Pemetrexed disodium for the treatment of malignant pleural mesothelioma:
a systematic review and economic evaluation

Final Version

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The Liverpool Reviews and Implementation Group (LRiG) was established within the Department of Pharmacology and Therapeutics, University of Liverpool in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance, is to conduct systematic reviews commissioned by the Health Technology Assessment Programme.

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Summary

Objectives

To assess the clinical and cost-effectiveness of pemetrexed disodium in combination with cisplatin for the treatment of unresectable pleural mesothelioma in chemotherapy naïve patients.

Background

Mesothelioma is a rare and rapidly progressive malignancy of the mesothelium. Ninety percent of cases involve the pleura (lining of the lungs), the remainder affect the peritoneum (lining of the abdomen). Epidemiological studies indicate that incidence is increasing worldwide, and this increase is being attributed to previous exposure to asbestos.

Currently there is no gold-standard treatment for mesothelioma. Surgical treatment is only an option for a small minority of patients whose disease is at stage I or II. Other treatment options may include chemotherapy, radiotherapy or supportive care.

Benefit of chemotherapy may include an improvement in symptoms and/or, occasionally, shrinkage in the size of cancer. Various chemotherapy regimens (either as single agent or in combination) are used, including mitomycin, vinorelbine, platinum compounds, doxorubicin, and antifolates.

Pemetrexed disodium, a new multitargeted antifolate, is the first and only chemotherapy agent that has been granted marketing approval for use in combination with cisplatin (administered with vitamin B12 and folic acid) for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Methods

The review was conducted following accepted guidelines for conducting systematic reviews including the identification of clinical and economic studies (1980 to May 2005), application of inclusion criteria, quality assessment of included studies and data extraction and analysis.

Inclusion criteria

Studies that compared pemetrexed disodium plus cisplatin with other cytotoxic agents or supportive care were considered for inclusion in the review. Data on the following outcome measures were considered: overall survival, toxicity, health-related quality of life, tumour response, and progression-free survival.

Full economic evaluations that compared two or more options and considered both costs and consequences including cost-effectiveness, cost-utility analysis or cost-benefit analysis undertaken in the context of high quality randomised controlled trials were considered for inclusion in the review.

Clinical findings

One randomised controlled trial (RCT) comparing pemetrexed and cisplatin with cisplatin alone, and involving a total study population of 448 patients, met the inclusion criteria. The search failed to identify any other studies that compared the effectiveness of pemetrexed disodium and cisplatin with other commonly used alternatives such as vinorelbine, MVP (mitomycin C, vinblastine and cisplatin) or supportive care.

Pemetrexed in combination with cisplatin in this trial showed a 2.8 months gain in median survival compared with cisplatin alone in intention-to-treat (ITT) population (12.1 and 9.3 months, respectively, p=0.020, hazard ratio of 0.77). During the trial, increased reporting of severe toxicity in the pemetrexed arm led to a change in the protocol to add folic acid and vitamin B12 supplementation to therapy. For fully supplemented patients (n = 331) the hazard ratio for median survival in favour of pemetrexed plus cisplatin was also comparable (0.75), but of borderline significance between treatment arms (p=0.051).

The trial inclusion criteria restricted recruitment to those with Karnofsky performance status of 70 or greater (equivalent to ECOG/WHO 0 or 1 scales more widely used in the UK). Quality of life scores using lung cancer symptom scale (LCSS) demonstrated significantly greater improvement for pain and dyspnoea for patients in the combination group compared to those in the cisplatin group.

In the ITT population, the incidence of serious toxicities with pemetrexed plus cisplatin was higher compared with cisplatin alone. However, the grade 3/4 toxicities of the combination arm, particularly leucopenia, neutropenia and diarrhoea, were found to be greatly improved by the addition of B12 and folic acid.

Economic evaluation

The existing published economic literature is very limited. Only one economic evaluation, available as a conference presentation, was identified for inclusion in the review.

The economic evaluation that we conducted (and that submitted by the manufacturer) suggests that pemetrexed is not cost effective at conventionally accepted thresholds for all

patients. This is mainly owing to the high cost of pemetrexed itself compared with cisplatin. These findings were better for some patient subgroups, e.g. especially for fully supplemented (FS) patients with good performance status (0/1) and advanced disease (AD). These findings seem robust.

Our estimated cost-effectiveness results were as follows:

- FS population: incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained = £59,600
- FS with AD population: ICER per QALY = £47,600
- FS with performance status 0/1 population: ICER per QALY = £49,800
- FS with performance status 0/1 and AD population: ICER per QALY = £36,700

Implications for the NHS

Given the relatively small (albeit increasing) numbers of patients with mesothelioma, the overall budget impact to the NHS is likely to be in the range of £3 - £6 million. This assumes only 25% of the malignant pleural mesothelioma (MPM) population are eligible for pemetrexed therapy. The majority of this cost is the acquisition cost of pemetrexed itself. Whether pemetrexed plus cisplatin is to be recommended to the NHS requires careful consideration, given the extent by which the ICER exceeds conventional thresholds, and the size of the NHS budget impact.

Recommendations for further research

Other agents including anthracyclines and antimetabolites require further evaluation in mesothelioma, in combination with pemetrexed. The use of sequential as well as combination chemotherapy should be considered.

The role of supportive care needs to be defined and evaluated. In order to generalise the treatment findings, further studies including patients with poor performance status are needed. Such trials also need to include an assessment of appropriate quality of life data to better inform subsequent economic evaluations.

ABBREVIATIONS:

AD	Advanced disease
AE	Adverse event
ASC	Active symptom control/ Active supportive care
BSA	Body surface area
BSC	Best supportive care
BTS	British Thoracic Society
CBA	Cost benefit analysis
CEA	Cost effectiveness analysis
CI	Confidence intrerval
Cis	Cisplatin
CMA	Cost minimisation analysis
CR	Complete response
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Chemotherapy
CUA	Cost utility analysis
DLT	Drug limiting toxicity
EMEA	European Agency for the Evaluation of Medicinal Products/European Medicines Agency
EMPHACIS	Evaluation of mesothelioma in a phase III trial with alimta and cisplatin (Also known as JMCH trial)
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
FS	Fully supplemented patients
HR	Hazard ratio
HRQOL	Health-related quality of life

ICER	Incremental cost effectiveness ratio
IM	Intramuscular
IPD	Individual patient data
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplain-Meier
KPS	Karnofsky Performance Status
MLE	Maximum likelihood estimation
MPM	Malignant pleural mesothelioma
MVP	Mitomycin C, vinblastine and cisplatin
NS	Never supplemented patients
NSCLC	Non-small cell lung cancer
PD	Progressive disease
Pem	Pemetrexed disodium
PR	Partial response
PS	Partially supplemented patients
PS 0/1	Performance status 0 or 1
QALY	Quality adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
TTP	Time to progressive disease

DEFINITIONS OF TERMS:

National Cancer Institute (NCI) Common Toxicity Criteria	Standard grading system for reporting adverse events (AEs). Grades refer to the severity of the AE: Grade 1: mild AE, Grade 2: moderate AE, Grade 3: serious AE, Grade 4: life-threatening or disabling AE, Grade 5: death relating to an AE.
Karnofsky performance scale	A subjective performance scale that rates a person's performance of activities of daily living.
Complete response	Total disappearance of all detectable clinical and radiographic evidence of disease and disease related symptoms.
Partial response	A decrease in tumour bulk by a predefined, though subjective, percentage (e.g. decrease of at least 50% of the tumour mass).
Performance status	A method of grading a patient's health at the time of diagnosis.
Phase I studies	Phase I studies are defined as the first clinical studies involving a small group of participants to obtain early evidence on the pharmacokinetics, effectiveness, safety, and the maximum tolerated dose of a new drug. Researchers use information from phase I studies to design phase II studies.
Phase II studies	Phase II studies include early controlled clinical studies to further evaluate safety and estimate the efficacy of the drug or treatment for a particular indication in patients with the disease or condition.
Phase III studies	These studies are longer-term research studies, conducted after phase I and II studies (usually involving several hundred to several thousand participants), to evaluate effectiveness and safety of the study drug or treatment. Most phase III studies are randomized and blinded trials.
Progressive disease	Cancer that is growing, spreading, or getting worse.
Stable disease	No change or less than 25% change in assessable lesions for at least 4 to 8 weeks with no new lesions appearing.
Time to progressive disease	The length of time from the start of treatment or randomisation to the date of documented progression of disease or death from any cause.

Time to treatment failure	The length of time from the start of treatment or randomisation to the date of documented progression of disease, death, or treatment discontinuation for any other reason or initiation of new chemotherapy.
Tumour response rate	The percentage of patients who had either a complete or partial response.

1 REVIEW AIMS

To assess the comparative clinical and cost-effectiveness of pemetrexed disodium (*trade name* Alimta, *synonym* multitargeted antifolate (MTA), LY231514) in combination with cisplatin for the treatment of unresectable malignant pleural mesothelioma in chemotherapy naïve patients.

2 BACKGROUND

2.1 Description of health problem

2.1.1 Disease

The mesothelium is a thin membrane that lines the chest and the abdomen and surrounds the organs in these areas. Mesothelioma is a rare and usually rapidly progressive malignancy of the mesothelium. The most common sites of mesothelioma are the pleura (over 90%), followed by the peritoneum. The presentation is often insidious with diagnosis at a late stage, with an extremely poor prognosis for patients.

2.1.2 Pathogenesis

The mesothelium is a single layer of cells which has the capacity to respond to chemical, infective or physical damage to the pleural or peritoneal cavities. Asbestos is a silicate which is mined in different forms that are associated with different fibre sizes. The ability of a fibre to penetrate into the lung or pleural space varies, but the common factor seems to be release of reactive oxygen species which induce DNA damage, and consequently lead to the non-malignant condition asbestosis and in some cases mesothelioma.[1] There are also less well characterised associations between radiation and mesothelioma, as well as infection with the SV40 virus, which has been demonstrated in up to 40% of diagnosed cases, although a causal relationship has not been demonstrated. The SV40 virus was widely disseminated in the 1950s and 1960s in the Salk polio vaccine.[2, 3]

2.1.3 Epidemiology

Mesothelioma is strongly associated with asbestos exposure which can produce localised and diffuse scarring of the pleural lining of the chest cavity. It has a long latency period varying between 20 and 50 or more years.[4] Epidemiological studies indicate occupational risks associated with mesothelioma. The greatest risks are linked with a variety of settings and occupations including asbestos manufacture, insulation work, working in shipyards, and construction work. The majority of patients are men, with a male to female ratio of 5:1, and in the 60 to 79 years age range.[5]

Although mesothelioma is rare, its incidence is increasing due to the large number of individuals who experienced occupational exposure to asbestos before the risk of mesothelioma was acknowledged. A peak incidence is expected in men in the 1948 to 53 birth cohort. For men born in the 1940s, mesothelioma may account for as many as 1% of all deaths in the United Kingdom in the future.[6]

Approximately 1700 people in the UK (2004 figures) are diagnosed with malignant pleural mesothelioma (MPM) each year.[7] Due to the high utilisation of asbestos principally in the construction industry in the 1970s, it is estimated that the annual mesothelioma mortality in the UK will peak at between 1950 to 2450 deaths/annum some time between the years 2011 and 2015.[6] An estimated 65,000 cases are expected to occur between 2002 and 2050.[6, 8]

2.1.4 Clinical presentation

When mesothelioma affects the pleura, the most common symptoms include breathlessness, and persistent chest pain. A persistent cough or hoarseness of voice may also occur, and a pleural effusion is frequently identified. Weight loss, difficulty in swallowing and fatigue may be associated with advanced disease. The prognosis is poor, with overall median survival ranging from 9 to 13 months.[9] In contrast to many other malignancies, mesothelioma is frequently disabling soon after diagnosis, and patients have a poor quality of life and require considerable supportive care. Death is usually due to compression of the heart and lungs by local spread of the tumour mass.

2.1.5 Diagnosis and staging

Diagnosis is problematic and mesothelioma is not generally diagnosed until 2 or 3 months after the onset of symptoms. Detection may occur incidentally at an advanced stage on routine chest radiographs.[10] Careful assessment of clinical and radiological findings in addition to cytologic findings is essential for accurate diagnosis. In a small proportion of patients the diagnosis may not be possible even after surgery.[11] The median time from first presentation to diagnosis is approximately 3 months.[5]

Studies have shown poor performance status (functional status), more advanced stage of disease, older age at diagnosis, a high white blood cell count and a sarcomatous histologic subtype to be prognostic factors.[12-14] The value of clinicopathological stage is less well accepted as an aid to clinical management, except to identify the small proportion of patients who may benefit from surgery. However, staging is essential for correct selection of patients for surgery[11] and can be used to predict prognosis. The following grouping based on the Tumour, Nodes Metastasis (TNM) system is generally used:[15]

- *Stage I:* mesothelioma affects one layer of the pleura only. It may have grown into the covering of the pericardium and the diaphragm.
- *Stage II:* mesothelioma has spread to both layers of the pleura on one side of the body only.
- *Stage III:* mesothelioma has spread to the chest wall, oesophagus or lymph nodes on the same side of the chest.
- *Stage IV:* mesothelioma has spread via the bloodstream to other organs in the body such as the liver, brain or bone or to lymph nodes on the other side of the chest.

2.1.6 Performance status

Assessment of performance status to quantify the functional status of the patient is important for treatment planning. Performance status is a prognostic factor which is useful in comparison of patient characteristics between studies or groups in randomised trials and may also be an eligibility criterion for inclusion of patients in a clinical trial.

The most commonly used performance status scoring systems include the Karnofsky Performance Status Scale (KPS) and the Eastern Cooperative Oncology Group (ECOG) scores (also called the WHO or Zubrod score). KPS is a 10-point scale from 0 to 100, with the higher scores representing better activity. ECOG is now more widely used and is a five-point scale with zero representing normal activity. In general, phase III trials exclude patients with ECOG performance status 3 or 4, but vary in whether they restrict entry to ECOG 0 and 1 (KPS 70-100), or include category 2 (KPS 60).

2.1.7 Treatment options

Surgery is only an option for a small minority of patients (1 to 5%)[11] whose disease is at stages I or II, and the survival rate for this selected subgroup may be as high as 15% at 5 years.[11] However, for most patients, the disease is surgically unresectable (beyond stage II) at the time of diagnosis and the outlook is bleak, with treatments aimed at palliation of symptoms, including pleural cavity drainage, radiotherapy, and chemotherapy.

Radiotherapy is an effective modality in the treatment of mesothelioma, but the large volumes required for pleural coverage limit its utility because of toxicity and failure to affect survival. However, more localised radiation may be used to achieve pain control or in the prophylaxis of implants along the tracts of drains or biopsy sites.[16]

Currently there is no standard chemotherapy treatment for mesothelioma in the UK. [17] A variety of chemotherapy regimens are used, including the alkylating agents, the anthracyclines, mitomycin C, the platinum compounds, and antifolates, with response rates in trials ranging from 0 to 45%.[18]

Cisplatin has been used as a single agent comparator in a number of phase I and II studies[19-21] although is not the most widely used agent for the treatment of pleural mesothelioma and is not considered as standard treatment in the UK.[17]

Chemotherapy may reduce symptoms and/or, occasionally, produce some actual reduction in the size of the tumour, although assessment of this is difficult and is usually based on computed tomography determined pleural thickness.

A total of 122 published studies (including those available as abstracts) of single agent or combination chemotherapy have been reported in a systematic review by Ellis and colleagues.[22] Of these, a large phase III trial randomized 250 patients to either raltitrexed and cisplatin or cisplatin alone.[23] Response rates and median survival rates were higher for the combination treatment arm, but the differences between treatment groups were not statistically significant. Grade 3/4 adverse events were slightly higher in the combination arm compared to cisplatin alone, with the exception of pleuritic pain.

The phase II studies reported by Ellis and colleagues[22] included many older studies with alkylating agents demonstrating low response rates. There were 10 trials of anthracyclines involving 309 patients, and a total of 35 trials of platinum agents either alone or in combination. The anthracycline data showed, in general, low response rates, although one study reported that symptoms improved in 53% of patients with chest pain.[24] Studies with the vinca alkaloids, taxanes, topoisomerase inhibitors and antimetabolites, in general, showed single figure response rates, the exception being the phase II study of pemetrexed disodium reported by Scagliotti and colleagues[25] which showed significant improvement in the global quality of life (QoL) score in responding patients, which comprised 14% of the 64 patients entered.

This review identified nine trials of single agent platinum chemotherapy at various doses and schedules, which showed a single agent response rate of 20% for cisplatin compared to the three trials of carboplatin where the response rate was 10%. A total of 790 patients were assessed on platinum based combinations, where an overall response rate of 24.9% (95% CI 22.0 to 27.9%) was seen. The MVP (mitomycin C, vinblastine and cisplatin combination) is

widely used in the UK, and has been shown to give good symptom relief with acceptable toxicity.[26]

2.1.8 Best/Active supportive care

All reports of treatment for all cancer patients include some form of supportive/palliative care. It may be termed 'best supportive care' (BSC), 'active supportive care' (ASC) or by the newer more medical term 'active symptom control'. Generally these terms refer to treatment or procedures that relieve symptoms and make the patient more comfortable. They may include the use of steroids, analgesics, appetite stimulants, bronchodilators and/or palliative radiotherapy.

However, no matter what term is used, with few exceptions the definition/description of such treatment/care is universally vague. A recent examination of systematic reviews included in the Cochrane Library, indicates that in those that used BSC or ASC as a comparator there was no clear definition of the care provided nor a clear description within trials of the care that had been provided. (personal communication: Rumona Dickson, Liverpool Reviews and Implementation Group, 30 November 2005)

The area of treatment of MPM is no exception to this generalisation and given that BSC or ACS is frequently the comparator in trials assessing new treatments a detailed description of components of such care is required to assess both treatment and cost-effectiveness.

In a recent overview of care for MPM patients, palliative care has been described as including care that addressed psychosocial problems, pain and dyspnoea.[9] The protocol for a recently completed study of second line treatment in MPM provides a more detailed definition of the components of best supportive care albeit sometimes by exclusion rather than inclusion.[27]

> '*BSC for this trial is defined as treatment given with the intent to maximise quality of life without a specific antineoplastic regimen. BSC specifically excludes surgery, immunotherapy, radiotherapy (with the exception of palliative radiotherapy), anticancer hormonal therapy and systemic chemotherapy in which the goal is to either eradicate or slow the progression of the disease .Those therapies considered acceptable include, but are not limited to, treatment with antibiotics, analgesics, thoracentesis, pleurodesis, blood transfusions, nutritional support (enteral or parenteral), and/or focal external beam radiation given for symptom control for pain, cough, dyspnea or haemoptysis.'*

The current British Thoracic Society (BTS) trial of treatment for MPM utilises active symptom control as the comparator.[28] Their definition of this care includes:

- ‘r*egular follow up in a specialist clinic by an identified physician or team*
- *structured assessments at every clinic visit of physical, psychological, and social problems with appropriate treatment or other action. Rapid involvement of additional specialists such as a pain relief service, specialist palliative care team, medical social worker, or physiotherapist*
- *parallel nursing support from a named specialist nurse or similar person*
- *active symptom control could include treatment with palliative radiotherapy and steroids’* [28]

In addition, the actual identification of components of care may vary. Patient involvement in the assessment of care is required as research by Stephens and colleagues[29] indicates a discrepancy in assessment of severity of symptoms between patients and clinicians with a ‘consistent bias towards doctors underestimating the severity’. Recent qualitative research described, from the patient perspective, the experiences and needs in relation to palliative care following a diagnosis of cancer and identified a desire by patients to have earlier referral to specialist palliative care.[30] From a different perspective Willard and Luker[31] examined the experience of implementing a new role for specialist cancer nurses (SCN). Although the stated role of these nurses was to provide supportive care they found themselves challenged by care organisations that prioritise treatment over other supportive care activities.

The Department of Health Cancer Plan (2002)[32] highlighted a need for delivery of supportive care services for all cancer patients. National guidance being developed by NICE is out for consultation and includes a review of supportive care[33] that takes a global perspective in relation to the development of supportive care services.

In conclusion, although supportive care (best or active) is included in the care of all cancer patients, the exact nature of this care is variable and frequently incompletely defined. This lack of detail makes comparison across trials difficult and the assessment of cost of care almost impossible.

2.2 The technology

Pemetrexed disodium (trade name *Alimta*™, referred to as pemetrexed throughout this report) is an antifolate drug that exerts its antineoplastic action by disturbing folate-

dependent metabolic processes essential for cell replication. This group of agents acts by inhibiting thymidylate synthetase and dihydrofolate production, and hence suppressing the synthesis of purines and pyrimidines.[9] Cisplatin is a platinum compound chemotherapeutic agent that is used either as a single agent or in combination, for treatment of a wide variety of cancers including those of the lung, bladder, testis, stomach and ovary.

Pemetrexed is the first and only chemotherapy agent that has been granted marketing approval for use in combination with cisplatin (administered with vitamin B12 and folic acid) for the treatment of chemotherapy naïve patients (i.e. patients who have not previously had chemotherapy) with unresectable MPM. Marketing approval was granted by the US Food and Drug Administration (FDA) in February 2004 and by European Medicines Agency (EMEA) in September 2004.

In patients treated for MPM the recommended dose of pemetrexed is 500mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes, followed 30 minutes later by cisplatin at a dose of 75mg/m^2 BSA infused over two hours, on the first day of each 21 day cycle.[34] In order to reduce toxicity, patients must receive oral folic acid and intramuscular injection of vitamin B12 one to three weeks prior to the start of chemotherapy and continually throughout treatment.[35] A corticosteroid (equivalent to 4mg of dexamethasone) should also be given orally the day prior to, on the day of, and the day after pemetrexed administration to reduce the incidence and severity of skin reactions.[34]

2.3 Outcome measures

Survival is the most critical and reliable outcome measure. The local spread of mesothelioma makes accurate serial measurements of tumour following intervention by chemotherapy subjective, and lesions such as pleural effusions may also be difficult to assess unless there is complete resolution, which is rare. The inclusion of small numbers of patients with peritoneal tumours, and variation in prior chemotherapy in the phase II studies may also complicate their interpretation. There is no international consensus on quality of life assessment, which is usually based on questionnaires. The most commonly used scales include Lung Cancer Symptom Scale (LCSS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ), LC13 (13 item lung cancer-specific questionnaire) and Functional Assessment of Cancer Therapy (FACT-L) scores.

2.4 Adverse events

The most commonly reported side effects with pemetrexed include nausea, vomiting, fatigue and leukopenia (reduced total white blood cells) particularly in the neutrophil component. Other grade 2 toxicities include skin rash, mucositis, nausea and liver function abnormalities.[36] Cisplatin is associated with nausea and vomiting, controllable in about 80% of cases by HT_3 antagonists, and renal and neurological (motor or sensory) toxicity may well be dose-limiting at doses in excess of $75mg/m^2$.

2.5 Current service provision

There is no current nationally agreed pathway for the management of patients diagnosed with MPM. Most are managed by the same teams which manage the much commoner lung cancers. These teams generally involve chest physicians working in district general hospitals in association with oncologists working in cancer centres. The precise arrangements vary with geography, and in particular the availability of specialist nurses with a lung cancer focus. Links with district nurses and palliative care teams will depend on local arrangements.

3 METHODS

3.1 Methods for reviewing clinical effectiveness

3.1.1 Search strategy

The search incorporated a number of strategies. Search terms for electronic databases included a combination of index terms (e.g. mesothelioma, mesothelial neoplasms and antineoplastic agents) and free text words (e.g. pleural mesothelioma and chemotherapy).

The electronic databases were searched for the period from 1980 to May 2005. Search strategies had no language restrictions, and did not include methodological filters that would limit results to specific publication types or study designs. Details of the search strategies used and the number of references retrieved for each search are provided in Appendix 1.

Reference lists of retrieved articles and pharmaceutical company submissions were searched to identify further studies. Internet resources (including industry supported websites) were examined for information on clinical trials. In addition, handsearching of the American Society of Clinical Oncology (ASCO) conference proceedings (2003 to 2005) was conducted.

An advisory panel was established to guide the review process. The role of the advisory panel was to comment on the review protocol, to answer specific questions as the review progressed and to comment on an early draft of the review including the identification of missed or ongoing studies.

All references were exported and managed using *EndNote* reference database, *Version 8.2*, ISI Research Soft, Cal., USA.

3.2 Inclusion and exclusion criteria: clinical effectiveness

The identified citations were assessed for inclusion through two stages and disagreements were resolved by discussion at each stage. Two reviewers (YD, CMcL) independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. Full text copies of the selected papers were obtained and each assessed by two reviewers for inclusion (YD, SD).

Details of inclusion and exclusion criteria are presented in *Table* 3A.

Table 3A: Databases searched and inclusion and exclusion criteria

	Clinical effectiveness	Cost-effectiveness
Electronic databases	MEDLINE (1980-2005) EMBASE (1980-2005) SCI/Web of Science (1981-2005) SCI/ISI Proceedings (1990-2005) The Cochrane Library 2005*	MEDLINE (1980-2005) EMBASE (1980-2005) SCI/Web of Science (1981-2005) SCI/ISI Proceedings (1990-2005) The Cochrane Library 2005*
Study design	RCT Non-RCT (e.g. non randomised phase I, phase II trials)	RCT Non-RCT Economic analyses
Patient population	Chemotherapy naïve patients with unresectable malignant pleural mesothelioma	Chemotherapy naïve patients with unresectable malignant pleural mesothelioma
Interventions	Pemetrexed disodium (Alimta, LY231514, MTA) and cisplatin in combination, supplemented by folic acid and vitamin B12	Pemetrexed disodium (Alimta, LY231514, MTA) and cisplatin in combination, supplemented by folic acid and vitamin B12
Comparators	• Cisplatin • Supportive care • Other commonly used alternatives (e.g. vinorelbine, or MVP (mitomycin C, vinblastin and cisplatin)	• Cisplatin • Supportive care • Other commonly used alternatives (e.g. vinorelbine, or MVP (mitomycin C, vinblastin and cisplatin)
Outcomes	• Overall survival • Toxicity • Symptom palliation • Health-related quality of life • Tumour response • Progression-free survival	• Incremental cost per life year gained • Incremental cost per quality adjusted life year gained
Exclusion criteria	• Study populations other than those described above	• No attempt to synthesise costs and benefits • Letters, editorials, commentaries or methodological papers

* Includes The Cochrane Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database and the NHS Economic Evaluation Database (NHS EED).

3.2.1 Data extraction

Data extraction was carried out by two reviewers (YD and SD). Individual study data relating to study design and findings were extracted independently by one reviewer into a pre-designed data extraction form and checked by a second reviewer.

3.2.2 Quality assessment

Two reviewers (YD, SD) independently evaluated the included studies for methodological quality. This involved methodological assessment for clinical effectiveness based on Centre for Reviews and Dissemination, York, Report 4 (see Appendix 2).[37] Any discrepancies were resolved through discussion.

3.2.3 Methods of analysis/synthesis

Individual study data and quality assessment were summarised in structured tables and as a narrative description. Results from non-randomised controlled trials were tabulated and presented narratively.

For binary outcomes, relative treatment effects were presented in the form of relative risks (RR) with 95% confidence intervals.

3.3 Methods for reviewing cost-effectiveness

3.3.1 Search strategy

A comprehensive review of the literature was undertaken to identify all published articles that could provide evidence with regard to the cost-effectiveness of pemetrexed plus cisplatin for the treatment of malignant pleural mesothelioma. This was carried out in conjunction with the search strategy for clinical effectiveness studies.

The reviewers undertaking the review of clinical effectiveness made note of the papers which appeared to contain economic or cost evidence and made this available to the economic reviewers. Reference lists of retrieved articles and pharmaceutical company submissions were also searched to identify further studies.

3.3.2 Inclusion and exclusion criteria

The aim of the economic review was to identify economic evaluations informed by clinical data from randomised and/or non-randomised controlled trials. After scanning the abstracts, all papers that appeared to be of potential value to the study were obtained. Using explicit, predetermined criteria, two reviewers (CMcL, YD) independently identified studies for

inclusion in the cost-effectiveness review process. Disagreements were resolved through discussion. The inclusion and exclusion criteria used in the review are presented in *Table 3A*.

All the references were exported and managed using *Endnote* reference database Version 8.2, ISI Research Soft, Cal., USA.

3.3.3 Data extraction: cost-effectiveness

All cost-effectiveness data were abstracted by a single reviewer (CMcL) and then checked by a second reviewer (YD).

3.3.4 Quality assessment: cost-effectiveness

Cost-effectiveness studies were quality assessed by two reviewers (CMcL and YD) using criteria updated from the checklist developed by Drummond and Jefferson (see Appendix 2).[38]

3.3.5 Methods of analysis for economic studies

Individual study data and quality assessment were presented in structured tables and as a narrative description.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the industry submissions to NICE, were collated and presented as appropriate.

4 RESULTS: CLINICAL EFFECTIVENESS

4.1 Introduction

A total of 881 titles and abstracts of references identified in literature searches were screened for inclusion in the review. Of these, 135 references were obtained as full papers.

One randomised controlled trial (RCT) comparing pemetrexed plus cisplatin with cisplatin alone met the inclusion criteria (Evaluation of Mesothelioma in a phase III trial with Alimta and Cisplatin (EMPHACIS)). Results from this trial were reported in one peer-reviewed journal article,[39] one conference abstract,[40] and two Food and Drug Administration (FDA) reports.[36, 41] In addition, Eli Lilly and Company Limited provided a full trial report.[27]

The search did not identify any other studies that compared the effectiveness of pemetrexed and cisplatin with other commonly used alternatives such as vinorelbine, MVP (mitomycin C, vinblastine and cisplatin) or active supportive care (ACS).

We identified seven additional non-comparative studies examining the effectiveness of pemetrexed used either as a single agent or in combination with other agents for the treatment of mesothelioma. Given the paucity of clinical trial evidence in this area, the Assessment Group decided it was appropriate to extract relevant outcome data and present a summary of the results from these excluded studies.

In addition, an ongoing randomised phase III trial (H3-MC-JMEW)[42, 43] involving 240 patients and comparing pemetrexed (administered with folic acid and vitamin B12) plus best supportive care (BSC) with BSC alone in previously treated patients (i.e. not chemonaïve) with advanced or metastatic malignant pleural mesothelioma (MPM) was excluded from the review.

4.2 Quality assessment of included studies

Methodological quality of the included trial, available as a published journal article and an unpublished trial report provided by Eli Lilly,[27] was assessed using the checklist described in CRD Report 4 (Appendix 2). A summary of the assessment is provided in *Table* 4A.

The trial comprised 574 patients who signed a consent form, of whom 456 were eligible, and of these, 448 were analysed on an intention-to-treat (ITT) basis. The ITT population was defined as all participants, who were randomly assigned to, and received, treatment (for the remainder of this report this group is referred to as the ITT population). No reasons are

provided to explain the exclusion of 118 patients who consented to the trial but were not eligible for the study.

The trial scored well on the key aspects of study design and quality. Although the number of participants randomised and participant eligibility criteria for study enrolment were reported in the published paper, the process of randomisation and the concealment of allocation were not described. However, in the trial report provided by the pharmaceutical company, it was stated that the randomisation process was controlled by a computerised voice response unit at a central location, and allocation of participants was unknown until the time of randomisation.

Baseline characteristics including gender, age, ethnic origin, and factors considered of potential significance (e.g. performance status, histological subtypes) were presented and were generally comparable in each intervention arm.

This was a single-blind trial where participants were blinded to the nature of treatment they received. The blinding procedure is described in detail in the unpublished trial report.[27] It was stated that a single-blind trial design was chosen to allow clinicians to treat severe toxicities without needing to break the randomisation code. The lack of a double-blind design (i.e. outcome assessors were not blind) may have introduced bias in investigator assessments. Considerable discrepancy in tumour response evaluations among the study investigators, the independent reviewers, and the U.S. Food and Drug Administration (FDA) reviewers occurred. In fact, an independent review by the FDA indicated that the tumour response could only be confirmed for approximately 50% of patients (47 of 94) in the combination treatment group.[36]

The trial reports the number of, and reason for, withdrawals.

Table 4A: Quality assessment of the included trial

	Randomisation:			Baseline comparability				Blinding:				Withdrawals		Intention to treat
Checklist items	Truly Random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	
VOGELZANG 2003*	✔	✔	✔	✔	✔	✔	✔	✘	✘	✔	✘	✔	✔	✔

✔ **yes** (item adequately addressed), ✘ no (item not adequately addressed). * Quality assessment based on journal article and trial report provided by Eli Lilly and Company Limited.

4.3 Study characteristics

The only included trial (EMPHACIS),[39] investigated the use of pemetrexed in combination with cisplatin compared to cisplatin alone for the treatment of MPM. This was a randomised, multicentre and single-blind trial carried out in 20 treatment centres in Europe (11 countries), America (five countries), Asia (three countries) and Australia, involving 456 chemotherapy naïve patients. The trial was funded and supported by Eli Lilly and Company Limited, USA.

Patients aged 18 years and over (life expectancy greater than or equal to 12 weeks) with histologically confirmed MPM, unidimensionally or bidimensionally measurable disease, not eligible for curative surgery and with a Karnofsky performance status of greater than or equal to 70 were eligible to participate in the trial. Those who had received prior chemotherapy or had a second primary malignancy or brain metastases were not eligible for the trial.

Of the 456 eligible patients, 448 were randomly assigned to two treatment groups of pemetrexed plus cisplatin (226 patients) and cisplatin alone (222 patients). Eight randomised patients were withdrawn from the study before receiving treatment. Reasons reported were: patient decision (four patients), inclusion criteria not met (two patients), hypertension (one patient), and death from study disease (1 patient).

Patients in the pemetrexed plus cisplatin group received a median of 6 treatment cycles (range: 1 to 12) and those in the cisplatin alone group received a median of 4 cycles (range: 1 to 9). In the pemetrexed plus cisplatin group, pemetrexed was given intravenously (IV) over 10 minutes at a dose of 500 mg/m^2, followed by IV cisplatin 30 minutes later at a dose of 75 mg/m^2 over two hours. Both drugs were administered on day one of each 21 day cycle. In the cisplatin arm, normal saline was given over 10 minutes instead of pemetrexed followed by the same dose of IV cisplatin 30 minutes later at a dose of 75 mg/m^2 over two hours.

During the trial, increased reporting of severe toxicity in the pemetrexed arm (including drug-related death, neutropenia, febrile neutropenia, and diarrhoea) led to a change in the protocol to add folic acid and vitamin B12 supplementation to therapy. As a result, all subsequent patients in both treatment arms received dietary folic acid (350 to 1000 µg, daily one to three weeks before and during study) and vitamin B12 (1000 µg IM injection, before treatment and repeated every nine weeks) supplementation. This resulted in three patient subgroups in the study defined by the patients' supplementation status:

- never supplemented patients (NS) (before the protocol change, n=70 patients),

- partially supplemented patients (PS) (those who commenced treatment before the protocol change and completed treatment after the change, n=47 patients), and
- fully supplemented patients (FS) (those who commenced treatment after the protocol change, n=331 patients).

In addition, all patients enrolled were given dexamethasone 4 mg orally (or an equivalent corticosteroid and dose) twice daily on the day before, the day of, and the day after each dose of pemetrexed plus cisplatin or cisplatin alone for primary prophylaxis against rash.

Trial characteristics are summarised in *Table* 4B.

Table 4B: EMPHACIS trial characteristics

Study name	Interventions, drug & dose, no of patients	Folic acid & vitamin B_{12} supplementation	Study design	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Follow-up
EMPHACIS 2003	Pemetrexed 500 mg/m^2 plus Cisplatin 75 mg/m^2 n=226 Cisplatin 75 mg/m^2 n=222	*Never supplemented:* Pem + cisplatin: 32 Cisplatin: 38 *Partially supplemented:* Pem +cisplatin: 26 Cisplatin: 21 *Fully supplemented:* Pem + cisplatin: 168 Cisplatin: 163	RCT Single-Blind	Primary outcome: survival Secondary outcomes: time to progressive disease, time to treatment failure, tumour response rate, duration of response	International, Multicentre (20)	Age ≥18, life expectancy ≥12 weeks, uni- or bidimensionally measurable disease, KPS ≥70	Prior chemotherapy, second primary malignancy, or brain metastases, and those who were unable to interrupt NSAIDs	10 months (median)

KPS: Karnofsky performance status; NSAID: non-steroidal anti-inflammatory drugs; RCT: randomised controlled trial; Pem: pemetrexed

4.4 Participant characteristics

Patient demographics were similar in both groups. Overall, 81% (n=365) of the patient population were male and 92% (n=410) were Caucasian with a median age of 61 (range: 19 to 85 years). Over half of the patients had a Karnofsky performance status of 90/100 (52% in the pemetrexed plus cisplatin group, 56% in the cisplatin group).

Over two-thirds of the patients had an epithelial histology (n=306), and 78% (n=350) had stage III or IV disease. None of the patients in the trial had prior systemic chemotherapy; however 12% had received prior radiotherapy.

Patient characteristics are presented in *Table* 4C.

Table 4C: EMPHACIS trial- patient characteristics

	ITT Analysis		Fully supplemented		Partially supplemented		Not supplemented	
	Pemetrexed + Cisplatin (n=226)	**Cisplatin (n=222)**	**Pemetrexed + Cisplatin, (n=168)**	**Cisplatin (n=163)**	**Pemetrexed + Cisplatin, (n=26)**	**Cisplatin (n=21)**	**Pemetrexed + Cisplatin, (n=32)**	**Cisplatin (n=38)**
Age, years	Median: 61 Range: 29-85	Median: 60 Range: 19-84	Median: 60 Range: 29-85	Median: 60 Range: 19-82	Median: 62.5 Range: 38-75	Median: 62 Range: 36-81	Median: 61 Range: 32-77	Median: 59.5 Range: 35-84
Sex	Male: 184 (81.4%) Female: 42 (18.6%)	Male: 181 (81.5%) Female: 41 (18.5%)	Male: 136 (81.0%) Female: 32 (19.0%)	Male: 134 (82.2%) Female: 29 (17.8%)	Male: 22 (84.6%) Female: 4 (15.4%)	Male: 18 (85.7%) Female: 3 (14.3%)	Male: 26 (81.3%) Female: 6 (18.8%)	Male: 29 (76.3%) Female: 9 (23.7%)
Race	White 204 (90.3%) Other: 22 (9.7%)	White: 206 (92.8%) Other: 16 (7.2%)	White: 150 (89.3%) Other: 18 (10.7%)	White: 153 (93.9%) Other: 10 (6.1%)	White: 23 (88.5%) Other: 3 (11.5%)	White: 19 (90.5%) Other: 2 (9.5%)	White: 31 (96.9%) Other: 1 (3.1%)	White: 34 (89.5%) Other: 4 (10.5%)
Performance status	70: 37 (16.4%) 80: 72 (31.9%) 90/100: 117 (51.8%)	70: 31 (14.0%) 80: 66 (29.7%) 90/100: 125 (56.3%)	70: 25 (14.9%) 80: 58 (34.5%) 90/100: 85 (50.6%)	70: 22 (13.5%) 80: 47 (28.8%) 90/100: 94 (57.7%)	70: 3 (11.5%) 80: 7 (26.9%) 90/100 16 (61.5%)	70: 3 (14.3%) 80: 7 (33.3%) 90/100: 11 (52.4%)	70: 9 (28.1%) 80: 7 (21.9%) 90/00: 16 (50.0%)	70: 6 (15.8%) 80: 12 (31.6%) 90/100: 20 (52.6%)
Histology	Epi: 154 (68.1%) Sar: 18 (8.0%) Mix: 37 (16.4%) Uns: 17 (7.5%)	Epi: 152 (68.5%) Sar: 25 (11.3%) Mix: 36 (16.2%) Uns: 9 (4.1%)	Epi: 117 (69.6%) Sar: 14 (8.3%) Mix: 25 (14.9%) Uns: 12 (7.1%)	Epi: 113 (69.3%) Sar: 17 (10.4%) Mix: 25 (15.3%) Uns: 8 (4.9%)	Epi: 18 (69.2%) Sar: 2 (7.7%) Mix: 4 (15.4%) Uns: 2 (7.7%)	Epi: 14 (66.7%) Sar: 3 (14.3%) Mix: 4 (19.0%) Uns: 0 (0.0%)	Epi: 19 (59.4%) Sar: 2 (6.3%) Mix: 8 (25.0%) Uns: 3 (9.4%)	Epi: 25 (65.8%) Sar: 5 (13.2%) Mix: 7 (18.4%) Uns: 1 (2.6%)
Stage	I: 16 (7.1%) II: 35 (15.6%) III: 73 (32.4%) IV: 102 (45.1%)	I: 14 (6.3%) II: 33 (15.0%) III: 68 (30.9%) IV: 107 (48.2%)	I: 15 (8.9%) II: 27 (16.2%) III: 51 (30.5%) IV: 75 (44.6%)	I: 12 (7.4%) II: 27 (16.8%) III: 49 (30.4%) IV: 75 (46.0%)	I: 1 (3.8%) II: 5 (19.2%) III: 12 (46.2%) IV: 8 (30.8%)	I: 0 (0.0%) II: 2 (9.5%) III: 9 (42.9%) IV: 10 (47.6%)	I: 0 (0.0%) II: 3 (9.4%) III: 10 (31.3%) IV: 19 (59.4%)	I: 2 (5.3%) II: 4 (10.5%) III: 10 (26.3%) IV: 22 (57.9%)

ITT: Intention-to-treat; Epi: Epithelial; Sar: Sarcomatoid; Mix: Mixed cell; Uns: Unspecific

4.5 Clinical results

The primary end point of the trial was survival. Secondary outcomes included time to progressive disease, time to treatment failure, tumour response rate, duration of response, toxicities and quality of life.

The primary analysis in this trial was performed on all patients randomly assigned to treatment who received study drug (randomised and treated). A subgroup analysis was also performed on patients who received folic acid and vitamin B12 supplementation during the entire course of the study therapy (fully supplemented).

All patients were followed up every 6 weeks for clinical assessment and lesion evaluation. Patients were followed thereafter approximately every 3 months until death or they were lost to follow-up.

Key outcomes as identified in the review protocol were extracted from the included trial and are presented in *Table* 4D.

4.5.1 Survival

Survival was described as the time from randomisation to the time of death due to any cause. The difference between the two study treatment groups was assessed using the log rank test. The Wilcoxon test was also used as a secondary analysis to further explore differences in early events. Kaplan-Meier analyses were used to compare survival between treatment groups in the ITT population, as well as on the FS and on FS plus PS patients.

The median survival time was significantly longer (P=0.02) for patients treated with the combination of pemetrexed plus cisplatin than for those treated with cisplatin alone when considering the ITT population (12.1 months versus 9.3 months, respectively).

In the FS subgroup, median survival was 13.3 months in the combination arm, compared with 10.0 months in the cisplatin alone group (P=0.051). Similar differences in survival times were observed between the combination and control groups when both FS and PS subgroups were included (13.2 versus 9.4 months, respectively, P=0.022). No statistically significant differences were observed between treatment groups in the NS subgroup.

One-year survival rates were also significantly longer for patients in the combination arm compared with those in the cisplatin alone arm when all patients were included in the analysis (50.3% versus 38.0%, respectively, P=0.012). This difference remained significant when the FS and FS/PS subgroups were analysed.

4.5.2 Time to progressive disease

Time to progressive disease was defined as the date from randomisation to the date of documented progression of disease or death from any cause.

The median time to progression (ITT population) was 5.7 months in the pemetrexed plus cisplatin arm compared with 3.9 months in the cisplatin single agent arm. The difference between the two treatment groups was significant (P=0.001), and a similar difference was observed in both the FS and combined FS/PS subgroups.

In the ITT population, as well as the FS and FS/PS subgroups, a significantly longer time to treatment failure was observed for patients treated with pemetrexed plus cisplatin than for those treated with cisplatin only.

4.5.3 Tumour response

A responder was defined as any patient who experienced a complete response (CR; complete disappearance of disease with no new lesions, and no disease-related symptoms) or a partial response (PR; e.g. ≥50% reduction in the measurable lesions, measured in two directions).

Tumour response rate was defined as the percentage of patients who had either a complete or partial response.

No patients experienced a complete response. The rate of partial response was 41.3% in the combination therapy group and 16.7% in the single agent cisplatin group (Fisher's exact P<0.001).

Table 4D: EMPHACIS trial- outcomes

Outcomes	ITT Analysis		Fully supplemented		Fully and partially supplemented	
	Pemetrexed+Cisplatin (n=226)	**Cisplatin (n=222)**	**Pemetrexed+Cisplatin (n=168)**	**Cisplatin (n=163)**	**Pemetrexed+Cisplatin (n=194)**	**Cisplatin (n=184)**
Survival Median (mo)	12.1 95% CI 10.0-14.4	9.3 95% CI 7.8-10.7	13.3 95% CI 11.4-14.9	10.0 95% CI 8.4-11.9	13.2 95% CI 10.9-14.8	9.4 95% CI 8.4-11.6
	HR 0.77 Log-rank *P* 0.020 Wilcoxon *P* 0.028		HR 0.75 Log-rank *P* 0.051 Wilcoxon *P* 0.039		HR 0.71 Log-rank *P* 0.022 Wilcoxon *P* 0.019	
1 year survival, %	50.3	38.0	56.5	41.9	54.1	40.9
	P 0.012		*P* 0.011		*P* 0.014	
Time to PD Median (mo)	5.7 95% CI 4.9-6.5	3.9 95% CI 2.8-4.4	6.1 95% CI 5.3-7.0	3.9 95% CI 2.8-4.5	6.1 95% CI 5.4-6.7	4.3 95% CI 3.0-4.9
	HR 0.68 Log-rank *P* 0.001 Wilcoxon *P* < 0.001		HR 0.64 Log-rank *P* 0.008 Wilcoxon *P* < 0.001		HR 0.70 Log-rank *P* 0.003 Wilcoxon *P* < 0.001	
Tumour response rate (%)	41.3 95% CI 34.8-48.1	16.7 95% CI 12.0-22.2	45.5 95% CI 37.8-53.4	19.6 95% CI 13.8-26.6	45.6 95% CI 38.4-52.9	19.0 95% CI 13.6-25.4
	Fisher's *P* < 0.001		Fisher's *P* < 0.001		Fisher's *P* < 0.001	

Mo: months; PD: progressive disease; ITT: intention-to-treat; HR: hazard ratio; 95% CI: 95% confidence intervals for median

4.5.4 Toxicity

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria.

Results are presented in *Tables* 4E and 4F. Comparisons of the incidence of toxicities between the groups were analysed using Fisher's exact test.

In the pemetrexed plus cisplatin arm, the most commonly reported severe adverse events were grade 3/4 neutropenia (n=63, 27.9%) and grade 3/4 leukopenia (n=40, 17.7%).

In the ITT population, the incidence of serious toxicities (including grade 3/4 neutropenia, thrombocytopenia, nausea, and vomiting) with pemetrexed plus cisplatin was higher than that with cisplatin alone (22.5% versus 7.2%). However supplementation of folic acid and vitamin B12 resulted in a consistent reduction in the severity and incidence of toxicity (except for dehydration) in the pemetrexed plus cisplatin group. Grade 3/4 neutropenia observed with FS patients was significantly lower (23.2%) compared with PS plus NS patients (41.4%) (P=0.011).

Of the 14 deaths occurring in the pemetrexed plus cisplatin arm (while receiving study treatment or within 30 days of the last dose of study drug), three were likely to be drug-related. No deaths occurred during this period after adding vitamin supplementation in this group. There were a total of eight deaths in the single agent cisplatin group, which were not thought to be drug-related.

Relative risks calculated from data provided in the published paper and the FDA reports are presented in *Figures* 4A to 4D. For grade 3/4 toxicities when including the entire ITT population, the relative risks generally favour cisplatin arm only (*Figure* 4A).

When considering the combination arm only, the relative risks indicate that grade 3/4 toxicities are consistently less frequent in the fully supplemented subgroup compared to the never supplemented subgroup, significantly so for febrile neutropenia, infection with 3/4 neutropenia, leucocytes, nausea and vomiting (*Figure* 4B).

For all grade toxicities when only FS patients are included, the relative risks generally favour the cisplatin only arm (*Figure* 4C), this is also the case when considering only grade 3/4 toxicities (*Figure* 4D).

Table 4E: Grade 3/4 toxicities

	Pemetrexed + Cisplatin, ITT (n=226)		Cisplatin ITT (n=222)		*P**
	No. of patients	**%**	**No. of patients**	**%**	
Haematologic laboratory toxicity					
Hb	11	4.8	0	0	0.001
Neutrophils	63	27.9	5	2.3	< 0.001
Leukocytes	40	17.7	2	0.9	< 0.001
Platelets	13	5.8	0	0	< 0.001
Nonlaboratory toxicity					
Nausea	33	14.6	14	6.3	0.005
Fatigue	23	10.2	19	8.6	0.628
Vomiting	30	13.3	8	3.6	0.000
Diarrhoea	10	4.4	0	0	0.002
Dehydration	9	4.0	1	0.5	0.020
Stomatitis	9	4.0	0	0	0.004
Anorexia	5	2.2	1	0.5	0.216
Febrile neutropenia	4	1.8	0	0	0.123
Infection with G 3/4 neutropenia	3	1.3	1	0.5	0.623
Rash	3	1.3	0	0	0.248

*P values were obtained from Fisher's exact test.

Figure 4A: Relative risks of grade 3/4 toxicities for pemetrexed plus cisplatin versus cisplatin

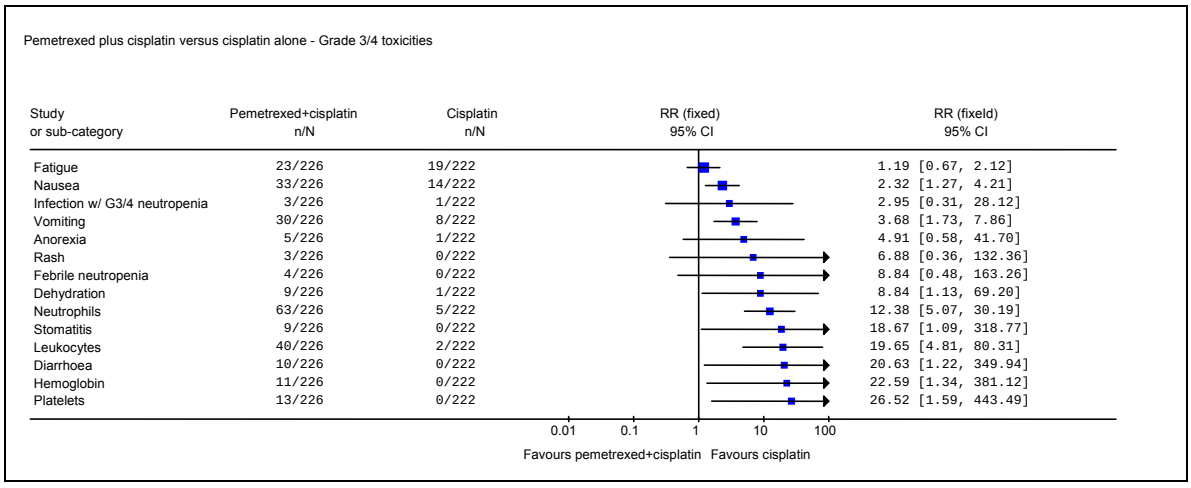


Table 4F: Grade 3/4 toxicities from pemetrexed plus cisplatin-treated patients

	Full versus partial supplementation and never supplemented					Full supplementation and partial supplementation versus never supplemented				
	FS (n=168)		PS+NS (n=58)		P-value	FS+PS (n=194)		NS (n=32)		P-value
	n	%	n	%		n	%	n	%	
Haemoglobin	7	4.2	4	6.9	0.479	8	4.1	3	9.4	0.192
Leukocytes	25	14.9	15	25.9	0.072	29	14.9	11	34.4	0.012
Neutrophils	39	23.2	24	41.4	0.011	51	26.3	12	37.5	0.205
Platelets	9	5.4	4	6.9	0.744	10	5.2	3	9.4	0.403
Nausea	20	11.9	13	22.4	0.082	23	11.9	10	31.3	0.012
Fatigue	17	10.1	6	10.3	0.999	18	9.3	5	15.6	0.338
Vomiting	18	10.7	12	20.7	0.071	20	10.3	10	31.3	0.003
Diarrhoea	6	3.6	4	6.9	0.284	7	3.6	3	9.4	0.154
Dehydration	7	4.2	2	3.4	0.999	7	3.6	2	6.3	0.619
Stomatitis	5	3.0	4	6.9	0.240	8	4.1	1	3.1	0.999
Anorexia	2	1.2	3	5.2	0.108	3	1.5	2	6.3	0.148
Febrile neutropenia	1	0.6	3	5.2	0.053	1	0.5	3	9.4	0.009
Infection with G 3/4 neutropenia	0	0	3	5.2	0.016	1	0.5	2	6.3	0.053
Rash	1	0.6	2	3.4	0.163	3	1.5	0	0.0	0.999

* P-values obtained from Fisher's exact test for within pemetrexed plus cisplatin arm comparisons for the full supplementation versus partial supplementation plus never supplemented subgroups, and for the full supplementation plus partial supplementation versus never supplemented subgroups. PS: Partially supplemented; NS: never supplemented; FS: fully supplemented

Figure 4B: Relative risks of grade 3/4 toxicities for fully supplemented versus never supplemented patients treated with pemetrexed plus cisplatin

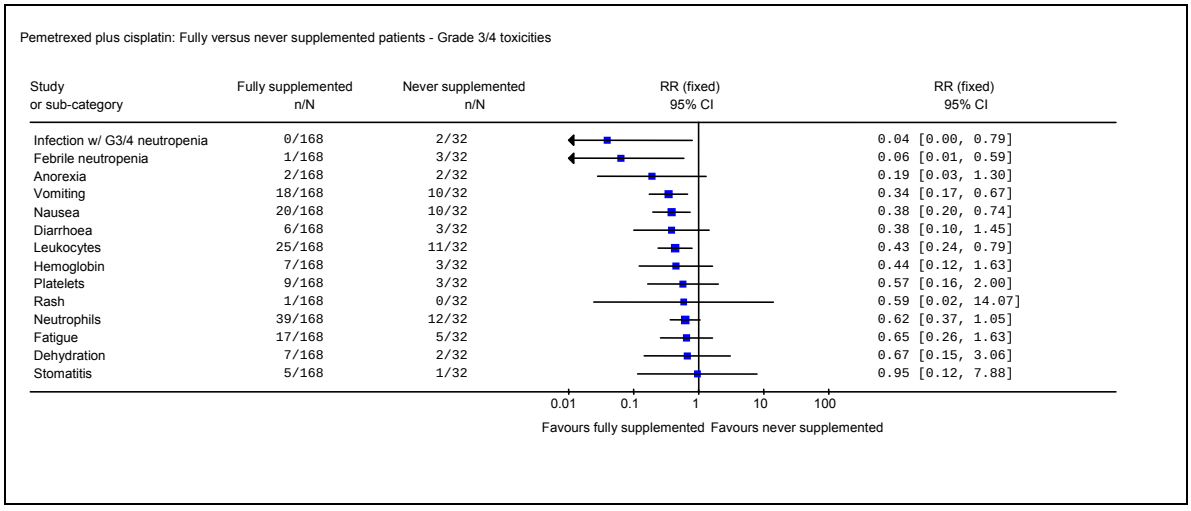


Figure 4C: Relative risks of all grade toxicities for fully supplemented pemetrexed plus cisplatin versus cisplatin

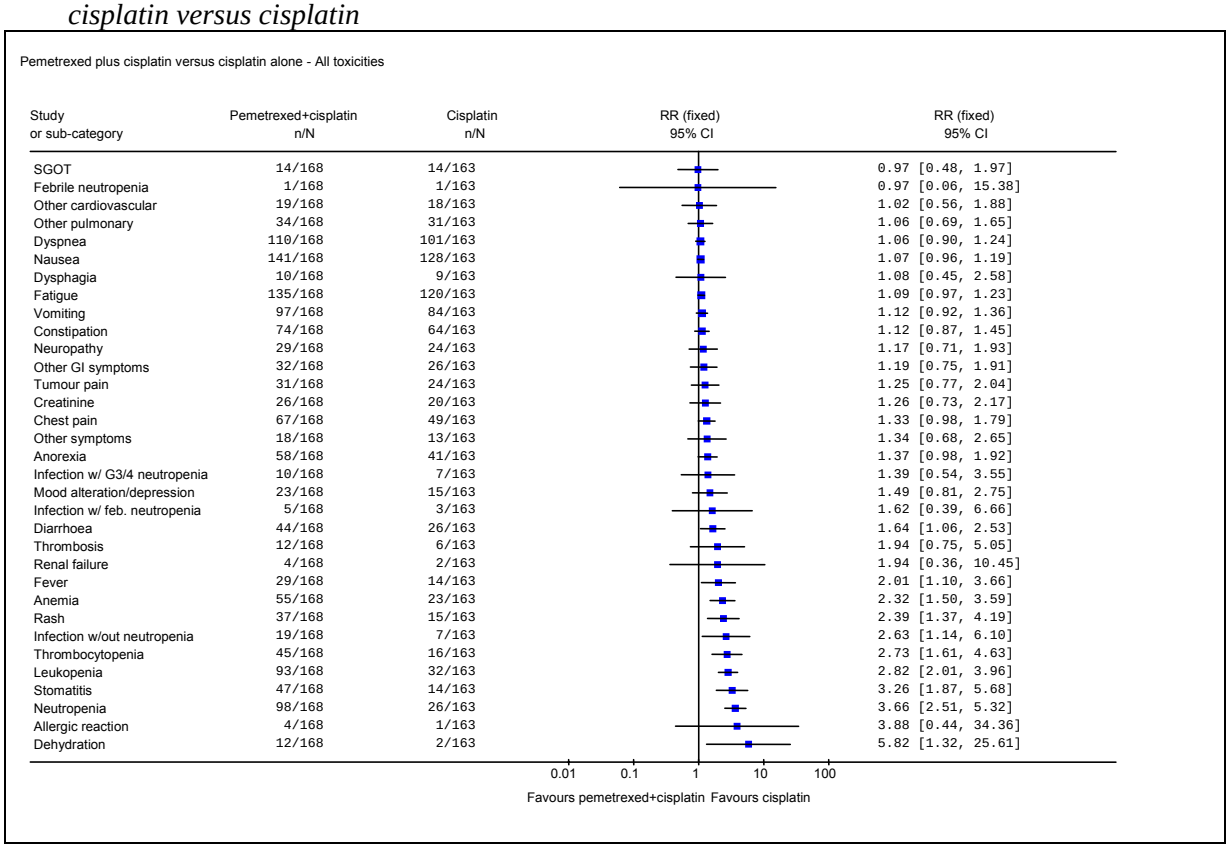
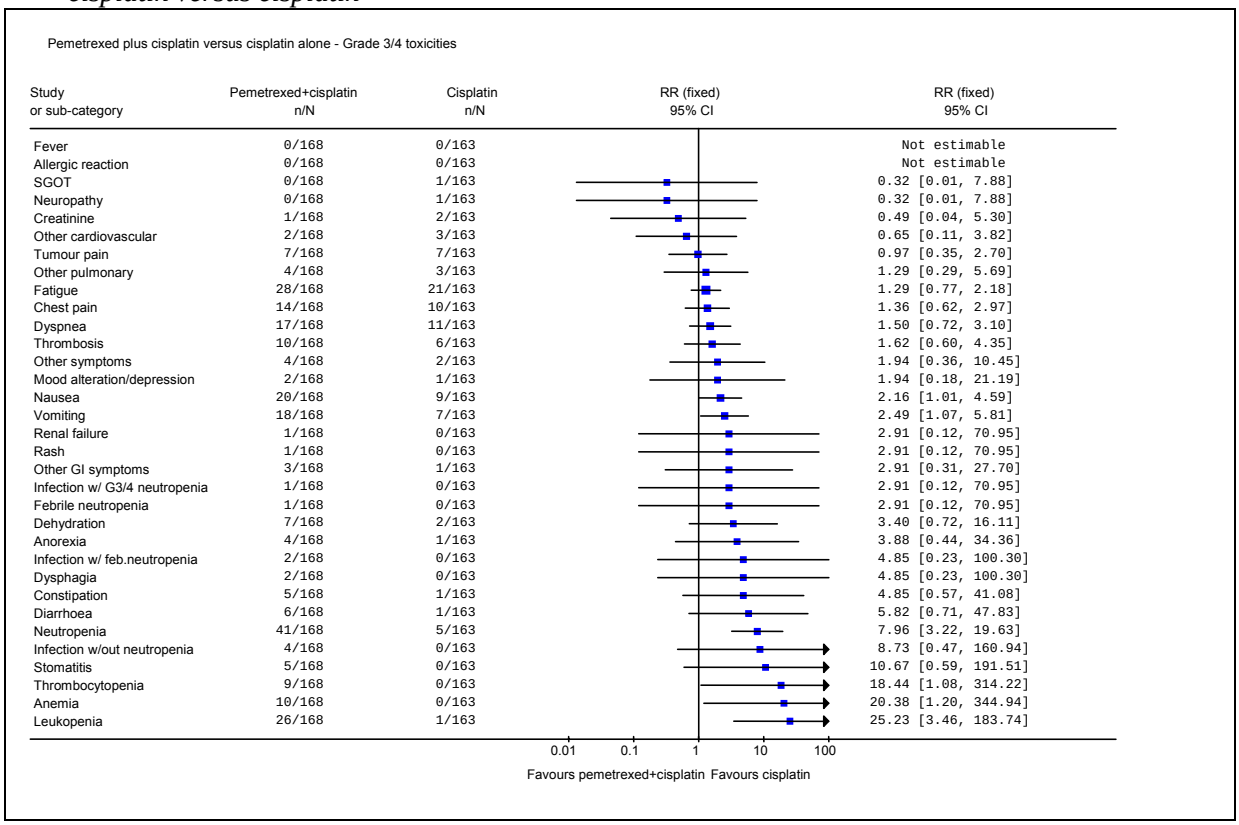


Figure 4D: Relative risks of grade 3/4 toxicities for fully supplemented pemetrexed plus cisplatin versus cisplatin



4.5.5 Quality of life

The assessment of quality of life (QoL) has been published only in conference abstract form.[40] Data were obtained from all randomised patients (n=448) using the validated lung cancer symptom scale (LCSS-meso instrument). Several aspects of QoL were evaluated including pain, dyspnoea, fatigue, anorexia and cough.

By week 18, the results demonstrate a significant greater improvement in global QoL (HR-QOL P=0.012) and symptom relief (all symptoms P<0.05) in the group of patients treated with pemetrexed plus cisplatin when compared to those treated with cisplatin alone in the ITT population. These results remain significant for the FS population by week 18 (P=0.024).[27]

4.6 Uncontrolled studies of pemetrexed

4.6.1 Introduction

Although not included in the review, non-comparative studies of pemetrexed used either as a single agent or in combination with other agents for the treatment of malignant mesothelioma and other cancers are briefly described and available data from these studies are provided within this section.

A total of seven non-comparative studies investigating the safety and efficacy of pemetrexed for the treatment of mesothelioma patients were identified. Of these, one study investigated pemetrexed as a single agent, and in the remainder pemetrexed was used in combination with other agents (two with carboplatin, two with gemcitabine, one with cisplatin, and one with vinorelbine).

Results from these studies were available from four peer-reviewed journal articles and three conference abstracts (*Tables* 4G and 4H).

4.6.2 Pemetrexed single agent studies

In the phase II study by Scagliotti,[25] 64 chemotherapy naïve patients were treated with single agent pemetrexed at a dose of 500 mg/m^2. Of these, 43 patients were supplemented with folic acid and vitamin B12 in order to improve safety.

With all patients included, there was a median survival time of 10.7 months, median time to progression of 4.7 months and a response rate of 14.1%.

Patients in the folic acid and vitamin B12 supplemented group experienced lower incidence of grade 3/4 haematological toxicities (neutropenia, leukopenia, and thrombocytopenia) compared with the non-supplemented group.

4.6.3 Pemetrexed combination studies

Phase I studies

Four phase I studies[19, 44-46] including a total study population of 161 patients investigated the efficacy and safety of pemetrexed combined with platinum-containing agents (cisplatin, carboplatin, gemcitabine, and vinorelbine) and explored feasible and alternative scheduling and dosing regimens. Of these, one study conducted by Milward and colleagues was available only in a conference abstract form.[44]

Only one study (by Hughes and colleagues)[46] solely included patients with MPM with no prior chemotherapy treatment. The remaining three studies included patients with advanced solid tumours (e.g. pleural mesothelioma, non-small-cell lung cancer, head and neck tumours, and colorectal cancer).

Millward and colleagues[44] reported the use of pemetrexed (300 to 600 mg/m^2) combined with vinorelbine (15 to 30 mg/m^2) in 24 patients with advanced cancer (including four with mesothelioma). All patients received folic acid and vitamin B12. A partial response was observed in four patients, including one patient with mesothelioma. Myelosuppression was the primary toxicity (not dose limiting) with grade 3/4 neutropenia.

In an open-label, dose-finding study conducted by Hughes and colleagues,[46] 27 chemotherapy-naïve patients with malignant pleural mesothelioma were treated with pemetrexed (400 to 500 mg/m^2) combined with carboplatin, without folic acid or vitamin B12 supplementation. Maximum tolerated dose for pemetrexed was 500 mg/m^2. Eight out of 25 assessable patients (32%) experienced partial responses. Median time to progression was 10.2 months (305 days), and median survival time was 15 months (451 days). The main dose-limiting toxicity was haematological, particularly neutropenia.

Thodtmann and colleagues[19] investigated the combination treatment of pemetrexed and cisplatin in 54 previously treated patients with advanced solid tumours (including 13 patients with mesothelioma). Only patients with grade 4 neutropenia (lasting longer than 7 days) were given folic acid. Two 3 week schedules were explored: pemetrexed plus cisplatin were given on day one, and pemetrexed on day one followed by cisplatin on day two. Study results showed that the 21-day cycle with both drugs given on day one was well tolerated and

clinically active. A total of five out of 11 evaluable patients with pleural mesothelioma experienced a partial response, representing an estimated response rate of 45%. The dose limiting toxicity for both schedules was neutropenia. Other adverse events included nausea, vomiting, and mucositis.

Adjei and colleagues[45] investigated the combination treatment of pemetrexed and gemcitabine in 56 patients with solid tumours (only three patients had mesothelioma). Forty-seven patients had prior chemotherapy. It was however not reported whether these included patients with mesothelioma. Pemetrexed was given at doses ranging 200 to 600 mg/m^2, after gemcitabine on day one. Partial response was observed in one out of three patients with mesothelioma in this study. The dose-limiting toxicity was neutropenia. Other toxicities included nausea, rash, and transaminase elevation.

Phase II studies

Two phase II studies (available as conference abstracts) involving a total of 198 patients with malignant pleural mesothelioma were identified.[47, 48]

The study by Janne and colleagues[47] included 96 chemotherapy-naïve patients treated with gemcitabine 1250 mg/m^2 given on days one and eight and pemetrexed 500 mg/m^2 on day eight immediately before gemcitabine (cohort 1), or immediately before gemcitabine on day one (cohort 2). All patients received folic acid, vitamin B12 and dexamethasone. Partial response rates were 24.5% in cohort 1, compared with 10.0% in cohort 2. Neutropenia was the most common grade 3/4 toxicity in both groups (cohort 1: 43.4%, cohort 2: 47.6%). Clinical toxicities included dyspnoea (20.8% in cohort 1, 7.1% in cohort 2) and fatigue (15.1% in cohort 1, 14.3% in cohort 2).

Another phase II study (presented recently at the 2005 American Society of Clinical Oncology meeting by Ceresoli and colleagues[48]included 102 chemo-naïve patients, and explored the efficacy and safety of the combination of pemetrexed given 500 mg/m^2 followed by carboplatin (AUC 5 mg/ml every min). All patients received folic acid and vitamin B12 supplementation, and steroid prophylaxis. Of the 92 patients assessed, overall response (CR+PR) was observed in 19 patients (21%). Stable disease was observed in 42 patients (46%) and progressive disease in 31 patients (33%). Median time to disease progression was 6 months. Grade 3/4 toxicities included neutropenia (18%), anaemia (13%), thrombocytopenia in (6%), and diarrhoea (3%). Overall time to survival was not reported.

Table 4G: Non-comparative studies of pemetrexed as single agent for the treatment of mesothelioma

Study name	Interventions drug & dose, no of patients	Study design	Histology	Inclusion criteria	No. of responders	Response rate (%)	PFS/TTP (months)	Overall median survival (months)	Adverse events, G3/4
SCAGLIOTTI 2003	Pemetrexed 500 mg/m^2 D1. After each dose, dose adjustments were made depending on platelet and neutrophil nadir counts *All patients:* 64 *Supplemented*: 43 *Not supplemented.* 21	Phase II, Non RCT	Epi: 45 (70.3%) Sar: 8 (12.5%) Mix: 9 (14.1%) Uns: 2 (3.1%)	MPM, no prior CT, life expectancy ≥12 weeks, bi/uni-dimensional lesions, KPS ≥ 70	*Supplemented:* CR 0 PR: 7 SD: 27 *Not Supplemented:* CR: 0 PR: 2 SD: 6 *All:* CR: 0 PR: 9 SD: 33	*Supplemented:* 16.3 (95% CI 6.8-30.7) *Not Supplemented:* 9.5 (95% CI 1.2-30.4) *All:* 14.1 (95% CI 6.6-25.0)	PFS: *Supplemented:* 4.8 (95% CI 4.4-6.1) *Not Supplemented:* 3.0 (95% CI 1.7-5.8) *All:* 4.7 (95% CI 4.2-5.8) TTP: 4.4 (95% CI 3.1-5.5)	*Supplemented:* 13.0 (95% CI 8.2-∞) *Not Supplemented:* 8.0 (95% CI 4.8-14.5) *All:* 10.7 (95% CI 7.7-14.5)	*Supplemented:* Neu: 4 (9.3%) Leu: 4 (9.3%) Thr: 1 (2.3%) *Not Supplemented:* Neu: 11 (52.3%) Leu: 8 (38.1%) Thr: 1 (4.8%)

D: day; CR: complete response; PR: partial response; SD: stable disease; PFS: progression free survival; TTP: time to progression; KPS: Karnofsky performance scale; CT: Chemotherapy; Epi: Epithelial; Sar: Sarcomatoid; Mix: Mixed cell; Uns: Unspecific; Thr: Thrombocytopenia; Neu: Neutrophils; Leu: Leukocytes; RCT: randomised control trial

Table 4H: Non-comparative studies of pemetrexed in combination with other agents

Study name	Interventions drug & dose, no of patients	Study design, n	Histology	Inclusion criteria	Response	Time to progression, Stable disease	Overall median survival	Adverse events, Grade 3/4
	Phase I studies							
MILWARD **2001** **(abstract)**	Pemetrexed with vinorelbine. Pemetrexed: 300-600 mg/m^2, vinorelbine 15-30 mg/m^2 All patients received FA and B_{12}	Phase I, n=24 Male: 17 Female: 7	*Tumour type:* *Mesothelioma:* 4 Other: 20	Age ≥ 18 years, PStat 0-2, life expectancy 12 weeks	*Mesothelioma patients:* PR: 1/4	NR	NR	*Not reported separately for mesothelioma patients.* Principal toxicity was myelosuppresion with G 3/4 neutropenia.
HUGHES **2002**	Pemetrexed with carboplatin Pemetrexed given at doses ranging 400 to 500 mg/m^2, followed by carboplatin AUC of 4-6 mg/mL.min	Phase I, n=27 (25 were assessable)	Epi: 16 Sar: 2 Mix: 5 Uns: 4	MPM, no prior CT, WHO PStat 0-2	PR: 8/25 (32%) SD: 14/25	Median TTP:305 days	451 days	The primary toxicity was haematological, particularly neutropenia. Other adverse events included nausea, vomiting, diarrhoea, stomatitis, and rash.
THÖDTMANN **1999**	Pemetrexed with cisplatin Cohort I (n=42): both agents given day I (pemetrexed: 300 mg/ m^2, cisplatin 60 mg/ m^2) Cohort II (n=12): pemetrexed given D 1 (500 or 600 mg/m^2) and cisplatin 75 mg/ m^2 on D 2.	Phase I, n=54	*Tumour type:* Mesothelioma: 13 Other: 41	Patients with solid tumours, no prior tx (platinum-based tx within 6 mo, CT within 3 weeks before entry), WHO P SAT ≤2, life expectancy ≥ 12 weeks.	*Mesothelioma patients:* PR: 5/11 (2 patients were not assessable for response)	NR	NR	*Not reported separately for mesothelioma patients.*

Study name	Interventions drug & dose, no of patients	Study design, n	Histology	Inclusion criteria	Response	Time to progression, Stable disease	Overall median survival	Adverse events, Grade 3/4
ADJEI **2000**	Pemetrexed with gemcitabine Gemcitabine initially given 1000 mg/m^2 and 1250 mg/m^2 on D 1 and 8, and pemetrexed given at doses ranging 200 to 600 mg/m^2, after gemcitabine on D 1. Due to excessive neutropenia, remaining 21 pts received pemetrexed on D 8.	Phase I, n=56 Group I: 35 Group II: 21	*Tumour type:* Mesothelioma: 3 Other: 53	Age ≥ 18 years, ECOG PStat ≤2 47 pts had prior CT.	*Mesothelioma patients:* PR: 1/3			*Not reported separately for mesothelioma patients.* (The most common DLT was neutropenia)
	Phase II studies							
JANNE **2005** **(abstract)**	Pemetrexed with gemcitabine. Gemcitabine 1250 mg/m^2 (over 30 min) on D 1 and D 8 with Pemetrexed 500 mg/m^2 (over 10 min) on D 8, immediately before gemcitabine (Cohort 1), or immediately before gemcitabine on D 1 (Cohort 2). All patients received FA and B_{12}	Phase II, non RCT n=96 Cohort 1: 53 Cohort 2: 43 *No. evaluated for response:* Cohort 1: 49 Cohort 2: 30	Cohort 1: Epi: 67.9% Mix: 13.2% Sar: 5.7% Uns: 13.2% Cohort 2: Epi: 58.1% Mix: 4.7% Sar: 16.3% Uns: 20.9%	NR (Study includes chemo-naïve MPM patients, implied by title)	Cohort 1: CR: 0% PR 12 (24.5%) ORR: 24.5% (95% CI 13-39%) Cohort 2: CR: 0% PR: 3 (10.0%) ORR: 10.0% (95% CI 2-27%)	Cohort 1: SD: 26 (53.1%) PD: 11 (22.4%) DCR: 78% TTP (mo, 95% CI): 4.17 (3.35, 5.39) Cohort 2: SD: 20 (66.7%) PD: 7 (23.3%) DCR: 77% TTP (mo, 95% CI): 7.56 (2.63, -)	NR	*Cohort 1:* Neu: 43.4% Anemia: 3.8% Feb neu: 7.5% Thr: 11.3% Dyspnea: 20.8% Fatigue: 15.1% Nausea: 5.7% *Cohort 2:* Neu: 47.6% Anemia: 0% Feb neu: 9.5% Thr: 2.4% Dyspnea: 7.1% Fatigue: 14.3% Nausea: 2.4%

Study name	Interventions drug & dose, no of patients	Study design, n	Histology	Inclusion criteria	Response	Time to progression, Stable disease	Overall median survival	Adverse events, Grade 3/4
CERESOLI **2005** **(abstract)**	Pemetrexed with carboplatin. Pemetrexed 500 mg/m^2 on D 1, followed by carboplatin AUC 5 mg/ml xmin. Tx repeated every 21 days (max of 6 cycles) All patients received FA and B_{12}	Phase II, Non RCT, n=102 Male: 76 (75%) Female: 26 (25%) (data reported for 92 patients evaluable for response, toxicity and survival)	Epi: 80 (78%) Sar: 7 (7%) Mix: 8 (8%) Uns: 7 (7%)	Age ≥18, MPM, no prior CT, ECOG PStat ≤2, life expectancy ≥ 12 wks	*Major response (2 CR and 17 PR)* CR+PR: 19 (21%) (95% CI: 13-30%)	Median TTP: 6 (Range: 0.3-14.8 mo) PD: 31 (33%) (95% CI: 24-44%) SD: 42 (46%) (95% CI: 35-56%)	NR	Neu: 17 (18%) Thr: 6 (6%) Anemia: 12 (13%) Feb neut: 1 (1%) Nau/vom: 0% Diarrhoea: 3(3%) Stomatitis: 0%

D: day; MPM: Malignant pleural mesothelioma; FA: Folic acid; PStat: Performance status; CR: complete response; PR: partial response; SD: stable disease; PFS: progression free survival; TTP: time to progression Epi: Epithelial; Sar: Sarcomatoid; Mix: Mixed cell; Uns: Unspecific; Neu: Neutrophils; Leu: Leukocyts; Thr: Thrombocytopenia; Feb neu: Febrile neutropenia; Nau/Vom: Nausea/Vomiting; ORR: Overall response rate; Eastern Cooperative Oncology Group (ECOG); DCR: Disease control rate; DLT: Drug limiting toxicity; NR: Not reported; RCT: randomised controlled trial

4.7 Discussion

Historically, the treatment of malignant mesothelioma has relied heavily on supportive care, with only a small proportion of patients benefiting from surgery or radiation. Studies in the last 15 years have evaluated the role of cytotoxic chemotherapy. This technology assessment is based on one randomised trial (EMPHACIS) which demonstrates that pemetrexed in combination with cisplatin improves survival compared to cisplatin alone. There is no comparison of any form of chemotherapy for mesothelioma with active/best supportive care in the literature.

The phase II studies prior to the introduction of pemetrexed are dominated by doxorubicin and cisplatin, used alone or in combination, with the marginally higher response rates in cisplatin-treated groups than among those who received other agents. Complete responses are rare, and the overall rates of response are less than 20% in most studies. The duration of remission, where reported, is of the order of a few months, but interpretation is limited by the extent of heterogeneity between the studies.

There is insufficient evidence base for current practice involving the use of MVP chemotherapy, the combination widely used in the UK. We found one published phase II trial of 39 patients using MVP,[26] which is under further evaluation by the British Thoracic Society randomised feasibility study (comparing active symptom control with or without chemotherapy) involving 420 patients with malignant pleural mesothelioma.[28]

The data on the less toxic analogue carboplatin is less extensive than cisplatin, but response rates appear lower than with cisplatin.[18, 22]

Where reported, the phase II data for pemetrexed show modest activity, in terms of response rate and time to progression. Phase I studies had previously shown 15 partial responses out of 47 patients treated at varying doses and combinations, and the rationale for the EMPHACIS trial is based largely on the 11 assessable patients in the study by Thodtmann and colleagues[19] given pemetrexed in combination with cisplatin, where five responses were seen and the dose limiting toxicity was neutropenia. However, the authors also justified the use of the cisplatin based combination in the EMPHACIS trial on a large phase II trial in non-small lung cancer.[49] The two large phase II studies[47, 48] in mesothelioma were with pemetrexed in combination with gemcitabine and carboplatin respectively, in fully supplemented patients.

However, differences in the inclusion criteria in terms of performance status, previous treatment, and drug regimens make comparisons with the phase III trial difficult.[39]

Interpretation of the EMPHACIS trial is complicated by several factors. The grade 3/4 toxicity of the combination therapy, particularly leukopenia, neutropenia and diarrhoea was found to be greatly improved by the addition of B12 and folic acid. It is clear that full supplementation is necessary for an acceptable toxicity profile, based on data from a sponsor initiated multivariate analysis initially published as an abstract in 2001,[50] subsequently published in 2002,[51] and confirmed by comparison of the groups in the EMPHACIS trial.[52]

Fifty-two percent of the trial population were WHO performance status zero, representing only minimal impairment of activity level at trial entry. This is a considerably higher proportion than would present to UK specialist clinicians. Only 67% of the randomised and treated patients had the pathological diagnosis confirmed by independent review.[36] The site and mode of spread of mesothelioma, in sheets of cells lining the pleura rather than well circumscribed lesions, complicates the assessment of response, which is usually based on computerised topography scan measurement. Hence, claims of response rates and time to progression have to be interpreted with caution.

An analysis by the company,[27] in the fully supplemented group with stages III/IV disease (n=247), also showed a significant survival benefit comparable to the published data. However, the trial was restricted to those with Karnofsky performance status 70 or greater (equivalent to ECOG/WHO 0 or 1 scales more widely used in the UK) and inconsistent with expected patient population.

Quality of life scores demonstrated significantly greater improvement for pain and dyspnoea in the combination group compared to the cisplatin group.[27, 40]

Reported response rates in the experimental arm in the Vogelzang publication[39] were higher than in many published phase II studies. In addition, only 50% of the response rates were confirmed by independent review.[41] This is a lower proportion of agreement than would normally be expected.

4.8 Conclusions

The data from one RCT shows pemetrexed plus cisplatin give a modest survival benefit for the patients with high performance status. These data are supported by a trend in improved QoL.

Full supplementation with folic acid and vitamin B12 is necessary for pemetrexed to reduce toxicity to acceptable levels and the modest survival gain for combination chemotherapy has to be carefully weighed against the potential toxicity demonstrated in the trial results.

No conclusions can be drawn about the appropriateness of treatment for patients with poor performance status (ECOG performance status of 2, 3, or 4), who may comprise the majority of patients presenting to a cancer centre or specialist clinicians in the UK.

Recommendations for research

Other agents including anthracyclines and antimetabolites require further evaluation in mesothelioma, in combination with pemetrexed. The use of sequential as well as combination chemotherapy should be considered.

The role of supportive care needs to be defined and evaluated. In order to generalise the treatment findings, further studies including patients with poor performance status are needed. Such trials also need to include an assessment of appropriate quality of life data to better inform subsequent economic evaluations.

5 RESULTS: REVIEW OF THE ECONOMIC LITERATURE

5.1 Introduction

In this chapter, we explore the published literature on the costs and benefits of pemetrexed in combination with cisplatin for the management of malignant pleural mesothelioma (MPM). We begin by discussing the economic impact of pemetrexed plus cisplatin therapy, and look at the costs and health outcomes of MPM within the framework of an economic evaluation. We then go on to describe the results of a literature search on the economics of pemetrexed in combination with cisplatin for MPM.

5.2 Economic impact of pemetrexed plus cisplatin for MPM

Currently there is no standard chemotherapy for MPM. Many treatment strategies have been employed but most have shown relatively low response rates[18, 22] and have not demonstrated a survival gain.

The new combination therapy of pemetrexed plus cisplatin has shown a modest mean survival gain of 2.4 months[39] compared with cisplatin alone in the ITT population, together with a partial tumour response rate of 41.3%. Toxicities are greater with the combination therapy.[39] Early results indicate that QoL is not diminished, but may in fact be improved compared with cisplatin alone.[40, 53]

Pemetrexed plus cisplatin therapy involves a substantial additional cost compared to cisplatin alone, as pemetrexed is over 40 times the price of cisplatin. Hence, the economic question is can the high additional costs of treatment be justified by the modest survival gains and the potential small benefits in terms of quality of life?

5.2.1 Costs of MPM

When estimating the costs associated with malignant pleural mesothelioma, it is important to be explicit about the perspective adopted for the analysis. From the viewpoint of the National Health Service and Personal Social Services, the costs of interest include direct healthcare costs (such as the costs of medication, hospitalisations, treatment of side-effects etc) and the direct non-healthcare costs (such as transport, home help etc).

With the introduction of pemetrexed plus cisplatin the total direct costs of MPM will increase substantially owing to the high costs of pemetrexed. However, since treatment is only for a relatively short period of time, the lifetime costs should be low in relation to other disease areas.

5.2.2 Health outcomes of MPM

In the published literature, health outcomes of interest can be divided into (i) quality of life (which is dependant on relief of pain and symptoms together with any adverse events caused by the treatment) and (ii) survival. Pemetrexed in combination with cisplatin appears to offer a modest survival gain together with an unknown variation in QoL (positive if the therapy improves the patient's experience, but negative if adverse events are dominant). In terms of an economic analysis, ideally a QALY would be constructed and a cost-utility analysis undertaken. However, this is dependant upon the availability of reliable quality of life data.

5.3 Review of economic literature

We conducted a systematic search for comparative economic evidence concerning pemetrexed alone, cisplatin alone, and pemetrexed in combination with cisplatin. The aim of the review was to identify published cost-effectiveness analyses of pemetrexed plus cisplatin versus cisplatin alone for the management of malignant pleural mesothelioma.

5.3.1 Identification of studies

The search strategy is outlined in the methods section (see Chapter 3). This search did not provide any published full economic reports. However, one conference abstract/presentation was found by handsearching.[54]

5.3.2 Characteristics of economic study

The study by Davey and colleagues, 2004,[54] was an incremental cost-effectiveness analysis of pemetrexed plus cisplatin versus cisplatin alone for the treatment of MPM in Australia, over 27 months (*Table* 5A). The study population was that of EMPHACIS trial of pemetrexed combination therapy versus cisplatin monotherapy included in this review (Chapter 4).

Personal communications with Peter Davey (M-TAG, Australia, 26-August_2005: personal communication), indicate that the model presented at the conference is a forerunner of the Eli Lilly submission to NICE,[27] which has been updated and expanded to the UK setting. Our review of the literature only concerns publicly available information, which currently is only available in the form of a conference abstract and presentation. Both of these are of limited detail, which is reflected in the review and quality assessment. A thorough analysis and critical assessment of the industry submission to NICE is given in Chapter 6.

5.3.3 Economic models

In the identified publication, an economic evaluation was undertaken based on data from the one randomised trial included in the assessment of effectiveness, although very limited details were provided. Life expectancy was taken from the Kaplan-Meier analysis of the ITT population presented in the randomised controlled trial (RCT). The perspective adopted was that of the Australian National Health Service (*Table* 5B).

5.3.4 Cost data and data sources

Resource use was applied as per trial (study drug utilisation, concomitant medications, supplementary medications, post-study chemotherapy and treatment of serious drug related adverse events), and costed accordingly using Australian prices (*Table* 5C). No mention of discounting was given, although from personal communication with the authors (personal communication: Anna Cordony, MTAG Australia; 21-Nov-2005), it appears that some form of discounting was undertaken, although no details of the discount rates were given. The incremental cost was estimated at A$14,032, with the costs of pemetrexed accounting for the majority of this increment.

5.3.5 Health outcome data and data sources

Health outcome was assessed on the basis of life years saved, which was derived from trial estimates of survival, which may be underestimated as some people are alive at the end of the trial (see *Table* 5D).

Given the survival data available in the presentation (1.147 mean life years saved for the pemetrexed plus cisplatin arm versus 0.949 for the cisplatin arm), the mean incremental life years saved would be expected to be 0.198, not the 0.191 presented. Following personal communication with the authors of the presentation (personal communication: Anna Cordony, MTAG Australia; 21-Nov-2005) it became apparent that the life years saved were reported in the undiscounted format whilst the incremental life years saved had been presented in the discounted form. Hence the value of 0.191 was correct, and the presentation error did not impact upon the CE ratios provided. However, the discounted life years saved should have been presented rather than the undiscounted values, for consistency, and so we have included them in Table 5D for reference.

5.3.6 Cost-effectiveness results

The mean and median incremental cost-effectiveness ratios (ICER) were estimated at A$73,470, and A$60,226 per life year saved, respectively (*Table* 5E). No subgroup analysis was undertaken, nor was any sensitivity analysis presented. The authors concluded that the

cost-effectiveness ratios were acceptable for MPM patients in Australia, although this has since been rejected by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) on the basis of unfavourable cost-effectiveness and uncertainty about the impact on QoL.[55]

5.3.7 Quality of research available

One full economic evaluation of pemetrexed plus cisplatin versus cisplatin monotherapy was identified, and subsequently quality assessed using a standard checklist[38] (see *Table* 5F). Owing to its nature (conference abstract/presentation) little detailed information was available. Details of the model utilised were not given nor were details of any sensitivity analysis provided. Hence, it is not possible to assess the validity of modelling assumptions and conclusions.

However one small presentation error was found. In terms of the life years saved, the presentation reported figures which were undiscounted, whilst the incremental life years saved were presented in a discounted form. However, this presentation error did not impact the CE ratios. Nevertheless, the discounted survival rates should have been presented for consistency.

5.4 Conclusion

Results of the literature review indicate that little evidence is available related to the economic value of pemetrexed combined with cisplatin versus cisplatin alone for the management of MPM. The only source of publicly available information was a conference abstract and presentation by Davy and colleagues.[54] We were unable to assess the model assumptions or the validity of the accompanying conclusions due to insufficient information provided.

Table 5A: Characteristics of economic studies

	Davey, et al.[54]
Type of evaluation and synthesis	Cost-effectiveness analysis
Interventions	Cisplatin monotherapy versus pemetrexed plus cisplatin
Study population	Trial population
Country	Australia
Time period of study	27 months

Table 5B: Economic model

	Davey, et al.[54]
Type of model	Unclear
Perspective	Australian health care system
Model assumptions	Unclear
Life expectancy method	Survival estimates taken from Kaplain Meier plot presented in trial

Table 5C: Cost data and data sources

	Davey, et al.[54]		
Currency and currency year	Australian $ (A$), year not stated		
Discount rate	Not stated		
Cost items		Pemetrexed plus cisplatin	Cisplatin
	Study drug use	A$14,553 (4.7 cycles)	A$418 (4 cycles)
	Serious adverse events	A$531	A$56
	Treatment-emergent side-effects	A$47	A$18
	Supportive medications	A$25	A$23
	Post-study chemotherapy	A$1,307	A$1915
	TOTAL	A$,16,463	A$2,431
Sources of costs items	Resource use taken from trial and costed accordingly using Australian prices		

Table 5D: Health outcome data and data sources

	Davey, et al.[54]		
Discount rate	Not stated		
Health outcomes		Pemetrexed plus cisplatin Mean (median)	Cisplatin Mean (median)
	Survival (months)	13.8 (12.1)	11.4 (9.3)
	Patient life years saved undiscounted[a]	1.147 (1.008)	0.949 (0.775)
	Patient life years saved discounted[b]	1.127	0.936
	Incremental life years saved discounted[c]	0.191	
Sources of health outcomes	Trial data		

A: These values were reported in the presentation, and from communication with authors they were found to be undiscounted (presentation does not state whether discounting was undertaken)
B: These values were provided by the authors through personal communication
C: This value was reported in presentation but through personal communication it was found to be the discounted value

Table 5E: Cost-effectiveness results

	Davey, et al.[54]
Mean ICER (median)	A$73,470 (A$60,226)
Subgroup analysis	None undertaken
Sensitivity analysis	None presented
Author conclusions	The cost-effectiveness ratio is acceptable for the small population of MPM patients in Australia.
Author funding	Eli Lilly Australia

Table 5F: Critical appraisal of economic evaluation

Checklist item[38]	Davey, et al.
1. The research question is stated	✔
2. The economic importance of the research question is stated	/
3. The viewpoint(s) of the analysis are clearly stated and justified	✔
4. The rationale for choosing the alternative programmes or interventions compared is stated	✔
5. The alternatives being compared are clearly described	/
6. The form of economic evaluation used is stated	✔
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✔
8. The source(s) of effectiveness estimates used are stated	✔
9. Details of the design and results of effectiveness study are given (if based on a single study)	/
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✔
11. The primary outcome measure(s) for the economic evaluation are clearly stated	✔
12. Methods to value health states and other benefits are stated	NA
13. Details of the subjects from whom valuations were obtained are given	NA
14. Productivity changes (if included) are reported separately	NA
15. The relevance of productivity changes to the study question is discussed if included.	NA
16. Quantities of resources are reported separately from their unit costs	✘
17. Methods for the estimation of quantities and unit costs are described	✔
18. Currency and price data are recorded	✔
19. Details of currency price adjustments for inflation or currency conversion are given	✘
20. Details of any model used are given	✘
21. The choice of model used and the key parameters on which it is based are justified.	✘
22. Time horizon of costs and benefits is stated	✔
23. The discount rate(s) is stated	NA
24. The choice of rate(s) is justified	NA
25. An explanation is given if costs or benefits are not discounted	NA
26. Details of statistical tests and confidence intervals are given for stochastic data	NS
27. The approach to sensitivity analysis is given	✘
28. The choice of variables for sensitivity analysis is justified	✘
29. The ranges over which the variables are varied are stated	✘
30. Relevant alternatives are compared	✔
31. Incremental analysis is reported	✔
32. Major outcomes are presented in a disaggregated as well as aggregated form	✔
33. The answer to the study question is given	✔
34. Conclusions follow from the data reported	✔
35. Conclusions are accompanied by the appropriate caveats.	✔

✔ yes (item adequately addressed), ✘ no (item not adequately addressed), / partially (item partially addressed), ? unclear or not enough information, NA not applicable, NS not stated.

6 CRITICAL REVIEW OF ECONOMIC SUBMISSION

6.1 Introduction

This chapter deals with the economic submission received from Eli Lilly and Company Limited,[27] the manufacturer of pemetrexed. Copies of two *Microsoft Excel* spreadsheet models were received together with supporting documentation. The next section provides a general description of the models, followed by details of the critical assessment.

The submission was split into two sections each employing a separate economic model. The first model is based on trial data of pemetrexed plus cisplatin versus cisplatin. The second model was not based on any single trial but undertaken using an amalgamation of data from several published sources to estimate how pemetrexed plus cisplatin would compare with MVP, vinorelbine and active symptom control (ASC).

6.2 Model 1

6.2.1 General description

Model 1 is based on individual patient data (IPD) taken from the phase III trial of cisplatin versus pemetrexed plus cisplatin (only fully supplemented patients included) over a period of 29 months. The justification for cisplatin as a comparator is based on the assumption that cisplatin is likely to be at least as good as active symptom control (ASC), and at the time of trial design was considered the best available single agent, owing to no clear evidence of efficacy for either MVP or vinorelbine.

Four subgroups were analysed; fully supplemented (FS) patients; FS patients with advanced (Stage III/IV) disease (the majority of patients presenting); FS patients with good (0/1) performance status (patients most likely to receive chemotherapy); FS patients with advanced disease and good performance status. The justification for choice of subgroups was based on the assumption that these groups of patients most closely relate to UK clinical practice, and the fact that they demonstrate the greatest degree of cost-effectiveness.

Only direct healthcare costs were included, as the perspective was that of the health care provider (see *Table* 6A for a summary of costs). No discounting of costs was undertaken as all treatment costs were incurred within 1 year. Drug acquisition costs, administration costs, hospitalisation costs, and post-study chemotherapy costs were calculated from the trial. Pre-medication costs for dexamethasone and folic acid were not taken directly from the trial as the formulations varied between doses and countries, but were calculated as the product of unit cost, dose and mean number of cycles.

Outcomes are expressed in terms of life years gained and QALYs, and discounted at 3.5% (see *Table* 6B for a summary of outcomes). Life years gained were estimated using K-M survival curves of trial data and expressed in terms of both mean and median. However, only means will be considered in this discussion as medians are of limited economic importance. Utility values were taken from an Eli Lilly ongoing observation study (ACTION) in NSCLC (non-small cell lung cancer) patients using EQ-5D and EQ-VAS just prior to treatment with chemotherapy, grouped by WHO performance status. These values are used for all phases of care, including pre-chemotherapy, undergoing chemotherapy, and post-chemotherapy. Although the utility values are not for an MPM population, this may not affect the analysis if it can be assumed that MPM patients have similar utility to other lung cancer patients.

Results of Model 1 indicate that the technology is not cost-effective at the conventional £30,000 per QALY, with mean incremental cost per QALYs ranging from £47,567 to £68,598 for the different subgroups explored (see *Table* 6C). The best cost-effectiveness results relate to fully supplemented patients with both advanced disease and good performance status (0/1).

One-way and two-way sensitivity analysis was undertaken on several variables, including drug costs, administration costs, hospitalisation costs, post-study chemotherapy, discount rate, mean survival outcomes, and utility estimates (see *Table* 6D for a summary of sensitivity analysis for FS population). Results for the one-way sensitivity analysis for the fully supplemented population ranged from £41,681 to £202,719 per QALY. Results for the two-way sensitivity analysis ranged from £33,691 to £237,931 per QALY. Results for other subgroups were comparable although slightly improved owing to the fact that for the remaining subgroups survival is expected to be greater (see *Table* 6B).

The authors of the submission concluded that pemetrexed plus cisplatin did not fall within the conventional range of cost-effectiveness. However, they believe that the therapy should be given special consideration owing to the lack of any other proven alternative to supportive care.

Table 6A: Summary of costs in Model 1

	Value	Reference
Pemetrexed 500mg	£800	MIMS May 2005
Pemetrexed 100mg	£160	Lilly attestation letter
Cisplatin 100mg	£55.64	MIMS May 2005
Cisplatin 50mg	£28.11	MIMS May 2005
In patient administration	£876.00	NHS reference costs 2004
Out patient administration	£266.00	NHS reference costs 2004
Total incremental costs:-		
FS population	£8,839	Calculation
FS population with advanced disease	£8,779	Calculation
FS population with good performance	£9,019	Calculation
FS population with good performance & advanced disease	£8,920	Calculation

FS: fully supplemented; MIMS: Monthly Index of Medical Specialities

Table 6B: Summary of outcomes in Model 1

	Value	Reference
Incremental life years gained:-		
FS population	0.2	K-M survival curves
FS population with advanced disease	0.250	K-M survival curves
FS population with good performance	0.285	K-M survival curves
FS population with good performance & advanced disease	0.285	K-M survival curves
Basecase utility cisplatin	0.688	ACTION
Basecase utility pemetrexed plus cisplatin	0.681	ACTION
Incremental QALYs per patient:-		
FS population	0.129	Calculation
FS population with advanced disease	0.165	Calculation
FS population with good performance	0.188	Calculation
FS population with good performance & advanced disease	0.188	Calculation

FS: fully supplemented; K-M: Kaplan-Meier; QALY: Quality adjusted life year

Table 6C: Summary results of Model 1

	Mean incremental cost/LYG	Mean incremental cost/QALY
FS population, n=331	£44,264	£68,598
FS with advanced disease (Stage III/IV), n=247	£35,065	£53,314
FS with good performance (0/1), n=284	£31,688	£48,099
FS with advanced disease and good performance, n=207	£31,337	£47,567

FS: fully supplemented; LYG: life year gained; QALY: Quality adjusted life year

Table 6D: Sensitivity analyses performed in Model 1

Type of sensitivity analysis	**Univariate sensitivity analyses**			**Two-way sensitivity analyses**
Parameters varied	**Parameter**	**Range varied**	**Cost per QALY (FS population)***	Survival estimates +/- 1.5 months versus drug costs +/- 20% Cost/QALY £33,691-£237,931
	Drug costs	+/- 5%, 10%, 20%	£55,948 - £81,239	
	100mg vial	Introduction of 100mg vial to explore wastage	£62,557	
	Administration costs	100% inpatient - 100% outpatient	£66, 743- £71,085	
	Hospitalisation costs	+/- 5%, 10%, 20%	£68,127 - £69,070	
	Post-study chemotherapy	Fully included - excluded	£68,599 - £68,721	
	Discount rate	Outcomes discount rate varied 0-6%	£67,573-£70,233	
	Mean survival outcomes	+/- 1.5 months	£41,681-£202,719	
	Median versus mean	95% CI around median	-	
	Utility estimates	Utility lowered and presented graphically	-	
Most influential parameters	By far the most influential parameter was survival estimates. Reducing survival by 1.5 months has a large impact on CU ratios, rendering the technology not cost-effective. However, it should be noted that pemetrexed plus cisplatin was not cost-effective at a £30,000/QALY threshold for any of the sensitivity analyses performed on the FS population.			If survival estimates are 1.5 months less, the technology is not cost-effective even if drug costs decrease by 20%.

* Base case £68,599

6.2.2 Critical assessment

Using a standard checklist[56] the economic submission for Model 1 was quality assessed (see *Table* 6E). In general the modelling and supporting documentation was of a high standard, as assessed by the checklist. The question posed was clearly stated and answerable, and the submission contained a clear description of the competing alternatives. Since Model 1 was based on individual patient data taken from the phase III clinical trial, the clinical effectiveness used in the model was justifiable and supported by evidence.

Most relevant costs and consequences were identified, and measured and valued credibly. No attempt was made to consider adverse event, investigational and therapy costs where patients were not hospitalised, or any additional costs in primary and community health care services. In principle this could make a difference although experience suggests that primary and community care costs for late stage cancers are generally small relative to hospital based costs, and should not greatly differ between treatment arms. Utility values were taken from a NSCLC population, although this may not bias the analysis if utility values for MPM patients are assumed to be similar to those for other lung cancer patients. Furthermore looking at *Table* 6B, the utility value is highest for cisplatin monotherapy; hence, no systematic favouring of pemetrexed has been unjustifiably introduced. Survival was taken from the trial, which may underestimate the ICER as true benefits may be greater. Outcomes were adjusted for differential timing, although costs were not, owing to the fact that all costs were incurred within the first year. Results were expressed in terms of incremental cost-effectiveness and cost utility ratios, both of which are appropriate to the technology and economic analysis.

The company submission presents univariate sensitivity analysis for the main model variables, together with selected two-way sensitivity analyses. Survival and drug costs were found to be the key parameters in terms of uncertainty, and were fully explored in the sensitivity analysis, using appropriate ranges. However, this does not take full account of the various sources of quantifiable parametric uncertainty which, can be estimated from full access to trial IPD and ideally should have been undertaken by Eli Lilly as part of their submission.

Formula errors were detected in the estimation of the costs of supplementation with dexamethasone, folic acid and vitamin B12, attributing erroneous patient numbers in

the calculation of treatment rates per cycle. However, this only had a minor effect on model results, although in our model we corrected this calculation prior to analysis (see Chapter 7). In addition there is a methodological issue relating to these costs: although in the trial supplementation was undertaken for both trial arms, it was designed specifically to address toxicity in the pemetrexed plus cisplatin arm. In normal practice outside of a clinical trial, patients undergoing cisplatin therapy would not receive such supplementation routinely, and examination of the adverse event/toxicity profiles of cisplatin patients fully supplemented and never supplemented shows that no discernible benefit accrued to these patients as a consequence. Therefore it is arguable that supplementation costs should only be applied in the model to the pemetrexed plus cisplatin arm. In practice, the cost per patient of supplementation is small, and such an amendment is likely to alter the incremental cost per patient by less than £10 and is therefore insufficient to affect cost-effectiveness assessments.

Table 6E: Quality assessment of submitted economic Model 1

Checklist items	**Model 1**
1. Was a well-defined question posed in answerable form?	Yes
2. Was a comprehensive description of the competing alternatives given?	Yes
3. Was there evidence that the programmes' effectiveness has been established?	Yes
4. Were all the important costs and consequences for each alternative identified?	No
5. Were costs and consequences measured accurately in appropriate physical units?	Yes
6. Were costs and consequences valued credibly?	Costs: Yes Outcomes: Probably
7. Were costs and consequences adjusted for differential timing?	Yes
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes
9. Was a sensitivity analysis performed?	Yes
10. Did the discussion of study results include all issues of concern to users?	Yes

6.2.3 Summary of critical review of submitted Model 1

- Model 1 and its parameters are explicit and generally justifiable. The only exception may be the utility values which were taken from a NSCLC population. This should not affect the analysis if it can be assumed that utility values for MPM patients will be similar to those NSCLC patients.
- Some additional costs occurring in an out-patient or primary/community care setting have not been included. These may be relatively minor but no attempt has been made to justify their omission.
- The results from the model indicate that the technology is not cost-effective at the conventional £30,000 threshold. This is mainly owing to the high price of the therapy, which yields a small gain in survival, insufficient to justify the extra costs.
- A wide-ranging sensitivity analysis was undertaken, in which survival and drug costs were found to be the key parameters. Results from the univariate analysis indicate that drug costs would need to be more than 20% lower for the therapy to be in the generally acceptable range of cost-effectiveness.
- The company model argues that although the therapy is not within the acceptable range of cost-effectiveness, the fact that MPM is an orphan disease for which there is no standard chemotherapy warrants special consideration.

6.3 Model 2

There is a fundamental problem with the evidence provided to support outcome gains claimed in Model 2, which is highlighted by the following passage from the company submission:

> *"There have been few studies investigating the use of MVP, vinorelbine (+/- platinum) in MPM, however most are small, non-randomised phase II trials. There are no randomised controlled trials comparing chemotherapy to ASC. The patient population characteristics varied widely between studies that make comparison of agents problematic and hence inconclusive."*

Despite these limitations, the authors have assembled data apparently showing important survival gains for the pemetrexed plus cisplatin combination therapy, particularly in comparison to supportive care. Unfortunately the evidence base

underpinning Model 2 is not credible since it is not founded upon direct or even indirect comparisons of RCTs, and there is no evidence to support comparability of the patient populations between the various studies quoted, nor with the EMPHACIS trial. The crucial issue is the extent of survival gain to be expected between pemetrexed plus cisplatin and the various comparators offered, and we have concluded that there is no objective basis on which to estimate such gains nor to assess the uncertainty associated with such estimates. Without these figures the Model 2 endeavour is fruitless, and therefore we have not pursued this approach any further.

7 ECONOMIC EVALUATION OF PEMETREXED FOR TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

7.1 Decision problem

In this chapter we attempt to assess the cost-effectiveness of pemetrexed in combination with cisplatin for the treatment of unresectable pleural mesothelioma in chemotherapy naïve patients. Due to limitations in data, only one comparator, cisplatin, was available with credible data from a randomised controlled trial comparing it with pemetrexed. However, cisplatin is not the standard therapy in the UK, hence it is not an ideal comparator.

A cost-utility model was developed based on the industry submission Model 1, using a health care provider perspective. The following sections discuss the limitations in data, before going on to discuss the model structure, and parameter estimates, together with a discussion and analysis of our model results.

7.2 Model selection and adaptation

7.2.1 Data requested and received

At the outset it was clear to the Assessment Group that their ability to carry out a thorough and independent assessment of the economic case for use of pemetrexed in treating malignant pleural mesothelioma (MPM) would be dependent upon access to detailed information from the clinical trial. Since there is no other established and well researched chemotherapy regimen routinely offered to this patient population, it was evident that the assessment team could not expect to find much supporting information in the medical or economic literature. Instead we believed that the only route to understanding the factors influencing effectiveness and cost-effectiveness of this novel therapy was to have full access to the anonymized clinical trial data at the level of individual patient (IPD). This was requested from the representatives of Eli Lilly and Company Limited at the NICE Consultee Information meeting held on 15 June 2005, and we were assured that the company wished to assist us in this respect.

Subsequently, but prior to the formal date for receipt of submissions, we again requested early access to these data to allow us to begin the complex process of analysing the IPD to expedite the review process, but received a negative response indicating that we would receive IPD along with the submission and associated economic models. As an alternative route to accelerating the process we approached

the Food and Drug Administration (FDA) in the US asking if we could have access to the clinical dataset submitted to them as part of the US regulatory approval process. However we were informed that this would require a formal application by a UK government department and might take many months for a decision to be reached.

Examination of the company submission in August 2005 revealed that the full trial IPD had not been provided to NICE and the Assessment Group. Instead a limited amount of resource/cost information for individual patients was incorporated into one of the two economic models submitted. Although of some value, these data did not allow any examination of crucial issues concerning patient survival and indicators of clinical efficacy within the trial, nor did it facilitate exploration of factors influencing differential survival benefit beyond those presented in aggregate form by the company.

In an attempt to rectify some of these shortcomings, we looked in detail at the Clinical Study Report (CSR) of the EMPHACIS trial dated 10 October 2002,[39] and identified a total of 16 charts of survival analyses shown in the report where further information would be valuable to the team. We requested copies of the full text report relating to these charts, which are produced by default when such charts are generated by the SAS LIFETEST function. In all this same request was submitted three times to the company between July and August 2005, and we finally received a restricted aggregated summary of the information requested in respect of just three of the requested analyses.

7.2.2 Implications for assessment

It has not been stated to the team by Eli Lilly why they were not willing to allow access to the full IPD for the single source of significant clinical data supporting their submission under terms of strict confidentiality, nor why they would not provide the much more limited information requested from survival analyses already undertaken by them and featured in the CSR.

In the circumstances the assessment team have not been able to carry out the full and detailed assessment of evidence they considered to be necessary when there are no other independent studies to corroborate claims made on the basis of results from one trial. Instead it has been necessary to explore the limited information made available, with the proviso that any conclusions reached cannot be considered independent of

the process which has restricted access to a narrow range of preselected and in important respects pre-processed aggregated data. This necessarily increases the likelihood that subsequent independent trials may provide ambiguous or conflicting evidence, possibly suggestive that caution should be exercised in the interpretation of the economic assessment results shown in this report.

7.3 Economic modelling

7.3.1 Model selection and adaptation

In Chapter 6, the two submitted models are described and assessed. As previously discussed, Model 2 is very speculative and seeks to make comparisons with other potential chemotherapy regimens and with supportive care without any underlying evidence. It was not used in our analysis due to a lack of data to support the numerous modelling assumptions, making any results coined from the model incredulous.

Model 1 in the Eli Lilly submission is limited to exploring the cost-effectiveness of the pemetrexed plus cisplatin combination in comparison to Cisplatin monotherapy as used in the EMPHACIS trial. There are important questions concerning the appropriateness of Cisplatin as the control therapy, but it does at least offer a genuine test of the incremental effects of Pemetrexed where the alternative is a relatively low cost agent.

We have reformulated the Model 1 structure in the form of the following simple equations (below) in order to carry out our own exploration of economic performance, drawing on the resource/cost IPD incorporated in the submitted Model 1.

Equations:

Incremental Cost per Life-year gained	=	Incremental Cost / Incremental Life-years gain
Incremental Cost per QALY gained	=	Incremental Cost / Incremental QALYs gain
Incremental Cost per patient	=	$C_1 + C_2 + C_3 + C_4 + C_5$
Where:		
C_1	=	Mean drug cost per patient of pemetrexed plus cisplatin therapy *minus* Mean drug cost per patient of cisplatin monotherapy
C_2	=	Mean administration cost per patient of pemetrexed plus cisplatin therapy *minus* Mean administration cost per patient of cisplatin monotherapy
C_3	=	Mean supplementation cost per patient required with pemetrexed plus cisplatin therapy
C_4	=	Mean cost per patient of Adverse Event hospital episodes with pemetrexed plus cisplatin therapy *minus* Mean cost per patient of Adverse Event hospital episodes with cisplatin monotherapy
C_5	=	Mean cost per patient of post-study chemotherapy after pemetrexed plus cisplatin therapy *minus* Mean cost per patient of post-study chemotherapy after cisplatin monotherapy
C_1, C_2 and C_3 are estimated from IPD on a per cycle basis as follows:		
Mean drug cost per patient	=	Mean cycles per patient * Mean drug cost per cycle
Mean administration cost per patient	=	Mean cycles per patient * Mean administration cost per cycle
Mean supplementation cost per patient	=	Mean cycles per patient * Mean supplementation cost per cycle
Incremental life years gained	=	Mean survival time with pemetrexed plus cisplatin therapy *minus* Mean survival time with cisplatin monotherapy
Incremental quality adjusted life years gained	=	Q_{pc} *minus* Q_c
W*here:*		
Q_{pc}	=	Mean survival time * Mean EQ-5D score, with pemetrexed plus cisplatin therapy
Q_c	=	Mean survival time * Mean EQ-5D score, with cisplatin monotherapy

QALY: Quality adjusted life year; /: divided by; +: addition; *: multiplied by

The ‘base case’ considered in this section relates only to ‘fully supplemented’ patients (and specific subgroups thereof) within the JHCM trial, which corresponds to the licensed mode of treatment for MPM patients. Results have also been generated for a second analysis assuming the future availability of a smaller 100 mg vial to avoid wastage as described in the company submission.

The costs included here are limited to those which feature in the submitted model. It has not been possible to explore other potential sources of cost differentiation (e.g. adverse events which did not lead to hospitalisation but may incur medication costs) without access to the full IPD.

7.3.2 Survival estimation

In order to calculate cost-effectiveness ratios involving patient survival it is necessary to estimate the mean expected survival time (i.e. from randomisation to anticipated

time of death). Although median survival (the time when 50% of patients have died) is a useful outcome measure of clinical effect, it is not meaningful to relate median survival to mean costs in the calculation of ratios. Moreover, the median takes no account of information relating to the 'tail' of the survival distribution which is often very influential in determining the true value of the mean. As a consequence attempts to estimate the mean from an observed median are prone to large and unpredictable errors. Where observational data is not complete and does not extend to the death of all patients in the cohort, it is often more reliable to fit an explicit parametric survival model to the trial data, and use this as a basis for estimating the eventual mean survival.

Since the extent of survival gain is the primary benefit claimed for pemetrexed, we aimed to develop independent estimates of mean survival for each of the patient populations referred to in the submission, despite the failure to gain access to IPD for patient survival. For this purpose we had two sources of information:

- aggregate monthly data on patients alive, dying and censored for three populations (ITT, FS, FS/AD); and
- Kaplan-Meier survival charts in the company submission document and appendices relating to the ITT population and the four sub-populations (FS, FS/AD, FS/performance status 0/1 (PS 0/1), FS/AD and PS 0/1)

Although the aggregated data did not allow us to assign specific timings to each event, we were able to assign notional times within each month, and carry out approximate K-M analysis for the three populations. The results are shown in the left-most vertical segment of *Table* 7A, and show that the K-M estimated means are systematically lower than the corresponding medians due to the truncation of the data required for estimation of the mean when not all patients have complete follow-up to death.

Exploratory analysis of suitable parametric survival models indicated that a constant hazard (exponential) model was inadequate to account for the observed data, but that a two-parameter Weibull model provided a robust fit to all patient populations. Using the aggregated monthly data we estimated Weibull model parameters by Maximum Likelihood Estimation (MLE), and calculated the expected mean survival for each of

the three populations (ITT, FS, FS/AD). The results are displayed in the third vertical segment of *Table* 7A. Comparison with the corresponding K-M results demonstrates:

- the extent to which K-M estimated means under represent true survival; and
- the lack of precision of observed medians leading to unreliable estimates of survival gains between trial arms.

For the two remaining populations (FS/PS 0/1, FS/AD and PS 0/1) no aggregate data were provided, and so a different approach had to be adopted, based on the CSR K-M charts. This involved digitising the chart images as closely as possible, to provided approximations to the survival patterns in the trial. By calculating the total area under the curve (AUC) we obtained estimates which should correspond quite closely to the K-M mean estimates generated from the aggregate data for three populations. Comparing results in the first and second vertical segments of *Table* 7A indeed confirms this expectation.

Establishing parameters for a Weibull model from the digitised K-M plots proved more problematic, since we had little information on which to judge how to weight the multiple observations underlying each point on a K-M plot. To address this problem we used point-wise standard errors from the approximate K-M analyses (i.e. from the first segment of *Table* 7A) and fitted polynomial functions of time to each population-arm so that we could obtain interpolated estimates of point standard errors for every point of the digitised K-M plot. This then facilitated the fitting of a Weibull survival model by weighted least squares, using the inverse of the standard error to weight each observation. In the case of the two populations without aggregate data, we used the FS polynomial functions to provide proxy weights. The results are shown in the final segment of *Table* 7A and graphically the fit between observational data and fitted models is shown in *Figures* 7A-7E. There is good correspondence between MLE estimates of mean expected survival, and those using weighted least squares and digitised data. It is also clear the extent to which projected mean survival estimates generally exceed those obtained by truncated observational data.

A significant problem associated with the weighted least squares method is that it is not possible to estimate confidence ranges around the estimates directly. In the left-most vertical section of *Table* 7B approximate confidence intervals have been derived by reference to the distribution of mean survival estimated by the MLE method. *Table*

7B also shows the effect of discounting estimated survival and survival gains at the standard rate of 3.5% per annum.

Table 7A: Estimates of mean and median expected survival for five patient populations

Population		Approximate analysis using summary data				Available digitised data				Projection to death using Weibull model					
		K-M				AUC				MLE for summary data			Weighted LS estimation		
		P/C	C	Difference	Max data	P/C	C	Difference	Max data	P/C	C	Difference	P/C	C	Difference
ITT	mean	13.80	11.79	**+ 2.08**	28.5	13.23	11.60	**+ 1.63**	27.9	14.39	11.68	**+ 2.71**	14.24	11.68	**+ 2.56**
	LCL	12.49	10.62	+ 0.32	-	-	-	**-**	-	12.88	10.53	+ 0.81	-	-	**-**
	UCL	15.12	12.95	+ 3.84	-	-	-	**-**	-	15.91	12.83	+ 4.61	-	-	**-**
	median	12.50	9.50	**+ 3.00**	-	12.07	9.14	**+ 2.93**	-	12.02	10.09	**+ 1.93**	-	-	**-**
	LCL	10.37	8.05	+ 0.42	-	-	-	**-**	-	10.13	8.65	- 0.44	-	-	**-**
	UCL	14.63	10.95	+ 5.58	-	-	-	**-**	-	13.90	11.52	+ 4.30	-	-	**-**
Fully Supplemented	mean	13.63	11.99	**+ 1.64**	25.5	13.38	11.78	**+ 1.60**	23.7	15.32	12.31	**+ 3.01**	15.33	12.25	**+ 3.08**
	LCL	12.27	10.72	- 0.22	-	-	-	**-**	-	13.48	10.95	+ 0.72	-	-	**-**
	UCL	15.00	13.26	+ 3.50	-	-	-	**-**	-	17.16	13.67	+ 5.30	-	-	**-**
	median	13.50	10.50	**+ 3.00**	-	13.28	10.12	**+ 3.16**	-	12.88	10.65	**+ 2.23**	-	-	**-**
	LCL	11.87	8.63	+ 0.52	-	-	-	**-**	-	10.60	8.95	- 0.61	-	-	**-**
	UCL	15.13	12.37	+ 5.48	-	-	-	**-**	-	15.16	12.34	+ 5.07	-	-	**-**
Fully Supplemented stage III or IV	mean	13.02	10.25	**+ 2.73**	23.5	12.83	10.35	**+ 2.48**	28.0	14.43	10.28	**+ 4.15**	13.59	10.00	**+ 3.59**
	LCL	11.6	8.93	+ 0.79	-	-	-	**-**	-	12.41	9.04	+ 1.78	-	-	**-**
	UCL	14.45	11.56	+ 4.67	-	-	-	**-**	-	16.44	11.53	+ 6.52	-	-	**-**
	median	13.50	8.50	**+ 5.00**	-	10.91	7.90	**+ 3.01**	-	12.13	8.97	**+ 3.16**	-	-	**-**
	LCL	11.41	6.56	+ 2.15	-	-	-	**-**	-	9.63	7.42	+ 0.22	-	-	**-**
	UCL	15.59	10.44	+ 7.85	-	-	-	**-**	-	14.62	10.51	+ 6.09	-	-	**-**
Fully Supplemented PS 0 or 1	mean	-	-	-	-	13.99	12.21	**+ 1.78**	23.2	-	-	-	16.53	12.99	**+ 3.55**
	LCL	-	-	-	-	-	-	**-**	-	-	-	-	-	-	**-**
	UCL	-	-	-	-	-	-	**-**	-	-	-	-	-	-	**-**
	median	-	-	-	-	14.49	10.46	**+ 4.03**	-	-	-	-	-	-	**-**
Fully Supplemented stage III / IV & PS 0 or 1	mean	-	-	-	-	13.3	10.25	**+ 3.04**	23.7	-	-	-	15.47	10.34	**+ 5.12**
	LCL	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	UCL	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	median	-	-	-	-	13.90	8.95	**+ 4.95**	-	-	-	-	-	-	**-**

ITT: Intention-to-treat; LCL: lower confidence interval; UCL: upper confidence interval; PS 0 or 1: Performance status 0 or 1; AUC: Area under curve; MLE: Maximum likelihood estimation; LS: least squares; P/C: Pemetrexed and cisplatin combination therapy; C: Cisplatin monotherapy

Table 7B: Estimates of mean survival gains and health-related utility gains per patient

Population		Life-months						Quality adjusted life years					
		Undiscounted			Discounted			Undiscounted			Discounted		
		P/C	C	Difference	P/C	C	Difference	P/C	C	Difference	P/C	C	Difference
ITT	mean	14.24	11.68	**+ 2.56**	14.01	11.55	**+ 2.46**	0.606	0.480	**+ 0.127**	0.597	0.474	**+ 0.122**
	LCL	12.74	10.53	+ 0.67	12.57	10.43	+ 0.65	0.538	0.416	+ 0.032	0.531	0.412	+ 0.031
	UCL	15.74	12.83	+ 4.45	15.43	12.66	+ 4.27	0.676	0.545	+ 0.221	0.663	0.537	+ 0.213
Fully Supplemented	mean	15.33	12.25	**+ 3.08**	15.05	12.10	**+ 2.95**	0.678	0.528	**+ 0.151**	0.666	0.521	**+ 0.145**
	LCL	13.49	10.89	+ 0.79	13.29	10.79	+ 0.77	0.593	0.466	+ 0.045	0.585	0.461	+ 0.043
	UCL	17.17	13.61	+ 5.37	16.79	13.40	+ 5.14	0.765	0.590	+ 0.257	0.749	0.583	+ 0.247
Fully Supplemented Stage III or IV	mean	13.59	10.00	**+ 3.59**	13.37	9.92	**+ 3.45**	0.592	0.408	**+ 0.185**	0.583	0.404	**+ 0.179**
	LCL	11.69	8.79	+ 1.34	11.55	8.74	+ 1.29	0.506	0.356	+ 0.083	0.500	0.353	+ 0.081
	UCL	15.49	11.21	+ 5.84	15.19	11.10	+ 5.62	0.679	0.461	+ 0.286	0.666	0.456	+ 0.276
Fully Supplemented PS 0 or 1	mean	16.53	12.99	**+ 3.55**	16.18	12.81	**+ 3.37**	0.744	0.559	**+ 0.185**	0.728	0.551	**+ 0.177**
	LCL	14.33	11.36	+ 0.81	14.09	11.24	+ 0.77	0.640	0.486	+ 0.057	0.631	0.480	+ 0.056
	UCL	18.73	14.62	+ 6.29	18.25	14.38	+ 5.98	0.849	0.634	+ 0.313	0.827	0.623	+ 0.299
Fully Supplemented Stage III / IV & PS 0 or 1	mean	15.47	10.34	**+ 5.12**	15.18	10.26	**+ 4.92**	0.683	0.436	**+ 0.247**	0.671	0.433	**+ 0.238**
	LCL	13.25	8.95	+ 2.50	13.07	8.90	+ 2.41	0.582	0.375	+ 0.128	0.575	0.373	+ 0.124
	UCL	17.69	11.73	+ 7.74	17.28	11.61	+ 7.43	0.786	0.498	+ 0.366	0.768	0.493	+ 0.352

ITT: Intention-to-treat; LCL: lower confidence interval; UCL: upper confidence interval; PS 0 or 1: Performance status 0 or 1; P/C: Pemetrexed and cisplatin combination therapy; C: Cisplatin monotherapy

Figure 7A: Survival from randomization - ITT population

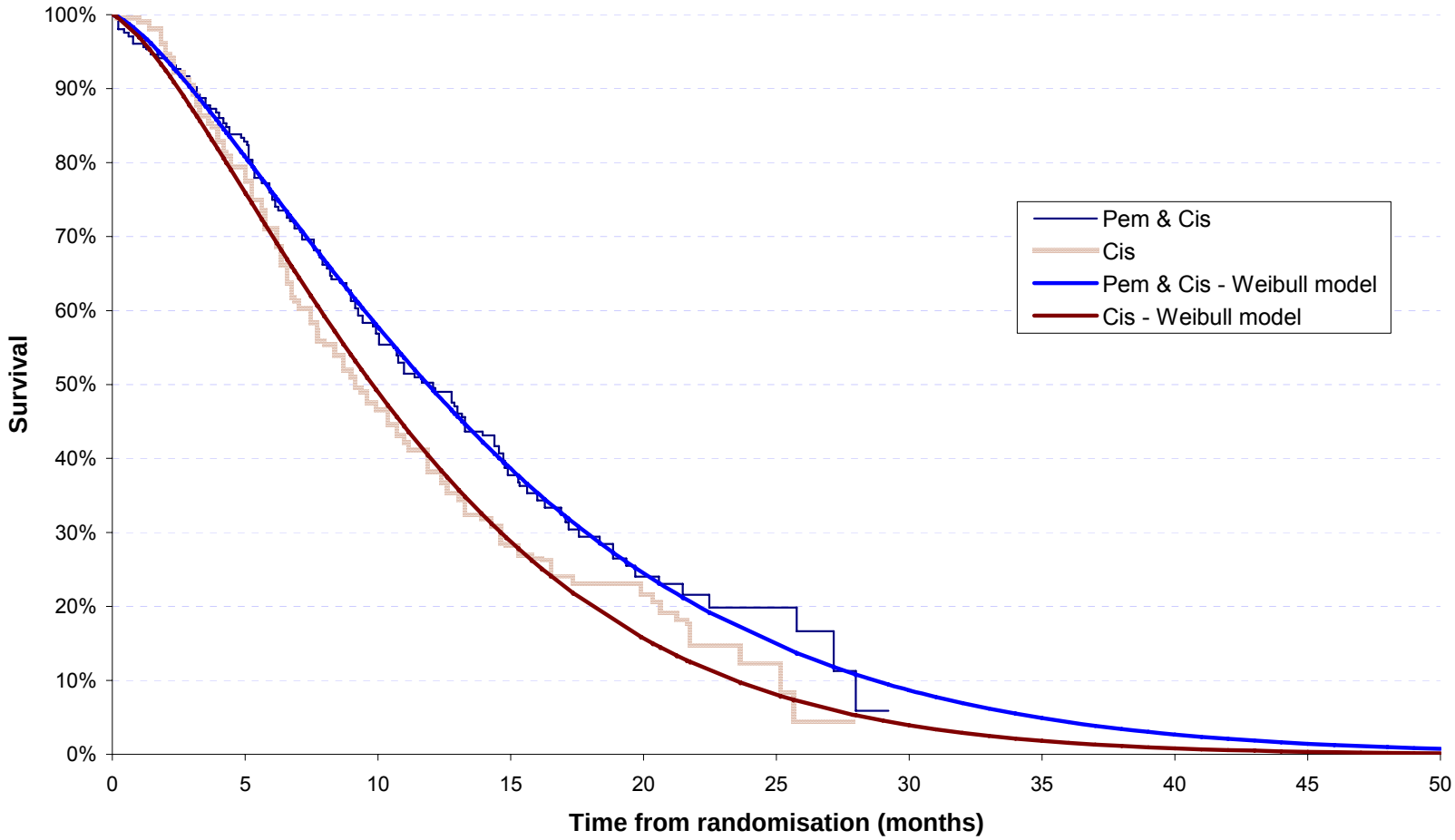


Figure 7B: Survival from randomization - fully supplemented (FS) population

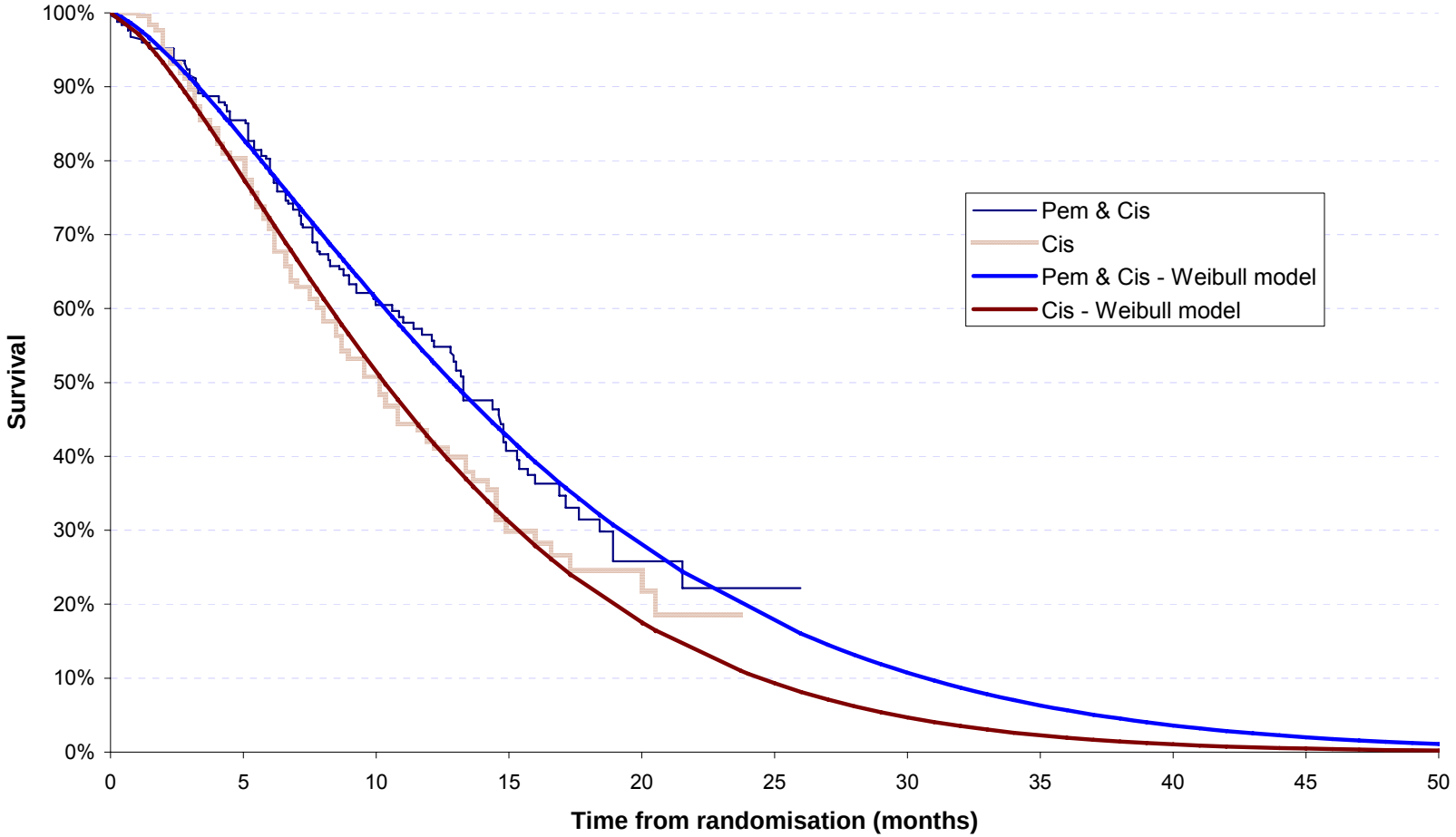


Figure 7C: Survival from randomization - fully supplemented with advanced disease (FS/AD) population

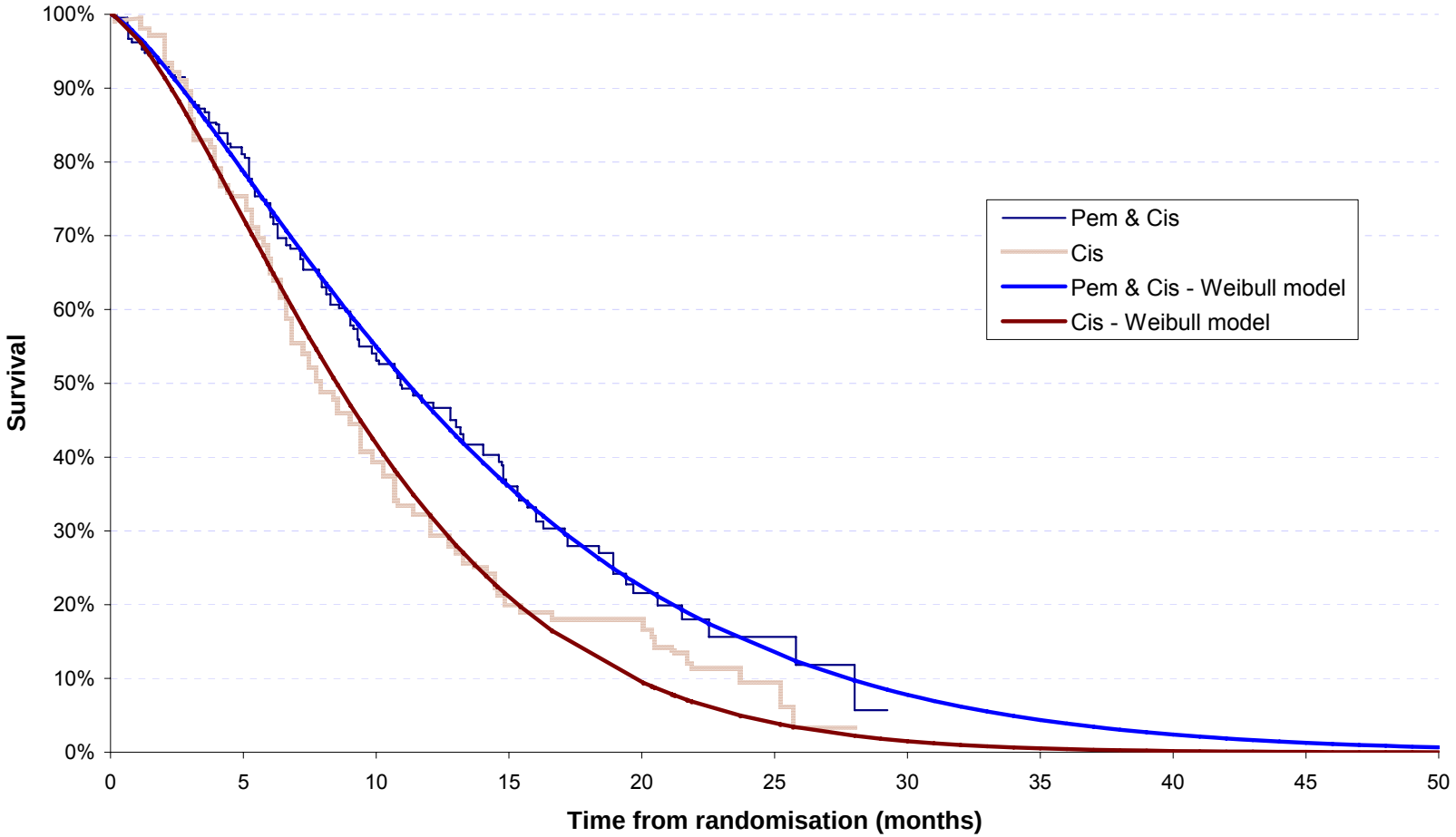


Figure 7D: Survival from randomization - fully supplemented with performance status 0 or 1 (FS/PS01) population

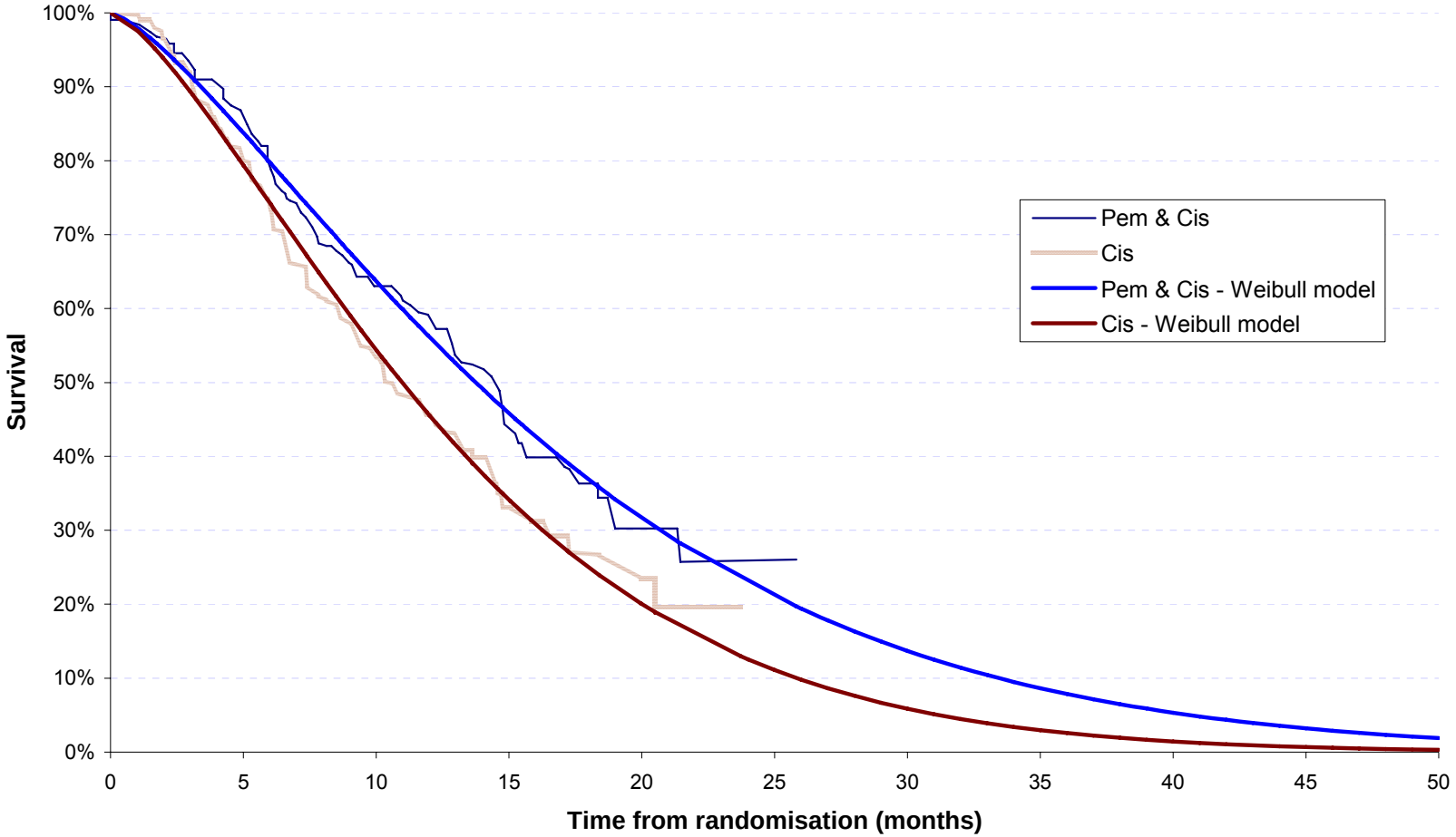
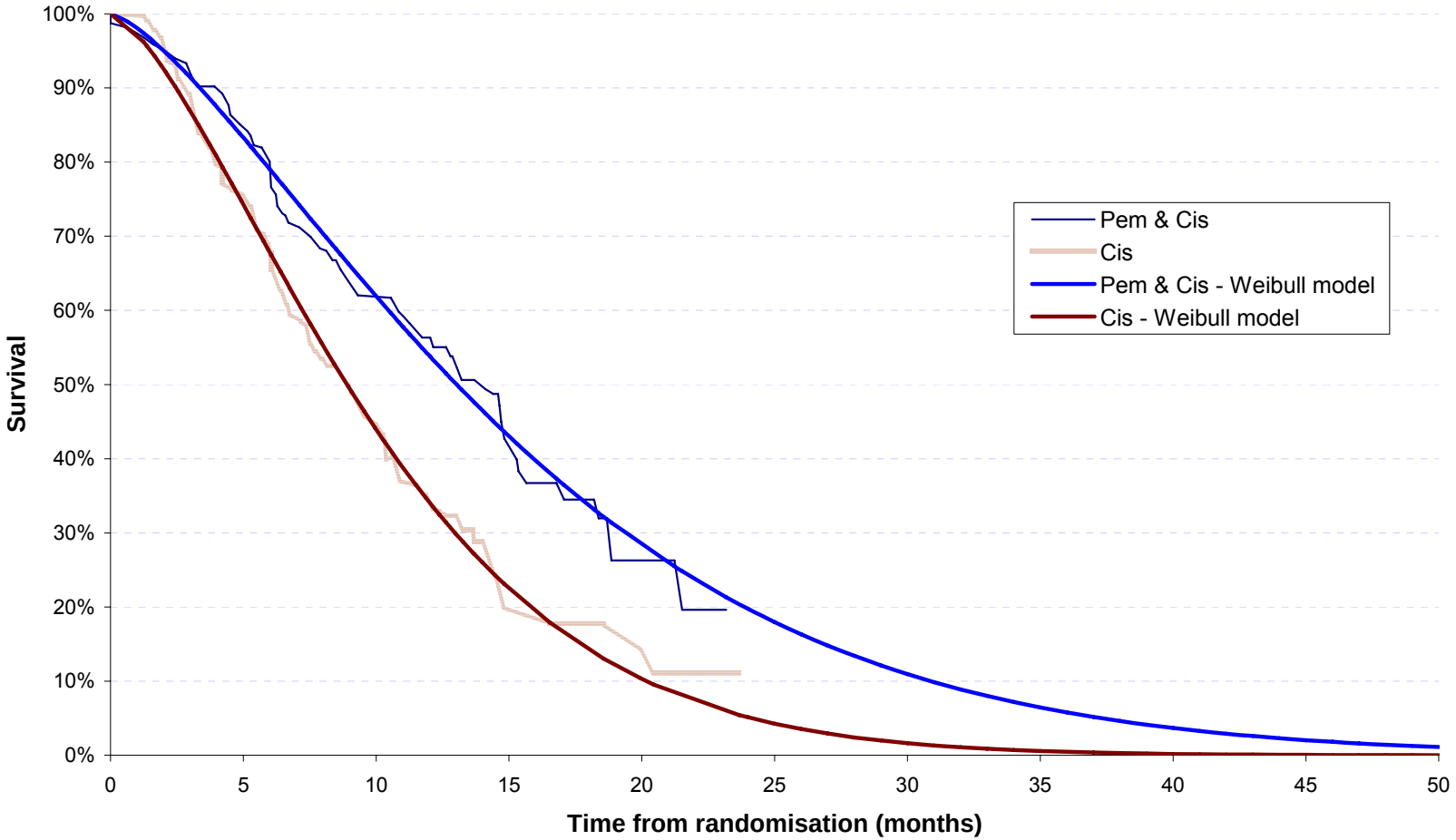


Figure 7E: Survival from randomization - fully supplemented with advanced disease & performance status 0 or 1 (FS/AD&PS01) population



7.3.3 Health-related quality of life

In order to obtain values for utility gains ascribable to use of pemetrexed, it is necessary to multiply estimates of mean survival time by a mean health-related quality of life score. In Model 1, Eli Lilly has employed the findings of a survey of patients suffering from non-small cell lung cancer, weighting EuroQoL EQ-5D results by the performance status of patients in the two arms on the EMPHACIS trial. Though MPM patients suffer from a cancer located in the thorax, it is not clear whether NSCLC values are directly comparable with the experience of MPM patients of equivalent performance status.

A further difficulty concerns the appropriateness of using a single mean value of EQ-5D. In the submitted Model 1 values of 0.68 or 0.69 are used throughout taking no account of the evident effect of loss of quality of life affecting those patients approaching death. Multiple observations by van den Hout[57] of quality of life from patients with various cancers undergoing radiotherapy demonstrates clearly that during that last few months of life, patients can expect to suffer an accelerating decline in quality of life from a previously stable level. Parametric modelling of van den Houts results allows us to account for this effect using a stable mean EQ5-D score of 0.65, followed by a terminal period of about 100 days during which an average score of 0.4 is applied. Using these values together with the aggregated survival data allows the derivation of mean quality of life values appropriate to each population-arm in the range 0.51-0.54. The right-hand columns of *Table* 7B shows the results of applying these values to the previously described survival estimates, and provides the incremental utility estimates (Q_{pc} - Q_c) employed in the model described in 7.2.1.

7.3.4 Resource use and costs

Unit costs in Model 1 are drawn from the British National Formulary (BNF)[58] or Monthly Index of Medical Specialities (MIMS) [59] for drugs and from NHS Reference Costs for hospital treatments: these appear to be well-founded and are used in our reformulation. *Table* 7C shows the parameter values used to calibrate our model based on the unit costs from the submitted model combined with IPD resource use patterns. These have been expressed in terms of either normal or beta distributed variables for use in probabilistic sensitivity analysis (PSA), as in the absence of IPD data these distributions suitably represent the distribution of the mean of each variable.

Table 7C: Resource use and unit cost uncertainty distributions and parameter estimates

				Population							
			Distribution	FS		FS/AD		FS/PS01		FS/AD&PS0/1	
		Parameters	Normal	Mean	St. Error	Mean	St. Error	Mean	St. Error	Mean	St. Error
			Beta	Alpha	Beta	Alpha	Beta	Alpha	Beta	Alpha	Beta
Topic	Item	Treatment									
AE hospitalisations	Events per cycle	P/C	Beta	63	761	52	532	44	673	33	463
		C	Beta	27	623	15	447	24	555	13	389
	Cost per event	P/C & C	Normal	811.4	34.3	802.8	36.7	805.8	42.2	796.9	47.6
Treatment	Cycles per patient	P/C	Beta	824	1192	584	916	717	999	496	752
		C	Beta	650	1306	462	1002	579	1113	402	834
Drug cost	Cost per cycle	P/C	Normal	1746.7	10.1	1752.5	12.4	1754.6	10.1	1762.7	12.2
		P/C adjusted	Normal	91.9	0.6	92.0	0.7	91.4	0.6	91.8	0.7
		C	Normal	1576.6	7.7	1585.4	8.9	1588.8	7.5	1603.0	8.1
Treatment mode	%IP administered	P/C	Beta	340	484	267	317	289	428	216	280
		C	Beta	266	384	165	297	235	344	137	265
Post-study chemotherapy	Events per patient	P/C	Beta	65	168	51	125	58	143	46	104
		C	Beta	68	163	51	122	60	141	43	103
	Cost per event	P/C & C	Normal	2768.1	132.2	2770.0	156.2	2931.0	150.0	2788.2	171.2
Utility gain	Discounted	-	Normal	0.145	0.052	0.179	0.050	0.177	0.062	0.238	0.058

FS: Fully supplemented; AD: Advanced disease; PS 0 or 1: Performance status 0 or 1; P/C: Pemetrexed and cisplatin combination therapy; C: Cisplatin monotherapy

7.4 Economic model findings

7.4.1 Base case cost-effectiveness results

Table 7D displays central estimates of cost-effectiveness (incremental cost per life-year gained and per QALY gained), comparing the results obtained with our amended model with those included within the company submission.

In almost all cases our results are more favourable to the use of pemetrexed, due mainly to the extended survival times and gains in life expectancy obtained by parametric survival modelling, but partially offset by our lower assessed utility values throughout patients' remaining lifetimes. Relative to indicative 'value for money' thresholds (£30,000 to £40,000 per QALY gained), these modest net improvements in ICER estimates do not materially alter the position of pemetrexed combination, except that the smallest subgroup (FS/AD and PS01) now falls below the £40,000 per QALY gained level.

7.4.2 Alternate analysis

Table 7E shows similar results based on the projected patient costs likely to be incurred if and when the smaller 100 mg vial of pemetrexed becomes available (2008 or later). As expected this has the effect of reducing the incremental costs of treatment, but the magnitude of this change is only modest and does not alter the assessment of cost-effectiveness for any of the four populations considered.

7.4.3 Sensitivity analysis

The limited access to selected IPD granted to the Assessment Group does not allow a comprehensive probabilistic sensitivity analysis to be carried out on either the submitted Model 1 or the LRiG modified version. In particular we were unable to explore the nature of covariance among the various model variables, especially those involving survival data. As a consequence we have undertaken an indicative PSA on the assumption that all model variables are mutually statistically independent. It has been possible to validate this assumption only for relationships between the main model cost elements (drug cost, administration cost, adverse event hospitalisation costs and post-study chemotherapy costs). On *a priori* grounds it is plausible that significant positive covariance should be present between patient survival and drug cost, but this cannot be confirmed: for example, patients dying early in the treatment

period will necessarily receive fewer cycles of treatment than those with extended survival, which should lead to a positive correlation between survival and number of cycles of treatment received. If such interactions could be confirmed and estimated, the effect would probably be to reduce the extent of variation in model results around the central estimates. The results of the PSA exercise are shown in *Table* 7F.

The PSA confirms the findings of the central estimates of cost-effectiveness:

- that it is probably not cost-effective for pemetrexed plus cisplatin combination therapy to be used for all patients of the types recruited into the EMPHACIS trial;
- that restricting use to those with either advanced disease (Stages III or IV) or good performance status (0 or 1) but not both, performs somewhat better but still does not provide a convincing case relative to generally used acceptability thresholds;
- that restricting use to only those patients with both advanced disease (Stages III or IV) and good performance status (0 or 1) provides the strongest (but not unequivocal) case for use of pemetrexed plus cisplatin combination therapy.

Table 7D: Cost-effective results for base case pemetrexed costs

Patient population	Cost per patient			Life years per patient			Incremental QALYs	Incremental cost per life year gained	Incremental cost per QALY gained
	Pemetrexed + cisplatin	Cisplatin	Incremental Cost	Pemetrexed + cisplatin	Cisplatin	Incremental Life-years			
Fully supplemented	£11,752	£3,119	+ £8,633	1.254	1.008	+ 0.246	+ 0.145	£35,062	£59,598
Fully supplemented with advanced disease	£11,407	£2,898	+ £8,509	1.115	0.827	+ 0.288	+ 0.179	£29,560	£47,628
Fully supplemented with good performance status (0 or 1)	£12,071	£3,237	+ £8,834	1.349	1.068	+ 0.281	+ 0.177	£31,424	£49,788
Fully supplemented with advanced disease & good performance status (0 or 1)	£11,656	£2,932	+ £8,723	1.265	0.855	+ 0.410	+ 0.238	£21,274	£36,676

Table 7E: Cost-effectiveness for alternative pemetrexed costs

Patient population	Cost per patient			Life years per patient			Incremental QALYs	Incremental cost per life year gained	Incremental cost per QALY gained
	Pemetrexed + cisplatin	Cisplatin	Incremental Cost	Pemetrexed + cisplatin	Cisplatin	Incremental Life-years			
Fully supplemented	£10,917	£3,119	+ £7,799	1.254	1.008	+ 0.246	+ 0.145	£31,674	£53,838
Fully supplemented with advanced disease	£10,626	£2,898	+ £7,728	1.115	0.827	+ 0.288	+ 0.179	£26,848	£43,257
Fully supplemented with good performance status (0 or 1)	£11,240	£3,237	+ £8,002	1.349	1.068	+ 0.281	+ 0.177	£28,467	£45,103
Fully supplemented with advanced disease & good performance status (0 or 1)	£10,894	£2,932	+ £7,962	1.265	0.855	+ 0.410	+ 0.238	£19,417	£33,474

Table 7F: *Key results of probabilistic sensitivity analysis for base case and alternative pemetrexed costs*

	Base case scenario					Alternative drug costs scenario				
	Acceptability threshold for probability cost-effective of			Probability cost-effective		Acceptability threshold for probability cost-effective of			Probability cost-effective	
Patient population	50%	2.5%	97.5%	£30,000 threshold	£40,000 threshold	50%	2.5%	97.5%	£30,000 threshold	£40,000 threshold
Fully supplemented	£59,434	£34,473	£191,532	0.7%	8.7%	£53,580	£31,080	£173,755	1.5%	17.7%
Fully supplemented with advanced disease	£47,360	£30,744	£106,226	1.8%	24.6%	£43,006	£28,028	£96,536	5.7%	38.0%
Fully supplemented with good performance status (0 or 1)	£49,648	£29,212	£152,281	3.1%	24.5%	£45,010	£26,535	£138,071	7.5%	35.6%
Fully supplemented with advanced disease & good performance status (0 or 1)	£36,472	£24,818	£71,663	18.5%	63.5%	£33,243	£22,727	£65,497	32.2%	74.4%

7.4.4 Other unquantified costs

Although at first sight the case put forward in the submitted Model 1 (and by implication in the modified LRiG version) appears plausible, there remain some concerns about the absence of a number of other costs from the model formulation.

7.4.4.1 Concomitant medications

In the company submission Table 20, provided in Appendix 10, purports to estimate the cost of concomitant medications in the two arms of the trial, and on the basis of these calculations the authors claim that the difference is too small to warrant including in the model. Unfortunately, the method of calculation appears to be flawed, in that percentages of patients receiving each treatment are multiplied by the cost of a typical dose/prescription, and no account is taken of the duration of treatment which patients may have received. For example, 10.1% of patients in the pemetrexed plus cisplatin arm required treatment with erythropoetin for anaemia, and were costed on the basis of a single dose. However, erythropoetin is routinely given prophylactically in US practice for patients with a history of anaemia and is often continued every few weeks over a very long period. By contrast, erythropoetin is very rarely used in the UK, blood transfusion being the normal treatment. When medications are correctly costed on the basis of doses used, rather than patients numbers, the difference between trial arms may be rather larger than is suggested. Without access to full IPD, this issue cannot be resolved.

7.4.4.2 Procedures and tests

Although all elements of the treatment of adverse events requiring hospitalisation should have been captured by the use of NHS Reference Costs, there are likely to have been a larger number of tests, investigations and therapeutic procedures carried out without formal admission to hospital and arising from adverse events of various levels of severity. These can range from simple blood tests to radiological scans and even minor surgery undertaken on an outpatient basis for relief of symptoms. These have not been mentioned in the CSR or in the company submission, and do not feature in the models submitted. It is not clear whether these data were collected during the trial, though it would be unusual if they had not. Once again failure to allow access to IPD has prevented resolution of this question.

7.4.4.3 Blood product transfusions

The CSR indicates a substantially heavier use of blood transfusions, primarily for anaemia, in the pemetrexed plus cisplatin arm of the EMPHACIS trial. Given that the largest national group of enrolled patients (nearly 20%) originated in USA, where erythropoetin is often used instead of transfusion, and the UK contributed less than 5% of trial patients, it is reasonable to expect that the difference in the need for transfusions due to use of pemetrexed would be greater in UK practice than that actually recorded. Without access to IPD we cannot determine how many of these events occurred whilst patients were resident in hospital, or on an out-patient basis so that it is difficult to assess what additional costs should have been included in the submitted models.

7.4.4.4 Community treatment costs

The evidence of the location of administered drugs during the trial suggests that at least 50% (and probably more) of patients were normally cared for in a community setting, incurring a continuing stream of costs both in terms of health professional contacts, and additional supportive therapies (e.g. home oxygen service). Once again there is considerable scope in this area for cost differences to arise between the trial arms. No mention of this aspect of care is made in the submission, even in order to discount it. It may be that no such data were collected in the trial, but that need not preclude its consideration for modelling, albeit in the form of an alternative scenario.

7.5 Summary

Of the two models submitted by Eli Lilly as evidence of cost-effectiveness, we concluded that Model 2 lacked credibility since the outcome data for putative comparators to pemetrexed plus cisplatin combination therapy was not drawn from comparable studies and also did not satisfy the requirements for indirect comparison.

Despite difficulties arising from the absence of patient level outcome data it proved possible to obtain improved estimates of survival gains, confirming the evidence submitted that pemetrexed in combination with cisplatin appears to confer real benefit to the type of MPM patients included in the trial.

By reformulating Model 1 and reanalysing some of the cost data supplied we were able to confirm that a reasonable case could be made for the sub-population of patients with both

good performance status and advanced disease, if the assumed content of the submitted cost model were accepted.

However, we have identified a number of potentially significant errors or omissions from the costs included in the models, which cannot be resolved without access and detailed study of the trial IPD, and could compromise these apparently positive findings.

8 BUDGET IMPACT ANALYSIS

8.1 Introduction

This section deals with the potential cost implications to the NHS of the introduction of pemetrexed plus cisplatin for the management of malignant pleural mesothelioma (MPM). The cost to the NHS will depend on two factors:

1. costs associated with pemetrexed plus cisplatin treatment
2. eligible population for such treatment

Each of these factors is examined in greater detail below.

8.2 The costs of pemetrexed plus cisplatin treatment

8.2.1 Direct therapy costs

In patients treated for MPM the recommended dose of pemetrexed is 500mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes, followed 30 minutes later by cisplatin at a dose of 75mg/m^2 BSA infused over two hours, on the first day of each 21 day cycle.[41] The LRiG modified version of Model 1 allows incorporation of the experience of trial patients in overall estimates of the costs directly associated with pemetrexed plus cisplatin therapy: the number of cycles/dose received, the cost of supplementation, the cost of administration, and the cost of hospitalisations associated with serious adverse events. If it is assumed that patients would otherwise receive active/best supportive care then the additional direct cost to the NHS is £10,980 per patient (varying slightly for each subgroup between £10,604 and £11,225). Since only the cost of hospital episodes resulting from adverse events is included in these estimates, we can expect some additional costs for community care and minor prescribing for the more numerous lower grade adverse effects of chemotherapy. As with other chemotherapy regimens pemetrexed plus cisplatin generates a large number of grade 1/2 adverse events, particularly nausea, vomiting, fatigue, constipation, anorexia, stomatitis as well as haematological problems. If we conservatively assume that on average each patient requires one additional GP surgery visit, with dispensed prescription, and one additional home visit by a District Nurse, an extra cost of around £70 per patient should be included in the budget impact calculation (Personal Social Services Research Unit (PSSRU) costs).[60]

For patients who might otherwise expect to receive an alternative chemotherapy regimen, the estimation of the net additional cost of pemetrexed plus cisplatin is more difficult, since it depends on the acquisition and administration costs of the drug(s) used, and adverse event profile relative to pemetrexed plus cisplatin. If cisplatin monotherapy is taken as a general guide, the net additional NHS cost per patient may be around £8,700.

8.2.2 Consequential supportive costs

Although not normally considered in the calculation of cost-effectiveness ratios, there are additional costs incurred by the NHS as a consequence of the survival gain produced by the use of pemetrexed plus cisplatin therapy. The apparent evidence of the various survival charts included in the CSR suggests that the extended survival reported occurs mainly in the period preceding disease progression/treatment failure when the patient can be expected to be in a generally stable condition and supported in a community setting. The cost of additional NHS services during this period must also be considered a potentially important impact on the NHS budget.

Unfortunately there are no research findings providing a profile of the normal components of care provided to MPM patients in the community, and therefore no reliable estimates of the cost of such care. If we make some simple assumptions, based on clinical advice, that each patient would see their GP once per month, a community-based palliative care nurse once a month, and that a proportion of patients would need additional supportive services (e.g. domiciliary oxygen), we may conservatively estimate extra supportive care costs of about £100 per month will be incurred by NHS budgets.

8.3 The eligible population

Currently approximately 1700 people are diagnosed with malignant pleural mesothelioma (MPM) each year in the UK.[4] However this is expected to rise to a peak between 2011 and 2015 of about 2450. Due to the advanced stage of disease, poor patient condition and other morbidities many patients would not be considered fit to undergo chemotherapy. Moreover, the recruitment criteria for the EMPHACIS trial[39] further restrict the number of patients who would be eligible for treatment with pemetrexed plus cisplatin, ensuring that the trial population is not comparable with the general patient population in England and Wales. Unfortunately there are no reliable contemporary statistics available relating to the stage and performance status of MPM patients at diagnosis, so there is no firm basis on which to assess the number of patients equivalent to the EMPHACIS sub-populations.

8.3.1 Cost estimates

With this proviso we present below estimated costs making crude assumptions about likely patient numbers for each population (equivalent to up to 20 to 25% of overall annual numbers being eligible) as broadly indicative of the potential impact of using pemetrexed plus cisplatin in place of supportive care (see Table 8A).

Table 8A: Estimated NHS budget impact of pemetrexed plus cisplatin

Population	Patients treated p.a.	Pemetrexed acquisition cost	Administration, supplementation & SAE costs	Community NHS costs	Extra maintenance costs	Total budget impact
FS	500	£4,283,800	£1,206,200	£35,000	£154,000	£5,679,000
FS/AD	400	£3,275,200	£966,400	£28,000	£143,600	£4,413,200
FS/PS0/1	400	£3,519,000	£971,000	£28,000	£142,000	£4,660,000
FS/AD&PS0/1	300	£2,522,100	£718,200	£21,000	£153,600	£3,414,900

PA: per annum; SAE: Serious adverse event; FS: Fully supplemented; AD: Advanced disease; PS0/1: Performance status 0 or 1

A realistic maximum estimate would probably be about double these figures if pemetrexed plus cisplatin were to become generally adopted as a standard regimen for suitable MPM patients.

8.4 Conclusion

The major factor determining cost impact to the NHS of pemetrexed plus cisplatin is the cost of pemetrexed itself. It is estimated that the total annual impact on NHS budgets would be between £3.4 million to £5.7 million depending on the population treated, and assuming that patients would otherwise receive active/best supportive care. If only patients already treated with inexpensive chemotherapy were to receive pemetrexed plus cisplatin, the budget impact may be about 25% less than that shown. However, it is possible that if pemetrexed plus cisplatin were to be widely adopted as a standard therapy for eligible patients these estimates should probably be doubled.

9 GENERAL DISCUSSION AND CONCLUSIONS

Mesothelioma will be a growing challenge for the NHS over the next 15 to 20 years, as patient numbers increase. Its poor prognosis is in part the result of late diagnosis but mainly due to the natural history of the tumour. This prognosis and the clinical course in which pain is often a prominent feature commands our attention. That it is a condition brought on by occupational exposure may increase our sense of needing to respond to these patients.

Any new treatment promising palliation or increased life expectancy therefore may seem very attractive. In evaluating a new treatment however, we need to consider what current best care is for such patients. Many patients as we have seen receive only supportive care, in part related to the late stage of presentation. The concept of best supportive care is somewhat nebulous: it is almost synonymous with active symptom control and ideally it would consist of adequate pain relief managed by an experienced palliative care team who would also offer other forms of support to both patients and their families. But this low technology and low cost approach is in practice not available to all patients. It would be sad if any new therapy attracted attention and resources away from this fundamental approach which should be available to all patients.

The new therapy examined in this document demonstrates an extension of life expectancy and palliation, as measured by time to progression of disease and other endpoints. The comparator in this trial was cisplatin, itself an unproven therapy in mesothelioma but justified on the grounds that there are no established regimens of chemotherapy proven to be of benefit in mesothelioma. This is strictly correct and the evidence presented is compelling, in several analyses, including those of the FDA looking at fully supplemented patients at various stages of disease. This is the largest trial yet conducted in mesothelioma, an impressive achievement, and will remain the best available evidence for some time to come.

However the absolute benefit obtained is small, and it needs to be weighed against the benefits of effective palliative care services. The limited benefit was also at the expense of considerable toxicity to patients. While the severe toxicities in early use were ameliorated by folate and B12 supplementation, even thereafter the incidence of toxicity was high.

The information on quality of life, which might be expected to capture the patient's perception of the balance between benefit and toxicity and of effective palliative care, is

limited at present, and for the economic evaluation presented here, it has been necessary to assume that data from other forms of lung cancer apply in this condition also.

Interestingly, the extension of life (2.8 months) was less than that previously suggested to be acceptable to patents with non small cell lung cancer when weighed against the toxicity of a cisplatin based chemotherapy regiment.[61] While the dose of cisplatin is important in determining toxicity, the extent to which patients would weigh the pemetrexed plus cisplatin regimen with its greater toxicity than cisplatin alone, against a limited extension of life is unknown. It would seem that this is an issue of providing enough information about the risks and benefits of this therapy to allow them to make their choice.

The comparator in this study, cisplatin as monotherapy, is not the form of chemotherapy most widely used in the UK for mesothelioma. A large multicentre phase III randomised trial of the most widely used treatments, mitomycin, vinblastine and cisplatin against vinorelbine and compared to active symptom control (ASC) is underway. Currently the trialists have recruited 380 patients with a target of 420 by early 2006 (personal communication: Richard Stephens, Cancer Division, MRC Clinical Trials Uni,t, 07 11 2005). Given that this trial also addresses the important question of whether any chemotherapy is better than supportive care, it would be unfortunate if this trial could not be carried on as a consequence of the pemetrexed plus cisplatin trial or a NICE appraisal.

Any decision to use pemetrexed plus cisplatin in an individual patient needs to be in full collaboration with that patient, against a background of high quality palliative care services. The patient needs to be well informed of the benefits and toxicities of the regimen. Much more research is needed into the optimum chemotherapy for these patients, and a clear definition of what constitutes best supportive care.

The economic evaluation conducted here and that of the manufacturers suggest that pemetrexed is not cost-effective at conventional thresholds for all patients. These findings seem robust. Cost-effectiveness seems better for some patient subgroups, e.g. especially for patients with good performance status and with advanced diseases, whereby our estimates, the ICER/QALY would be £36,700. Given the relatively small number of patients with mesothelioma, albeit increasing, the overall budget impact of pemetrexed would be unlikely to be no more than £5milion per year at present costs.

Appendix 1: Search strategy - clinical and economic evidence

Table A1: Search strategy and search results

Database	Years	Search strategy	References identified
MEDLINE	1980-2005	See below	620
EMBASE	1980-2005	See below	788
Science Citation Index/Web of Science	1981-2005	pleural mesothelio* and chemotherapy*	282
Science Citation Index/ ISI Proceedings	1990-2005	As above	54
The Cochrane Library 2005 (2)*	2005 (2)	As above	48
Handsearching			1
	Total references identified		**1793**
	Duplicates		**912**
	Total		**881**

*Includes The Cochrane Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database and the NHS Economic Evaluation Database (NHS EED)

Search strategy: MEDLINE 1980 – May 2005

1. mesotheio$.tw.
2. pleural mesothelioma.tw.
3. exp mesothelioma
4. exp neoplasms, mesothelial
5. exp antineoplastic agents
6. chemothera$.tw
7. or/1-4
8. or/5-6
9. 7 and 8
10. animal
11. human
12. 10 not 11
13. 9 not 12
14. limit 13 to yr=1980-2005

Search strategy: EMBASE 1980 - May 2005

15. mesotheio$.tw.
1. exp meotheioma or exp pleura mesothelioma
2. chemothera$.tw
3. exp cancer chemotherapy
4. exp cancer combination chemotherapy
5. or/1-2

6. or/3-5
7. 6 and 7
8. limit 7 to human
9. limit 8 to yr=1980-2005

Appendix 2: Quality assessment - clinical and economic evidence

a) Clinical evidence:

RCTs of clinical effectiveness were assessed using the following criteria, based on CRD Report No. 4.[37]

- Was the method used to assign participants to the treatment groups really random? *(Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)*
- Was the allocation of treatment concealed? *(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque)*
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention-to-treat analysis included?

Items will be graded in terms of ✔ **yes** (item adequately addressed), ✘ **no** (item not adequately addressed), ✔/✘ *partially* (item partially addressed), **?** **unclear** or not enough information, **NA** not applicable or **NS** not stated.

b) Economic evidence:

Studies of cost effectiveness were assessed using the following criteria, which is an updated version of the checklist developed by Drummond and Jefferson.[38]

Study design:

- The research question is stated
- The economic importance of the research question is stated
- The viewpoint(s) of the analysis are clearly stated and justified
- The rationale for choosing the alternative programmes or interventions compared is stated
- The alternatives being compared are clearly described
- The form of economic evaluation used is stated
- The choice of form of economic evaluation is justified in relation to the questions addressed.

Data collection:

- The source(s) of effectiveness estimates used are stated
- Details of the design and results of effectiveness study are given (if based on a single study)
- Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
- The primary outcome measure(s) for the economic evaluation are clearly stated
- Methods to value health states and other benefits are stated
- Details of the subjects from whom valuations were obtained are given
- Productivity changes (if included) are reported separately
- The relevance of productivity changes to the study question is discussed
- Quantities of resources are reported separately from their unit costs
- Methods for the estimation of quantities and unit costs are described
- Currency and price data are recorded
- Details of currency of price adjustments for inflation or currency conversion are given
- Details of any model used are given
- The choice of model used and the key parameters on which it is based are justified.

Analysis and interpretation of results:

- Time horizon of costs and benefits is stated
- The discount rate(s) is stated
- The choice of rate(s) is justified
- An explanation is given if costs or benefits are not discounted
- Details of statistical tests and confidence intervals are given for stochastic data
- The approach to sensitivity analysis is given
- The choice of variables for sensitivity analysis is justified
- The ranges over which the variables are varied are stated
- Relevant alternatives are compared
- Incremental analysis is reported
- Major outcomes are presented in a disaggregated as well as aggregated form
- The answer to the study question is given
- Conclusions follow from the data reported

- Conclusions are accompanied by the appropriate caveats.

All items will be graded as either ✔ **yes** (item adequately addressed), ✖ no (item not adequately addressed), **?** **unclear** or not enough information, **NA** not appropriate or **NS** not stated.

References:

1. Jaurand MC, Fleury-Feith J. Pathogenesis of malignant pleural mesothelioma. Respirology 2005;10(1):2-8.
2. Cavazza A, Travis LB, Travis WD, Wolfe JT, 3rd, Foo ML, Gillespie DJ, et al. Post-irradiation malignant mesothelioma. Cancer 1996;77(7):1379-1385.
3. Bocchetta M, Di Resta I, Powers A, Fresco R, Tosolini A, Testa JR, et al. Human mesothelial cells are unusually susceptible to simian virus 40-mediated transformation and asbestos cocarcinogenicity. Proc Natl Acad Sci U S A 2000;97(18):10214-10219.
4. Cancerbacup. Mesothelioma information centre. 2004 [cited 02/08/2005]; Available from: http://www.cancerbacup.org.uk/Cancertype/Mesothelioma
5. Hughes RS. Malignant pleural mesothelioma. Am J Med Sci 2005;329(1):29-44.
6. Hodgson JT, McElvenny DM, Darnton AJ, Price MJ, Peto J. The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. Br J Cancer 2005;92(3):587-593.
7. Wan Y. Pemetrexed (Alimta) for malignant pleural mesothelioma. APC/DTC Briefing. London& South East Medicines Information Service on behalf of the London New Drugs Group. 2005 [cited September 2005]; Available from: http://www.druginfozone.nhs.uk/new_drugs
8. Peto J, Hodgson JT, Matthews FE, Jones JR. Continuing increase in mesothelioma mortality in Britain. Lancet 1995;345(8949):535-539.
9. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. Lancet 2005;366(9483):397-408.
10. Robinson BW, Lake RA. Advances in malignant mesothelioma. N Engl J Med 2005;353(15):1591-1603.
11. British Thoracic Society Standards of Care Committee. Statement on malignant mesothelioma in the UK. Thorax 2001;56(2):250-265.
12. Curran D, Sahmoud T, Therasse P, Van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: The European organization for research and treatment of cancer experience. J Clin Oncol 1998;16(1):145-152.
13. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 1998;113(3):723-731.
14. Van Gelder T, Damhuis R, Hoogsteden H. Prognostic factors and survival in malignant pleural mesothelioma. Eur Respir J 1994;7(6):1035-1038.
15. Pistolesi M, Rusthoven J. Malignant pleural mesothelioma: update, current management, and newer therapeutic strategies. Chest 2004;126(4):1318-1329.
16. Sterman D, Albelda S. Advances in the diagnosis, evaluation and management of malignant pleural mesothelioma. Respirology 2005;10(3):266-283.
17. NICE Health Technology Appraisal: Pemetrexed disodium for the treatment of malignant pleural mesothelioma. Comments on behalf of the Roral College of

Physicians, Royal College of Radiologists, the Association of Cancer Physicians and the Joint Collegiate Council for Oncology. August 2005.

18. Tomek S, Manegold C. Chemotherapy for malignant pleural mesothelioma: Past results and recent developments. Lung Cancer 2004;45(SUPPL):S103-S119.

19. Thodtmann R, Depenbrock H, Dumez H, Blatter J, Johnson RD, van Oosterom A, et al. Clinical and pharmacokinetic phase I study of multitargeted antifolate (LY231514) in combination with cisplatin. J Clin Oncol 1999;17(10):3009-3016.

20. Zidar BL, Green S, Pierce HI, Roach RW, Balcerzak SP, Militello L. A phase II evaluation of cisplatin in unresectable diffuse malignant mesothelioma: a Southwest Oncology Group Study. Invest New Drugs 1988;6(3):223-226.

21. Mintzer DM, Kelsen D, Frimmer D, Heelan R, Gralla R. Phase II trial of high-dose cisplatin in patients with malignant mesothelioma. Cancer Treat Rep 1985;69(6):711-2.

22. Ellis P, Davies AM, Evans WK, Haynes AE, Lloyd NS. The use of chemotherapy in patients with advanced malignant pleural mesothelioma. Evidence summary report #7-14-1 (Program in evidence-based care. A Cancer Care Ontario program); 2004.

23. van Meerbeeck JP, Manegold C, Gaafar R, van Klaveren RJ, Vincent M, Legrand C. A randomized phase III trial of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an Intergroup study of the EORTC Lung Cancer Group and NCIC (abstract). Journal of clinical oncology 2004;22(14 (Suppl)):A7021.

24. Colbert N, Vannetzel JM, Izrael V, Schlienger M, Milleron B, Blanchon F, et al. A prospective study of detorubicin in malignant mesothelioma. Cancer 1985;56(9):2170-2174.

25. Scagliotti GV, Shin DM, Kindler HL, Vasconcelles MJ, Keppler U, Manegold C, et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. J Clin Oncol 2003;21(8):1556-1561.

26. Middleton GW, Smith IE, O'Brien MER, Norton A, Hickish T, Priest K, et al. Good symptom relief with palliative MVP (mitomycin-C, vinblastine and cisplatin) chemotherapy in malignant mesothelioma. Ann Oncol 1998;9(3):269-273.

27. Eli Lilly and Company Limited. Manufacturer submission to the National Institute for Health and Clinical Excellence (Pemetrexed disodium for the treatment of malignant pleural mesothelioma). London: National Institute for Health and Clinical Excellence; 2005.

28. Muers MF, Rudd RM, O'Brien ME, Qian W, Hodson A, Parmar MK, et al. BTS randomised feasibility study of active symptom control with or without chemotherapy in malignant pleural mesothelioma. Thorax 2004;59(2):144-148.

29. Stephens R, Hopwood P, Dirling D, Machin D. Randomised trials with quality of life endpoints: are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? Quality of Life Research 1997;6:225-236.

30. Fincham L, Copp G, Caldwell K, Jones L, Tookman A. Supportive care: experiences of cancer patients. European Journal of Oncology Nursing 2004;9:258-268.

31. Willard C, Luker K. Supportive care in the cancer setting: rhetoric or reality? Palliative Medicine 2005;19:328-333.

32. Department of Health. NHS Cancer Plan. London: HMSO; 2000.

33. Gysels M, Higginson I, Rajasekaran M, Davies E, Harding R. Improving supportive and palliative care for adults with cancer. London: Kings College London; 2003.

34. Electronic Medicines Compendium (Summaries of Product Characteristics (SPCs). Alimta 500mg powder for concentrate for solution for infusion [eMC entry]. electronic Medicines Compendium 2004 [cited 2005 11/11/2005]; Available from: http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=15513

35. European Medicines Agency. Summary of product characteristics (Annex I). 2004 [cited 11/11/2005]; Available from: http://www.emea.eu.int/humandocs/PDFs/EPAR/alimta/H-564-PI-en.pdf

36. Hazarika M, White RM, Booth BP, Wang YC, Lee Ham DY, Cheng YL, et al. Pemetrexed in malignant pleural mesothelioma. Clinical Cancer Research 2005;11(3):982-992.

37. Khan K, Ter Riet G, Glanville J, Sowdon A, Kleijnen J. Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews. CRD Report Number 4 (2nd Edition). York: Centre for Reviews and Dissemination, University of York; 2001.

38. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working. BMJ 1996;313(7052):275-283.

39. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21(14):2636-2644.

40. Gralla RJ, Hollen PJ, Liepa AM, Symanowski JT, Boyer MJ, Abraham R, et al. Improving quality of life in patients with malignant pleural mesothelioma: results of the randomized pemetrexed + cisplatin vs. cisplatin trial using the LCSS-Meso instrument abstract. Proceedings of the American Society of Clinical Oncology 2003:621.

41. Hazarika M, White RM, Johnson JR, Pazdur R. FDA drug approval summaries: Pemetrexed (Alimta). Oncologist 2004;9(5):482-488.

42. Favaretto A. Overview on ongoing or planned clinical trials in Europe. Lung Cancer 2005;49 Suppl 1:S117-21.

43. Tomek S, Manegold C. Chemotherapy for malignant pleural mesothelioma. Current Opinion in Oncology 2003;15(2):148-156.

44. Milward M, Clarke S, Beale P, Boyer M, Childs A, Bishop J, et al. Phase I trial of pemetrexed (Alimta) and vinorelbine in patients with advanced cancer (abstract). In: American Society of Clinical Oncology (ASCO) Annual Meeting; 2001; 2001.

45. Adjei AA, Erlichman C, Sloan JA, Reid JM, Pitot HC, Goldberg RM, et al. Phase I and pharmacologic study of sequences of gemcitabine and the multitargeted antifolate agent in patients with advanced solid tumors. J Clin Oncol 2000;18(8):1748-1757.

46. Hughes A, Calvert P, Azzabi A, Plummer R, Johnson R, Rusthoven J, et al. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. J Clin Oncol 2002;20(16):3533-3544.

47. Janne PA, Simon GR, Langer RN, Taub RN, FDowlati P, Fidias P, et al. Un update of pemetrexed plus gemcitabine as front-line chemotherapy for patients with malignant pleural mesothelioma (MPM): a phase II clinical trial (abstract). 2005 ASCO Meeting, Abstract No: 7067 2005.

48. Ceresoli GL, Zucali PA, Favaretto A, Marangalo M, Del Conte G, Ceribelli A, et al. A phase II study of pemetrexed and carboplatin as front-line chemotherapy in patients with malignant pleural mesothelioma (MPM) (conference presentation). In: American Society of Clinical Oncology (ASCO) Annual Meeting; 2005; 2005.

49. Shepherd FA, Dancey J, Arnold A, Neville A, Rusthoven J, Johnson RD, et al. Phase II study of pemetrexed disodium, a multitargeted antifolate, and cisplatin as first-line therapy in patients with advanced nonsmall cell lung carcinoma: a study of the National Cancer Institute of Canada Clinical Trials Group. Cancer 2001;92(3):595-600.

50. Bunn P, Paolett P, Niyizika C, et a. Vitamin B12 and folate reduce toxicity of pemetrexed, a novel antifolate antometabolite (abstract). Proc Soc Clin Oncol 2001;20:300.

51. Niyizika C, Baker SD, Seitz DE, et a. Homocysteine and methylmalonic acid: markers to predict and avoid toxicity from pemetrexed therapy. Mol Cancer Ther 2002;1:545-552.

52. Vogelzang NJ, Boyer MJ, et a. Effect of folic acid and vitamin B12 supplementation on risk-benefit ratio from phase III study of pemetrexed + csiplatin versus cisplatin in malignant pleural mesothelioma (abstract). Proc Am Soc Clin Oncol 2003;22:667.

53. Boyer M, Jassem J, Liepa A. Symptom and quality of life advantages for pemetrexed plus cisplatin versus cisplatin in the treatment of MPM. 10th World Conference on Lung Cancer, August 10-14, 2003, Vancouver, British Columbia 2003.

54. Davey P, Cordony A, Rajan N, Arora B, Pavlakis N. Value for money of pemetrexed plus csiplatin versus cisplatin alone in the treatment of MPM (conference presentation). International Society For Pharmacoeconomics and Outcomes Research (ISPOR) conference 2004.

55. Australian Government Department of Health and Ageing. Recommendations made by the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2005 relating to the listing of drugs on the Pharmaceutical Benefits Scheme (PBS). 2005 [cited October 2005]; Available from:

http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-mar05-neg1

56. Drummond M, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programmes. 2 ed. Oxford: 2nd Edition. Oxford University Press; 1997.

57. van den Hout WB, van der Linden YM, Steenland E, Wiggenraad RG, Kievit J, de Haes H, et al. Single versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. J Natl Cancer Inst 2003;95(3):222-229.

58. BNF 50. British National Formulary: [electronic resource]. British Medical Association, Royal Pharmaceutical Society. 2005 [cited 28/11/2005]; Available from: http://bnf.org/

59. MIMS. Monthly index of medical specialities. Haymarket Medical Publications. London; May 2005.

60. PSSRU. Personal Social Services Research Unit costs. 2004 [cited 11/11/2005]; Available from: http://www.pssru.ac.uk/

61. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ 1998;317(7161):771-775.