estimate for adverse events is not including as this varies so widely between patients.

Table 67: **Chemotherapy acquisition and administration costs, based on per vial costs for a patients with BSA of 1.8m^2**

Cost	Pem/cis	Gem/cis	Gem/carbo	Doc/cis
Chemotherapy (per vial costing)	£1,516	£857	£972	£1,099
Administration Cost	£430	£619	£368	£430
Total cost per cycles	**£1,946**	**£1,476**	**£1,340**	**£1,529**
Mean no. treatment cycles	*3.00*	*3.00*	*3.00*	*3.00*
Total cost per patient	**£5,838**	**£4,428**	**£4,020**	**£4,587**

Detailed chemotherapy treatment costs are provided in table 68 and administration costs are provided in table 69.

Table 68: **Detailed chemotherapy treatment costs (BNF 55, 2008)**

	Unit cost per vial	Calculated cost per mg	DOSE	Cost per dose
Chemotherapy				
Pemetrexed (100mg vial)	£160.00	£1.60		
Pemetrexed (500mg vial)	£800.00	£1.60	500mg/m^2	£1440.00
Gemcitabine (200mg vial)	£32.55	£0.16	1250mg/m^2	£390.62
Gemcitabine (1000mg vial)	£162.76	£0.16		
Docetaxel (20mg vial)	£162.75	£8.14	75mg/m^2	£1023.00
Docetaxel (80mg vial)	£534.75	£6.68		
Platinum				
Cisplatin (50mg vial)	£25.37	£0.51	75mg/m^2	£75.59
Cisplatin (100mg vial)	£50.22	£0.50		
Carboplatin (50mg vial)	£22.04	£0.44	AUC=5 500mg/cycle	£190.89
Carboplatin (150mg vial)	£56.29	£0.38		
Carboplatin (450mg vial)	£168.85	£0.38		
Carboplatin (600mg vial)	£260.00	£0.43		

	Mean cost per patient per cycle	Mean number of cycles per patient	Mean total cost per patient
Pem/cis	£1440 + £75.59	3	£4547
Gem/cis	(£390.62 x 2*) + £75.59	3	£2570
Gem/carbo	(£390.62 x 2*) + £190.89	3	£2916
Doc/cis	£1023 + £75.59	3	£3296

*Day 1 and Day 8 gemcitabine

Table 69: **National schedule of reference costs 2006-07 NHS Trusts, Chemotherapy inpatients and outpatients (DH, 2008)**

HRG Code	HRG Label	Unit cost	
		Outpatients	***Inpatients***
SB12Z	Deliver simple parenteral chemotherapy at first attendance	£170	£309
SB13Z	Deliver more complex parenteral chemotherapy at first attendance	£104	£298
SB14Z	Deliver complex chemotherapy including prolonged infusional treatment at first attendance.	£179	£430
SB15Z	Deliver subsequent elements of a chemotherapy cycle	£189	£255

The administration costs are based on the most up to date HRGs available from the Department of Health. It is important to note that it is the platinum part of the chemotherapy doublet that drives the administration classification, because cisplatin requires hydration it is more often associated with an inpatient stay. Carboplatin is generally given in an outpatient setting. It is possible to give cisplatin as a long day-case.

For the purposes of this budget impact analysis it is assumed that all therapies are SB14Z: 'Deliver complex chemotherapy including prolonged infusional treatment at first attendance' with cisplatin therapies being all inpatient administration, at £430, and carboplatin based being outpatient administration at £179. Gemcitabine also requires Day 8 administration (without a platinum) and so is classed as SB15Z (outpatient), 'Deliver subsequent elements of a chemotherapy cycle'.

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 mean number of treatment cycles is assumed to be three, which is based on the number of cycles estimated in the economic model and a likely average assuming a maximum of four cycles in routine clinical practice with patients who progress or do not exhibit response not receiving the maximum number of cycles. The only difference between observed and recommended doses is in regards to gem/carbo, in which the SPC reports a dose of 400mg/m^2 but clinical papers and clinical experts suggest this is too high a dose in the advanced NSCLC patient and 500mg (an estimate of AUC = 5) is used.

We discuss administration costs in question 8.5.

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

Pemetrexed would provide direct savings in the form of fewer adverse events and reduced clinic visits compared to gemcitabine. However, pemetrexed is more expensive than gemcitabine, so the savings would be off-set by higher acquisition costs.

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 or reduced toxicity with pem/cis.

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