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

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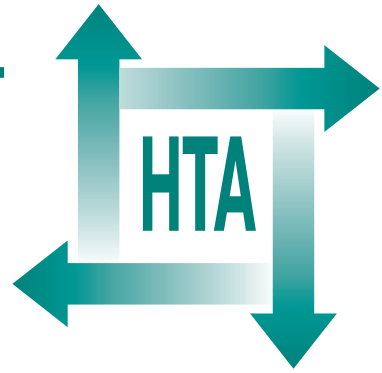



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# Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/17/01. The protocol was agreed in June 2005. The assessment report began editorial review in May 2006 and was accepted for publication in July 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

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

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**Objectives:** To assess the clinical effectiveness and cost-effectiveness of pemetrexed disodium in combination with cisplatin for the treatment of unresectable pleural mesothelioma in chemotherapy-naïve patients.
**Data sources:** Electronic databases were searched up to May 2005.
**Review methods:** The systematic review was conducted following accepted guidelines. An assessment of the economic submission received from the manufacturer of pemetrexed was also carried out. This comprised two sections, each employing an economic model. One of these models was then reformulated in order to carry out a separate exploration of economic performance.
**Results:** One randomised controlled trial comparing pemetrexed and cisplatin with cisplatin alone, and involving a total study population of 448 patients, met the inclusion criteria. Pemetrexed in combination with cisplatin in this trial showed a 2.8-month gain in median survival compared with cisplatin alone in an 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 $B_{12}$ 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 a 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 the Lung Cancer Symptom Scale demonstrated significantly greater improvement for pain and dyspnoea for patients in the combination group compared with 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 vitamin $B_{12}$ and folic acid. The existing published economic literature was very limited. The economic evaluation conducted by the study (and that submitted by the manufacturer) suggested that pemetrexed is unlikely to be considered cost-effective at conventionally accepted thresholds in the UK for all patients, mainly because of 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. The estimated cost-effectiveness results were for the FS population, incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained = £59,600; for the FS with AD population, ICER per QALY = £47,600; for the FS with performance status 0/1 population, ICER per QALY = £49,800; and for the FS with performance status 0/1 and AD population, ICER per QALY = £36,700.
**Conclusions:** 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 end-points. 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. The economic evaluation conducted in this study and

that of the manufacturers suggest that pemetrexed is not cost-effective at conventional thresholds for all patients. Cost-effectiveness seems better for some patient subgroups, e.g. especially for patients with good performance status and with advanced diseases, where it is estimated the ICER per 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 more than £5 million per year at present costs. Much more research is needed into the optimum chemotherapy for patients with mesothelioma and a clear definition of what constitutes best supportive care.

# Contents

# Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

## Glossary

**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, although subjective, percentage (e.g. a 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 evaluate safety further 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 randomised 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 4–8 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.

## List of abbreviations

| | |
|---|---|
| AD | advanced disease |
| AE | adverse event |
| ASC | active symptom control/active supportive care |
| AUC | area under the curve |
| BNF | British National Formulary |
| BSA | body surface area |
| BSC | best supportive care |
| BTS | British Thoracic Society |
| CI | confidence interval |
| CR | complete response |
| CRD | Centre for Reviews and Dissemination |
| CSR | Clinical Study Report |
| ECOG | Eastern Cooperative Oncology Group |
| 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 |
| ECOG | Eastern Cooperative Oncology Group |
| FDA | US Food and Drug Administration |
| FS | fully supplemented |
| HRQoL | health-related quality of life |
| ICER | incremental cost-effectiveness ratio |
| IPD | individual patient data |
| ITT | intention-to-treat |
| KPS | Karnofsky Performance Status |
| LCSS | Lung Cancer Symptom Scale |
| MIMS | Monthly Index of Medical Specialities |
| MLE | maximum likelihood estimation |
| MPM | malignant pleural mesothelioma |
| MVP | mitomycin C, vinblastine and cisplatin |
| NICE | National Institute for Health and Clinical Excellence |
| NS | never supplemented |
| NSCLC | non-small cell lung cancer |
| PR | partial response |
| PS | partially supplemented |
| PS 0/1 | performance status 0 or 1 |
| PSA | probabilistic sensitivity analysis |
| QALY | quality-adjusted life-year |
| QoL | quality of life |
| RCT | randomised controlled trial |
| RR | relative risk |
| SEER | Surveillance Epidemiology and End Results |
| WHO | World Health Organization |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

# Executive summary

## Objectives

The review aimed to assess the clinical effectiveness 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. About 90% of cases involve the pleura (lining of the lungs) and 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 an option for only a small minority of patients whose disease is at Stage I or II. Other treatment options may include chemotherapy, radiotherapy or supportive care.

Benefits of chemotherapy may include an improvement in symptoms and/or, occasionally, shrinkage in the size of the 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 $B_{12}$ 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 (RCTs) were considered for inclusion in the review.

An assessment was also carried out of the economic submission received from the manufacturer of pemetrexed comprising two sections, each employing a separate economic model. One of these models was then reformulated in order to carry out a separate exploration of economic performance.

## Results

### Clinical findings

One 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-month gain in median survival compared with cisplatin alone in an 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 vitamin $B_{12}$ and folic acid

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 a 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 the Lung Cancer Symptom Scale demonstrated significantly greater improvement for pain and dyspnoea for patients in the combination group compared with 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 vitamin $B_{12}$ 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 unlikely to be considered cost-effective at conventionally accepted thresholds in the UK for all patients. This is mainly due 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 that only 25% of the malignant pleural mesothelioma (MPM) population are eligible for pemetrexed therapy. Most 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.

## Conclusions

Mesothelioma will be a growing challenge for the NHS over the next 15–20 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 command 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 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. However, 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 end-points. 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 US Food and Drug Administration 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 vitamin $B_{12}$ and folic acid 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 regimen. Although 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 with active symptom control, is under way. 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 National Institute for Health and Clinical Excellence appraisal.

We believe that 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 manufacturer 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 disease, where it is estimated the ICER per 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 more than £5 million per year at present costs.

## Recommendations for further research

Other agents including anthracyclines and antimetabolites require further evaluation in mesothelioma, in combination with pemetrexed. The use of sequential and also 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 inform subsequent economic evaluations better.

# Chapter 1

## Objective of the review

The review aimed to assess the comparative clinical effectiveness 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 (MPM) in chemotherapy-naïve patients.

# Chapter 2
# Background

## Description of health problem

### 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.

### 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, and 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]

### 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 the incidence two to six times higher in males, and in the 50–70 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 1948–53 birth cohort. For men born in the 1940s, mesothelioma may account for as many as 1% of all deaths in the UK in the future.[6]

Approximately 1700 people in the UK (2004 figures) are diagnosed with 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 and 2450 deaths per 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]

### 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.

### Diagnosis and staging

Diagnosis is problematic and mesothelioma is not generally diagnosed until 2–3 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 cytological 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 histological 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.

## 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 comparisons 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 (KPS) scale 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).

## Treatment options

Surgery is an option for only a small minority of patients (1–5%)[11] whose disease is at Stage 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 alkylating agents, anthracyclines, mitomycin C, 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 it 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 randomised 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 with 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 with 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 mitomycin C, vinblastine and cisplatin combination (MVP) is widely used in the UK, and has been shown to give good symptom relief with acceptable toxicity.[26]

## 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' or by the newer more medical term 'active symptom control' (ASC). 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 or a clear description within trials of the care that had been provided.

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:

> "• Regular 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."

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. 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 the National Institute for Health and Clinical Excellence (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.

## 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 act by inhibiting thymidylate synthetase and dihydrofolate production, 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 the 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 $B_{12}$ 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 500 mg/m$^2$ body surface area (BSA) administered as an intravenous infusion over 10 minutes, followed 30 minutes later by cisplatin at a dose of 75 mg/m$^2$ BSA infused over 2 hours, on the first day of each 21-day cycle.[34] In order to reduce toxicity, patients must receive oral folic acid and an intramuscular injection of vitamin $B_{12}$ 1–3 weeks prior to the start of chemotherapy and continually throughout treatment.[35] A corticosteroid (equivalent to 4 mg of dexamethasone) should also be given orally on the day prior to, the day of and the day after pemetrexed administration to reduce the incidence and severity of skin reactions.[34]

## 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 QoL assessment, which is usually based on questionnaires. The most commonly used scales include the 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–Lung (FACT-L) scores.

## Adverse events

The most commonly reported side-effects with pemetrexed include nausea, vomiting, fatigue and leucopenia (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 75 mg/m$^2$.

## 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.

# Chapter 3
# Methods

## Methods for reviewing clinical effectiveness

### 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 (2003–2005) 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 the EndNote reference database, Version 8.2 (ISI ResearchSoft, Berkeley, CA, USA).

### Inclusion and exclusion criteria
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 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 predesigned data extraction form and checked by a second reviewer.

### 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 (CRD), York, Report 4 (see Appendix 2).[37] Any discrepancies were resolved through discussion.

### 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 (RCTs) were tabulated and presented narratively.

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

## Methods for reviewing cost-effectiveness

### 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 MPM. 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.

***TABLE 1*** *Databases searched and inclusion and exclusion criteria*

| | Clinical effectiveness | Cost-effectiveness |
|---|---|---|
| Electronic databases | MEDLINE (1980–2005)<br>EMBASE (1980–2005)<br>SCI/Web of Science (1981–2005)<br>SCI/ISI Proceedings (1990–2005)<br>The Cochrane Library (2005)[a] | MEDLINE (1980–2005)<br>EMBASE (1980–2005)<br>SCI/Web of Science (1981–2005)<br>SCI/ISI Proceedings (1990–2005)<br>The Cochrane Library 2005[a] |
| Study design | RCT<br>Non-RCT (e.g. non-randomised Phase I, Phase II trials) | RCT<br>Non-RCT<br>Economic analyses |
| Patient population | Chemotherapy-naïve patients with unresectable MPM | Chemotherapy-naïve patients with unresectable MPM |
| Interventions | Pemetrexed disodium (Alimta, LY231514, MTA) and cisplatin in combination, supplemented by folic acid and vitamin $B_{12}$ | Pemetrexed disodium (Alimta, LY231514, MTA) and cisplatin in combination, supplemented by folic acid and vitamin $B_{12}$ |
| Comparators | Cisplatin<br>Supportive care<br>Other commonly used alternatives (e.g. vinorelbine or MVP) | Cisplatin<br>Supportive care<br>Other commonly used alternatives (e.g. vinorelbine or MVP) |
| Outcomes | Overall survival<br>Toxicity<br>Symptom palliation<br>Health-related quality of life<br>Tumour response<br>Progression-free survival | Incremental cost per life-year gained<br>Incremental cost per quality-adjusted life-year gained |
| Exclusion criteria | Study populations other than those described above | No attempt to synthesise costs and benefits<br>Letters, editorials, commentaries or methodological papers |

RCT, randomised controlled trial.
[a] 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).

## Inclusion and exclusion criteria

The aim of the economic review was to identify economic evaluations informed by clinical data from RCTs and/or non-RCTs. 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 1*.

All the references were exported and managed using the Endnote reference database, Version 8.2 (ISI Research Soft).

## Data extractions

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

## Quality assessment

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]

## Methods of analysis for economic studies

Individual study data and quality assessments 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.

# Chapter 4

# Results: clinical effectiveness

## 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 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 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 or ASC.

Seven additional non-comparative studies were identified 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 that 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 $B_{12}$) plus BSC with BSC alone in previously treated patients (i.e. not chemotherapy-naïve) with advanced or metastatic MPM was excluded from the review.

## 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 2*.

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 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 2*** *Quality assessment of the included trial*

| Study name | Randomisation | | | Baseline comparability | | | | Blinding | | | | Withdrawals | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | ITT |
| Vogelzang, 2003[39a] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | × | ✓ | × | ✓ | ✓ | ✓ |

✓, Yes (item adequately addressed); ×, no (item not adequately addressed).
[a] Quality assessment based on journal article and trial report provided by Eli Lilly and Company Limited.

## Study characteristics

The only included trial (EMPHACIS)[39] investigated the use of pemetrexed in combination with cisplatin compared with 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 ≥12 weeks) with histologically confirmed MPM, unidimensionally or bidimensionally measurable disease, not eligible for curative surgery and with a KPS of ≥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), inclusion criteria not met (two), hypertension (one) and death from study disease (one).

Patients in the pemetrexed plus cisplatin group received a median of six treatment cycles (range: 1–12) and those in the cisplatin alone group received a median of four cycles (range: 1–9). In the pemetrexed plus cisplatin group, pemetrexed was given intravenously over 10 minutes at a dose of 500 mg/m$^2$, followed by cisplatin intravenously 30 minutes later at a dose of 75 mg/m$^2$ over 2 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 intravenous dose of cisplatin 30 minutes later at a dose of 75 mg/m$^2$ over 2 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 $B_{12}$ supplementation to therapy. As a result, all subsequent patients in both treatment arms received dietary folic acid (350–1000 μg daily 1–3 weeks before and during study) and vitamin $B_{12}$ (1000-μg intramuscular injection, before treatment and repeated every 9 weeks) supplementation. This resulted in three patient subgroups in the study defined by the patients' supplementation status:

- never supplemented (NS) patients (before the protocol change, $n = 70$ patients)
- partially supplemented (PS) patients (those who commenced treatment before the protocol change and completed treatment after the change, $n = 47$ patients)
- fully supplemented (FS) patients (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 3*.

## 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 years (range: 19–85 years). Over half of the patients had a KPS 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 had prior systemic chemotherapy; however, 12% had received prior radiotherapy.

Patient characteristics are presented in *Table 4*.

## 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 QoL.

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 $B_{12}$ supplementation during the entire course of the study therapy (FS).

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 5*.

### 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, and also 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 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.

### 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, and also 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.

### Tumour response

A responder was defined as any patient who experienced a complete response (CR) (complete

***TABLE 3*** *EMPHACIS trial characteristics*

| Study name | Interventions, drug and dose, no. of patients | Folic acid and vitamin $B_{12}$ supplementation | Study design | Outcomes | Location and centres | Inclusion criteria | Exclusion criteria | Follow-up |
|---|---|---|---|---|---|---|---|---|
| EMPHACIS, 2003[39] | Pemetrexed 500 mg/m$^2$ + cisplatin 75 mg/m$^2$ $n$ = 226<br>Cisplatin 75 mg/m$^2$ $n$ = 222 | *NS*<br>Pemetrexed + cisplatin: 32<br>Cisplatin: 38<br>*PS*<br>Pemetrexed + cisplatin: 26<br>Cisplatin: 21<br>*FS*<br>Pemetrexed + cisplatin: 168<br>Cisplatin: 163 | RCT single-blind | Primary outcome: survival<br>Secondary outcomes: time to progressive disease, time to treatment failure, tumour response rate, duration of response | International, multicentre (20) | Age ≥18 years, 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) |

NSAID, non-steroidal anti-inflammatory drugs.

***TABLE 4*** *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 | 60 | 60 | 60 | 62.5 | 62 | 61 | 59.5 |
| Range | 29–85 | 19–84 | 29–85 | 19–82 | 38–75 | 36–81 | 32–77 | 35–84 |
| Sex | | | | | | | | |
| Male | 184 (81.4%) | 181 (81.5%) | 136 (81.0%) | 134 (82.2%) | 22 (84.6%) | 18 (85.7%) | 26 (81.3%) | 29 (76.3%) |
| Female | 42 (18.6%) | 41 (18.5%) | 32 (19.0%) | 29 (17.8%) | 4 (15.4%) | 3 (14.3%) | 6 (18.8%) | 9 (23.7%) |
| Race | | | | | | | | |
| White | 204 (90.3%) | 206 (92.8%) | 150 (89.3%) | 153 (93.9%) | 23 (88.5%) | 19 (90.5%) | 31 (96.9%) | 34 (89.5%) |
| Other | 22 (9.7%) | 16 (7.2%) | 18 (10.7%) | 10 (6.1%) | 3 (11.5%) | 2 (9.5%) | 1 (3.1%) | 4 (10.5%) |
| Performance status | | | | | | | | |
| 70 | 37 (16.4%) | 31 (14.0%) | 25 (14.9%) | 22 (13.5%) | 3 (11.5%) | 3 (14.3%) | 9 (28.1%) | 6 (15.8%) |
| 80 | 72 (31.9%) | 66 (29.7%) | 58 (34.5%) | 47 (28.8%) | 7 (26.9%) | 7 (33.3%) | 7 (21.9%) | 12 (31.6%) |
| 90/100 | 117 (51.8%) | 125 (56.3%) | 85 (50.6%) | 94 (57.7%) | 16 (61.5%) | 11 (52.4%) | 16 (50.0%) | 20 (52.6%) |
| Histology | | | | | | | | |
| Epi | 154 (68.1%) | 152 (68.5%) | 117 (69.6%) | 113 (69.3%) | 18 (69.2%) | 14 (66.7%) | 19 (59.4%) | 25 (65.8%) |
| Sar | 18 (8.0%) | 25 (11.3%) | 14 (8.3%) | 17 (10.4%) | 2 (7.7%) | 3 (14.3%) | 2 (6.3%) | 5 (13.2%) |
| Mix | 37 (16.4%) | 36 (16.2%) | 25 (14.9%) | 25 (15.3%) | 4 (15.4%) | 4 (19.0%) | 8 (25.0%) | 7 (18.4%) |
| Uns | 17 (7.5%) | 9 (4.1%) | 12 (7.1%) | 8 (4.9%) | 2 (7.7%) | 0 (0.0%) | 3 (9.4%) | 1 (2.6%) |
| Stage | | | | | | | | |
| I | 16 (7.1%) | 14 (6.3%) | 15 (8.9%) | 12 (7.4%) | 1 (3.8%) | 0 (0.0%) | 0 (0.0%) | 2 (5.3%) |
| II | 35 (15.6%) | 33 (15.0%) | 27 (16.2%) | 27 (16.8%) | 5 (19.2%) | 2 (9.5%) | 3 (9.4%) | 4 (10.5%) |
| III | 73 (32.4%) | 68 (30.9%) | 51 (30.5%) | 49 (30.4%) | 12 (46.2%) | 9 (42.9%) | 10 (31.3%) | 10 (26.3%) |
| IV | 102 (45.1%) | 107 (48.2%) | 75 (44.6%) | 75 (46.0%) | 8 (30.8%) | 10 (47.6%) | 19 (59.4%) | 22 (57.9%) |

Epi, epithelial; Mix, Mixed cell; Sar, sarcomatoid; Uns, unspecific.

***TABLE 5*** *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 (months) | 12.1<br>95% CI 10.0 to 14.4 | 9.3<br>95% CI 7.8 to 10.7 | 13.3<br>95% CI 11.4 to 14.9 | 10.0<br>95% CI 8.4 to 11.9 | 13.2<br>95% CI 10.9 to 14.8 | 9.4<br>95% CI 8.4 to 11.6 |
| | HR = 0.77<br>Log-rank $p = 0.020$<br>Wilcoxon $p = 0.028$ | | HR = 0.75<br>Log-rank $p = 0.051$<br>Wilcoxon $p = 0.039$ | | HR = 0.71<br>Log-rank $p = 0.022$<br>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 (months) | 5.7<br>95% CI 4.9 to 6.5 | 3.9<br>95% CI 2.8 to 4.4 | 6.1<br>95% CI 5.3 to 7.0 | 3.9<br>95% CI 2.8 to 4.5 | 6.1<br>95% CI 5.4 to 6.7 | 4.3<br>95% CI 3.0 to 4.9 |
| | HR = 0.68<br>Log-rank $p = 0.001$<br>Wilcoxon $p < 0.001$ | | HR = 0.64<br>Log-rank $p = 0.008$<br>Wilcoxon $p < 0.001$ | | HR = 0.70<br>Log-rank $p = 0.003$<br>Wilcoxon $p < 0.001$ | |
| Tumour response rate (%) | 41.3<br>95% CI 34.8 to 48.1 | 16.7<br>95% CI 12.0 to 22.2 | 45.5<br>95% CI 37.8 to 53.4 | 19.6<br>95% CI 13.8 to 26.6 | 45.6<br>95% CI 38.4 to 52.9 | 19.0<br>95% CI 13.6 to 25.4 |
| | Fisher's $p < 0.001$ | | Fisher's $p < 0.001$ | | Fisher's $p < 0.001$ | |

HR, hazard ratio; PD, progressive disease.

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 CR or PR.

No patients experienced a CR. 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 test, $p < 0.001$).

## Toxicity

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria. Results are presented in *Tables 6* and *7*. 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 leucopenia ($n = 40$, 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 $B_{12}$ 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.

RRs calculated from data provided in the published paper and the FDA reports are presented in *Figures 1–4*. For grade 3/4 toxicities when including the entire ITT population, the RRs generally favour the cisplatin arm only (*Figure 1*).

When considering the combination arm only, the RRs indicate that grade 3/4 toxicities are consistently less frequent in the FS subgroup than the NS subgroup, significantly so for febrile neutropenia, infection with grade 3/4 neutropenia, leucocytes, nausea and vomiting (*Figure 2*).

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

***TABLE 6*** *Grade 3/4 toxicities*

| | Pemetrexed + cisplatin ITT ($n$ = 226) | | Cisplatin ITT ($n$ = 222) | | $p^a$ |
|---|---|---|---|---|---|
| | No. of patients | % | No. of patients | % | |
| **Haematological laboratory toxicity** | | | | | |
| Haemoglobin | 11 | 4.8 | 0 | 0 | 0.001 |
| Neutrophils | 63 | 27.9 | 5 | 2.3 | <0.001 |
| Leucocytes | 40 | 17.7 | 2 | 0.9 | <0.001 |
| Platelets | 13 | 5.8 | 0 | 0 | <0.001 |
| **Non-laboratory 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 grade 3/4 neutropenia | 3 | 1.3 | 1 | 0.5 | 0.623 |
| Rash | 3 | 1.3 | 0 | 0 | 0.248 |

[a] The $p$-values were obtained from Fisher's exact test.

***TABLE 7*** *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 |
| Leucocytes | 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 grade 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 |

[a] The $p$-values were obtained from Fisher's exact test for within pemetrexed plus cisplatin arm comparisons for the FS versus PS plus NS subgroups, and for the FS plus PS versus NS subgroups.

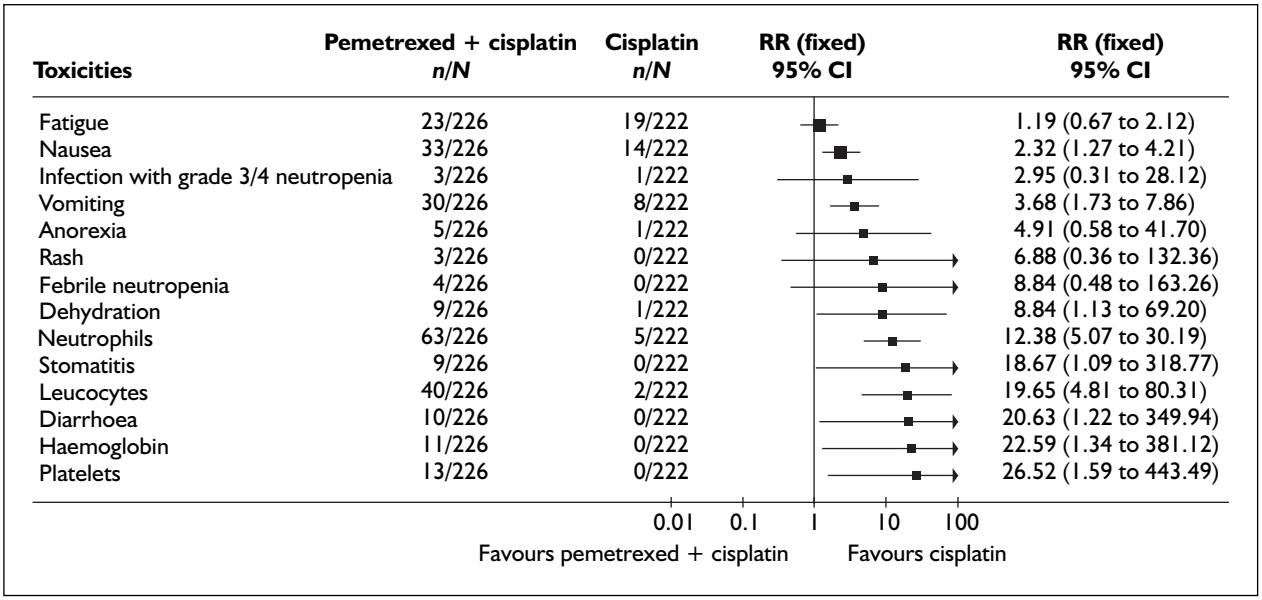


***FIGURE 1*** *RRs of grade 3/4 toxicities for pemetrexed plus cisplatin versus cisplatin*

## Quality of life

The assessment of 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 [health-related quality of life (HRQoL), $p$ = 0.012] and

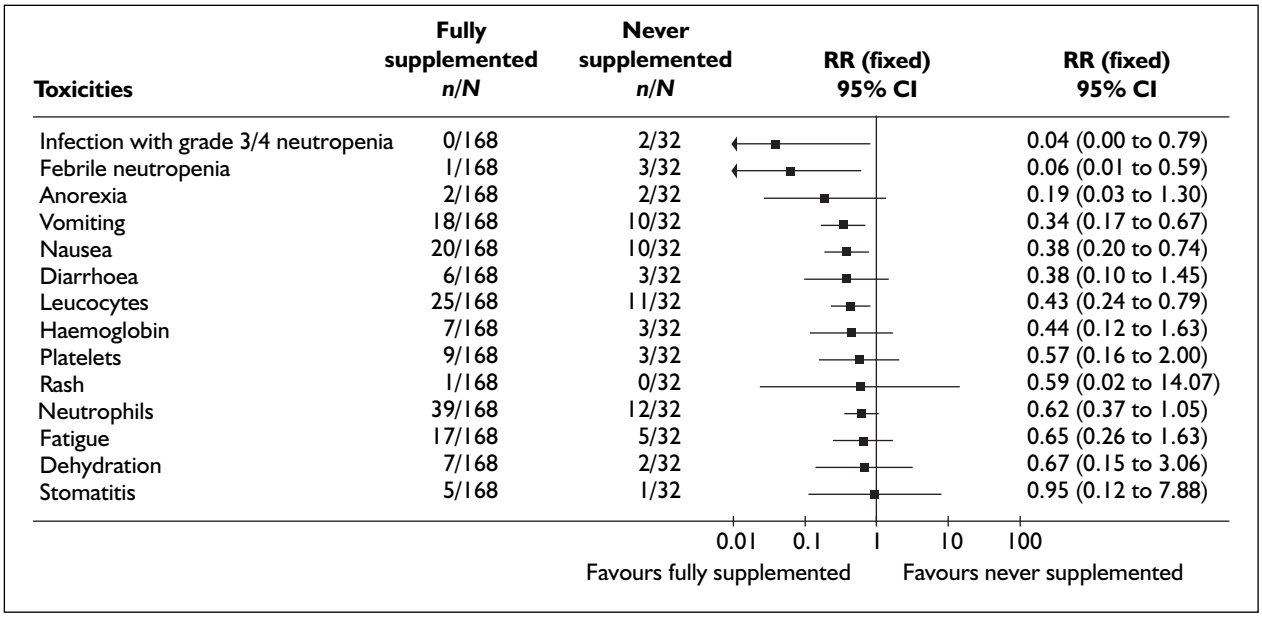


***FIGURE 2*** *RRs of grade 3/4 toxicities for FS versus NS patients treated with pemetrexed plus cisplatin*

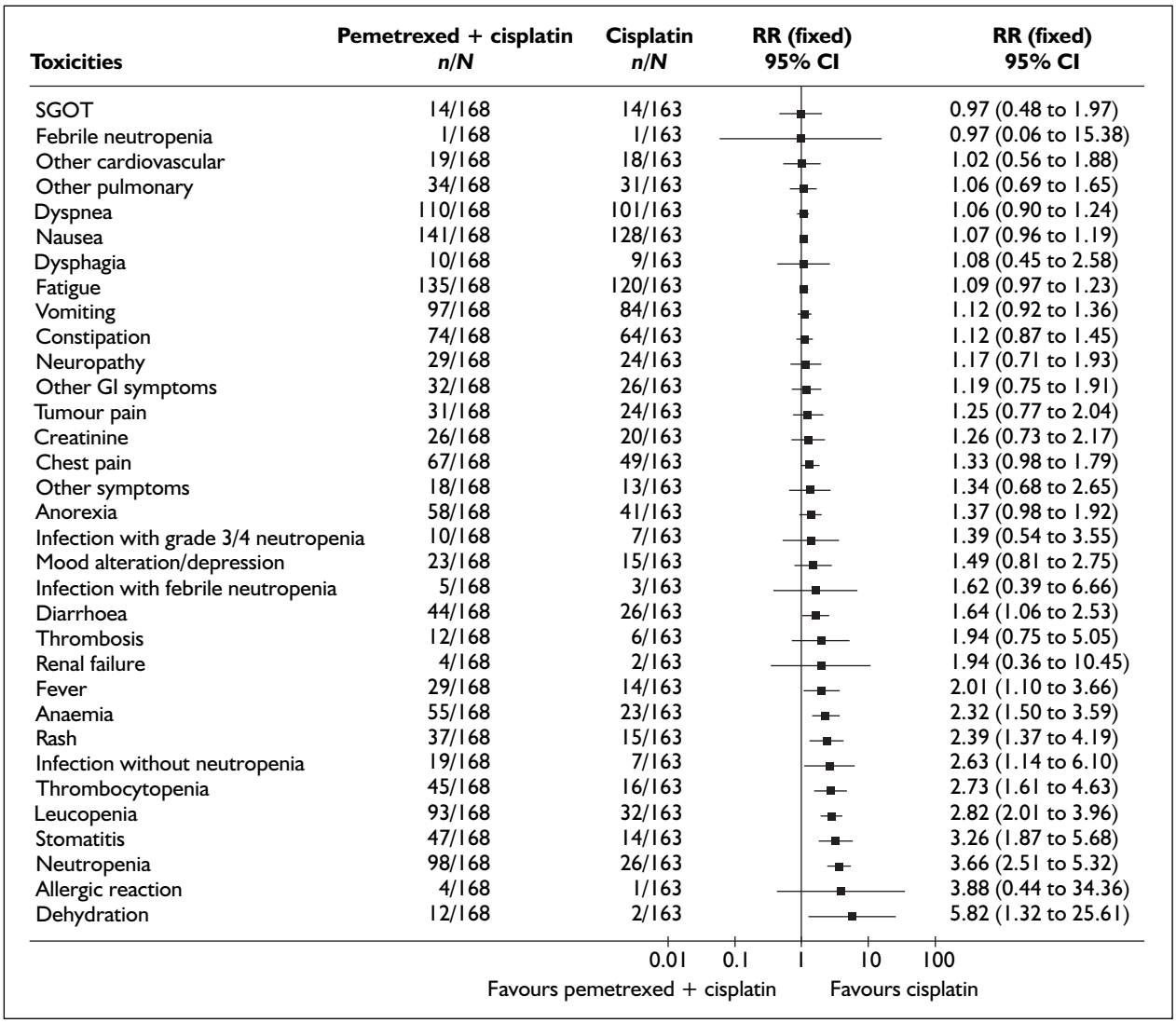


***FIGURE 3*** *RRs of all grade toxicities for FS pemetrexed plus cisplatin versus cisplatin*

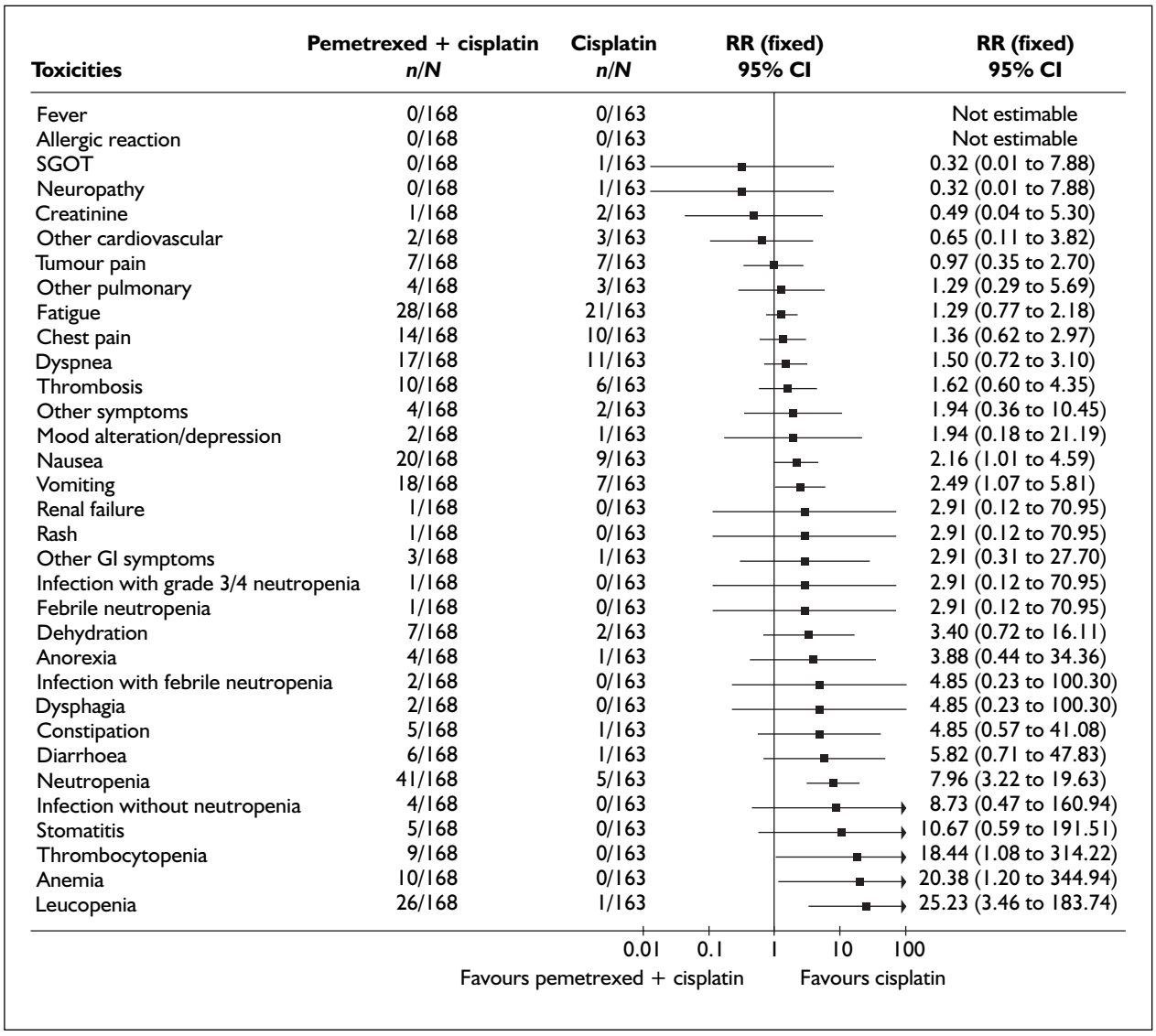


***FIGURE 4*** *RRs of grade 3/4 toxicities for FS pemetrexed plus cisplatin versus cisplatin*

symptom relief (all symptoms, $p < 0.05$) in the group of patients treated with pemetrexed plus cisplatin compared with those treated with cisplatin alone in the ITT population. These results remain significant for the FS population by week 18 ($p = 0.024$).[27]

# Uncontrolled studies of pemetrexed

## 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 MPM and other cancers are briefly described and available data from these studies are provided in this section.

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 8* and *9*).

## Pemetrexed single agent studies

In the Phase II study by Scagliotti and colleagues,[25] 64 chemotherapy-naïve patients were treated with single agent pemetrexed at a dose of 500 mg/m$^2$.

***TABLE 8*** *Non-comparative studies of pemetrexed as single agent for the treatment of mesothelioma*

| Study name | Interventions drug and dose, no. of patients | Study design, *n* | Histology | Inclusion criteria | No. of responders | Response rate (%) | PFS/TTP (months) | Overall median survival (months) | Adverse events, grade 3/4 |
|---|---|---|---|---|---|---|---|---|---|
| Scagliotti, 2003[25] | Pemetrexed 500 mg/m$^2$ D1<br>After each dose, dose adjustments were made depending on platelet and neutrophil nadir counts | Phase II, non-RCT<br>All patients: 64<br>*Supplemented*: 43<br>*Not supplemented*: 21 | Epi: 45 (70.3%)<br>Sar: 8 (12.5%)<br>Mix: 9 (14.1%)<br>Uns: 2 (3.1%) | MPM, no prior CT, life expectancy ≥ 12 weeks, bi/uni-dimensional lesions, KPS ≥ 70 | *Supplemented*:<br>CR 0<br>PR: 7<br>SD: 27<br>*Not supplemented*:<br>CR: 0<br>PR: 2<br>SD: 6<br>*All*:<br>CR: 0<br>PR: 9<br>SD: 33 | *Supplemented*: 16.3 (95% CI 6.8 to 30.7)<br>*Not supplemented*: 9.5 (95% CI 1.2 to 30.4)<br>*All*: 14.1 (95% CI 6.6 to 25.0) | PFS:<br>*Supplemented*: 4.8 (95% CI 4.4 to 6.1)<br>*Not supplemented*: 3.0 (95% CI 1.7 to 5.8)<br>*All*: 4.7 (95% CI 4.2 to 5.8)<br>TTP: 4.4 (95% CI 3.1 to 5.5) | *Supplemented*: 13.0 (95% CI 8.2 to ∞)<br>*Not supplemented*: 8.0 (95% CI 4.8 to 14.5)<br>*All*: 10.7 (95% CI 7.7 to 14.5) | *Supplemented*:<br>Neu: 4 (9.3%)<br>Leu: 4 (9.3%)<br>Thr: 1 (2.3%)<br>*Not supplemented*:<br>Neu: 11 (52.3%)<br>Leu: 8 (38.1%)<br>Thr: 1 (4.8%) |

CR, complete response; CT, chemotherapy; D, day; Epi, epithelial; KPS, Karnofsky performance scale; Leu, Leucocytes; Mix, mixed cell; Neu, neutrophils; PFS, progression-free survival; PR, partial response; Sar, sarcomatoid; SD, stable disease; Thr, thrombocytopenia; TTP, time to progression; Uns, unspecific.

***TABLE 9*** *Non-comparative studies of pemetrexed in combination with other agents*

| Study name | Interventions drug and dose | 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[44] (abstract) | Pemetrexed with vinorelbine<br>Pemetrexed 300–600 mg/m$^2$, vinorelbine 15–30 mg/m$^2$<br>All patients received FA and $B_{12}$ | Phase I, *n* = 24<br>Male: 17<br>Female: 7 | *Tumour type*:<br>Mesothelioma: 4<br>Other: 20 | Age ≥18 years, PStat 0–2, life expectancy 12 weeks | *Mesothelioma patients*:<br>PR: 1/4 | NR | NR | *Not reported separately for mesothelioma patients*<br>Principal toxicity was myelosuppresion with grade 3/4 neutropenia |
| Hughes, 2002[46] | Pemetrexed with carboplatin<br>Pemetrexed given at doses ranging from 400 to 500 mg/m$^2$, followed by carboplatin AUC of 4–6 mg/ml/minute | Phase I, *n* = 27<br>(25 were assessable) | Epi: 16<br>Sar: 2<br>Mix: 5<br>Uns: 4 | MPM, no prior CT, WHO PStat 0–2 | PR: 8/25 (32%) | Median TTP: 10.2 mo<br>SD: 14/25 | 14.8 mo | The primary toxicity was haematological, particularly neutropenia. Other adverse events included nausea, vomiting, diarrhoea, stomatitis and rash |
| Thödtmann, 1999[19] | Pemetrexed with cisplatin<br>Cohort 1 (*n* = 42): both agents given D 1 (pemetrexed 300 mg/m$^2$, cisplatin 60 mg/m$^2$)<br>Cohort 2 (*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*:<br>Mesothelioma: 13<br>Other: 41 | Patients with solid tumours, no prior treatment (platinum-based treatment within 6 months, CT within 3 weeks before entry), WHO PStat ≤2, life expectancy ≥12 weeks | *Mesothelioma patients*:<br>PR: 5/11<br>(2 patients were not assessable for response) | NR | NR | *Not reported separately for mesothelioma patients* |

*continued*

***TABLE 9*** *Non-comparative studies of pemetrexed in combination with other agents (cont'd)*

| Study name | Interventions drug and dose | Study design, *n* | Histology | Inclusion criteria | Response | Time to progression, stable disease | Overall median survival | Adverse events, grade 3/4 |
|---|---|---|---|---|---|---|---|---|
| Adjei, 2000[45] | Pemetrexed with gemcitabine<br>Gemcitabine initially given 1000 and 1250 mg/m$^2$ on D 1 and 8, and pemetrexed given at doses ranging from 200 to 600 mg/m$^2$, after gemcitabine on D 1. Due to excessive neutropenia the remaining 21 patients received pemetrexed on D 8 | Phase I, *n* = 56<br>Group I: 35<br>Group II: 21 | *Tumour type*:<br>Mesothelioma: 3<br>Other: 53 | Age ≥18 years, ECOG PStat ≤2<br>47 pts had prior CT | *Mesothelioma patients*:<br>PR: 1/3 | | | *Not reported separately for mesothelioma patients*<br>(The most common DLT was neutropenia) |
| **Phase II studies** | | | | | | | | |
| Janne, 2005[47] (abstract) | Pemetrexed with gemcitabine<br>Gemcitabine 1250 mg/m$^2$ (over 30 minutes) on D 1 and 8 with Pemetrexed 500 mg/m$^2$ (over 10 minutes) on D 8, immediately before gemcitabine (Cohort 1), or immediately before gemcitabine on D 1 (Cohort 2)<br>All patients received FA and $B_{12}$ | Phase II, non-RCT, *n* = 96<br>Cohort 1: 53<br>Cohort 2: 43<br>*No. evaluated for response*:<br>Cohort 1: 49<br>Cohort 2: 30 | *Cohort 1*:<br>Epi: 67.9%<br>Mix: 13.2%<br>Sar: 5.7%<br>Uns: 13.2%<br>*Cohort 2*:<br>Epi: 58.1%<br>Mix: 4.7%<br>Sar: 16.3%<br>Uns: 20.9% | NR<br>(Study includes chemo-naïve MPM patients, implied by title) | *Cohort 1*:<br>CR: 0%<br>PR 12 (24.5%)<br>ORR: 24.5% (95% CI 13 to 39%)<br>*Cohort 2*:<br>CR: 0%<br>PR: 3 (10.0%)<br>ORR: 10.0% (95% CI 2 to 27%) | *Cohort 1*:<br>SD: 26 (53.1%)<br>PD: 11 (22.4%)<br>DCR: 78%<br>TTP (mo, 95% CI): 4.17 (3.35 to 5.39)<br>*Cohort 2*:<br>SD: 20 (66.7%)<br>PD: 7 (23.3%)<br>DCR: 77%<br>TTP (mo, 95% CI): 7.56 (2.63 to –) | NR | *Cohort 1*:<br>Neu: 43.4%<br>Anaemia: 3.8%<br>Feb neu: 7.5%<br>Thr: 11.3%<br>Dyspnea: 20.8%<br>Fatigue: 15.1%<br>Nausea: 5.7%<br>*Cohort 2*:<br>Neu: 47.6%<br>Anaemia: 0%<br>Feb neu: 9.5%<br>Thr: 2.4%<br>Dyspnea: 7.1%<br>Fatigue: 14.3%<br>Nausea: 2.4% |

*continued*

***TABLE 9*** *Non-comparative studies of pemetrexed in combination with other agents (cont'd)*

| Study name | Interventions drug and dose | Study design, *n* | Histology | Inclusion criteria | Response | Time to progression, stable disease | Overall median survival | Adverse events, grade 3/4 |
|---|---|---|---|---|---|---|---|---|
| Ceresoli, 2005[48] (abstract) | Pemetrexed with carboplatin<br>Pemetrexed 500 mg/m$^2$ on D 1, followed by carboplatin AUC 5 mg/ml *x* min. Treatment repeated every 21 D (max. of 6 cycles)<br>All patients received FA and $B_{12}$ | Phase II, non-RCT, *n* = 102<br>Male: 76 (75%)<br>Female: 26 (25%)<br>(data reported for 92 patients evaluable for response, toxicity and survival) | Epi: 80 (78%)<br>Sar: 7 (7%)<br>Mix: 8 (8%)<br>Uns: 7 (7%) | Age ≥18 years, MPM, no prior CT, ECOG PStat ≤2, life expectancy ≥12 weeks | *Major response (2 CR and 17 PR)*<br>CR + PR: 19 (21%)<br>(95% CI 13 to 30%) | Median TTP: 6 (range: 0.3–14.8 mo)<br>PD: 31 (33%)<br>(95% CI 24–44%)<br>SD: 42 (46%)<br>(95% CI 35 to 56%) | NR | Neu: 17 (18%)<br>Thr: 6 (6%)<br>Anaemia: 12 (13%)<br>Feb neut: 1 (1%)<br>Nau/vom: 0%<br>Diarrhoea: 3 (3%)<br>Stomatitis: 0% |

AUC, area under the curve; CR, complete response; CT, chemotherapy; D, day; DCR, disease control rate; DLT, drug-limiting toxicity; Epi, epithelial; FA, folic acid; Feb neu, febrile neutropenia; Leu, Leucocytes; Mix, mixed cell; Nau/vom, nausea/vomiting; Neu, neutrophils; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PR, partial response; PStat, Performance status; Sar, sarcomatoid; SD, stable disease; Thr, thrombocytopenia; TTP, time to progression; Uns, unspecific.

Of these, 43 patients were supplemented with folic acid and vitamin $B_{12}$ 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 $B_{12}$-supplemented group experienced a lower incidence of grade 3/4 haematological toxicities (neutropenia, leucopenia and thrombocytopenia) compared with the non-supplemented group.

## Pemetrexed combination studies

### *Phase I studies*

Four Phase I studies[19,44–46] with 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]) included solely 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 (NSCLC), head and neck tumours and colorectal cancer].

Milward and colleagues[44] reported the use of pemetrexed (300–600 mg/m$^2$) combined with vinorelbine (15–30 mg/m$^2$) in 24 patients with advanced cancer (including four with mesothelioma). All patients received folic acid and vitamin $B_{12}$. A PR was observed in four patients, including one 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 MPM were treated with pemetrexed (400–500 mg/m$^2$) combined with carboplatin, without folic acid or vitamin $B_{12}$ supplementation. The maximum tolerated dose for pemetrexed was 500 mg/m$^2$. Eight out of 25 assessable patients (32%) experienced PRs. The median time to progression was 10.2 months (305 days) and the median survival time was 14.8 months (451 days). The main dose-limiting toxicity was haematological, particularly neutropenia.

Thödtmann 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. The study results showed that the 21-day cycle with both drugs given on day one was well tolerated and clinically active. Five out of 11 evaluable patients with MPM experienced a PR, 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 combination treatment with pemetrexed and gemcitabine in 56 patients with solid tumours (only three patients had mesothelioma). Forty-seven patients had prior chemotherapy. It was not reported, however, whether these included patients with mesothelioma. Pemetrexed was given at doses ranging from 200 to 600 mg/m$^2$, after gemcitabine on day one. PR 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 MPM 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 $B_{12}$ and dexamethasone. PR 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 at the 2005 American Society of Clinical Oncology meeting by Ceresoli and colleagues[48]) included 102 chemotherapy-naïve patients, and explored the efficacy and safety of the combination of pemetrexed given at 500 mg/m$^2$ followed by

carboplatin (AUC 5 mg/ml every minute). All patients received folic acid and vitamin $B_{12}$ 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%). The 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.

## Discussion

Historically, the treatment of MPM 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 with cisplatin alone. There is no comparison of any form of chemotherapy for mesothelioma with ASC/BSC 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 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 an 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 ASC with or without chemotherapy) involving 420 patients with MPM.[28]

The data on the less toxic analogue carboplatin are less extensive than those on 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 PRs 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 Thödtmann 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 NSCLC.[49] The two large Phase II studies[47,48] in mesothelioma were with pemetrexed in combination with gemcitabine and carboplatin, respectively, in FS 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 leucopenia, neutropenia and diarrhoea, was found to be greatly improved by the addition of vitamin $B_{12}$ and folic acid. It is clear that FS 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]

About 52% 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, complicate the assessment of response, which is usually based on computed tomography scan measurement. Hence claims of response rates and time to progression have to be interpreted with caution.

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

QoL scores demonstrated significantly greater improvement for pain and dyspnoea in the combination group compared with the cisplatin group.[27,40]

Reported response rates in the experimental arm in the study by Vogelzang and colleagues[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.

## Conclusions

The data from one RCT show that 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 $B_{12}$ 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 both sequential and 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 QoL data to inform subsequent economic evaluations better.

# Chapter 5

# Results: review of the economic literature

## Introduction

This chapter explores the published literature on the costs and benefits of pemetrexed in combination with cisplatin for the management of MPM. It begins by discussing the economic impact of pemetrexed plus cisplatin therapy and looks at the costs and health outcomes of MPM within the framework of an economic evaluation. It then goes on to describe the results of a literature search on the economics of pemetrexed in combination with cisplatin for MPM.

## 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, and may in fact be improved compared with cisplatin alone.[40,53]

Pemetrexed plus cisplatin therapy involves a substantial additional cost compared with cisplatin alone, as the price of pemetrexed is approximately 20 times that of cisplatin. Hence the economic question is whether the high additional costs of treatment be justified by the modest survival gains and the potential small benefits in terms of QoL.

### Costs of MPM

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

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

### Health outcomes of MPM

In the published literature, health outcomes of interest can be divided into (1) QoL (which is dependent on relief of pain and symptoms together with any adverse events caused by the treatment) and (2) 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 quality-adjusted life-year (QALY) would be constructed and a cost–utility analysis undertaken. However, this is dependent on the availability of reliable QoL data.

## 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 MPM.

### Identification of studies

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

### Characteristics of economic study

The study by Davey and colleagues[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 10*). The study population was that of EMPHACIS trial of pemetrexed combination therapy versus cisplatin monotherapy included in this review (Chapter 4).

**TABLE 10** *Characteristics of economic study* [54]

| | |
|---|---|
| Type of evaluation and synthesis | Cost-effectiveness analysis |
| Interventions | Cisplatin monotherapy versus pemetrexed plus cisplatin |
| Study population | Trial population |
| Country | Australia |
| Period of study | 27 months |

**TABLE 11** *Economic model*[54]

| | |
|---|---|
| Type of model | Unclear |
| Perspective | Australian healthcare system |
| Model assumptions | Unclear |
| Life expectancy method | Survival estimates taken from Kaplain–Meier plot presented in trial |

**TABLE 12** *Cost data and data sources*[54]

| | | | |
|---|---|---|---|
| Currency and currency year | Australian $ (A$), year not stated | | |
| Discount rate | Not stated | | |
| Cost items | | *Pemetrexed plus cisplatin (A$)* | *Cisplatin (A$)* |
| | Study drug use | 14,553 (4.7 cycles) | 418 (4 cycles) |
| | Serious adverse events | 531 | 56 |
| | Treatment-emergent side-effects | 47 | 18 |
| | Supportive medications | 25 | 23 |
| | Post-study chemotherapy | 1,307 | 1,915 |
| | Total | 16,463 | 2,431 |
| Sources of costs items | Resource use taken from trial and costed accordingly using Australian prices | | |

A personal communication (Davey P, M-TAG, Australia: personal communication, 26 August 2005) indicated 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 are given in Chapter 6.

## 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 RCT. The perspective adopted was that of the Australian NHS (*Table 11*).

## 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 12*). No mention of discounting was made, although from personal communication with the authors (Cordony A, M-TAG, Australia: personal communication, 21 November 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.

***TABLE 13*** *Health outcome data and data sources*[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 personal 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 the presentation, but through personal communication it was found to be the discounted value.

***TABLE 14*** *Cost-effectiveness results*[54]

| | |
|---|---|
| Mean ICER (median) | A$73,470 (A$60,226) |
| Subgroup analysis | None undertaken |
| Sensitivity analysis | None presented |
| Author conclusions | The ICER is acceptable for the small population of MPM patients in Australia |
| Author funding | Eli Lilly Australia |

## Health outcome data and data sources

Health outcome was assessed on the basis of life-years saved, which were derived from trial estimates of survival, which may be underestimated as some people are alive at the end of the trial (*Table 13*).

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 (Cordony A, M-TAG, Australia: personal communication, 21 November 2005) it became apparent that the life-years saved were reported in the undiscounted format whereas 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 cost-effectiveness 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 13* for reference.

## Cost-effectiveness results

The mean and median incremental cost-effectiveness ratios (ICERs) were estimated at A$73,470 and A$60,226 per life-year saved, respectively (*Table 14*). No subgroup analysis was undertaken, nor was any sensitivity analysis presented. The authors concluded that the ICERs 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]

## 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] (*Table 15*). 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, whereas the incremental life-years saved were presented in a discounted form. However, this presentation error did not impact the ICERs. Nevertheless, the discounted survival rates should have been presented for consistency.

***TABLE 15*** *Critical appraisal of economic evaluation*

| Checklist item[38] | Davey *et al.*[54] |
|---|---|
| 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. The 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 both a disaggregated and an 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.

## 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 Davey and colleagues.[54] We were unable to assess the model assumptions or the validity of the accompanying conclusions due to insufficient information provided.

# Chapter 6

# Critical review of economic submission

## 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 ASC.

## Model 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 FS 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 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; 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); and 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 healthcare provider (see *Table 16* 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. Premedication 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 are discounted at 3.5% (see *Table 17* for a summary of outcomes).

***TABLE 16*** *Summary of costs in Model 1*

| | Value (£) | Reference |
|---|---|---|
| Pemetrexed 500 mg | 800 | MIMS, May 2005 |
| Pemetrexed 100 mg | 160 | Lilly attestation letter |
| Cisplatin 100 mg | 55.64 | MIMS, May 2005 |
| Cisplatin 50 mg | 28.11 | MIMS, May 2005 |
| Inpatient administration | 876.00 | NHS reference costs, 2004 |
| Outpatient administration | 266.00 | NHS reference costs, 2004 |
| Total incremental costs: | | |
| FS population | 8839 | Calculation |
| FS population with advanced disease | 8779 | Calculation |
| FS population with good performance | 9019 | Calculation |
| FS population with good performance and advanced disease | 8920 | Calculation |

MIMS, *Monthly Index of Medical Specialities*.

***TABLE 17*** *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 and advanced disease | 0.285 | K–M survival curves |
| Base-case utility cisplatin | 0.688 | ACTION |
| Base-case 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 and advanced disease | 0.188 | Calculation |

K–M, Kaplan–Meier.

***TABLE 18*** *Summary of results for 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 |

LYG, life-year gained.

Life-years gained were estimated using Kaplan–Meier 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 patients using EQ-5D and EQ-VAS instruments 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 for Model 1 indicate that the technology is not cost-effective at the conventional £30,000 per QALY, with mean incremental cost per QALY ranging from £47,567 to £68,598 for the different subgroups explored (*Table 18*). The best cost-effectiveness results relate to FS patients with both advanced disease and good performance status (0/1).

One-way and two-way sensitivity analyses were undertaken on several variables, including drug costs, administration costs, hospitalisation costs, post-study chemotherapy, discount rate, mean survival outcomes and utility estimates (see *Table 19* for a summary of sensitivity analysis for the FS population). Results for the one-way sensitivity analysis for the FS population ranged from £41,681 to £202,719 per QALY and those for the two-way sensitivity analysis ranged from £33,691 to £237,931 per QALY. Results for other subgroups were comparable although slightly improved because for the remaining subgroups survival is expected to be greater (*Table 17*).

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.

## Critical assessment

Using a standard checklist,[56] the economic submission for Model 1 was quality assessed (*Table 20*). 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

***TABLE 19*** *Sensitivity analyses performed in Model 1*

| Type of sensitivity analysis | Univariate sensitivity analyses | | | Two-way sensitivity analyses |
|---|---|---|---|---|
| | **Parameter** | **Range varied** | **Cost per QALY (FS population) (£)[a]** | |
| Parameters varied | Drug costs | ±5, 10, 20% | 55,948–81,239 | Survival estimates ±1.5 months versus drug costs ±20% cost/QALY £33,691–237,931 |
| | 100-mg vial | Introduction of 100-mg 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 cost–utility 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% |

[a] Base-case £68,599.

***TABLE 20*** *Quality assessment of submitted economic Model 1*

| Checklist item | 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 programme's 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 |

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 healthcare 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 differ greatly between treatment arms. Utility values were taken from an 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 from *Table 17*, 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, because all costs were incurred within the first year. Results were expressed in terms of ICERs 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 $B_{12}$, attributing erroneous patient numbers in the calculation of treatment rates per cycle. However, this only had a minor effect on the 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 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.

## 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 an NSCLC population. This should not affect the analysis if it can be assumed that utility values for MPM patients will be similar to those for NSCLC patients.
- Some additional costs occurring in an outpatient 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 due 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.

## 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 with 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, or 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 or 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.

# Chapter 7

# Economic evaluation of pemetrexed for treatment of malignant pleural mesothelioma

## Part A: economic evaluation completed for appraisal report

### Decision problem

This chapter attempts to assess the cost-effectiveness of pemetrexed in combination with cisplatin for the treatment of unresectable MPM in chemotherapy-naïve patients. Due to limitations in data, only one comparator, cisplatin, was available with credible data from an RCT 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 healthcare 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.

### Model selection and adaptation

#### *Data requested and received*

At the outset it was clear to the assessment team that their ability to carry out a thorough and independent assessment of the economic case for use of pemetrexed in treating MPM would be dependent on 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, the only route to understanding the factors influencing effectiveness and cost-effectiveness of this novel therapy was believed to be full access to the anonymised clinical trial data at the IPD level. This was requested from the representatives of Eli Lilly and Company Limited at the NICE Consultee Information meeting held on 15 June 2005, and an assurance was given that the company wished to assist us in this respect.

Subsequently, but prior to the formal date for receipt of submissions, early access to these data was again requested to allow us to start the complex process of analysing the IPD to expedite the review process, but a negative response was received indicating that IPD would be supplied along with the submission and associated economic models. As an alternative route to accelerating the process, the FDA in the USA was approached for access to the clinical dataset submitted to them as part of the US regulatory approval process. However, the response indicated that this would require a formal application from a UK government department and it 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 team. 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 they 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, the Clinical Study Report (CSR) of the EMPHACIS trial dated 10 October 2002 was examined,[39] and 16 charts of survival analyses shown in the report providing valuable information to the team were identified. Copies were requested of the full text report relating to these charts, which are produced by default when such charts are generated by the SAS LIFETEST function. This same request was submitted three times to the company between July and August 2005, and a restricted aggregated summary of the information requested in respect of just three of the requested analyses was finally received.

#### *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

***TABLE 21*** *Equations representing Model 1*

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 QALYs gained = $Q_{pc} - Q_c$

where:

$Q_{pc}$ = mean survival time × mean EQ-5D score, with pemetrexed plus cisplatin therapy

$Q_c$ = mean survival time × mean EQ-5D score, with cisplatin monotherapy

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 preprocessed 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.

## Economic modelling

### *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 the 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 with 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.

The Model 1 structure was reformulated in the form of the simple equations shown in *Table 21* in order to carry out exploration of economic performance, drawing on the resource/cost IPD incorporated in the submitted Model 1.

The 'base case' considered in this section relates only to 'fully supplemented' patients (and specific subgroups thereof) within the EMPHACIS 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.

### *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 expected 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 are not complete and do 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, independent estimates of mean survival were developed 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 there were two sources of information:

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

Although the aggregated data did not allow specific timings to be assigned to each event, the notional times were able to be assigned within each month and approximate Kaplan–Meier analysis could be carried out for the three populations. The results are given in the left-most block of *Table 22*, and show that the Kaplan–Meier 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, Weibull model parameters were estimated by maximum likelihood estimation (MLE), and the expected mean survival calculated for each of the three populations (ITT, FS, FS/AD). The results are displayed in the third block of *Table 22*. Comparison with the corresponding Kaplan–Meier results demonstrates:

- the extent to which the Kaplan–Meier method estimated means underrepresent true survival
- 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, so a different approach had to be adopted, based on the CSR Kaplan–Meier charts. This involved digitising the chart images as closely as possible, to provide approximations to the survival patterns in the trial. By calculating the total AUC, estimates were obtained which should correspond fairly closely to the Kaplan–Meier mean estimates generated from the aggregate data for three populations. Comparing results in the first and second blocks in *Table 22* confirms this expectation.

Establishing parameters for a Weibull model from the digitised Kaplan–Meier plots proved more problematic, since there was little information on which to judge how to weight the multiple observations underlying each point on a Kaplan–Meier plot. To address this problem, point-wise standard errors were used from the approximate Kaplan–Meier analyses (i.e. from the first block of *Table 22*) and polynomial functions of time were fitted to each population arm so that interpolated estimates of point standard errors could be obtained for every point of the digitised Kaplan–Meier 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, the FS polynomial functions were used to provide proxy weights. The results are shown in the final block of *Table 22* and graphically the fit between observational data and fitted models is shown in *Figures 5–8*. There is good correspondence between MLE estimates of mean expected survival

***TABLE 22*** *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 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Kaplan–Meier | | | | 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 | – | – | – |
| FS | | | | | | | | | | | | | | |
| 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 | – | – | – |
| FS Stage III/IV | | | | | | | | | | | | | | |
| Mean | 13.02 | 10.25 | +2.73 | 23.5 | – | – | – | – | 14.43 | 10.28 | +4.15 | 13.59 | 10.00 | +3.59 |
| LCL | 11.60 | 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 | – | – | – | – | – | 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 | – | – | – |
| FS PS 0/1 | | | | | | | | | | | | | | |
| Mean | – | – | – | – | 13.99 | 12.21 | +1.78 | 23.2 | – | – | – | 16.53 | 12.99 | +3.55 |
| LCL | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| UCL | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Median | – | – | – | – | 14.49 | 10.46 | +4.03 | – | – | – | – | – | – | – |
| FS Stage III/IV and PS 0/1 | | | | | | | | | | | | | | |
| Mean | – | – | – | – | 13.30 | 10.25 | +3.04 | 23.7 | – | – | – | 15.47 | 10.34 | +5.12 |
| LCL | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| UCL | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Median | – | – | – | – | 13.90 | 8.95 | +4.95 | – | – | – | – | – | – | – |

C, cisplatin monotherapy; LCL, lower confidence interval; LS, least squares; P/C, pemetrexed and cisplatin combination therapy; UCL, upper confidence interval.

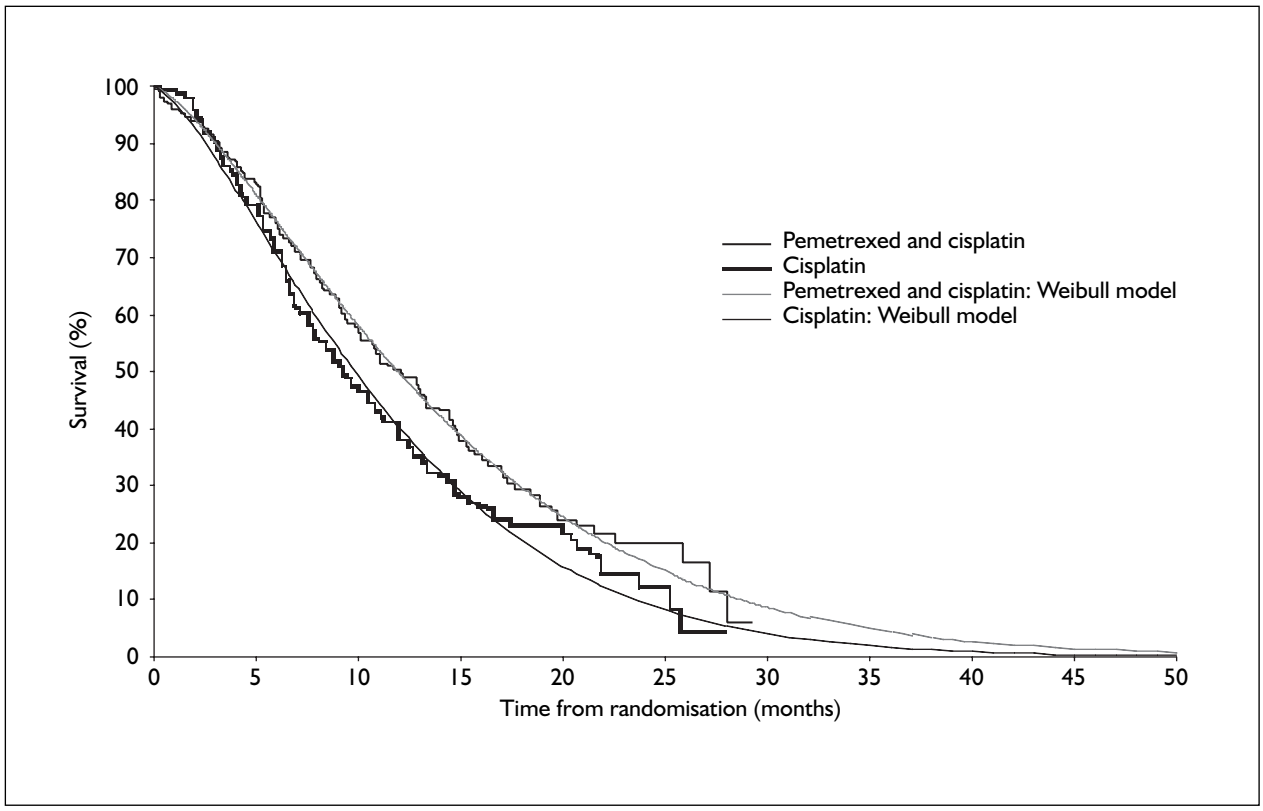


***FIGURE 5*** *Survival from randomisation: ITT population*

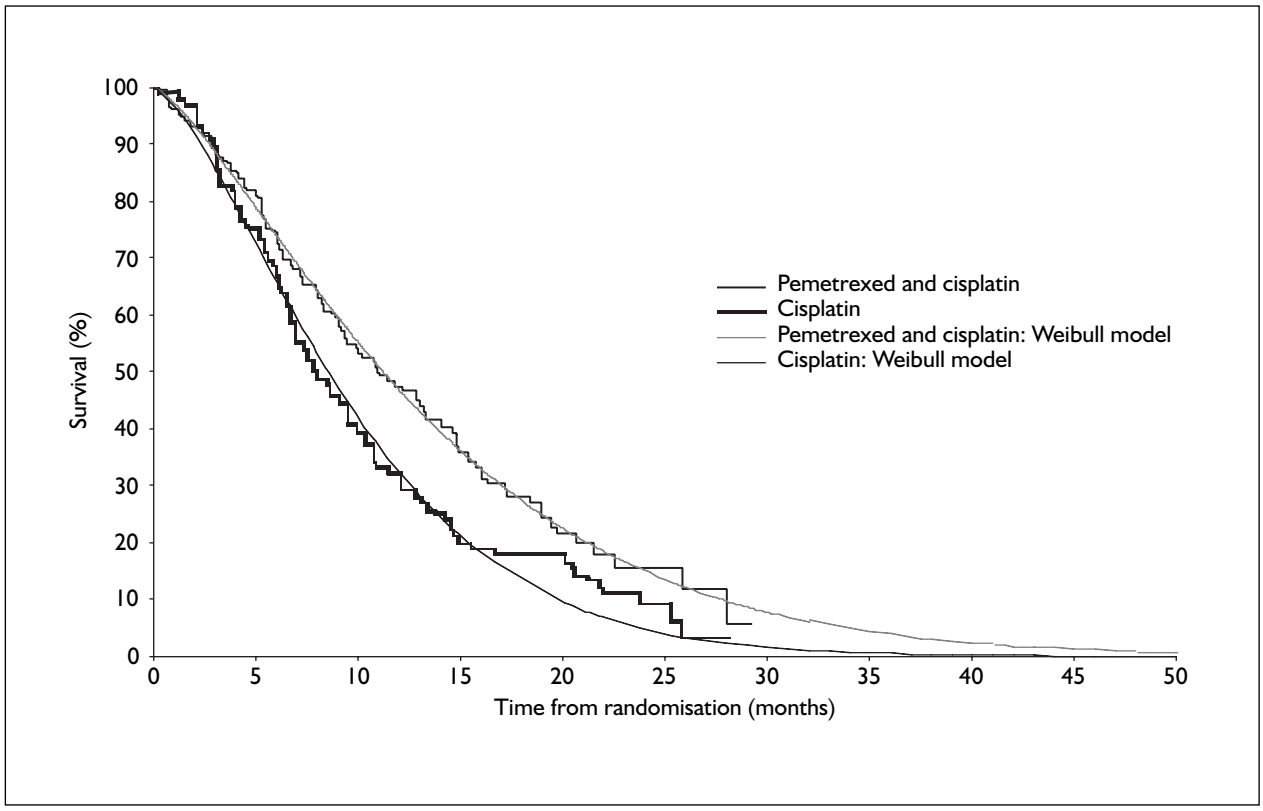


***FIGURE 6*** *Survival from randomisation: fully supplemented with advanced disease (FS/AD) population*

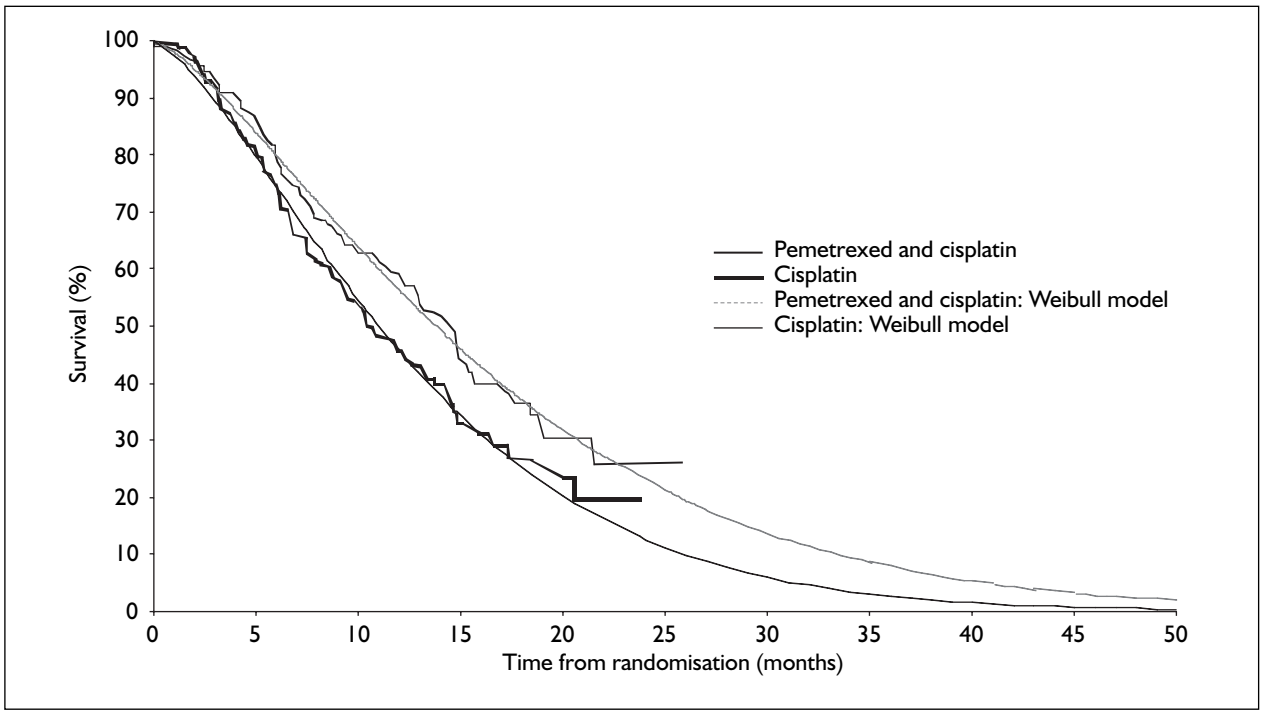


***FIGURE 7*** *Survival from randomisation: fully supplemented with performance status 0 or 1 (FS/PS 0/1) population*

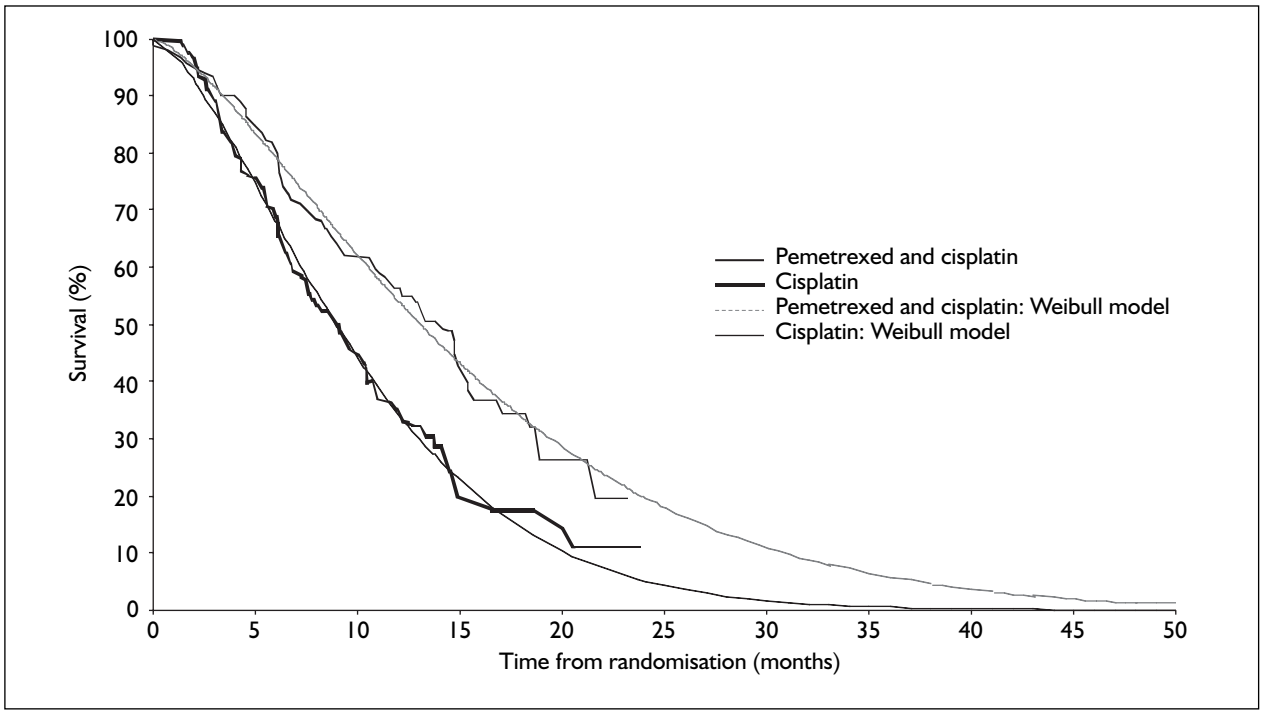


***FIGURE 8*** *Survival from randomisation: fully supplemented with advanced disease and performance status 0 or 1 (FS/AD and PS 0/1) population*

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 block of *Table 23* approximate CIs have been derived by reference

***TABLE 23*** *Estimates of mean survival gains and health-related utility gains per patient*

| | Life-months | | | | | | QALYs | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 |
| FS | | | | | | | | | | | | |
| 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 |
| FS 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 |
| FS PS 0/1 | | | | | | | | | | | | |
| 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 |
| FS Stage III/IV and PS 0/1 | | | | | | | | | | | | |
| 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 |

Abbreviations as in *Table 22*.

to the distribution of mean survival estimated by the MLE method. *Table 23* also shows the effect of discounting estimated survival and survival gains at the standard rate of 3.5% per annum.

#### *Health-related quality of life*

In order to obtain values for utility gains ascribable to the use of pemetrexed, it is necessary to multiply estimates of mean survival time by a mean HRQoL score. In Model 1, Eli Lilly employed the findings of a survey of patients suffering from NSCLC, weighting EuroQoL EQ-5D results by the performance status of patients in the two arms on the EMPHACIS trial. Although 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 QoL affecting those patients approaching death. Multiple observations by van den Hout and colleagues[57] of QoL 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 QoL from a previously stable level. Parametric modelling of van den Hout and colleagues' 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 QoL values appropriate to each population arm in the range 0.51–0.54. The right-hand columns of *Table 23* show the results of applying these values to the previously described survival estimates, and provide the incremental utility estimates ($Q_{pc} - Q_c$) employed in the model.

#### *Resource use and costs*

Unit costs in Model 1 are drawn from the 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 the reformulation. *Table 24* shows the parameter values used to calibrate the 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, as in the absence of IPD data these distributions suitably represent the distribution of the mean of each variable.

## Economic model findings

#### *Base-case cost-effectiveness results*

*Table 25* displays central estimates of cost-effectiveness (incremental cost per life-year gained and per QALY gained), comparing the results obtained with the amended model with those included within the company submission.

In almost all cases the 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 the lower assessed utility values throughout patients' remaining lifetimes. Relative to indicative 'value for money' thresholds (£30,000–40,000 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 PS 0/1) now falls below the £40,000 per QALY gained level.

#### *Alternative analysis*

*Table 26* 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.

#### *Sensitivity analysis*

The limited access to selected IPD granted to the assessment team does not allow a comprehensive probabilistic sensitivity analysis (PSA) to be carried out on either the submitted Model 1 or the modified version. In particular, the team were unable to explore the nature of covariance among the various model variables, especially those involving survival data. As a consequence, the team 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 costs, administration costs, 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

***TABLE 24*** *Resource use and unit cost uncertainty distributions and parameter estimates*

| Topic | Item | Treatment | Distribution | Population | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | FS | | FS/AD | | FS/PS 0/1 | | FS/AD and PS 0/1 | |
| | | | Normal Beta | Mean Alpha | SE Beta | Mean Alpha | SE Beta | Mean Alpha | SE Beta | Mean Alpha | SE Beta |
| AE hospitalisations | Events per cycle | P/C | Beta | 63 | 761 | 52 | 532 | 44 | 673 | 33 | 463 |
| | Cost per event | C | Beta | 27 | 623 | 15 | 447 | 24 | 555 | 13` | 389 |
| | | P/C and 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 | % inpatient 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 | 103 | 51 | 74 | 58 | 85 | 46 | 58 |
| | Cost per event | C | Beta | 68 | 95 | 51 | 71 | 60 | 81 | 43 | 60 |
| | | P/C and 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 |

AE, adverse event; C, cisplatin monotherapy; P/C, pemetrexed and cisplatin combination therapy; SE, standard error.

***TABLE 25*** *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 | | | |
| FS | 12,495 | 3,723 | +8,773 | 1.254 | 1.008 | +0.246 | +0.145 | 35,629 | 60,561 |
| FS with AD | 12,211 | 3,448 | +8,763 | 1.115 | 0.827 | +0.288 | +0.179 | 30,444 | 49,051 |
| FS with good performance status (0 or 1) | 12,815 | 3,880 | +8,935 | 1.349 | 1.068 | +0.281 | +0.177 | 31,783 | 50,357 |
| FS with AD and good performance status (0 or 1) | 12,441 | 3,483 | +8,958 | 1.265 | 0.855 | +0.410 | +0.238 | 21,847 | 37,664 |

***TABLE 26*** *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 | | | |
| FS | 11,661 | 3,723 | +7,938 | 1.254 | 1.008 | +0.246 | +0.145 | 32,241 | 54,802 |
| FS with AD | 11,430 | 3,448 | +7,982 | 1.115 | 0.827 | +0.288 | +0.179 | 27,731 | 44,681 |
| FS with good performance status (0 or 1) | 11,983 | 3,880 | +8,103 | 1.349 | 1.068 | +0.281 | +0.177 | 28,825 | 45,671 |
| FS with AD and good performance status (0 or 1) | 11,680 | 3,483 | +8,197 | 1.265 | 0.855 | +0.410 | +0.238 | 19,990 | 34,463 |

***TABLE 27*** *Key results of probabilistic sensitivity analysis for base-case and alternative pemetrexed costs*

| Patient population | 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 (%) | |
| | 50% | 2.5% | 97.5% | £30,000 threshold | £40,000 threshold | 50% | 2.5% | 97.5% | £30,000 threshold | £40,000 threshold |
| FS | 59,118 | 34,284 | 191,242 | 0.7 | 9.2 | 53,304 | 31,048 | 172,800 | 1.6 | 18.2 |
| FS with AD | 48,747 | 31,699 | 109,428 | 1.1 | 21.0 | 44,394 | 28,951 | 99,738 | 4.1 | 33.0 |
| FS with good performance status (0 or 1) | 50,155 | 29,626 | 154,219 | 2.8 | 23.3 | 45,425 | 26,973 | 140,009 | 6.6 | 34.3 |
| FS with AD and good performance status (0 or 1) | 37,451 | 25,526 | 73,365 | 16.4 | 60.1 | 34,287 | 23,410 | 67,201 | 27.9 | 70.9 |

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 27*.

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 (Stage 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 (Stage 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.

### *Other unquantified costs*

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

**Concomitant medications**

In the company submission, Table 20, provided in their 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 inclusion 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 erythropoietin for anaemia, and were costed on the basis of a single dose. However, erythropoietin 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, erythropoietin 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 patient numbers, the difference between trial arms may be larger than is suggested. Without access to full IPD, this issue cannot be resolved.

**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, although it would be unusual if they were not. Once again, failure to allow access to IPD has prevented resolution of this question.

**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 erythropoietin 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 while patients were resident in hospital, or on an outpatient basis, so that it is difficult to assess what additional costs should have been included in the submitted models.

**Community treatment costs**

The evidence of the location of administered drugs during the trial suggests that at least 50% of patients (and probably more) were normally cared for in a community setting, incurring a continuing stream of costs in terms of both 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.

## 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 subpopulation 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.

# Part B: further economic evaluation (prepared in evidence for the NICE Appraisals Committee)

## Introduction

Currently in the UK, there is no accepted standard treatment regimen for MPM. The most commonly used treatment regimens include MVP combination, single agent vinorelbine and supportive care. None of these agents, however, are licensed for the treatment of MPM.

This addendum presents additional material relating to questions regarding comparability between the innovative therapy (pemetrexed combined with cisplatin for the treatment of MPM) and other treatments, and the relevance of the choice of comparator to the assessment of effectiveness and cost-effectiveness in the treatment of MPM.

The issues addressed below are as follows:

- Is cisplatin monotherapy a suitable comparator for pemetrexed + cisplatin in the UK context?
- How well can effectiveness/survival be estimated for chemotherapy regimens commonly used in the UK to treat patients with MPM?
- How well can effectiveness/survival be estimated for active supportive care alone as provided in the UK to treat patients with MPM?
- What conclusions, if any, can be drawn on the cost-effectiveness of pemetrexed + cisplatin compared with other chemotherapy regimens and/or active supportive care?

Prior to dealing directly with these issues, it is appropriate to comment on two important topics. First, background information on survival estimation and trends relating to MPM. Second, to provide a more detailed description and critique of the industry-submitted Model 2 than was included in the main report.

## Survival in malignant mesothelioma

Five retrospective studies have been traced which describe survival experience in unselected patient series covering periods ranging between 1950 and 1985 (*Table 28*). Overall median survival from diagnosis varies between 7 and 12 months, with the median time from symptoms to diagnosis ranging between about 3 and 6 months.

There is no consistency of prognostic factors identified, even among the larger studies. The clear heterogeneity among the studies ensures that no deductions can be drawn in relation to the impact of treatment on survival or of any temporal trends.

However, the large American Surveillance Epidemiology and End Results (SEER) Program database[65] offers the opportunity to look in more detail at trends in survival, by contrasting experience over different time periods. The data in *Table 29* appear to demonstrate clear improvement over time among males, both those under and over 65 years old at diagnosis. However, the position relating to females is less compelling, with a declining trend in older patients and ambiguity among those under 65 years old. It is possible that the smaller number of females in the registries may be significant here. Even if we accept the improving trend among males over 20 years old, there are several potential confounding factors which should prompt caution in interpreting these figures:

- Secular case-mix changes could have a strong influence.

***TABLE 28*** *Early retrospective and registry studies of survival in malignant mesothelioma*

| Study name | Location | Indication | Patients | Period | Histology | Survival | Prognostic factors |
|---|---|---|---|---|---|---|---|
| Adams, 1986[60] | USA | Diffuse MM | 92 | 1950–80 | Epithelial 42, mixed 29, sarcomatous 21 | 12 months<br>5 months<br>3 months<br>(median from diagnosis) | Sex, epithelial |
| Chailleux, 1988[61] | France | Diffuse MM | 167 | 1955–85 | Epithelial 131, mixed 25, sarcomatous 7 | 1-year survival:<br>39% from diagnosis<br>54% from symptoms | Age, laterality, any treatment |
| Tammilehto, 1992[62] | Finland | Histologically confirmed MPM | 65 | 1960–80 | Not stated | 12 months from diagnosis<br>18 months from symptoms<br>(median) | Stage, performance status |
| Ruffie, 1989[63] | Canada | Diffuse MM | 332 | 1965–84 | Not stated | 3.5 months to diagnosis<br>9 months from diagnosis<br>(median) | Stage, platelet count, asbestos exposure |
| Spirtas, 1988[64] | USA<br>(9 States) | Histologically confirmed MPM | 1475 | 1973–84 | Only available for 20% of cases | 7 months<br>(median from diagnosis) | Age, sex, stage, any treatment, location |

MM, malignant mesothelioma.

***TABLE 29*** *5-year survival rates (%) for white SEER patients from time of diagnosis by age and sex*[65]

| Period | <65 years old | | 65+ years old | | All ages | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| 1975–9 | 5.0 | 27.2 | 2.6 | 12.5 | 4.0 | 21.9 |
| 1985–9 | 8.2 | 21.2 | 2.8 | 7.3 | 4.9 | 14.0 |
| 1995–2001 | 10.2 | 35.2 | 4.7 | 4.7 | 6.5 | 17.7 |

***TABLE 30*** *5-year conditional survival rates for white SEER patients by conditional survival period (SEER registries 1975–2001)*[65]

| Conditional survival period (years) | Probability of surviving a further 5 years (%) |
|---|---|
| 1 | 17.1 |
| 3 | 44.7 |
| 5 | 60.7 |
| 10 | 89.1 |

- Case-finding and reporting practices may have changed over time.
- The long-term trajectory of incidence following asbestos exposure may be interacting with variations in the inherent aggressiveness of disease, leading to temporal distortions in survival patterns.
- Changes in clinical practice and the availability of specific treatments may also be influential on survival.

*Table 30* (also from the SEER database[65]) is interesting in demonstrating the heterogeneity of MPM patients, with a small number of very long-term survivors. This is consistent with the need to employ a survival model with variable hazard rate, such as the Weibull model, rather than an exponential model (with constant hazard).

#### *Summary*

Consideration of the limited literature available from Europe and North America does not offer a basis for estimating typical expected survival in MPM, or for identifying an unambiguous set of prognostic indicators for better survival. Long-term time trends in survival may suggest some improvement in life expectancy at diagnosis, at least in men, but cannot rule out that this may be artefactual due to several confounding effects. However, the data do strongly suggest that despite the generally poor prospect, a small number of patients may survive for several years.

## Model 2: description and critique

The second spreadsheet model submitted by the manufacturer of pemetrexed is designed to estimate a set of economic comparisons between pemetrexed + cisplatin and various other chemotherapy regimens thought to be commonly used in the UK. The model is relatively simple in structure, relies on a variety of data sources to furnish parameter estimates and is not designed to allow PSA.

The model considers only the fully supplemented population from the primary trial. The main components of the model are as follows:

- *Survival*: for pemetrexed + cisplatin, the mean survival estimated in Model 1 was used. For other therapies (MVP, vinorelbine-based regimens and supportive care), evidence from various comparative and non-comparative studies was combined to obtain estimates of median survival and these were then translated into an estimated mean survival using a multiplier derived from the primary trial.
- *Pemetrexed + cisplatin costs*: the mean overall cost per patient estimated in Model 1 was used.
- *Drug costs*: each comparator regimen was costed separately based on body surface area, standard dose levels (mg/kg), mean treatments per cycle, mean cycles per course and list prices for the constituent drugs.
- *Administration costs*: these are based on the proportions of patients treated as inpatients or outpatients in the primary trial, multiplied by a corresponding NHS Reference Cost.
- *Serious adverse event/treatment-emergent adverse event costs*: various comparative and non-comparative studies were combined with results of a clinician survey to derive estimated frequencies of each type of event associated with particular regimens. These were then multiplied by NHS Reference Costs for corresponding inpatient episodes.

#### *Summary*

A number of issues and concerns with Model 2 have been identified by the assessment team and are detailed in *Table 31*. The most serious of these relate to the sources used and methods of calculation employed in obtaining estimates of mean survival for the various comparators. Since these values are fundamental to the remainder of the model, the lack of methodological validity and the consequent inherent unreliability of derived economic results led the assessment team to conclude that Model 2 results could not be considered a useful basis for decision-making.

## Cisplatin as comparator for malignant mesothelioma

#### *Cisplatin monotherapy*

Five published studies report information concerning treatment of malignant mesothelioma

***TABLE 31*** *Issues identified concerning the validity and reliability of Model 2*

| Model component | Issue | Present assessment | Impact on results |
|---|---|---|---|
| Survival | 1. Single arms of non-comparative trials were combined without correction for case-mix differences, when estimating comparator survival | 1. Results obtained cannot be considered meaningful, since variations between populations may serious alter estimates | 1. Estimates obtained by this method cannot be meaningfully compared with survival in the P + C arm of the primary trial |
| | 2. Median values from separate trial arms were combined by calculating a weighted average median | 2. This is methodologically unsound and can result in introducing potentially large and unpredictable errors | 2. Estimates obtained by this procedure are fundamentally unreliable |
| | 3. Estimated median survival for comparators is converted to estimated means by a ratio (1.24) obtained from the P + C arm of the primary trial | 3. This ratio varies for each treatment and the completeness of follow-up. The team's survival model implies ratios of 1.189 for P + C and 1.156 for C | 3. P + C survival estimates are not affected, but comparators may have survival overstated by 0.6–0.8 months. This would lead to slightly more favourable ICERs for P + C |
| | 4. Mean survival in the P + C arm is only estimated to 29 months (duration of trial data). Comparators are implicitly subject to the same limit by use of mean:median ratio derived from the P + C arm | 4. The team's survival estimates to end of life give slightly greater survival benefit | 4. Slightly conservative assumption for P + C |
| Pemetrexed + cisplatin costs | AE costs in the primary trial were restricted to those which incurred an inpatient episode. No attempt was made to distinguish treatment-related AEs from other serious events, or to consider costs arising from other AEs requiring ambulatory treatment | It is difficult to be sure that AE costs obtained from the trial (as used in the P + C arm of Model 2) are directly comparable to AE/treatment-emergent costs for comparators estimated in Model 2 | The potential size of any discrepancy in incremental costs is likely to be small, and is unlikely to impact significantly on estimated ICERs |
| Drug costs | Sources for the mean number of cycles of therapy given for each of the comparators are limited and confusing<br>MVP: both of the quoted studies report only a median number of cycles given (3), but not the mean, although this can be deduced to be 4 and <3.5, respectively<br>Vinorelbine: two small studies were used (monotherapy $n = 29$, vinorelbine + oxaliplatin $n = 26$) reporting only median cycles given as 2 and 4, respectively | This is important in driving both the acquisition and administration costs of each comparator.<br>The higher mean cycle values in the model (4.7 MVP, 6.125 vinorelbine, 4.0 vinorelbine ± platinum) are derived from the market research exercise. It is not clear whether these refer to maximum intended cycles of treatment or the actual mean cycles given (after withdrawals for any reason) | If mean cycles are smaller than those 'reported' it could have a large impact on ICERs, particularly for vinorelbine-based regimens |

*continued*

***TABLE 31*** *Issues identified concerning the validity and reliability of Model 2 (cont'd)*

| Model component | Issue | Present assessment | Impact on results |
|---|---|---|---|
| Administration costs | 1. See Drug costs above | 1. See Drug costs above | 1. See Drug costs above |
| | 2. In all the main analyses, it is assumed that 63% of patients required hospitalisation for treatment, in line with the primary trial | 2. This is an unreasonable assumption for vinorelbine-based therapies, since both the cited trials report 100% outpatient administration. The MVP references do not provide information on inpatient or outpatient status | 2. Requiring inpatient administration greatly increases the cost in the comparator arm for vinorelbine-based therapies, and may also do so for MVP. A sensitivity analysis is included assuming 100% outpatient administration, but this should be considered the base case |
| Serious adverse event/ treatment-emergent adverse event costs | 1. AE event frequencies for P + C are obtained from the primary trial and are restricted to events leading to hospitalisation. For comparators UK oncologist survey results are combined with source papers to obtain estimated figures | 1. It is not clear that reported frequencies in source papers, oncologist survey and the primary trial are compatible, either in magnitude (survey figures often much higher and usually in 'round figures') or in being limited only to hospitalisations | 1. Use of the survey data increases the frequencies and thus the associated costs for the comparators and may bias the results in favour of P + C |
| | 2. In both the primary trial and in estimation for comparators, it is not clear how hospitalisations are counted | 2. Frequently more than one serious AE may be reported in relation to the same incident, leading to the likelihood of significant 'double counting' | 2. AE hospitalisation costs generally may be overstated in either or both arms of the analysis |
| | 3. For P + C, AEs which are not associated with hospitalisation are not costed. For comparators, all AEs are assumed to require hospitalisation | 3. There is significant scope for undercosting the P + C arm and overcosting comparators | 3. Important unquantifiable potential for bias |
| Concomitant medications | Costs for concomitant medications are included in the P + C costs, but are excluded from the comparator costs due to lack of evidence | Costs are almost certainly underestimated for P + C, since the calculation appears not to take into account the duration of use, which in a number of cases may extend beyond the initial prescription | Unclear whether the combined effect of undercosting P + C and omission of costs for comparators will bias results in either direction. However, the overall effect is likely to be small |

C, cisplatin; P, pemetrexed.

with cisplatin monotherapy; these are detailed in *Table 32*. All but one are non-comparative Phase I or II studies with very limited patient numbers and response rates varying between 12.5 and 35.7%.

#### *Cisplatin combination therapies*

A further 26 non-comparative studies were found involving 18 different regimens (*Table 33*), involving between 11 and 69 patients, and reporting response rates in the range 6–48% and median survival in the range 6–15 months. The majority of these papers together with other non-cisplatin studies were the subject of a systematic review of Phase II trials published in 2002 by Berghmans and colleagues.[69] They grouped response rates into four classes based on the presence or absence of cisplatin and doxorubicin in the regimen and obtained results from meta-analysis shown in *Table 34*.

The manufacturer's submission provides evidence from market research of current usage of first-line therapies in the UK. This suggests that although the use of cisplatin is very low, there is no evidence of any use of doxorubicin with this group of patients.

#### *Summary*

There is limited evidence of efficacy for any cisplatin chemotherapy regimen for MPM. However, there is meta-analytic evidence suggesting that cisplatin is probably at least as active as other compounds, both as monotherapy and in combination. Since doxorubicin is not currently used at all in the UK and is more expensive than cisplatin, it is reasonable to consider cisplatin monotherapy as a reasonable comparator for pemetrexed + cisplatin, as compared in the primary trial.

### Other comparators: chemotherapy and active supportive care

The manufacturer's submission identified eight published studies as sources for information relating to potential UK comparator regimens for pemetrexed + cisplatin other than that used in the primary trial (cisplatin monotherapy). These are detailed in *Table 35*, and include four relating to chemotherapy and four to supportive care.

#### *MVP survival*

The manufacturers employed a median survival of 6.79 months as a weighted average of reported medians in the two studies (see *Table 31* for methodological problems with this), and derived from this an estimated mean survival of 8.4 months. However, Andreopoulou and colleagues[70] showed that median survival is strongly influenced by performance status with 10 months for PS 0/1 and only 6 months for PS 2/3. Using the PS case-mix in the primary trial, we may infer that a more reasonable median survival to use in Model 2 would be about 9.5 months. This would lead to an estimated mean survival of 11.8 months in Model 2, about 40% greater than that shown as the base case. This alteration alone changes the submitted incremental cost per QALY gained from £21,731 to £47,972.

#### *Vinorelbine survival*

The two studies cited in the manufacturer's submission are both small (29 and 26 patients only) and therefore subject to a large degree of uncertainty in terms of survival estimates. Steele and colleagues[71] reported a median survival of 10.6 months for monotherapy, whereas Fennell and colleagues[72] appeared to report a median of 8.8 months for vinorelbine + oxaliplatin. However, this is probably a misreading of the Fennell paper: examination of the published survival curves yields a median survival of 8.45 months and a mean of 8.9 months (AUC estimate). For Model 2, a strong assumption has been made that all vinorelbine regimens are of equal efficacy (i.e. that addition of other active treatments yields no additional benefit), which must be open to question. Only very small alterations in vinorelbine survival (about 1%) are necessary in Model 2 to increase the incremental cost per QALY gained from the submitted base value to more than £30,000.

#### *Active/best supportive care*

There is an essential difference between the majority of patients currently receiving supportive care, for whom any chemotherapy may not be suitable due to their performance status and life expectancy, and the much smaller numbers who might be suitable for chemotherapy. Not surprisingly, it would be difficult to mount a large-scale randomised trial of such patients on both ethical and human grounds. It is therefore not surprising that the evidence base for survival in patients receiving only supportive care is particularly weak and of questionable relevance to the cost-effectiveness of pemetrexed + cisplatin.

Three of the four studies cited in the manufacturer's submission are non-comparative retrospective case reviews, none of which can be considered to be drawn from equivalent patient populations. The single comparative trial[74] ($n$ = 36) involves patients clearly with much

***TABLE 32*** *Published studies including cisplatin monotherapy*

| Study name | Interventions | Study design, *n* | No. of patients | Tumour type | Overall median survival (months) | Response rate (%) |
|---|---|---|---|---|---|---|
| Van Meerbeeck, 2005[66] | Arm A: cisplatin<br>Arm B: cisplatin plus raltitrexed | Phase III, RCT | 250 (213 with measurable disease) | MPM | Cisplatin: 8.8<br>Raltitrexed: 11.4 | Cisplatin: 13.6<br>Raltitrexed: 23.6 |
| Planting, 1994[67] | High-dose cisplatin | Phase II, non-comparative | 14 | MPM, Stage II | NR | PR: 36 (ITT) |
| Rebattu, 1993[68] | High-dose cisplatin (200 mg/m$^2$) | Phase II, non-comparative | 13 (10 pleural, 3 peritoneal) | MM | 11 | PR: 23 (ITT) |
| Zidar, 1988[20] (SWOG study) | Cisplatin | Phase II, non-comparative | 35 (pleural 32, peritoneal 2, prior CT or RT allowed) | MM | 7.5 (all patients)<br>9 (responders) | PR: 14.3 |
| Mintzer, 1985[21] | Cisplatin | Phase II, non-comparative | 25 (24 evaluated, 7 received prior CT) | MM | 5 | PR: 12.5 |

CT, chemotherapy; MM, malignant mesothelioma; NR; not reported; RT, radiotherapy.

***TABLE 33*** *Published studies of cisplatin-containing combinations*[18,22]

| Study name | Interventions | No. of patients | Response rate (%) | Median survival (months) |
|---|---|---|---|---|
| Chahinian, 1993 | Cisplatin + doxorubicin | 35 | 14 | 8.8 |
| Ardizzoni, 1991 | Cisplatin + doxorubicin | 24 | 25 | 10 |
| Henss, 1988 | Cisplatin + doxorubicin | 19 | 46 | 12.3 |
| Parra, 2001 | Cisplatin + doxorubicin + IFN-α | 35 | 29 | 9.3 |
| Shin, 1995 | Cisplatin + doxorubicin cyclophosphamide | 23 | 26 | 14 |
| Pennucci, 1997 | Cisplatin + doxorubicin + mitomycin | 23 | 21 | 11 |
| Breau, 1991 | Cisplatin + doxorubicin + mitomycin + bleomycin | 25 | 44 | NA |
| Samuels, 1998 | Cisplatin + dihydro-5-azacytidine | 29 | 17 | 6.4 |
| Planting, 1995 | Cisplatin + etoposide | 25 | 24 | NR |
| Eisenhauer, 1988 | Cisplatin + etoposide | 29 | 12 | NA |
| Byrne, 1999 | Cisplatin + gemcitabine | 21 | 47.6 | 10.3 |
| Van Haarst, 2000 | Cisplatin + gemcitabine | 22 | 15 | 10 |
| Nowak, 2002 | Cisplatin + gemcitabine | 53 | 33 | 11.2 |
| Castagneto, 2005 | Cisplatin + gemcitabine | 35 | 26 | 13 |
| Soulie, 1996 | Cisplatin + IFN-α | 26 | 40 | 12 |
| Pass, 1995 | Cisplatin + IFN-α + tamoxifen | 36 | 19 | 8.7 |
| Trandafir, 1997 | Cisplatin + IFN-α | 30 | 27 | 15 |
| Nakano, 1999 | Cisplatin + irinotecan | 15 | 26.7 | 7.1 |
| Chahinian, 1993 | Cisplatin + mitomycin | 35 | 26 | 7.7 |
| Tansan, 1994 | Cisplatin + mitomycin + IFN-α | 20 | 11 | 15 |
| Middleton, 1998 | MVP | 39 | 20 | 6 |
| Metintas, 1999 | Cisplatin + mitomycin + IFN-α | 43 | 23 | 11.5 |
| Thödtman, 1999 | Cisplatin + pemetrexed (Phase I) | 11 | 45 | NA |
| Kaukel, 1990 | Cisplatin + pirarubicin | 39 | 15 | 10.5 |
| Fizazi, 2000 | Cisplatin + paclitaxel | 18 | 6 | 12 |
| Berghmans, 2005 | Cisplatin + epirubicin | 69 | 19 | 13.3 |

IFN, interferon; NA, not applicable; NR, not reported.

***TABLE 34*** *Response rates according to treatment groups*[69]

| Therapy group | No. of responders | No. exposed | Response rate (%) | 95% CI |
|---|---|---|---|---|
| Cisplatin, no doxorubicin | 127 | 547 | 23.2 | 19.7 to 26.8 |
| Doxorubicin, no cisplatin | 24 | 213 | 11.3 | 7.0 to 15.5 |
| Cisplatin + doxorubicin | 43 | 151 | 28.5 | 21.3 to 35.7 |
| Neither | 164 | 1409 | 11.6 | 10.0 to 13.3 |

poorer prospects than those in the primary trial. By combining these studies, the industry submission offers a median survival of 6.7 months and an estimated mean of 8.3 months.

An alternative approach may be offered by a meta-analysis undertaken by Curran and colleagues,[12] designed to consider prognostic factors for survival in MPM. This involved the analysis of patient data from five Phase II trials which failed to show efficacy for candidate compounds. The advantage of this patient group is that they are more likely to represent patients who might normally be considered appropriate for chemotherapy. If this is accepted, then the failure of efficacy suggests that their combined survival experience may be a reasonable proxy for supportive care without active chemotherapy. This study reported an overall median survival of 8.4 months, with a strong trend by performance status (10.7 months for PS 0, and 7.2 months for PS 1 or 2). Substituting this value into Model 2 increases the incremental cost per QALY gained from £32,066 to £48,779, indicating that the cost-effectiveness of pemetrexed + cisplatin relative to supportive care may be subject to very substantial uncertainty.

### *Summary*

The evidence base for estimating survival in other comparators (including supportive care) is too weak to be taken seriously as a basis for

***TABLE 35*** *Published studies of current treatment options in the UK*

| Study name | Data collection | Interventions | Study design, *n* | No. of patients | Tumour type | Overall median survival (months) | Response rate (%) |
|---|---|---|---|---|---|---|---|
| Middleton, 1998[26] | October 1986–June 1997 | MVP | Non-comparative, prospective study | 39 | MM (unclear whether pleural or peritoneal) | 6 (range: 1–16) | PR: 20<br>No complete response |
| Andreopoulou, 2004[70] | October 1986–May 2002 | MVP | Non-comparative, prospective study | 150 | MPM | 7 | 15.3 |
| Steele, 2000[71] | April 1998–January 1999 | Vinorelbine | Phase II, non-comparative open-label study | 29 | MPM | 10.6 | PR: 24 |
| Fennell, 2005[72] | November 2000 (cut-off date) | Vinorelbine and oxaliplatin | Phase II, non-comparative study | 26 | MPM | 8.8 | PR: 23 |
| Aziz, 2002[73] | 1989–98 | BSC | Retrospective study | 191 | MPM | 7 (range: 1–19) | NR |
| Calavrezos, 1988[74] | March 1981–February 1985 | Group A: combined chemotherapy (doxorubicin, vindesine, cyclophosphamide)<br>Group B: supportive care<br>Group C: patients not eligible for treatment (also received supportive care) | Prospective comparative study | Group B: 36<br>Group C: 39 (5 patients received chemotherapy) | MPM | Group B: 7<br>Group C: 5 | NR |
| Chan, 2003[75] | Review of medical records, between 1996 and 2001, Singapore General Hospital | Supportive care (12 patients), chemotherapy (4 patients) | Retrospective chart review | 16 | MPM (13 patients), Peritoneal mesothelioma (3 patients) | 7 | NR |
| Jubelirer, 1997[76] | Review of medical records between 1966 and 1992 | Supportive care only (26 patients)<br>Combination of 3 treatment modalities (24 patients) | Retrospective chart review | 50 | MPM | 4 | NR |

MM, malignant mesothelioma, NR, not reported.

***TABLE 36*** *Conclusions*

| Question | Response |
|---|---|
| Is cisplatin monotherapy a suitable comparator for pemetrexed + cisplatin in the UK context? | Cisplatin appears to be as active a compound as others in the literature, is used very occasionally in the UK and, because it has a low acquisition cost, represents a meaningful test of cost-effectiveness for pemetrexed + cisplatin |
| How well can effectiveness/survival be estimated for chemotherapy regimens commonly used in the UK to treat patients with malignant mesothelioma? | The evidence base for survival for MVP and vinorelbine regimens is very weak, and not based on comparative trials. Great caution should be exercised in the use of these results |
| How well can effectiveness/survival be estimated for ASC alone as provided in the UK to treat patients with malignant mesothelioma? | The direct evidence base for survival with support care only is even weaker. Also, there is a serious problem concerning the legitimacy of supportive care as a comparator for chemotherapy, since the great majority of patients currently receiving supportive care will not be suitable for chemotherapy. Indirect evidence may suggest that survival on supportive care may be rather better than it appears in the cited studies |
| What conclusions, if any, can be drawn on the cost-effectiveness of pemetrexed + cisplatin compared with other chemotherapy regimens and/or ASC? | On the basis of the above, we continue to believe that the results presented from Model 2 should be considered unreliable and potentially misleading. If it is accepted that cisplatin is a reasonable comparator for pemetrexed + cisplatin, then this would appear to be the most appropriate basis for assessing cost-effectiveness |

decision-making. The use to which these results have been put is in some instances misleading or at least open to question, and relatively small variations in estimated survival are likely to lead to substantially increased cost-effectiveness ratios and likely to yield values beyond the normal range of acceptability.

## Conclusions

Returning to the original questions posed, we make the observations set out in *Table 36*.

# Chapter 8

# Budget impact analysis

## Introduction

This chapter deals with the potential cost implications to the NHS of the introduction of pemetrexed + cisplatin for the management of MPM. The cost to the NHS will depend on two factors:

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

Each of these factors is examined in greater detail below.

## Costs of pemetrexed plus cisplatin treatment

### Direct therapy costs

In patients treated for MPM, the recommended dose of pemetrexed is 500 mg/m$^2$ BSA administered as an intravenous infusion over 10 minutes, followed 30 minutes later by cisplatin at a dose of 75 mg/m$^2$ BSA infused over 2 hours, on the first day of each 21-day cycle.[41] The modified version of Model 1 allows incorporation of the experience of trial patients in overall estimates of the costs directly associated with pemetrexed + 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 ASC/BSC, 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 + cisplatin generates a large number of grade 1/2 adverse events, particularly nausea, vomiting, fatigue, constipation, anorexia, stomatitis and 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].[77]

For patients who might otherwise expect to receive an alternative chemotherapy regimen, the estimation of the net additional cost of pemetrexed + 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 + cisplatin. If cisplatin monotherapy is taken as a general guide, the net additional NHS cost per patient may be around £8700.

### 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 + 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 and a community-based palliative care nurse once per month, and that a proportion of patients would need additional supportive services (e.g. domiciliary oxygen), we may conservatively estimate that extra supportive care costs of about £100 per month will be incurred by NHS budgets.

***TABLE 37*** *Estimated NHS budget impact of pemetrexed + cisplatin*

| Population | No. of patients treated p.a. | Pemetrexed acquisition cost (£) | Administration, supplementation and 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/PS 0/1 | 400 | 3,519,000 | 971,000 | 28,000 | 142,000 | 4,660,000 |
| FS/AD and PS 0/1 | 300 | 2,522,100 | 718,200 | 21,000 | 153,600 | 3,414,900 |

SAE, serious adverse event.

## Eligible population

Currently, approximately 1700 people are diagnosed with 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 + 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 subpopulations.

### Cost estimates

With this proviso, we present in *Table 37* estimated costs making crude assumptions about likely patient numbers for each population (equivalent to up to 20–25% of overall annual numbers being eligible) as broadly indicative of the potential impact of using pemetrexed plus cisplatin in place of supportive care.

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

## Conclusion

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

# Chapter 9

# General discussion and conclusions

Mesothelioma will be a growing challenge for the NHS over the next 15–20 years, as patient numbers increase. Its poor prognosis is in part the result of late diagnosis but is mainly due to the natural history of the tumour. This prognosis and the clinical course in which pain is often a prominent feature command 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 receive only supportive care, in part related to the late stage of presentation. The concept of BSC is somewhat nebulous: it is almost synonymous with ASC 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. However, 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 end-points. 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 folic acid and vitamin $B_{12}$ supplementation, even thereafter the incidence of toxicity was high.

The information on QoL, 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 NSCLC when weighed against the toxicity of a cisplatin-based chemotherapy regimen.[78] Although the dose of cisplatin is important in determining toxicity, the extent to which patients would weigh the pemetrexed + 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, MVP against vinorelbine and compared with ASC, is under way. Currently the trialists have recruited 380 patients with a target of 420 by early 2006 (Stephens R, Cancer Division, MRC Clinical Trials Unit: personal communication, 7 November 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 + cisplatin trial or a NICE appraisal.

Any decision to use pemetrexed + 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 BSC.

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, especially for patients with good performance status and with advanced disease, where the estimated ICER per 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 more than £5 million per year at present costs.

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## Contribution of authors

Yenal Dundar (Research Fellow, Clinical Effectiveness) was responsible for the review coordination, development of search strategies, data management and input into all aspects of clinical review, including writing and editing of the report. Adrian Bagust (Professor, Health Economics) carried out the economic analysis, including economic modelling. Rumona Dickson (Director of the Liverpool Reviews and Implementation Group) was responsible for project management and input into all aspects of the clinical component of the review. Susanna Dodd (Research Associate, Medical Statistics) checked data and gave statistical advice. John Green (Senior Lecturer, Medical Oncology) gave input into all aspects of the clinical component of the review. Alan Haycox (Senior Research Fellow, Health Economics) gave support to the economics team. Ruaraidh Hill (Research Fellow, Clinical Effectiveness) gave input into the development of the protocol. Claire McLeod (Training Fellow, Health Economics) was responsible for the economic analysis, evaluation of the submitted economic model and summary of the economic data. Tom Walley (Professor, Pharmacology and Therapeutics) carried out data assessment and interpretation of the clinical and economic data. All contributors took part in the editing and production of the report.

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# Appendix 1

## Search strategy: clinical and economic evidence

The search strategy and search results are given in *Table 38*.

### Search strategy: MEDLINE, 1980–May 2005

1. mesothelio$.tw.
2. pleural mesothelioma.tw.
3. exp mesothelioma
4. exp neoplasms, mesothelial
5. exp antineoplastic agents
6. chemothera$.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

1. mesothelio$.tw.
2. exp mesothelioma or exp pleura mesothelioma
3. chemothera$.tw
4. exp cancer chemotherapy
5. exp cancer combination chemotherapy
6. or/1-2
7. or/3-5
8. 6 and 7
9. limit 7 to human
10. limit 8 to yr=1980-2005

***TABLE 38*** *Search strategy and search results*

| Database | Years | Search strategy | References identified |
|---|---|---|---|
| MEDLINE | 1980–2005 | See above | 620 |
| EMBASE | 1980–2005 | See above | 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)[a] | 2005 (2) | As above | 48 |
| Handsearching | | | 1 |
| | Total references identified | | **1793** |
| | Duplicates | | **912** |
| | **Total** | | **881** |

[a] 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).

# Appendix 2

# Quality assessment: clinical and economic evidence

## 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, while 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 ITT 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.

## Economic evidence

Studies of cost-effectiveness were assessed using the following criteria, which represent 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

- The 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 CIs 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 both a disaggregated and an 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.

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