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Abstract

The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation

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Objectives: To assess the clinical effectiveness and cost-effectiveness of gemcitabine, used in combination with paclitaxel, as a second-line treatment for people with metastatic breast cancer who have relapsed following treatment with anthracycline-based chemotherapy.
Data sources: Electronic databases were searched from inception to March 2006. Clinical advisers were also consulted.
Review methods: A systematic review of the literature was undertaken to appraise the clinical and cost-effectiveness of gemcitabine. A Markov state transition model was developed for the economic evaluation.
Results: The systematic review identified only one randomised controlled trials (RCT), and this has not yet been fully published. The methodological quality and quality of reporting of the included trial were assessed to be poor using standard criteria, but this may be due to the lack of information in the limited publications rather than being a fair reflection of the trial's quality. This RCT compared gemcitabine and paclitaxel therapy with paclitaxel monotherapy in 529 patients with metastatic breast cancer who had previously received anthracyclines, but no prior chemotherapy for metastatic breast cancer. Approximately 71% of the gemcitabine/paclitaxel patients survived for 1 year, compared with 61% of the paclitaxel group. The hazard ratio showed a 26% lower chance of survival in the paclitaxel group, and time to progressive disease was also shorter in this group. The overall response rate was higher in the gemcitabine/paclitaxel group than in the paclitaxel group. Adverse events, particularly neutropenia, were more common with gemcitabine/paclitaxel combination therapy than with paclitaxel therapy alone. The economic model was run for a simulation of 1000 patients, assuming that chemotherapy continued until patients' disease progressed. This base-case analysis found an incremental cost-effectiveness ratio (ICER) of £58,876 per quality-adjusted life-year (QALY) gained and £30,117 per life-year gained. The model was re-run with treatment restricted to a maximum of six cycles per patient, reflecting normal practice. This yielded an ICER of £38,699 per QALY gained and £20,021 per life-year gained.
Conclusions: The review of clinical effectiveness is based on data from a single RCT that has not yet been fully published. While only tentative conclusions can be drawn from this, the evidence may indicate that treatment with gemcitabine and paclitaxel confers an improved outcome for patients in terms of survival and disease progression, but at the cost of increased toxicity. An economic model developed for this review reflects high costs per QALY for this treatment combination. The base-case analysis shows high ICERs, with costs per QALY gained close to £60,000. Adopting a more realistic treatment protocol, with chemotherapy limited to a maximum of six cycles, gives a more favourable cost-effectiveness estimate. However, this was still higher than would usually be considered to be a cost-effective treatment from the NHS's perspective. Future research recommendations include an update of this review in 12–18 months' time, by which time the included RCT should be fully published. It would also be useful to compare gemcitabine with currently used treatments for metastatic breast cancer, including capecitabine and vinorelbine.

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

Adjuvant therapy Treatment given after removal of a primary tumour which aims to prevent recurrence. Chemotherapy or hormone therapy may be used to destroy any remaining micrometastatic tumour cells

Anthracycline resistance Resistance to anthracycline therapy after initial response to first-line treatment with a treatment combination containing anthracyclines

Complete response No detectable malignant disease for at least 4 weeks following therapy

Cost–utility analysis Analysis estimating additional cost per quality-adjusted life-year gained

Cycle Course of chemotherapy followed by a recovery period

Cytotoxic Toxic to cells, resulting in cell death or slowed growth

Distant metastases Tumours which appear in other sites of the body, not attached to the primary tumour site. These develop when cancer cells spread via the blood circulation or lymphatic system

Endocrine therapy Manipulation of hormones to treat a condition

EORTC QLQ-BR32 A questionnaire specific to breast cancer for use with the EORTC QLQ-C30

EORTC QLQ-C30 A standard self-administered questionnaire for assessing health-related quality of life

First-line therapy Initial treatment for a particular condition that has previously not been treated. Chemotherapy or hormone therapy could be used as first-line treatment for metastatic breast cancer

Neoadjuvant Treatment taken by patients before their main treatment. This may be chemotherapy or radiotherapy before surgical removal of a tumour

Karnofsky Performance Status A subjective measure of how well a patient performs activities of daily living

Nulliparous A woman who has never given birth to a child

Oestrogen receptor A protein on some breast cancer cells that binds oestrogen. Tumours with cells of this type are suitable for hormonal treatment, and prognosis is generally better for patients with these tumours. Cells can also contain progesterone receptors

Progression Continued growth of the tumour or development of new metastases

Second-line therapy The second chemotherapy regimen administered either as a result of relapse after first-line therapy or immediately following on from first-line therapy in patients with progressive or stable disease

List of abbreviations

AE	adverse event
BNF	British National Formulary
BPI	Brief Pain Inventory
BRCA1	breast cancer 1 gene
BRCA2	breast cancer 2 gene
BSA	body surface area
CEAC	cost-effectiveness acceptability curve
CHEK2	checkpoint homolog-2 gene
CMF	cyclophosphamide–methotrexate–5-fluororacil
CRD	Centre for Reviews and Dissemination
CT	chemotherapy
DNA	deoxyribonucleic acid
ER	oestrogen receptor
FDA	Food and Drug Administration
FEC	5-fluororacicil–epirubicin–cyclophosphamide
GEM	gemcitabine
HER-2	human epidermal growth factor-2
HR	hazard ratio
HRT	hormone replacement therapy
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
KPS	Karnofsky Performance Status
MBC	metastatic breast cancer
MIMS	Monthly Index for Medical Specialties
MR	mortality rate
MRD	median response duration
MSD	median survival duration
NICE	National Institute for Health and Clinical Excellence
ONS	Office for National Statistics
ORR	overall response rate
OS	overall survival
PAC	paclitaxel
PCT	primary care trust
PFS	progression-free survival
PR	progesterone receptor
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RSCL	Rotterdam Symptom Checklist
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
TNM	tumour, node, metastases
TTP	time to progression

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

Background

Breast cancer is the most common cancer in the UK, accounting for one-third of all cancers in women. In 2003, the age-standardised incidence rates per 100,000 population were 120.3 for England and 120.83 for Wales. The high incidence of breast cancer in conjunction with relatively good survival rates, compared with many other cancers, has led to a relatively high prevalence. Increasing age is the strongest risk factor for breast cancer, and the disease is rare in women under the age of 40 years. Over 80% of cases occur in women over the age of 50 years, with the number of diagnoses reaching a peak in the 55–59-year age group.

Breast cancer is classified into four clinical stages. Metastatic breast cancer (Stage IV) is characterised by the spread of distant metastases to other parts of the body, such as the bones, brain, lung or liver. Approximately half of all women with breast cancer will develop metastatic disease, although the majority will have a long disease-free interval between treatment for early-stage breast cancer and the development of metastases.

Treatments for metastatic breast cancer are primarily palliative rather than curative, although high rates of response can prolong survival to some extent. Toxicity and adverse effects will therefore play an important role in treatment decisions, with quality of life being a key consideration.

Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.

The combination of gemcitabine with paclitaxel is appropriate because they have different anti-tumour activities and non-overlapping toxicity profiles.

Objectives

The aim of this systematic review and economic evaluation is to assess the clinical effectiveness and cost-effectiveness of gemcitabine, used in combination with paclitaxel, as a second-line treatment for people with metastatic breast cancer who have relapsed following treatment with anthracycline-based chemotherapy.

Methods

A systematic review of the literature was undertaken to appraise the clinical and cost-effectiveness of gemcitabine. A model was developed for the economic evaluation.

Data sources

Electronic databases were searched from inception to March 2006 and reference lists from retrieved papers were checked for additional publications not identified by the electronic searches. Clinical advisers were asked if they were aware of any additional studies.

Study selection

Studies were included if they met the following criteria:

- *Interventions*: gemcitabine in combination with paclitaxel.
- *Comparators for clinical effectiveness review*: any other licensed treatment for metastatic breast cancer.
- *Patients*: people diagnosed with metastatic breast cancer who have previously been treated with anthracycline-based therapies.
- *Types of studies*: systematic reviews of randomised controlled trials (RCTs) and RCTs of the intervention compared with other treatments for metastatic breast cancer.
- *Outcomes*: survival; time to disease progression; disease-related symptoms; health-related quality of life; and adverse effects of treatment.

The titles and abstracts of all identified studies were screened by two independent reviewers and full-text versions of relevant English-language papers were retrieved. Inclusion criteria for full-text papers were applied by one reviewer and checked by a second reviewer. Any differences in decision to include or exclude were resolved through discussion.

Data extraction and quality assessment

Data were extracted from the included studies by one reviewer and checked by a second reviewer using a data extraction form. Any disagreements were resolved through discussion. Studies with multiple publications were data extracted on to one form, with any differences between the publications identified and explicitly referenced. The quality of included RCTs was assessed using standard criteria developed by the NHS Centre for Reviews and Dissemination.

Data synthesis

The included study reports were tabulated and synthesised in a narrative summary. Meta-analysis was not appropriate for this report, due to the limited data identified.

Economic model

A Markov state transition model was developed to estimate the cost-effectiveness of gemcitabine with paclitaxel for patients with metastatic breast cancer. The model consisted of four states (responsive, stable disease, progressive disease and death) and applied transition probabilities derived from the literature and expert opinion. The model adopted a lifetime horizon, running until the majority of the cohort was in the absorbing health state (death). Sensitivity analyses were carried out to estimate the effect of treating for a maximum of six cycles of chemotherapy.

Results

The systematic review identified only one RCT, and this has not yet been fully published. The data are only available in three conference abstracts. The methodological quality and quality of reporting of the included trial were assessed to be poor using standard criteria, but this may be due to the lack of information in the limited publications rather than being a fair reflection of the trial's quality. This RCT compared gemcitabine and paclitaxel therapy with paclitaxel monotherapy in 529 patients with metastatic breast cancer who had previously received anthracyclines, but no prior chemotherapy for metastatic breast cancer.

Survival at 1 year was statistically significantly better in the gemcitabine/paclitaxel group than the paclitaxel group. Approximately 71% of the gemcitabine/paclitaxel patients survived for 1 year, compared with 61% of the paclitaxel group. The hazard ratio showed a 26% lower chance of survival in the paclitaxel group, and time to progressive disease was also shorter in this group. The overall response rate was higher in the gemcitabine/paclitaxel group than in the paclitaxel group. Adverse events, particularly neutropenia, were more common with gemcitabine/paclitaxel combination therapy than with paclitaxel therapy alone.

The economic model developed for this review was run for a simulation of 1000 patients, assuming that chemotherapy continued until patients' disease progressed. This base-case analysis found an incremental cost-effectiveness ratio (ICER) of £58,876 per quality-adjusted life-year (QALY) gained and £30,117 per life-year gained. In normal practice, patients are likely to receive chemotherapy for a fixed number of cycles, rather than until disease progression. As a result, the model was re-run with treatment restricted to a maximum of six cycles per patient, which yielded an ICER of £38,699 per QALY gained and £20,021 per life-year gained.

Discussion

The systematic review was restricted by the lack of published evidence for gemcitabine's licensed indication. In the absence of any fully published studies, data from three abstracts were used to form the basis of the review of clinical effectiveness. These did not generally contain sufficient data to allow a detailed review of the clinical effectiveness of gemcitabine with paclitaxel.

The economic model adopted a structure similar to that used in previous economic evaluations of chemotherapy regimes for metastatic breast cancer. Clinical trial data used to derive parameter estimates for the model were taken from published abstracts and supplementary information available on the American Society of Clinical Oncology website (http://www.asco.org/portal/site/ASCO). Although sufficient data were available to develop and populate the model, these publications were not fully peer reviewed and it was not possible to quality assess these data formally. Assumptions were necessary to convert the clinical trial data to the form required for the model and these need to be taken into account when interpreting the results from the model.

Conclusions

The review of clinical effectiveness is based on data from a single RCT which has not yet been

fully published. The trial did not rate particularly well on quality assessment criteria, although this was partly a reflection of publication status and lack of published information. Only tentative conclusions can therefore be drawn from our review.

Evidence from the included RCT may indicate that treatment with gemcitabine and paclitaxel confers an improved outcome for patients in terms of survival and disease progression, but at the cost of increased toxicity. An economic model developed for this review reflects high costs per QALY for this treatment combination. The base-case analysis shows high ICERs, with costs per QALY gained close to £60,000. Adopting a more realistic treatment protocol, with chemotherapy limited to a maximum of six cycles, gives a more favourable cost-effectiveness estimate. However, this was still higher than would usually be considered to be a cost-effective treatment from the NHS's perspective.

Future research recommendations include an update of this review in 12–18 months' time, by which time the included RCT should be fully published. It would also be useful to compare gemcitabine with currently used treatments for metastatic breast cancer, including capecitabine and vinorelbine.

Chapter 1

Aim of review

Gemcitabine (GEM) (Gemzar®, Lilly) is licensed for the treatment of people with metastatic breast cancer (MBC), when used in combination with paclitaxel (PAC) (Taxol®, Bristol-Myers Squibb). It is indicated for the treatment of patients with MBC who have relapsed following adjuvant/neoadjuvant chemotherapy. The National Institute for Health and Clinical Excellence (NICE) has issued guidance on the use of gemcitabine GEM for MBC as part of their Single Technology Appraisal programme (www.nice.org.uk). An appraisal of the clinical and cost-effectiveness of this drug is therefore of interest. The aim of this systematic review and economic evaluation is to assess the clinical effectiveness and cost-effectiveness of GEM, used in combination with PAC, as a second-line treatment for people with MBC.

Chapter 2
Background

Breast cancer is the most common cancer in the UK, with more than 100 new cases being diagnosed every day.[1] The disease accounts for one-third of all cancers in women[2] and it is the third most common cause of cancer death in the UK after lung cancer and large bowel cancer.[3] The highest numbers of breast cancer diagnoses are made for women aged between 50 and 64 years, although the incidence per 100,000 population continues to rise with age from this group onwards. The disease is also occasionally found in men, who account for approximately 1% of total cases.[3]

Breast cancer is classified on a clinical basis, according to the internationally recognised tumour, node, metastases (TNM) staging system (see Appendix 1). Staging involves physical examination in conjunction with evaluations made on laboratory and radiological data. The TNM system is based on three sets of codes, relating to the primary tumour, involvement of lymph nodes and evidence of distant metastases. Four clinical stages are defined by particular combinations of these codes. Stages I and II are sometimes referred to as primary or early breast cancer. Stage I indicates a small tumour (less than 2 cm in diameter) confined to the breast tissue. Stage II tumours can be up to 5 cm in diameter (or larger if lymph-node negative), with no metastatic spread to distant sites. Stages III and IV represent advanced breast cancer. By stage III, the primary tumour is usually larger than 5 cm, and may be attached to the skin or chest wall. It is likely that the cancer will have spread to the lymph nodes, but not to distant sites.

Stage IV is metastatic disease, regardless of lymph-node assessment or size of primary tumour.[4] For some patients, metastases can occur with a small primary tumour, although the chance of having metastatic disease at the time of diagnosis is higher with large (Stage III) tumours. Most patients who are going to develop metastases do so within 5 years of first diagnosis. Only a small group of patients relapse beyond 5 years, and these patients tend to have oestrogen receptor (ER)-positive disease.[5]

The sections below describe breast cancer in general terms, with a more specific focus on MBC in the section 'Metastatic breast cancer' (p. 6).

Epidemiology

Incidence

In 2003, there were 36,509 new cases of breast cancer diagnosed in England[6] and 2355 in Wales.[7] These figures represent age-standardised rates per 100,000 population of 120.3 for England and 120.83 for Wales.

The introduction of the UK's breast screening programme in 1988 made it possible to identify breast cancer at earlier stages. The initial target population was women aged 50–64 years, but in 2001 this was extended to include women up to the age of 70 years.[2] The incidence of breast cancer increased by 80% between 1971 and 2003 and by 16% between 1993 and 2003.[2] Early detection due to screening might have accounted for some of the rise, but there has been a progressive underlying increase in the incidence of breast cancer in addition to this. The 2003 age-standardised incidence rate for England was 120.3, which is slightly higher than that averaged over 2001–3 (116.9 per 100,000).[8]

Low levels of child bearing and later maternal age at first birth are associated with a higher incidence of breast cancer (see the section 'Reproductive history', p. 5), and the falling fertility rates in the UK could be one explanation for this trend. Following the 'baby boom' peak total fertility rate of 2.95 children per woman in 1964, fertility levels fell to 1.77 children per woman in 2004. In 2004, the mean age of women having their first birth was 27.1 years, compared with 23.7 years in 1971. Greater numbers of women are never having children – around one in five women in 2004 compared with one in 10 women born in the mid-1940s.[9]

Prevalence

The high incidence of breast cancer in conjunction with relatively good survival rates, compared with many other cancers, has led to a high prevalence. In 1992, there were estimated to be 172,836 women in the UK who had been diagnosed with breast cancer.[10] The most recent available data set from the Office for National Statistics (ONS) shows that approximately 81% (75,000) of people diagnosed with the disease in 1990–2, and 62%

(168,000) of those diagnosed in 1983–92 were still alive at the beginning of 1993.[11]

Detailed estimates of cancer prevalence are scarce, as their calculation requires long-term incidence data and reliable data on survival times. The most recent large-scale estimate of cancer prevalence in the UK[10] was based on data from eight UK cancer registries. At the end of 1992, female breast cancer was the most common form of cancer, with a prevalence of almost 1%.[10] Total prevalence for England was estimated to be 952 per 100,000 population. This is higher than the directly observed rate of 872 per 100,000 published by the ONS.[11] For the UK as a whole, Forman and colleagues presented prevalence estimates by three age bands and an overall total. Prevalence estimates of breast cancer per 100,000 population in 1992 were as follows: 947 for the whole of the UK; 89 for people aged 0–44 years; 1688 for the 45–64-year age group; and 2840 for people aged over 64 years.[10] Over half (55.7%) of prevalent cases in the UK were seen in people over the age of 64 years. More than one-third (38.7%) were in people aged 45–64 years, and only 5.6% of prevalent cases were in people under 45 years old.[10]

Mortality

In 2003, 10,553 women in England and 12,696 in the whole of the UK died from breast cancer.[3,12–14] This represents a rate of 29 deaths per 100,000 women.[2] Deaths from breast cancer in England and Wales resulted in about 47,000 lost potential working years in 2003.[15] Women diagnosed between 1998 and 2001 had a 5-year survival rate of 80%, which is higher than that for cervical, lung, colorectal and ovarian cancers.[2]

Relative survival is calculated as the ratio of the number of people still alive compared with the expected survival rates for people of the same age and sex. It therefore takes into account people who die from causes other than their cancer. Women who are diagnosed between the ages of 50 and 69 years have 10- and 20-year relative survival estimates of 73% and 64%, respectively. Women who were aged 70–99 years at diagnosis have the lowest levels of long-term relative survival, with only 63% surviving for 10 years and 59% surviving for 20 years.[16] Although breast cancer is rarer in younger women, it is the most common cause of all deaths (17%) in women aged 35–54 years.[3]

Improvements in the treatment of breast cancer have led to reduced mortality from this disease. Between 1988 and 2003, the mortality rate reduced by 38% for women aged 40–49 years and by 34% for women aged 50–64 years. Reductions in the mortality rate were 32% for women aged 65–69 years, and 17% for women aged 15–39 years. The lowest reduction in mortality was in women over 70 years old, whose mortality rates fell by 12% during this period.

Predicted trends in long-term survival from breast cancer[16] indicate that 72% of women diagnosed in 2001–3 are likely to survive for at least 10 years and 64% are likely to survive for at least 20 years. These long-term survival predictions are higher than those for women who were diagnosed in 1991–3, of whom 54% were predicted to survive for 10 years and 44% were likely to survive for 20 years.

Risk factors

Breast cancer is more common in economically developed countries. In 2002, the age-standardised incidence rate of female breast cancer per 100,000 population in the UK was 87.2. This ranked fifth behind the USA (101.1), France (91.9), Denmark (88.7) and Sweden (87.8).[17] Women who migrate from a country with a low prevalence to one with a high prevalence tend to have the same risk of developing breast cancer as other women in their host country. Major increases in risk have been observed between first-, second- and third-generation Asian migrants to the USA.[18] This indicates that environment and lifestyle factors play an important role in the risk of developing breast cancer.

Several risk factors for breast cancer have been identified, and these are summarised below. Since these relate to breast cancer in general and are not specific to MBC, they will not be discussed in detail.

Age

Increasing age is the strongest risk factor for breast cancer, and the disease is rare in women under the age of 40 years (approximately 0.5% of registrations in *Table 1*).

Changes in hormonal status are thought to be linked to the greater incidence in breast cancer observed in women just before the menopause.[3] Over 80% of cases occur in women over the age of 50 years, with the number of diagnoses reaching a peak in the 55–59-year age group (*Table 1*). The age-standardised incidence rate per 100,000

TABLE 1 *Breast cancer incidence in England and Wales, 2003*

Age band (years)	Registrations of newly diagnosed cases of female breast cancer by age in England and Wales, 2003[6,7]	Estimated incidence rate per 100,000 women in England and Wales
15–19	4	0.24
20–24	8	0.49
25–29	116	7.13
30–34	519	26.29
35–39	1314	62.54
40–44	2281	116.70
45–49	3064	178.15
50–54	4553	272.08
55–59	5395	314.65
60–64	4624	349.01
65–69	3987	328.69
70–74	3585	319.60
75–79	3432	347.93
80–84	2956	359.70
85+	3026	425.54

female population was estimated by dividing the number of registrations per age band by the ONS female population estimates for England and Wales for mid-2003.[19]

We used the ONS's age- and sex-adjusted population with the incidence rates for breast cancer in *Table 1* to provide an estimate of the incidence of breast cancer for an average population of a primary care trust (PCT). We assumed that there are an equal number of males and females in the average PCT, so a PCT with a population of 200,000 might expect to have 100,000 girls and women in its catchment area, of whom approximately 144 per year could be expected to present with breast cancer.

Reproductive history

Risk factors for breast cancer generally relate to exposure to oestrogen. Age at first birth increases the relative risk of developing breast cancer by 3% each year of passing time before pregnancy.[20] Number of pregnancies also has a protective effect, and nulliparous women have a 30% increase in risk compared with parous women.[21] Each subsequent birth (in the absence of breastfeeding) reduces the risk of developing breast cancer by 7%.[20] Breastfeeding has an additional protective effect against breast cancer, with the relative risk reducing by 4.3% for each year that a woman breastfeeds.[20]

Some breast cancer cells have hormone receptors, and tumours can be ER positive or progesterone receptor (PR) positive (or both). Approximately three-quarters of postmenopausal women and 50–60% of premenopausal women have hormone-sensitive tumours.[22] Breast cancers with hormone receptors on the surface of their cells are stimulated to grow by hormones, so hormone manipulation can be used to block their growth. A systematic review of 31 studies found that the risk associated with reproductive factors, such as delayed childbearing, nulliparity and early menarche, seemed to be restricted to hormone receptor-positive tumours. The authors of that review found no appreciable elevation in hormone receptor-negative cancers for women with these risk factors.[23]

Other risk factors

Other hormonal risk factors for breast cancer include current use (relative risk = 1.24) or use within past 5 years (relative risk = 1.16) of oral contraceptives[20] and current use of hormone replacement therapy (HRT) (relative risk = 1.66).[24]

In 24–30% of women, the breast tumour amplifies or overexpresses the proto-oncogene human epidermal growth factor-2 (HER-2)/neu or its protein receptor HER-2. Breast tumours that overexpress the HER-2 receptor are associated with poor prognosis and outcome.[25] High levels of HER-2 are more commonly found in women with ER- and PR-negative tumours.[1]

Family history can be an important risk factor for the small group of women who have mutations in the breast cancer susceptibility genes breast cancer 1 gene (BRCA1) and breast cancer 2 gene (BRCA2). Mutations in these genes account for up

to 50% of hereditary and familial breast cancer.[26] Women who carry this mutation have a 50–80% chance of developing the disease.[1] Other genetic factors which may affect a woman's likelihood of developing breast cancer include alterations of the checkpoint homolog-2 (CHEK2) gene.[1] Lifestyle factors such as overweight and obesity, alcohol consumption, physical activity and diet may also affect a woman's likelihood of developing breast cancer.

Metastatic breast cancer

As discussed at the beginning of this chapter (p. 3), MBC reflects disease that has spread beyond the local regional area, i.e. the breast and drainage lymph node, and has affected distant organs. Common metastatic sites include skin, lymph node, bone, lung, liver and brain.

Figures for the incidence and prevalence of MBC are not readily available, but some reports indicate that 50%[27,28] of women treated for early or localised breast cancer relapse and develop metastatic disease. However, these figures are based on rather old data, and disease-free survival from early-stage breast cancer continues to improve. For example, a recent review by the ONS found a 20-year survival rate of 64% for women diagnosed with breast cancer between the ages of 50 and 69 years.[16] Taking the average PCT's estimated incidence, calculated as 144 new cases of breast cancer per year, these rates suggest that approximately 52–72 women could be expected to relapse and develop metastatic cancer.

A smaller proportion (16–20%) of women are found to have MBC at first diagnosis.[29] Treatment effects and survival outcomes are thought to be similar, regardless of whether a patient presents initially with MBC or whether the metastasis is a recurrence of previous disease.[27]

Expert opinion indicates that the risk of developing metastatic disease is not related to age or to ER status of the primary tumour. Women who have lymph node-positive disease at diagnosis are at a higher risk of MBC than those women with lymph node-negative disease. If the lymph nodes are involved, then the histological grade of the tumour and the size of the tumour have little additional impact. If, however, the lymph nodes are not involved at the time of diagnosis, then the histological grade of the tumour and the size of the tumour assume considerable importance in determining prognosis. Patients who have HER-2-positive disease are at higher risk of relapse from breast cancer if all other factors (nodes, size, stage) are equal, and tend to relapse earlier than women without HER-2 amplification (anonymous expert: personal communication, April 2006).

MBC is currently considered to be incurable, and prognosis will be influenced by various predictive and prognostic factors. An American study[30] found a median survival time for Stage IV disease of 2–3 years, with a range of 5-year survival estimates from 12 to 35% and 10-year survival ranging from 5 to 22%. Improvements in treatment have increased survival times steadily by about 1% per annum in recent years, and the 5-year survival rate is now between 3 and 12%.[31]

There are a number of factors at the time of first metastases which dictate the likelihood of response to treatment. These include the disease-free interval from primary diagnosis and the number and sites of metastatic disease (with metastases in soft tissue and bone having a better prognosis than visceral sites such as the lung or liver). Women who develop metastases within 1 year of first diagnosis tend to have a lower chance of response to therapy than those patients who develop metastatic disease at a later time. MBC is likely to be resistant to any chemotherapy and/or hormonal therapy treatments that were used as adjuvant therapy for primary breast cancer if there has been less than 1 year between these and progression to metastatic disease.[32] Predictive factors such as ER status and HER-2 amplification will determine which treatments are used for MBC.

Current service provision

Treatments for MBC are primarily palliative rather than curative, although high rates of response can prolong survival to some extent.[31] Toxicity and adverse effects will therefore play an important role in treatment decisions, with quality of life (QoL) being a key consideration. Patients in the UK who require adjuvant therapy at the time of diagnosis of Stage I, II or III breast cancer are generally offered anthracycline-based chemotherapy (CT). This is commonly a regimen called FEC (5-fluororacil–epirubicin–cyclophosphamide) for six cycles or four cycles of epirubicin followed by four cycles of CMF (cyclophosphamide–methotrexate–5-fluororacil) (anonymous clinical expert: personal communication, April 2006). Patients who relapse and develop metastatic disease are therefore largely anthracycline pre-exposed, and will not be suitable for further anthracycline treatment.

Choice of first-line therapy generally depends on ER status:

- For ER-positive patients, hormone manipulation therapy is recommended by NICE as first-line treatment,[33] and this will generally involve a change from the hormonal treatment used in the adjuvant setting. Aromatase inhibitors are generally the hormonal manipulation of first choice in MBC as they have a higher response rate than tamoxifen (Murray N, Southampton University Hospitals Trust: personal communication, April 2006). Furthermore, the majority of women with ER-positive disease will have received tamoxifen as adjuvant therapy.
- CT is also used to treat life-threatening disease, particularly when the cancer has metastasised to critical visceral sites, when there has only been a short interval since previous treatment for early-stage disease, or disease progression after endocrine therapy.[29] Patients may receive more than one line of endocrine therapy for metastatic disease.
- For ER-negative patients with MBC, NICE guidance[29] recommends CT, including an anthracycline if one has not previously been used. However, the majority of women with ER-negative disease will have received an anthracycline as adjuvant treatment, since they will not have been suitable for hormonal therapy.

Docetaxel, PAC, capecitabine and vinorelbine are commonly used to treat MBC. Trastuzumab is used to treat women with tumours that over-express HER-2. NICE is currently developing guidelines on the diagnosis and treatment of advanced breast cancer, and this will replace existing guidance on the use of capecitabine, vinorelbine, trastuzumab and the taxanes. Existing NICE guidance on these therapies is summarised below.

Taxanes

NICE guidance[34] (2001) recommends docetaxel and PAC as options for the treatment of advanced breast cancer where initial cytotoxic CT (including an anthracycline) has failed or is inappropriate. If a patient has not received adjuvant anthracyclines, an anthracycline will be used as first-line treatment for metastatic disease. Docetaxel monotherapy given once every 3 weeks tends to be the first-choice CT for younger, generally healthier patients with metastatic breast cancer (Murray N, Southampton University Hospitals Trust: personal communication, April 2006). PAC (either once every 3 weeks or a lower dose weekly) may be used instead of docetaxel as a treatment for MBC for patients who have previously been treated with anthracyclines. For women unwilling to accept the hair loss associated with docetaxel, or who have already received taxane treatment in the adjuvant setting, the choice of treatment tends to be capecitabine or vinorelbine.

Capecitabine

Existing NICE guidance[29] (2003) recommends capecitabine in combination with docetaxel in preference to single-agent docetaxel for the treatment of locally advanced or metastatic breast cancer, in people for whom anthracycline-containing regimens are unsuitable or have failed. In practice, the combination of capecitabine and docetaxel is rarely used, due to increased toxicity. NICE also recommends capecitabine monotherapy as an option for people with locally advanced or metastatic breast cancer, if they have not previously received capecitabine in combination therapy and if anthracycline and taxane-containing regimens have failed, or further anthracycline therapy is contraindicated. Capecitabine is an oral therapy, and its toxicity profile includes mucositis (sore mouth and potentially diarrhoea), and sore hands and feet.

Vinorelbine

Existing NICE guidance[35] (2002) only recommends vinorelbine as an option for second-line or later treatment for advanced breast cancer, when anthracycline-based regimens have failed or are unsuitable. It is not currently recommended for use in combination therapies. Vinorelbine is administered intravenously, requiring attendance for treatment on 2 days in every 21.

Trastuzumab

Trastuzumab in combination with PAC or docetaxel is recommended by NICE[33] as an option for people with tumours expressing HER-2 at levels of 3+ who have not received CT for MBC, and in whom anthracycline treatment is inappropriate. The initial NICE recommendation was to use trastuzumab with PAC, but this has been modified so that docetaxel may be used. Treatment with trastuzumab is an option for patients who have tumours that over-express HER-2 at 3+ levels by immunohistochemistry, or who have confirmation of gene amplification of HER-2 by the fluorescent *in situ* hybridisation test.

Surgery may be indicated for patients who have a solitary parenchymal brain metastasis or vertebral metastases with spinal cord compression, isolated lung metastases, pathological (or impending) fractures or pleural or pericardial effusions. Radiation therapy is often used as palliative

treatment for painful bony metastases, unresectable central nervous system metastases (brain, meningeal and spinal cord) or bronchial obstruction. Radiation therapy should also be given following surgery for decompression of intracranial or spinal cord metastases and following fixation of pathological fractures.[36]

Description of technology under assessment

GEM, in combination with PAC, is licensed for the treatment of patients with MBC who have relapsed following adjuvant/neoadjuvant CT. GEM is an antimetabolite, and works by killing cells undergoing the second phase of DNA synthesis required for cell growth. It can also block the progression of cells from the first to the second phase of DNA synthesis under certain conditions (gemcitabine summary of product characteristics available from http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=596). Subsequent cell division and the growth of tumours are therefore prevented. PAC is a taxane, a type of anti-cancer drug originally derived from the bark of *Taxus brevifolia*, the Pacific yew tree. Cells exposed to taxanes cannot form the mitotic spindle required for cell division, and this leads to cell death.[37,38]

The recommended dosage for patients with MBC is PAC (175 mg/m^2) administered on day 1 over 3 hours as an intravenous infusion, followed by GEM (1250 mg/m^2) as a 30–60-minute intravenous infusion on days 1 and 8 of each 21-day cycle (www.nice.org.uk). The combination of GEM with PAC is appropriate because they have different antitumour activities and non-overlapping toxicity profiles.[39]

The US Food and Drug Administration (FDA) approved the combination of GEM and PAC for the first-line treatment of MBC in 2004. In March 2005, the Scottish Medicines Consortium (SMC) decided not to recommend its use within NHS Scotland for the treatment of patients with breast cancer that has spread beyond the breast, who have relapsed following CT. The SMC concluded that the economic case has not been demonstrated.

Patients with metastatic disease will generally have received anthracycline treatment as an adjuvant therapy, or as a first-line CT treatment. Further use of anthracyclines at the metastatic stage may be precluded by cumulative cardiotoxicity or the development of anthracycline resistance.[40] Anthracycline resistance is usually defined as disease progression during or within 6–12 months of completion of anthracycline therapy. Similarly, increasing numbers of patients are exposed to taxanes in the adjuvant setting which could prevent the licensed combination of GEM and PAC being used as a later line of therapy.

This review considered treatment with GEM and PAC for people diagnosed with Stage IV MBC who have previously been treated with anthracycline-based therapies. Possible subgroups included: pre-/postmenopausal women, ER status and HER-2 score. Possible comparators outlined in the protocol were any other licensed treatments for the second-line treatment of MBC, including the taxanes and capecitabine as monotherapies, combination docetaxel and capecitabine and rechallenge with anthracyclines. The choice of possible comparators reflects the original brief for this project, based on NICE's scoping exercise.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

The *a priori* methods for systematically reviewing the evidence of clinical effectiveness were described in the research protocol (Appendix 2). Expert comments on the protocol were obtained from members of the advisory group to the study (see Acknowledgements). Although helpful comments were received about the general content of the research protocol, none identified specific problems with the methods proposed. A concern was raised by an advisor that limiting the assessment to gemcitabine in combination with paclitaxel only would restrict its usefulness to clinical practice. The advisor felt that the assessment could examine the use of GEM as a single agent as well as in combination with platinum drugs and that the role of trastuzumab could be considered. Originally this assessment was commissioned by the HTA programme to inform the NICE appraisal programme and as a consequence has a specific scope to address. It was not possible within the scope to examine other comparators or unlicensed indications. Other ongoing or planned appraisals will consider some of the comparators identified.

The methods outlined in the protocol are summarised below.

Search strategy

Sources of information, search terms and a flowchart outlining the identification of studies for the systematic review are described in Appendices 3 and 4. The electronic search strategy aimed to generate a comprehensive list of studies meeting the inclusion criteria for the systematic review, to provide information on the epidemiology of breast cancer and to provide information for developing an economic evaluation (including costs and quality of life). The search included studies published in the English language only. Reference lists from all publications included were checked for additional publications not identified by the electronic searches, and clinical advisers were consulted for any further relevant studies. Searches were carried out from the inception of the databases until March 2006.

Inclusion and data extraction process

Studies identified in the search strategy were assessed for inclusion in the systematic review of clinical effectiveness depending on the interventions used, the patient groups, the outcomes assessed and the study design.

Inclusion criteria

- *Interventions*
  The review included studies that evaluated GEM in combination with PAC.
- *Comparators for clinical effectiveness review*
  The review considered studies comparing GEM and PAC with any other licensed treatments for MBC.
- *Patients*
  Participants were people diagnosed with MBC, who had previously been treated with anthracycline-based therapies. Trials including people with locally advanced breast cancer were included if the majority of the patient population had metastatic disease.
- *Types of studies*
  Systematic reviews of randomised controlled trials (RCTs) and RCTs of the intervention compared with other treatments for MBC were included.
- *Outcomes*
  Outcomes focused on survival, time to progression (TTP), disease-related symptoms, health-related QoL and adverse effects of treatment.

Studies identified by the search strategy were assessed for inclusion through two stages. The titles and abstracts of all identified studies were screened by two independent reviewers and full-text versions of relevant papers were retrieved. Any differences in decision to include or exclude were resolved through discussion. Studies included at this stage were obtained to allow examination of the full text of the study. Inclusion criteria of full-text papers were applied by one reviewer and checked by a second reviewer. Any disagreements were resolved by discussion. These procedures were used to reduce the effects of bias in study selection, which can occur due to the effects of pre-existing opinions of the researcher, and to minimise the risk of errors of judgement. Studies excluded from the review of clinical effectiveness are listed in Appendix 5.

TABLE 2 *Characteristics of included study O'Shaughnessy* et al.[42–44]

Methods	Participants	Outcomes
Design: RCT *Interventions:* Group A: GEM/PAC Group B: PAC *Number of centres:* 98 *Median duration of treatment:* 6 cycles (group A), 5 cycles (group B) *Sponsor:* Eli Lilly	*Inclusion criteria:* MBC previously treated with anthracyclines; no prior CT for MBC; score ⩾70 on activities of daily living scale [Karnofsky Performance Status (KPS)] *Numbers:* 529 participants Group A: 267 Group B: 262 *Mean age (range):* Group A 53 (26–83) years Group B 52 (26–75) years	*Primary outcomes:* overall survival, progression-free survival, overall response, QoL, palliation of pain, toxicity, TTP disease *Secondary outcomes:* Brief Pain Inventory (BPI), Rotterdam Symptom Checklist (RSCL), analgesic level *Length of follow-up:* median follow-up 15.6 months for overall survival outcome

Data were extracted from the included studies by one reviewer and checked by a second reviewer using a data extraction form developed *a priori*. Any disagreements were resolved through discussion. Studies with multiple publications were data extracted on to one form, with any differences between the publications identified and explicitly referenced.

Quality assessment

The methodological quality of the studies included in the systematic review of clinical effectiveness was assessed using criteria recommended by the NHS Centre for Reviews and Dissemination (CRD) (University of York) (see Appendix 6 for full details).[41] Quality assessment criteria were applied by one reviewer and checked by a second reviewer. As with other decisions in the systematic review, any disagreements were resolved through discussion.

Data synthesis

The included study reports were tabulated and synthesised in a narrative summary. Statistical synthesis by meta-analysis of the data was not appropriate owing to the limited data identified.

Results

Quantity and quality of research available

Searches identified 361 references, of which 330 were excluded in the initial stages of the review. We retrieved full copies of 31 articles, and 28 of these were excluded on further inspection. The majority of papers were excluded because the study design (e.g. Phase II, non-randomised) did not meet the inclusion criteria. Three reports of one RCT for the evaluation of GEM and PAC in patients with MBC met the inclusion criteria for the review.[42–44] All three reports were published in abstract format. Additional data are available in the form of unpublished conference presentations and this can be seen in Appendix 7. Details of the study characteristics are shown in *Table 2*.

Description of included study

The only included RCT[42–44] was a multicentre study investigating the use of GEM and PAC in patients with histologically confirmed, measurable MBC and previous adjuvant or neoadjuvant anthracycline therapy (or non-anthracyclines if clinically contraindicated). The comparator treatment was PAC therapy alone. In the GEM/PAC therapy group, patients received 1250 mg/m^2 of GEM on days 1 and 8 and 175 mg/m^2 of PAC on day 1. In the PAC therapy group, patients received 175 mg/m^2 of PAC on day 1. The study abstracts report that the drugs were given every 21 days until disease progression and that the median number of cycles was six for GEM/PAC therapy and five for PAC therapy. No details of any additional interventions were reported.

Baseline characteristics of treatment groups were not reported in the published abstracts. However, some baseline characteristics were available on the manufacturer's website and in conference presentations. Information from these sources is included in the data extraction form in Appendix 7. Participants had a median age of 53 (range 26–83) years in the GEM/PAC therapy group and 52 (range 26–75) years in the PAC group. Metastatic disease was present in 97.0% of the GEM/PAC treatment group and in 96.9% in the PAC treatment group. Approximately 3% of the participants in each group had unresectable, locally advanced breast cancer. This latter group

TABLE 3 *Summary of results presented in abstracts*

Outcomes	GEM + PAC (n = 267)	PAC (n = 262)	p-Value (GEM + PAC vs PAC)	Hazard ratio
Median time to progressive disease[45]	5.4 months (95% CI: 4.6 to 6.1 months)	3.5 months (95% CI: 2.9 to 4.0 months)	p = 0.0013	0.734 (95% CI: 0.607 to 0.889; p = 0.0015)
Overall response rate[45]	39.3% (95% CI: 33.5% to 45.2%)	25.6% (95% CI: 20.3% to 30.9%)	p = 0.0007	Not given
Median overall survival[43]	18.5 months (95% CI: 16.5 to 21.2)	15.8 months (95% CI: 14.4 to 17.4 months)	Not given	0.775 (95% CI: 0.627 to 0.959; p = 0.018)
One-year survival[43]	70.7% (95% CI: 65.1 to 76.3%)	60.9% (95% CI: 54.8 to 66.9%)	p = 0.019	0.740[a] (95% CI: 0.598 to 0.915; p = 0.006).

CI, confidence interval.
[a] After adjusting for baseline covariates.

falls outside the licensed indication for GEM use, but represents only a small proportion of the patients included in the trial. The trial has therefore been included in the current review. Prior anthracycline therapy was reported to have been given in 96.6% of the GEM/PAC group and 95.8% in the PAC group. Treatment was stopped due to disease progression in 38% of women from the GEM/PAC group and 55% of women from the PAC group; disease progression is not defined in the included RCT's available data. The included abstracts give no details of how missing data were handled in the analyses, and it is not clear exactly when treatment was stopped. Further information on the reasons for treatment discontinuation is included in the data extraction form in Appendix 7. The duration of follow-up is reported as a median of 15.6 months in the abstract reporting overall survival data.[43]

Quality assessment

Since the RCT has only been published as a series of abstracts, the quality of reporting and methodology rates poorly against standard quality assessment criteria (see Appendix 7). Both the method of randomisation and concealment of allocation were classified as unknown. Poor scores on these criteria increase the risk of selection bias, with the allocation sequence open to possible manipulation. Without further published information being available, it is not possible to assess whether such selection bias could have affected this trial. The trial reported adequate eligibility criteria, and although limited baseline characteristics were presented in the trial abstracts, further details were available in conference presentations. The assessment of blinding of the care provider, patient and outcome assessors are classed as inadequate, as there was a clear difference in treatments (two drugs versus one drug). This may lead to measurement bias, particularly for subjective outcomes such as QoL assessments. No appropriate intention-to-treat (ITT) analysis was undertaken, and inadequate detail was given as to the numbers of and reasons for withdrawals from the study. Some of the results on the quality assessment criteria may be due to the lack of peer-reviewed, fully published RCT data.

Assessment of effectiveness: results of included trials

The included abstracts' extractable data are shown in *Table 3*. Further data from conference presentation slides were included on the data extraction form, but these are not presented in the table as they are not published and their accuracy cannot be guaranteed.

Survival

The median overall survival was reported to be 18.5 months in the GEM/PAC group and 15.8 months in the PAC group. One-year survival was 70.7 versus 60.9% for the GEM/PAC and PAC groups, respectively. This difference in 1-year survival was statistically significant (p = 0.019). Eighteen-month survival was reported to be 50.7% in the GEM/PAC group and 41.9% in the PAC group, but no statistical analysis of the difference between the groups was presented. Using Kaplan–Meier analysis at approximately 75% (n = 343) of the deaths needed (n = 440) for the planned final overall survival analysis, the hazard ratio (HR) was 0.775 in favour of the GEM/PAC group (p = 0.018). In Cox regression, adjusting for baseline covariates (no detail reported), the HR of 0.74 persisted in favour of GEM/PAC (p = 0.006). However, the final overall survival

analysis is not yet reported. The included abstracts give no details of censoring or other methods of handling missing data. It is not clear how patients who had their treatment stopped due to disease progression (38% of the GEM/PAC group and 55% of the PAC group) were handled in the analysis of survival.

The abstracts report that one patient was not included in the overall survival analysis, but it is not clear which group this patient was from or why she was excluded from the analysis. If the excluded patient's survival was much shorter than that of the rest of her group, exclusion of her data could affect the treatment comparison. However, without further information, it is not really possible to speculate about how the data would be affected by this exclusion.

In an analysis of interim results,[42] progression-free survival was reported to be statistically significantly better with GEM/PAC ($p = 0.0021$), but no further data were presented.

The included trial did not report treatment cross-overs clearly, and it is possible that the overall survival analysis might be affected by patients in the PAC monotherapy subsequently being offered GEM. Most of the subsequent CT received by patients was reasonably well balanced between the two study groups,[45] but subsequent GEM was received by 3.8% of the GEM/PAC group and 14.1% of the PAC group.

Tumour response

Overall response rates were reported in the study abstracts, but no definition of overall response was described. The GEM/PAC group demonstrated an overall response rate of 39.3%. The group receiving PAC alone showed a statistically significantly lower overall response rate of 25.6% ($p = 0.0007$).

Duration of response

The median time to progressive disease was longer in the GEM/PAC group (5.4 months) than in the PAC group (3.5 months). This difference was statistically significant ($p = 0.0013$). The HR for TTP was 0.734 ($p = 0.0015$) in favour of GEM/PAC. It was also reported that the GEM/PAC group had an increased probability of approximately 50% of being disease progression free at 6 months.

Quality of life

The included RCT reports in one abstract[44] that global QoL, as measured by the Rotterdam Symptom Checklist (RSCL), was significantly better in the GEM/PAC group than in the PAC group (p-values for subscales ranged from 0.004 to 0.04). The abstract indicates that 350 out of 529 participants completed the RSC questionnaires, but no further data are presented for this outcome measure. In another of the published abstracts,[42] a statement is made that global QoL was not statistically significantly different between the two treatment groups. It is unclear if this is using the same or a different measure of global QoL.

One abstract[44] reports that 291 out of the 529 participants completed a BPI questionnaire, but does not present results for this outcome measure.

Of patients requiring analgesic at baseline ($n = 216$), the proportion able to decrease analgesic use for more than one treatment cycle was 25% in the GEM/PAC group and 15% in the PAC group. The significance value was not reported in this abstract.[44] Although no data were presented in another of the included abstracts,[42] it does report that there was no statistically significant difference in analgesic use between the two groups. It is unclear if these two reports relate to the same measure or to a different measure of analgesic use.

Adverse events

Adverse events (AEs) are reported in the abstracts of the included RCT, and can be seen in *Table 4*. GEM/PAC combination therapy tended to lead to more AEs than PAC monotherapy. The incidence of neutropenia in the GEM/PAC group was more than double that in the PAC monotherapy group (17.2 versus 6.6%, respectively). Other AEs were only marginally higher in the GEM/PAC group than in the PAC monotherapy group. One death from toxic effects of the drugs was noted in each of the treatment groups. Therapy was discontinued in 6.7% of participants treated with GEM/PAC and in 5.0% of participants treated with PAC. In the unpublished conference presentations, AEs were described in terms of grade 3 or 4 haematological and non-haematological toxicity. These can be seen in Appendix 7.

TABLE 4 *Adverse events*

Adverse event	GEM/PAC ($n = 267$) (%)	PAC ($n = 262$) (%)
Neutropenia	17.2	6.6
Anaemia	1.1	0.4
Thrombocytopenia	0.4	0
Febrile neutropenia	0.4	0

Summary and discussion

- One RCT comparing GEM/PAC combination therapy with PAC monotherapy met the inclusion criteria for this review of clinical effectiveness.
- The RCT was published in three abstracts. The full-text report is currently unpublished.
- The quality of reporting was poor, with an unknown method of randomisation and concealment of allocation. Methodological quality was low in some cases; for example, statistical analyses do not appear to have been undertaken using an ITT principle. Some of the poor ratings on methodological quality may be due to the publications only being available in abstract form, and the absence of a fully published report hampers further assessment of study quality.
- Survival at 1 year was statistically significantly better in the GEM/PAC group than the PAC group. The HR from a Cox regression analysis, adjusted for baseline covariates, was favourable to GEM/PAC and showed a 26% lower chance of survival in the PAC group.
- Treatment with GEM/PAC was also more favourable than treatment with PAC on measures of disease progression. TTP was longer in the GEM/PAC group than the PAC group and overall response rate was lower in the latter group.
- No data were reported relating to QoL.
- AEs were more common with GEM/PAC combination therapy than with PAC therapy alone. This was particularly the case with the incidence of neutropenia.
- Treatment with GEM/PAC confers an improved outcome for patients in terms of survival and disease progression, but with the disadvantage of increased toxicity.

Chapter 4

Assessment of cost-effectiveness

The aim of this section is to assess the cost-effectiveness of GEM and PAC in combination compared with PAC alone as treatment for women with MBC. The economic analysis comprises a systematic review of the literature on the cost-effectiveness of GEM and PAC in combination and the presentation of an economic model and cost-effectiveness results from the Southampton Health Technology Assessments Centre (SHTAC).

Systematic review of existing cost-effectiveness evidence

Methods for the systematic review of cost-effectiveness

A systematic literature search was undertaken to identify economic evaluations comparing the combination of GEM and PAC with existing treatments (single-agent PAC or other relevant comparators) provided as second-line treatment for women with MBC. The details of databases searched and search strategy are documented in Appendix 3.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by a health economist. Economic evaluations were eligible for inclusion if they reported on the cost-effectiveness of the combination of GEM and PAC versus existing treatments for women with anthracycline-resistant MBC. Studies reporting full economic evaluations of other CT regimes for MBC were also identified and obtained to enable a review of key methodological issues in the economic evaluation of treatment for this state of the disease and for the abstraction of any relevant clinical and cost data.

Results of the systematic review of cost-effectiveness

No fully published economic evaluations of GEM with PAC were identified by the systematic literature search. Five studies reporting economic evaluations of other CT regimes were identified from the initial literature search [Appendix 3, 'Health economics search strategy for MEDLINE (OVID)', p. 42] before applying the filters specific to the GEM and PAC combination. *Table 5* reports the CT regimes included in the published economic evaluations.

Chemotherapy for women with metastatic breast cancer: published economic evaluations

In the absence of published economic evaluations of the combination of GEM and PAC, this section presents a brief review of the methodology and assumptions adopted for the economic evaluations of other second-line CT for women with MBC. We present an overview of methods used to model disease progression, to estimate benefits/outcome and to estimate costs.

Summary of methods used in published economic evaluations

Five fully published economic evaluations of CT regimes for treatment of women with recurrent MBC were identified.[46–50] The studies used models that were structurally similar, with four using identical models. Brown and Hutton,[48] Brown and colleagues[49] and Cooper and colleagues[50] adopted the economic model developed by Hutton and colleagues[46] with updated clinical data, newer assumptions for health state utility values or applying the model to new treatment options.

TABLE 5 *Chemotherapy regimes*

Agent	Dosage (mg/m^2)	Source
Docetaxel	100	Hutton *et al.*,[46] Launois *et al.*,[47] Brown and Hutton,[48] Brown *et al.*,[49] Cooper *et al.*,[50]
Paclitaxel	175	Hutton *et al.*,[46] Launois *et al.*,[47] Brown and Hutton[48]
Paclitaxel	200	Brown *et al.*,[49]
Vinorelbine	30	Launois *et al.*,[47] Brown *et al.*,[49]
Doxorubicin	75	Cooper *et al.*,[50]

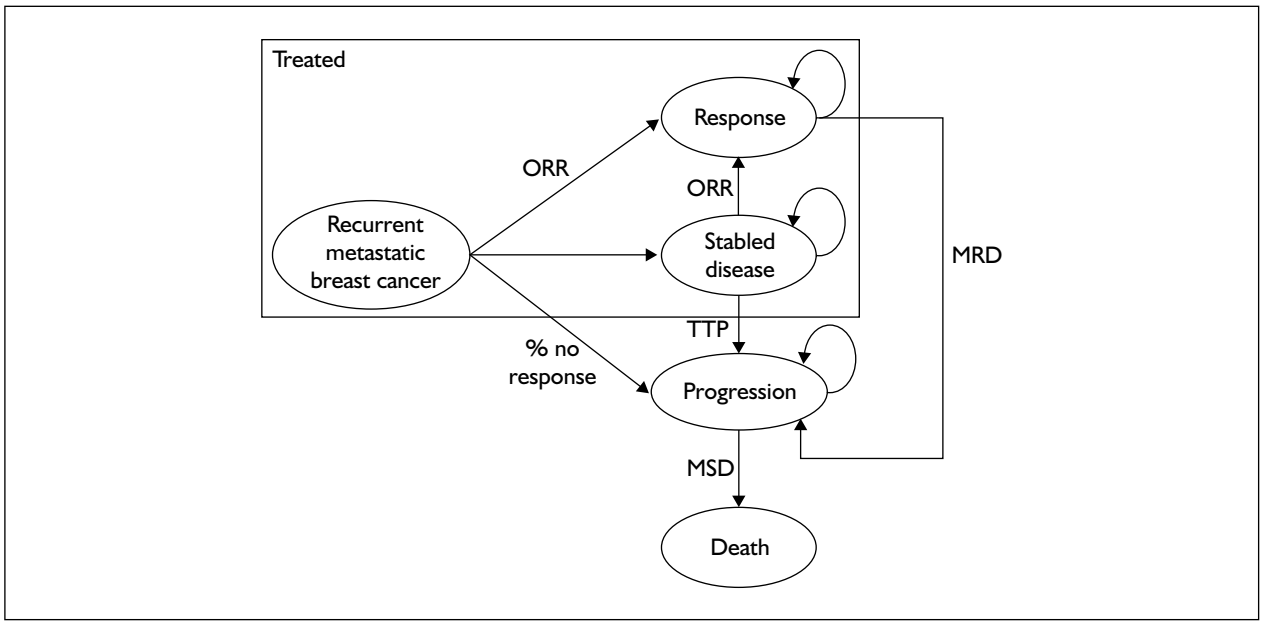

FIGURE 1 *Model structure adopted in economic evaluations of chemotherapy regimes for recurrent MBC: treatment response and disease progression*

The evaluations included data from trials which included patients with anthracycline-resistant disease. However, the proportion varied markedly between included trials. PAC prescribing data, used by Hutton and colleagues,[46] were pooled for a cohort of patients in which only 17% had anthracycline-resistant MBC. A similar proportion was reported for PAC data included by Launois and colleagues,[47] whereas the data extracted for docetaxel came from a pooled analysis in which 75% of patients had anthracycline-resistant disease. Patients in the trials included by Brown and Hutton[48] were all anthracycline-naïve.

Each of the published evaluations established the case for adopting decision analytical modelling of cost-effectiveness of new drugs for cancer CT. They based this on the rapid pace of development of new therapies, arguing that this precludes the collection of comprehensive empirical data on cost-effectiveness before these new therapies are in general use. As a result, Markov state transition models were adopted to extrapolate effects reported in clinical trials to cohorts of women with MBC. The principal treatment effects included in the models have been the proportion of patients responding to treatment (either partial or complete response) and the duration of response, and also progression-free survival for patients whose disease initially stabilises during treatment. These effects result in a delay in disease progression for patients who respond or whose disease stabilises, which may not increase overall survival but is expected to result in improved QoL.

The proportions of patients experiencing treatment-related toxicities were extracted from clinical trial reports or in one case general prescribing information.[46] In all cases, it was assumed that patients experiencing severe or life-threatening toxicities would discontinue treatment and would immediately enter the progressive disease state. The effect of less severe toxicity assumed in the models was to reduce QoL during the treatment cycle in which the toxicity occurred.

The Markov models were used to estimate patients' life expectancy, quality-adjusted life expectancy and lifetime costs. Life expectancy was estimated based on the number of model cycles that a cohort of patients spends in any health state (other than death), irrespective of disease progression or the development of toxicity. Quality-adjusted life expectancy was estimated by adjusting the life expectancy estimates according to weightings intended to reflect QoL in the different health states and the impact of treatment-related toxicity. It was assumed that QoL declines with disease progression and, for each health state, is lower when patients develop treatment-related toxicity.

Modelling response to treatment and disease progression

Figure 1 illustrates the general structure adopted in the economic evaluations reviewed in this section. All patients entering the model have either failed to respond to or have relapsed following first-line treatment for MBC. On

initiation of CT patients may respond to treatment [estimated from the overall response rates (ORRs) reported in clinical trials and converted to a probability of response per treatment cycle; see Cooper and colleagues,[50,51] for the method] or may experience stabilisation of their disease (typically estimated as the default transition, i.e. those patients who do not respond or whose disease does not progress). Patients responding to treatment remain in the response state until they develop progressive disease [using probabilities derived from the median response duration (MRD) reported in clinical trials; see Cooper and colleagues[50,51] for the method], and cannot enter the stable disease state. Patients whose condition stabilises may enter the response state (using a probability of response per treatment cycle derived from the ORR), may remain in the stable state or may develop progressive disease (using probabilities derived from the median TTP reported in clinical trials). All the models assume that patients in the response or stable disease states need to enter the progression state before dying from MBC – probability of death is derived from the median survival duration (MSD) reported in the clinical trials or based on expert opinion.

The studies vary substantially in the sources used for calculating transition probabilities for response to treatment and disease progression. Hutton and colleagues[46] derived the majority of their input data from drug-prescribing information data sheets, although the MRD, median duration of stable disease and 1-year mortality were all assumed (based on literature review and clinical opinion). Brown and Hutton[48] derived all transition probabilities from two trials where each of the drugs were compared with doxorubicin – where data for certain toxicities were not available for PAC, the values extracted for docetaxel were used. Launois and colleagues[47] used data from a pooled analysis of three Phase II trials for docetaxel, a single large trial for PAC and an uncontrolled clinical series for vinorelbine. Cooper and colleagues[50] were the only authors who sought to derive all their input data – treatment effects, median progression-free and overall survival and toxicity probabilities – through pooling and formal meta-analysis of trial reports.

The studies vary in the degree of detail provided on how the observed response rates, MSD data and proportion of patients experiencing toxicity were used in their models. Both Hutton and colleagues[46] and Brown and Hutton[48] report the observed values extracted from clinical trial reports and refer to these as probabilities – no indication is given on whether, or by what method, these observed values were converted to cycle probabilities. Launois and colleagues[47] and Cooper and colleagues[50] report the ORRs, MSD estimates and proportion of patients experiencing toxicity, but also clearly indicate how these data have been converted to cycle probabilities. Both studies use a standard approach for the survival data, deriving rates from the medians using the method described by Beck and colleagues.[52] Transition probabilities are then derived from the rates as described by Miller and Homan.[53] For observed data that are reported as proportions (ORR and toxicity), transition probabilities for each cycle were derived using the method described by Miller and Homan.[53] Each of these methods is based on the assumption that the survival functions follow an exponential decline with hazards that are constant with respect to time – neither study reports any empirical tests for this assumption or estimates of the impact of alternative parametric assumptions.

Overall survival in the studies by Hutton and colleagues[46] and Brown and Hutton[48] was constrained to be same for both treatments. In the former study the mortality rate (MR) at 1 year from the start of treatment was assumed to be 57% for both docetaxel and PAC – in the latter the corresponding figure was 35%, therefore life expectancy in the progressive health state was lower for treatments providing higher response rate.

Quality of life: disease progression and treatment toxicity

Quality-adjusted life expectancies in each of the evaluations were derived by applying health state utilities to the relevant health states. In each model, utility declines with disease progression and in each of the treatment eligible states (response or stable) utility values are lower for patients experiencing toxicity than for those who do not.

Three of the published evaluations[46–48] report primary empirical studies developing health state utilities for patients with MBC, with or without treatment-related toxicity. The studies used similar methodology in which health state descriptions, developed in collaboration with oncology nurses and clinical specialists in breast cancer treatment, were valued by samples of oncology nurses using the standard gamble method. The health state descriptions were based on six dimensions (ambulation, dexterity, emotion, cognition, pain/activities and personal care) from a generic

health status classification (Health Utilities Index Mark One[54] and Mark Two[55]) and six further dimensions (fear/anxiety, depression, energy, hair loss, pain relief and nausea) specific to oncology patients and those undergoing CT. Each dimension comprised between three and six levels. In the original study by Hutton and colleagues,[46] 23 health states were defined using these dimensions. These states, plus two additional marker states (best possible and worst possible health), were valued by participating nurses, although only eight states were used in the final model. In Launois and colleagues' study,[47] 24 states were valued, whereas Brown and Hutton[48] derived 13 health state values.

In all the studies, health state values were based on the responses of samples of oncology nurses (29 UK nurses,[46] 20 French nurses[47] and 29 US nurses[48]). Hutton and colleagues[46] and Brown and Hutton[48] compared the valuations they derived from the UK and US nurses to valuations derived from nurses practising in other countries (Germany, Italy, The Netherlands and Spain) and found that the average valuations were consistent across all countries. Cooper and colleagues[50] pooled health state valuations from these three studies to develop utility estimates for eight health states in their study.

None of the evaluations report whether outcomes have been discounted. Given the comparatively short overall survival for patients in these studies (median survival for all patients in Launois and colleagues' study[47] was 12 months), this is unlikely to have a substantial effect on the outcome estimates.

Modelling treatment and health state costs
None of the evaluations used prospectively recorded costs for clinical trial patients, although Launois and colleagues[47] used data from an observational study of patients undergoing CT for recurrent MBC to develop their intervention and health state costs.

Hutton and colleagues[46] and Brown and Hutton[48] used clinical experts to develop protocols of expected resource use for patients in each of their identified health states. These included estimates of drug use, hospitalisation and outpatient attendance, medical and nursing inputs, diagnostic tests and therapeutic procedures required in each health state (responsive, stable and progressive disease) and, where relevant, the additional resources required to manage treatment-related toxicity. The resource estimates were converted to health state costs using unit costs derived from national cost databases or from the published literature. CT costs were calculated for standard dosages, assuming a patient body surface area (BSA) of 1.7 m^2 and using prices quoted in the Monthly Index for Medical Specialties (MIMS)[56] for the UK and from Medicare and third-party payers for the USA.

Cooper and colleagues[50] based their health state costs on the resource assumptions for doctor and nursing inputs, outpatient attendance and diagnostic tests developed by Hutton and colleagues.[46] Costs for hospitalisations and treatment of toxicities were based on data from NHS Reference Costs or from the literature. Drug costs for each CT regime were calculated from unit costs reported in a systematic review of taxanes used in the treatment of advanced breast cancer,[37] which assumed a BSA of 1.75 m^2. Additional costs for each regime included hospital costs for the administration of CT and premedication costs for docetaxel.

Conclusion/summary
The evaluations reviewed in this section adopted similar methodology, using Markov state transition models to estimate the costs and outcomes of CT regimes for patients with recurrent MBC. The models consisted of four states (responsive, stable disease, progressive disease and death) and applied transition probabilities derived from the literature, including clinical trial reports and case series. Where data were missing, expert opinion was used. The models adopted a lifetime horizon, running until the majority of the cohort was in the absorbing health state (death).

All the evaluations included adjustment for QoL to take account of the differing rate of disease progression (in the absence of differences in overall life expectancy) and varying toxicity profiles of the different CT regimes. All the health state utility values were based on ratings provided by oncology nurses. These ratings appear to be consistent between studies and, where this was reported, between nurses working in different countries. However, no comparisons of these ratings against those derived from patients with MBC or undergoing CT have been reported.

SHTAC cost-effectiveness model

Methods

A Markov state transition model was developed, adopting the structure reported in previous

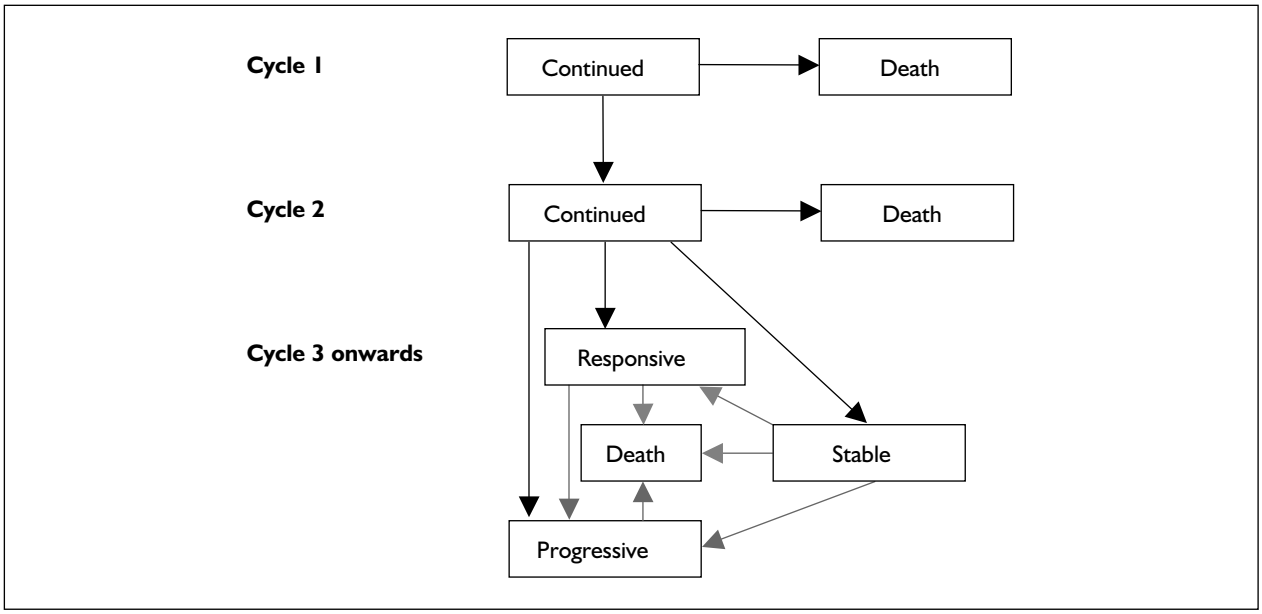

FIGURE 2 *Possible health state pathways in the model*

economic evaluations. The state transitions considered in this assessment, as shown in *Figure 2*, are modified from those shown in *Figure 1*. In the model, patients are classified into one of the following disease states:

- response: complete and partial (>50%) tumour disappearance
- stable: no change
- progression: tumour growth or spread to other sites
- death.

Assumptions

The main assumptions of the model were that:

- During treatment cycles, individuals could only enter the responsive state from the stable state.
- Having entered the responsive state individuals either remain in that state, move to the progressive state or die.
- Having entered the progressive state individuals either remain in that state or die.
- Individuals in all states are subject to a mortality risk, which increases with disease severity.
- Individuals in the responsive and stable states are subject to risk of disease progression, which increases with disease severity,
- Minor toxicities are treatable and CT continues.

Following the protocol for the clinical trial, it was assumed that patients who did not experience serious AEs continued CT until entering the progressive state.[42] The model adopted a lifetime horizon with a cycle length of 3 weeks, corresponding to the length of the CT cycle.

Figure 2 illustrates patient pathways through the model. All patients remain on CT during the first two cycles – during this time no assessment of response is made. At cycle 3, and in each subsequent cycle, patients are assessed for response to treatment. Patients classified into the progressive state discontinue treatment and remain in this state until death. Patients in the response or stable health states, who remain on CT, may develop treatment-related toxicity or may discontinue treatment due to serious AEs.

Model parameters

Transition probabilities

Death

Mortality risks were estimated from the reported survival functions for patients in each arm of the RCT reported by Albain and colleagues.[43] The survival probabilities for patients in the PAC arm of the trial were estimated from the reported survival plots[45] and a parametric survival function fitted to these data using the outputs from an ordinary least-squares regression on a log-cumulative hazard[57] (for full details, see Appendix 8). This provides an estimated survival function for the cohort of patients in the PAC arm of the trial. The reported HR was then used to obtain the estimated survival function for the cohort of patients in the GEM/PAC arm.

TABLE 6 *Adjustment for mortality risk and risk of disease progression*

Adjustment	Health state	Rate
Adjustment for mortality risk	Responsive	0.2
	Stable	0.5
	Progressive	1.0
Adjustment for risk of disease progression	Responsive	1.0
	Stable	1.5

TABLE 7 *Overall response rates and trial follow-up duration*

Parameter	GEM/PAC	PAC	Source of inputs
Overall response rate	0.393	0.256	Trial data[42]
No. of follow-up cycles	30	30	Trial data[42] (converted from 21 months assumed in trial follow-up)

It is likely that patients who have responded to treatment or whose disease has stabilised will be at a substantially lower risk of death than those whose disease has progressed. We adjusted the baseline mortality risk, derived from the estimated survival function for patients in each arm of the trial, using the factors reported in *Table 6*. These factors were derived using a clinician's input, and reflect the assumption that mortality risk increases with disease severity. To illustrate, the mortality risk in the responsive state is one-fifth of that for the progressive state, and mortality risk for the stable state is half of that for the progressive state.

Disease progression

Risk of disease progression was estimated from the plot of time to documented disease progression[45] and the HR reported from the trial, using the method described above. Since this provides an overall estimate for the cohort of patients in each arm of the trial (including both patients who respond to treatment and those whose disease stabilised), we adjusted the risk with a clinician's inputs, as reported in *Table 6*, which reflect the assumption that the risk of disease progression is lower for patients who show a response to treatment.

Response to chemotherapy

The ORRs to CT for each treatment arm reported in the trial are shown in *Table 7*. The probability of responding in each treatment cycle for those in the stable state was estimated using a standard formula,[53] which assumes that these rates follow an exponential function over time – see Appendix 9 for details.

Toxicities

It was assumed that toxicities are reversible and disappear once CT is discontinued. Therefore, the impact of toxicities on QoL were considered only for those in the stable and responsive states, since CT was discontinued on entering the progressive state. The proportions of patients demonstrating grade III and IV toxicities were reported in the trial and are shown in *Table 8*. The probability of developing each of the reported toxicities at each treatment cycle was estimated using the standard formula and assumptions described in the previous section. The risk of developing each toxicity in each treatment cycle was assumed to be independent of whether the individual had experienced any toxicity in previous cycles and was also independent of developing other toxicities at each cycle. The risk of developing any toxicity in each cycle was therefore the sum of the risks of developing each toxicity.

Discontinuation of chemotherapy

The proportion of patients discontinuing treatment was reported for each arm in the trial and is shown in *Table 8*. These proportions were converted to a transition probability using the approach described above for response to CT.

Utilities

Health state utilities for each of the disease states with or without treatment-related toxicities have been reported in other studies of CT for MBC. These values do not depend on the type of CT that patients receive, but do depend on the state of disease and on the development of toxicity. The health state utilities reported by Cooper and colleagues[50] are pooled estimates derived from the

TABLE 8 *Proportions of patients who developed toxicities and discontinued chemotherapy*

Parameter	Toxicity	GEM/PAC	PAC	Source of inputs
Proportion of patients developing treatment-related toxicity	Anaemia	0.07	0.025	Trial data[42]
	Neutropenia	0.48	0.03	
	Leucopenia	0.11	0.02	
	Thrombocytopenia	0.055	0.00	
	Neuropathy	0.06	0.04	
	Emesis	0.03	0.03	
	Fatigue	0.07	0.02	
	Diarrhoea	0.03	0.02	
	Dyspnoea	0.025	0.00	
	Elevated liver enzymes	0.07	0.01	
Proportion discontinuing treatment due to AEs		0.07	0.05	

TABLE 9 *Health state utilities*

Health state	Health state utility score		Source
	Without toxicity	With toxicity	
Responsive	0.81	0.67	Cooper *et al.*[50]
Stable	0.65	0.54	
Progressive	0.45	0.45	

health state valuation studies reviewed in the published section 'Chemotherapy for women with metastatic breast cancer: economic evaluations' (p. 15). They provide estimates for health states relevant to our model, with and without toxicity, and were adopted for this analysis (*Table 9*).

To calculate the expected utility for a given health state, it was assumed that toxicities are mutually independent and that their probability of occurrence in each cycle is the same in all treatment-eligible health states. Since the proportion of patients developing toxicities varies between treatment groups, as reported in the trial,[42] the expected utility for each health state would be different between the treatment groups.[50] The expected utility for each state, taking into account the development of treatment-related toxicity, is the sum of two calculations. First, the probability of developing any toxicity is multiplied by the utility score for the given health state in the presence of treatment-related toxicity. Second, the probability of not developing any toxicity is multiplied by the utility score for the state without toxicity. Expected utility is the sum of these two values – see Appendix 9 for details.

We assumed that toxicities do not persist upon discontinuation of CT. As CT is discontinued on entering the progressive state, the expected utility for patients in that state is identical in both treatment groups.

It should be noted that as disease state would only be determined from cycle 3, a general initial utility score independent of study group (0.64), as reported by Cooper and colleagues,[50] was assigned to all the patients.

Costs

Costs for the stable and response states at each cycle consisted of two components: drug and administration costs for patients continuing CT and the costs of managing treatment-related toxicity.

CT costs were based on the dose regimen specified in the trial protocol.[42] In each cycle, patients in the PAC arm received 175 mg/m^2 by 3-hour intravenous infusion on the first day of the cycle. Patients in the GEM/PAC group received GEM at 1250 mg/m^2 on days 1 and 8 in addition to PAC at 175 mg/m^2 on day 1. Drug unit costs were taken from the BNF, No. 50 (September 2005).[58] CT costs per cycle were calculated for a patient with an average BSA of 1.6 m^2. Other treatment-associated costs, such as administration and consultation costs, were considered for each CT regimen. The expected CT costs per cycle were

TABLE 10 *Costs of chemotherapy, consultation, administration and treatment of toxicities*

Parameter	Unit costs (£)[a]	Source
Consultation	61.24	Cooper *et al.*[50]
CT administration	84.81	
Drug:		
GEM/PAC	1766.84	Estimated from BNF 50[58]
PAC	985.60	
Treatment for toxicities:		
Anaemia	611.35	Cooper *et al.*[50]
Febrile neutropenia	1111.97	
Emesis	433.48	
Diarrhoea	154.31	
Thrombocytopenia	184.39	Nuijten *et al.*[59]
Neuropathy	151.87	Brown *et al.*[49]

[a] These are inflated costs based on inputs from various sources using the NHS Pay and Prices Index.

TABLE 11 *Base-case analysis*

Per patient	GEM/PAC	PAC	Difference
Cost (£)	26,202	16,653	9,549
Life-years gained	2.01	1.69	0.32
QALYs gained	1.00	0.83	0.16
Cost per QALY gained (£)			58,876
Cost per life year gained (£)			30,117

calculated by multiplying the CT unit costs shown in *Table 10* by the probability of continuing CT.

Unit costs for managing toxicities were developed with reference to other published studies.[49,50,59,60] The expected costs of managing toxicities per cycle were calculated by first multiplying the probability of developing each toxicity by the appropriate unit cost for treating the toxicity (see *Table 10*) and then taking the sum of these values.

The costs for the stable and responsive states at each cycle were therefore the sum of the expected treatment costs and the expected costs of managing toxicities – see Appendix 9 for details.

As CT discontinues on entering the progressive state, there are no associated CT costs or costs of managing toxicities. The costs for the progressive state are based on the frequency of GP and nursing visits and provision of palliative treatment reported in the literature.[50]

All unit costs, other than for CT drugs, were identified from other studies in the UK setting and then inflated using the NHS Pay and Prices Index.[61]

Results

Both the overall survival and TTP data estimated from the trial reports were shown to fit well to a Weibull distribution (for the estimates of distribution coefficients, see Appendix 10). A cohort of 1000 patients was run through the model with costs and outcomes discounted at 3.5%.[62]

Base case analysis

Table 11 reports the total costs, health outcomes [in terms of life-years and quality-adjusted life-years (QALYs)] for each treatment group and the incremental cost-effectiveness ratios (ICERs) for the combination of GEM and PAC compared with PAC alone.

Average costs are approximately 50% higher for the GEM/PAC combination compared with PAC alone. The majority of this difference is due to the cost of CT drugs rather than differences in the costs of managing toxicity or disease progression. Quality-adjusted life expectancy is lower than

TABLE 12 *Sensitivity analysis based on only six cycles of chemotherapy*

Per patient	GEM/PAC	PAC	Difference
Cost, £	20,980	14,903	6,078
Life years gained	1.96	1.66	0.30
QALYs gained	0.98	0.83	0.16
Cost per QALY gained (£)			38,699
Cost per life year gained (£)			20,021

TABLE 13 *Sensitivity analysis based on only responsive and stable state patients*

Per patient	GEM/PAC	PAC	Difference
Cost, £	16,115	7,749	8,366
PFS years gained	0.49	0.39	0.09
QAPFS gained	0.32	0.26	0.06
Cost per QAPFS gained (£)			136,251
Cost per PFS year gained (£)			91,926

PFS, progression-free survival; QAPFS, quality-adjusted progression-free survival.

unadjusted life expectancy for both CT regimens due to the substantial QoL decrements associated with treatment-related toxicity and disease progression.

The addition of GEM to PAC for treating MBC incurs an additional cost of £30,117 on average for each life-year gained. After adjusting life expectancy for QoL, the estimated ICER is £58,876 per QALY gained.

Sensitivity analyses

The base-case analysis reported above is based on the inputs from a clinical trial, and these may have limited generalisability to clinical practice. We consulted an oncologist from a teaching hospital for clinical inputs into the model. In practice, it is not realistic to treat the patients until they enter the progressive state. Very few people are offered more than six cycles of CT, after which patients would often consider moving to other treatments. The maximum of six cycles of CT in practice is due to the cumulative toxicities and standard limits on the length of CT. Therefore, it is less applicable to run the model until death, with CT given to patients until they enter the progressive state. Sensitivity analyses were conducted for the above scenarios separately. The results are given in *Tables 12* and *13*.

Probabilistic sensitivity analysis

Parameter uncertainty is addressed using probabilistic sensitivity analysis. Probability distributions around the point estimates used in the base-case analysis were assigned to the parameters. Appendix 10 reports the parameters included in the probabilistic sensitivity analysis, the sampling distribution used and the mean and standard error for each parameter. The parameters for each distribution were estimated from the point estimates and their standard errors using the method of moments.[63] Where no standard errors were reported or where no value could be estimated from the reported data, we assumed appropriate values.

The results of the probabilistic sensitivity analysis using 1000 evaluations of the model for each study group are presented on a cost-effectiveness plane in *Figure 3* and as a cost-effectiveness acceptability curve (CEAC) in *Figure 4*.

The majority of the results shown in *Figure 3* are found in the north-east quadrant of the cost-effectiveness map. They indicate that outcomes (in terms of quality-adjusted life expectancy) are higher with the GEM/PAC combination than with PAC alone, but that this treatment option also costs more. In all the simulations, costs were higher for the GEM/PAC combination. However, the QALY gain was close to zero or negative in some simulations. In all cases the QALY gain was <1, while the incremental costs for the GEM/PAC combination range from around £5000 to £20,000.

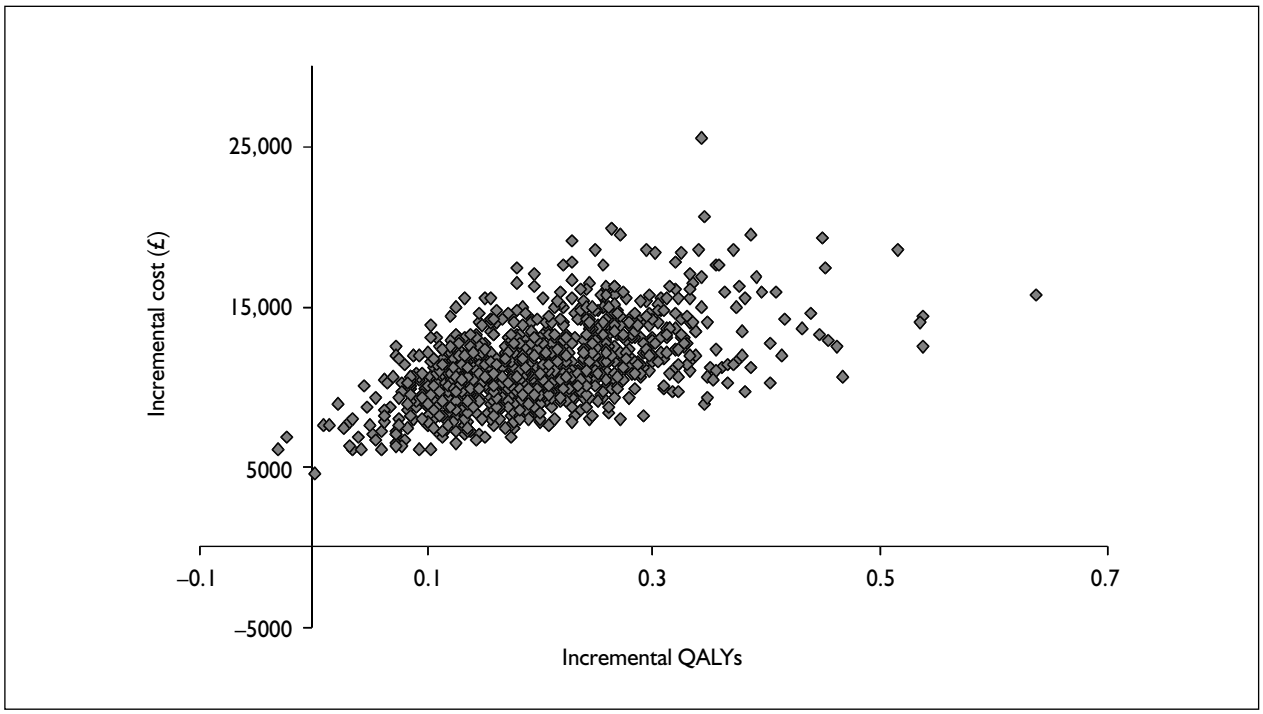

FIGURE 3 *Density of incremental costs versus incremental QALY gained: cost-effectiveness plane (based on Weibull survival function)*

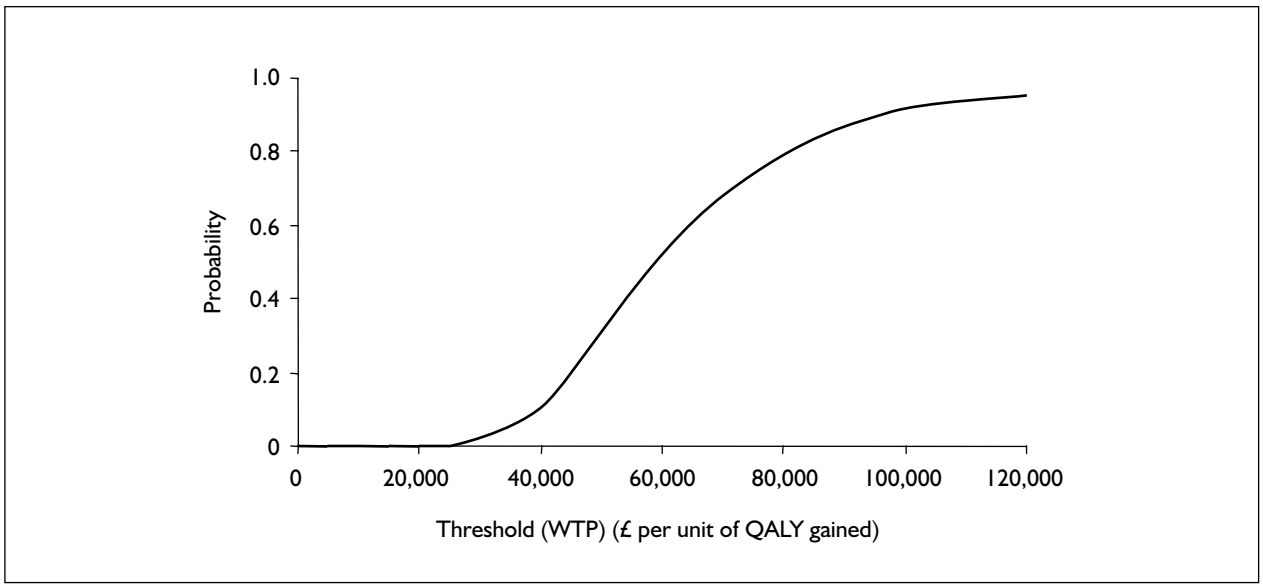

FIGURE 4 *CEAC for GEM/PAC combination (WTP, willingness to pay)*

The CEAC summarises the information shown in the cost-effectiveness map and reports, for a given intervention, the proportion of simulations showing a positive incremental net benefit for a range of values of willingness to pay per QALY gained. The curve can be interpreted as the probability that the GEM/PAC combination is more cost-effective than PAC alone, based on available evidence. *Figure 4* suggests that the GEM/PAC combination is unlikely to be a more cost-effective option until the willingness to pay per QALY is above £60,000.

Discussion

The base-case analysis shows high ICERs. Costs per QALY gained and per life-year gained were calculated to be £58,876 and £30,117, respectively (*Table 11*). The model predicts that addition of

GEM to PAC in treating patients with MBC results in a gain in life expectancy. However, the higher toxicity profile for the combination CT, shown in the clinical trial and reported in the section 'Adverse events' (p. 12) and *Table 4*, reduces a patient's QoL. This leads to a lower gain in quality-adjusted life expectancy than the initial gain in life expectancy would suggest. A trade-off between increased life expectancy and greater toxicity is often seen in CT studies which compare combination therapy with monotherapy.[64]

A potential limitation of this analysis is the fact that health state utilities were assumed to vary by disease state and toxicity, regardless of treatment received by patients. This approach was adopted in common with the previously published economic evaluations reviewed in the section 'Chemotherapy for women with metastatic breast cancer: published economic evaluations' (p. 15). The values adopted were pooled estimates[50] from other studies,[46–48] although these were all derived before GEM was available and were based on valuations by clinical staff experienced in caring for patients with MBC rather than by patients themselves. This could be improved if utility scores amongst MBC patients treated with GEM and PAC become available in the literature.

The sensitivity analyses demonstrate that different types of model structure could be considered. To reflect standard clinical practice, the model was modified by limiting CT to only six cycles. To be consistent with the base-case analysis, the cost for treating the toxicities was included in only those six cycles with CT. Both ICERs show a reduction of around 34%, with £38,699 per QALY gained and £20,021 per life-year gained.

It is common in clinical practice for patients to receive a different CT after discontinuation from a regimen of CT due to disease progression or its toxicities. It is unclear whether the overall survival analysis reported in the trial[42] includes follow-up of those patients after being discontinued from the study CTs. Therefore, the model was modified to evaluate the impact of GEM in disease progression. The respective ICERs, per PFS in years gained and per quality-adjusted PFS in years gained, are more than 1.3 and 2.0 times those estimated in the base-case analysis. This substantial increase in the ICERs is due to the smaller gain in both the PFS and quality-adjusted PFS between the two study groups, as shown in *Table 13*, in comparison with that under the base-case analysis. It also indicates that GEM added to PAC improves the overall survival more in the progression period than in the progression-free period.

The uncertainty around parameters was presented in *Figure 4*. It shows that GEM has an unfavourable probability profile, being cost-effective at high willingness-to-pay thresholds. At a threshold of £60,000 per QALY gained, GEM/PAC begins to be more likely to be cost-effective than PAC alone. The uncertainty around model parameters will be reduced when more trial data are published, thus improving future models of cost-effectiveness.

Chapter 5
Discussion

Statement of principal findings

The key findings of this review of GEM with PAC for the treatment of MBC are summarised below.

Clinical effectiveness

Only one RCT met the inclusion criteria for this review. As of February 2006, this has only been published as a series of three conference abstracts, with additional information available in conference presentations. It is difficult to assess the quality of this study from the available information. The included RCT reflects the licensed indication for GEM and PAC for the treatment of MBC. The nature of the treatment schedule (combination therapy versus monotherapy) prevented blinding of patients and of doctors administering the drugs.

Almost all of the patients in the RCT had metastatic disease (97%) and over 70% had visceral metastases. Approximately 75% of the included patients had two or more metastatic tumour sites and 96% of the group had received prior anthracycline therapy. Just under 40% of patients had ER- or PR-positive disease, and approximately 50% of the total patient group had received prior hormonal therapy. The RCT population had a median age of 53 years. Consultation with clinical advisors suggests that MBC patients seen in clinical practice tend to have higher rates of ER disease and be somewhat older than the RCT population, but are similar enough for the results of the included RCT to be extrapolated to the general population of patients with MBC (anonymous clinical expert: personal communication, April 2006).

The included RCT's interim results showed a statistically significant increase in 1-year survival rate for the patients receiving GEM. Approximately 71% of the GEM/PAC patients survived for 1 year, compared with 61% of the PAC-only group. Median survival was approximately 3.5 months longer in the GEM/PAC group than in the PAC monotherapy group.

The abstracts of the included study did not report detailed data on QoL measures, but it is likely that the higher toxicity associated with GEM would impact on a patient's QoL. AEs were more common in those patients receiving GEM and the incidence of neutropenia was considerably higher (17.2% for GEM/PAC versus 6.6% for PAC only).

The RCT did not include any detailed subgroup analyses. It is therefore not possible to report on the clinical effectiveness of GEM for patient subgroups, such as those with particular ER status or HER-2 scores.

Economic evaluation

A systematic review of the cost-effectiveness literature did not identify any fully published reviews of GEM with PAC for the treatment of MBC. Five fully published economic evaluations of other CT regimes for anthracycline-resistant MBC were identified.[46–50]

Since there were no published economic evaluations including the GEM/PAC combination for MBC, we developed a Markov state transition model to assess the cost-effectiveness of this CT regime. The base-case analysis shows high ICERs. Costs per QALY gained and per life-year gained were estimated to be £58,876 and £30,117, respectively.

GEM has an unfavourable probability profile, being cost-effective at high willingness-to-pay thresholds. GEM/PAC only begins to be more likely to be cost-effective at a threshold of £60,000 per QALY gained. The uncertainty around model parameters will be reduced when more trial data are published, thus improving future models of cost-effectiveness.

Strengths and limitations of the assessment

Clinical effectiveness

This report was guided by the principles for undertaking a systematic review, and our methods were stated in a protocol (Appendix 2). The protocol defined the research question, inclusion criteria, quality assessment criteria and data extraction process. A clinical advisory group has informed the review from the development of the research protocol to completion of the report.

The systematic review was restricted by the lack of published evidence for GEM's licensed indication. In the absence of any fully published studies, we used data from three abstracts to form the basis of the review of clinical effectiveness. The abstracts did not contain sufficient methodological detail to allow a fair assessment of study quality, and there was a lack of detailed data on QoL outcomes. Conference presentations were available via the Internet, but these were not peer-reviewed publications so their accuracy could not be guaranteed. Lack of data also hampered interpretation of results. For example, GEM was reported to have a statistically significant benefit in terms of overall response, but a 'response' was not clearly defined in the available information. It was not possible to say how well this relates to a clinically meaningful improvement.

This review was restricted to the licensed use of GEM (i.e. in combination with PAC) to reflect the scope issued by NICE as part of its appraisal process that was originally used to commission this assessment. Many oncologists are cautious about using a taxane as part of second-line therapy if the patient has previously been exposed to another drug of this type. Increasing numbers of patients are being exposed to taxanes in the adjuvant setting, so this may restrict the use of PAC as second-line therapy, and hence the use of GEM in its licensed form (with PAC). For patients who have already received treatment with a taxane, a doctor might consider using GEM alone or in combination with a platinum drug, rather than using the licensed combination of GEM with PAC. Despite these concerns, the assessment of GEM's use in such situations was considered to be outside the remit for this report.

Economic evaluation

A limitation of the economic model is the assumption that toxicities are mutually independent, whereas development of toxicities might be correlated from one to another and also from one cycle to the next cycle. Clinical experience suggests that there may be an increased risk of toxicity, particularly the same toxicity, if toxicity has been experienced in previous cycles. This assumption, which is common to other economic models of cancer CT, is generally adopted due to lack of data and also to avoid excessive computational complexity. This could theoretically result in an underestimated ICER, but the low transition probabilities of toxicities estimated from trial data suggest that the impact of this assumption on ICERs would be negligible.

The included trial did not report treatment cross-overs clearly, and it is possible that the overall survival and TTP analyses may have been affected by patients in the PAC monotherapy group subsequently being offered GEM. This is therefore a possible source of bias, which may have resulted in overestimation of the ICER. The majority of the subsequent CT received by patients was reasonably well balanced between the two study groups,[45] but subsequent GEM/PAC was received by 3.8% of the GEM/PAC group and 14.1% of the PAC group. It is difficult to judge the likely impact of this difference on cost-effectiveness estimates as the GEM regimen (single agent or in combination with PAC) is not clearly stated, nor are the durations of subsequent CT reported.

Since very few patients are offered more than six cycles of CT, the model was modified in the sensitivity analyses to provide cost-effectiveness estimates for standard clinical practice. The cost per QALY gained decreased from £58,876 to £38,631 on limiting CT to six cycles. However, as the patients in the trial received study CT until entering the progressive state, limiting study CT to six cycles would not be expected to produce the survival and TTP outcomes reported in the clinical trial. As a result, the ICERs reported in *Table 12* are likely to be underestimates, since lower gains in life expectancy and QALYs would be expected.

Chapter 6
Conclusions

The review of clinical effectiveness is based on data from a single RCT which has not yet been fully published. The trial rated poorly on quality assessment criteria, although this was partly a reflection of publication status and lack of published information. Only tentative conclusions can therefore be drawn from the review.

Evidence from the included RCT indicates that treatment with GEM/PAC confers an improved outcome for patients in terms of survival and disease progression, but at the cost of increased toxicity. An economic model developed for this review produced high costs per QALY for this treatment combination. The base-case analysis shows high ICERs, with costs per QALY gained exceeding £58,876. This is higher than would usually be considered to be a cost-effective treatment from the NHS's perspective.

Suggested research priorities

Given the lack of published data on the use of GEM with PAC for the treatment of MBC, it would be helpful to update this systematic review in 12–18 months' time. The conference abstracts included in this review were published in 2004, and publication of the full papers was expected to take place in 2005. However, they did not appear in our searches which were carried out up to March 2006.

The rationale behind adding GEM to PAC treatment is to improve on the effectiveness of PAC as a single-agent taxane. It would therefore be useful to compare this treatment combination with other trials investigating the use of a taxane in combination with other agents. For example, a trial has been conducted which compared docetaxel with or without capecitabine,[65–67] and another has compared docetaxel and GEM favourably with docetaxel and capecitabine.[68] Evaluation of these treatment comparisons would provide useful information, but was outside the scope of this review. Further work is therefore suggested in the form of a systematic review and economic evaluation of docetaxel and capecitabine compared with GEM. Given the lack of head-to-head trials in this area, indirect comparison could provide useful information for future economic models of treatments for MBC.

This review identified a lack of RCT data for GEM treatment of MBC, and more RCTs with economic evaluations, particularly head-to-head comparisons with other treatments for MBC, would be helpful. Vinorelbine and GEM have similar scheduling, and a head-to-head trial of these treatments is recommended. More QoL data would be useful to future economic evaluations in this area, and it would be appropriate to include QoL outcome measures in future RCTs.

The epidemiology of MBC was not clearly described in the literature reviewed for this report, and most identified sources of information were for breast cancer in general. Further epidemiology studies of the incidence and prevalence of MBC would be helpful.

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Contribution of authors

Emma Loveman (Senior Research Fellow) and Andrea Takeda (Senior Research Fellow) assisting in the development of the search strategy, were responsible for inclusion screening and carried out the data extraction/critical appraisal. Seng Chuen Tan (Research Fellow) and Jeremy Jones (Senior Research Fellow) worked on the health economics aspects of the report. Andrea Takeda, Emma Loveman, Jeremy Jones, Seng Chuen Tan and Andy Clegg (SHTAC Director) contributed to the development of the protocol and to drafting the report. Andrea Takeda was project coordinator.

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Appendix 1

Breast cancer staging

TNM staging system for breast cancer

T TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour <2 cm
T2	Tumour 2–5 cm
T3	Tumour >5 cm
T4	Tumour of any size with direct extension to chest wall or skin
N NX	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastases
N1	Metastasis to movable ipsilateral axillary nodes
N2	Metastases to fixed ipsilateral axillary nodes or to other structures
N3	Metastases to ipsilateral internal mammary lymph nodes
M M0	No evidence of distant metastasis
M1	Distant metastases

The TNM system is an internationally recognised staging system for breast cancer. It is based on the extent of the tumour, the involvement of the lymph nodes and the presence of metastases. The descriptions here are from Jones and colleagues,[69] adapted from the original system of Harris and colleagues.[4]

Clinical staging

Early breast cancer

- Stage I. Small tumour (<2 cm).
- Stage IIA. No evidence of primary tumour, lymph-node positive, no evidence of distant metastasis.
- Tumour <2 cm, lymph-node positive, no evidence of distant metastasis.
- Tumour 2–5 cm, lymph-node negative, no evidence of distant metastasis.
- Stage IIB. Tumour 2–5 cm, lymph-node positive, no evidence of distant metastasis.
- Tumour >5 cm, lymph-node negative, no evidence of distant metastasis.

Advanced breast cancer

- Stage IIIA. No evidence of primary tumour or tumour <2 cm, fixed lymph-node positive, no evidence of distant metastasis.
- Tumour 2–5 cm, fixed lymph-node positive, no evidence of distant metastasis.
- Tumour >5 cm, lymph-node positive, no evidence of distant metastasis.
- Stage IIIB. Tumour of any size with direct extension to chest wall or skin, lymph-node negative or positive, no evidence of distant metastasis.
- Any tumour size, mammary lymph-node positive, no evidence of distant metastasis.
- Stage IV. Any tumour size, lymph-node negative or positive, distant metastases.

Appendix 2

Research protocol: methods

Report methods for synthesis of evidence of clinical effectiveness

The review will be undertaken as systematically as time allows, following the general principles outlined in NHS CRD Report 4.[41] The research protocol will be updated as necessary as the research programme progresses.

Search strategy

- The draft search strategy for MEDLINE is listed in Appendix 3. Searches will be carried out from the inception date of the database until March 2006 and will be limited to the English language.
- Electronic databases that will be searched include: Cochrane Systematic Reviews Database; Cochrane Controlled Trials Register; NHS CRD (University of York) DARE and NHS EED; MEDLINE (Ovid); EMBASE; National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Bibliographies of related papers will be assessed for relevant studies.
- Experts will be contacted for advice and peer review, and to identify additional published and unpublished references.

Inclusion and exclusion criteria

- GEM in combination with PAC, is the only intervention that will be included in this review, as this is the licensed combination. Comparators for the clinical effectiveness review will be: any other agents licensed for the second-line treatment of cancer, including: the taxanes and capecitabine as monotherapies; combination docetaxel and capecitabine; rechallenge with anthracyclines. To isolate the effectiveness of GEM in combination with PAC, trials will be excluded if an additional intervention (e.g. epirubicin) is only used in the GEM arm of the trial and not in the control arm.
- Participants in the trials to be included in the review are people diagnosed with MBC who have previously been treated with anthracycline-based therapies. The licensed indication is for MBC only. If any trials include people with locally advanced breast cancer in addition to people with MBC, we will include them provided the majority of the patient population in the trial have metastatic disease.
- Systematic reviews of RCTs and RCTs comparing the stated intervention with listed comparators will be included in the review of clinical effectiveness.
- Full economic evaluations of GEM in combination with PAC for the treatment of MBC will be included. Systematic reviews of economic evaluations, where relevant, will be included.
- Studies published as abstracts or conference presentations will be included in the primary analysis of clinical and cost-effectiveness if sufficient details are presented to make appropriate decisions about the methodology of the study and the results.
- A range of designs for studies on QoL, and epidemiology/natural history will be considered.
- Outcome measures will include: survival; time to disease progression; disease-related symptoms; health-related QoL; adverse effects of treatment.
- Inclusion criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Data extraction strategy

- Data will be extracted from the included studies using standard tables for the clinical effectiveness studies (see Appendix 7 for format).
- Data extraction will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Quality assessment strategy

- The quality of included systematic reviews will be assessed using NHS CRD (University of York) criteria.[41] Quality assessment of RCTs will be judged in accordance with Chapter II.5 of CRD Report 4 (2nd ed.) (see Appendix 6).

- Economic evaluations will be assessed using criteria recommended by Drummond and colleagues[70] (see Appendix 6) and/or the format recommended and applied in the CRD NHS Economic Evaluation Database (CRD Report 6).[71]
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Methods of analysis/synthesis

- Clinical effectiveness will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quantity, quality and homogeneity, a meta-analysis of the clinical effectiveness studies will be performed, using Cochrane Review Manager Software.

Methods for estimating quality of life

- The primary aim of treatments for MBC is to palliate symptoms, prolong survival and maintain a good QoL with minimal AEs from treatment.
- This assessment will aim to identify AEs of treatment that are likely to have a substantial impact on patients' QoL, and to include these effects in estimates of health state utility while on treatment.
- Where presented, QoL information will be obtained from included RCTs. Where QoL data are insufficient to calculate utility estimates in terms of QALYs, data will be derived from the broader literature or estimated from other sources.

Report methods for synthesising evidence of cost-effectiveness

- Published cost-effectiveness studies identified as part of the search strategy documented above will be reviewed in detail, comprising a narrative review and tabulation of results where appropriate. Fully published cost-effectiveness studies will be assessed using a standard quality checklist. Studies reported in abstract form will be discussed, but not reviewed in detail or quality assessed.
- Where appropriate, an economic model will be constructed by adapting an existing model or developing a new one, using the best available evidence to estimate the cost-effectiveness of GEM in combination with PAC as second-line treatment for MBC in a UK setting. The perspective will be that of the NHS and Personal Social Services.
- Data on resource use and costs will be from the published literature and NHS sources, where appropriate and available. Effectiveness data, in terms of the outcomes described above, will be extracted from published trials and used in conjunction with cost data to populate the model.
- Cost-effectiveness will be from an NHS and Personal Social Services perspective (costs and benefits). Estimates of cost-effectiveness will be presented as incremental cost per QALY gained. Both costs and QALYs will be discounted at 3.5%.
- The robustness of the results to the assumptions made in the cost analysis and the cost-effectiveness model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

Appendix 3

Documentation of search strategy used

The following databases were searched for published and ongoing research:

- Cochrane Library – Cochrane Database of Systematic Reviews
- Cochrane Library – CENTRAL
- MEDLINE (OVID) 1966-
- EMBASE (OVID) 1980-
- Web of Science
- Web of Science Proceedings 2002–5
- BIOSIS
- DARE
- HTA database (on CRD databases)
- Current Controlled Trials, including MRC Trials
- http://controlled-trials.com/
- Food and Drug Administration (FDA)
- European Medicines Agency (EMEA)

Clinical effectiveness search strategy for MEDLINE (OVID)

1 (gemcitabin$ or gemcytabin$).mp. (3239)
2 gemzar$.mp. (249)
3 1 or 2 (3243)
4 (paclitaxel or taxol).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (12103)
5 (paclitac$ or paxene).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (5)
6 4 or 5 (12103)
7 3 and 6 (862)
8 exp Breast Neoplasms/ (125569)
9 (breast adj25 neoplasm$).ti,ab,sh. (4484)
10 (breast adj25 cancer$).ti,ab,sh. (93589)
11 adj25 tumo?r$).ti,ab,sh. (37735)
12 (breast adj25 carcinoma$).ti,ab,sh. (30059)
13 (breast adj25 adenocarcinoma$).ti,ab,sh. (3095)
14 (breast adj25 sarcoma$).ti,ab,sh. (1511)
15 (breast adj25 dcis).ti,ab,sh. (1000)
16 (breast adj25 ductal).ti,ab,sh. (4599)
17 (breast adj25 infiltrating).ti,ab,sh. (1625)
18 (breast adj25 intraductal).ti,ab,sh. (1020)
19 (breast adj25 lobular).ti,ab,sh. (1796)
20 (breast adj25 medullary).ti,ab,sh. (392)
21 or/9-20 (116184)
22 exp breast/ (19836)
23 breast.tw. (148393)
24 exp neoplasms/ (1617933)
25 (22 or 23) and 24 (117228)
26 exp mammary neoplasms/ (14567)
27 (mammary adj25 neoplasm$).ti,ab,sh. (628)
28 (mammary adj25 cancer$).ti,ab,sh. (6206)
29 (mammary adj25 tumo?r$).ti,ab,sh. (15626)
30 (mammary adj25 carcinoma$).ti,ab,sh. (7565)
31 (mammary adj25 adenocarcinoma$).ti,ab,sh. (2608)
32 (mammary adj25 sarcoma$).ti,ab,sh. (496)
33 (mammary adj25 dcis).ti,ab,sh. (70)
34 (mammary adj25 ductal).ti,ab,sh. (1141)
35 (mammary adj25 infiltrating).ti,ab,sh. (253)
36 (mammary adj25 intraductal).ti,ab,sh. (221)
37 (mammary adj25 lobular).ti,ab,sh. (281)
38 (mammary adj25 medullary).ti,ab,sh. (60)
39 or/26-38 (27595)
40 8 or 21 or 25 or 39 (166238)
41 (metasta$ or stage IV or stage 4).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (217694)
42 (stage III or stage 3 or advanc$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (226902)
43 (41 or 42) and 40 (41495)
44 43 and 3 (243)
45 43 and 7 (116)
46 45 or 44 (243)
47 limit 46 to english language (228)
48 40 and 3 (361)
49 40 and 7 (154)
50 48 or 49 (361)
51 limit 50 to english language (338)
52 randomized controlled trial.pt. (206082)
53 controlled clinical trial.pt. (69290)
54 randomized controlled trials/ (39086)
55 random allocation/ (53797)
56 double-blind method/ (83140)
57 single-blind method/ (9273)
58 exp evaluation studies/ (532914)
59 exp clinical trials/ (169622)
60 clinical trial.pt. (414986)
61 (clin$ adj5 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (201764)

62 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (921208)
63 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw. (80615)
64 exp placebos/ (24013)
65 placebo$.tw. (90652)
66 random$.tw. (318251)
67 exp research design/ (195557)
68 63 or 64 or 65 or 66 or 67 (481132)
69 62 or 68 (1105008)
70 69 and 47 (198)
71 69 and 51 (258)
72 from 71 keep 1-258 (258)

1 (gemcitabin$ or gemcytabin$).mp. (6930)
2 gemcitabine/ (6846)
3 gemzar$.mp. (634)
4 (paclitaxel or taxol).mp. (19907)
5 (paclitac$ or paxene).mp. (27)
6 paclitaxel/ (9239)
7 or/1-3 (6930)
8 or/4-6 (19907)
9 7 and 8 (3225)
10 breast metastasis/ (1514)
11 exp breast cancer/ (111180)
12 (breast adj25 neoplasm$).ti,ab. (1792)
13 (breast adj25 cancer$).ti,ab. (80649)
14 (breast adj25 tumo?r$).ti,ab. (33165)
15 (breast adj25 carcinoma$).ti,ab. (24744)
16 (breast adj25 adenocarcinoma$).ti,ab. (2385)
17 (breast adj25 sarcoma$).ti,ab. (1239)
18 (breast adj25 dcis).ti,ab. (958)
19 (breast adj25 ductal).ti,ab. (4261)
20 (breast adj25 infiltrating).ti,ab. (1474)
21 (breast adj25 intraductal).ti,ab. (862)
22 (breast adj lobular).ti,ab. (26)
23 (breast adj medullary).ti,ab. (8)
24 or/10-23 (127901)
25 (mammary adj25 neoplasm$).ti,ab. (419)
26 (mammary adj25 cancer).ti,ab. (4741)
27 (mammary adj25 tumo?r$).ti,ab. (12125)
28 (mammary adj25 adenocarcinoma$).ti,ab. (2069)
29 adj25 dcis).ti,ab. (64)
30 (mammary adj25 ductal).ti,ab. (954)
31 (mammary adj25 infiltrating).ti,ab. (213)
32 (mammary adj25 sarcoma).ti,ab. (219)
33 (mammary adj25 intraductal).ti,ab. (175)
34 (mammary adj25 lobular).ti,ab. (228)
35 (mammary adj25 medullary).ti,ab. (43)
36 (mammary adj25 carcinoma$).ti,ab. (6237)
37 or/25-36 (17729)
38 24 or 37 (133555)
39 (metasta$ or stage IV or stage 4).mp. (178167)
40 (stage III or stage3 or advanc$).mp. (194993)
41 39 or 40 (348638)
42 38 and 41 (34673)
43 9 and 42 (406)
44 limit 43 to (human and english language) (349)
45 randomized controlled trial/ (99670)
46 exp controlled study/ (2051031)
47 randomization/ (16465)
48 double blind procedure/ (57457)
49 single blind procedure/ (5558)
50 or/45-49 (2059637)
51 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).tw. (78065)
52 exp placebo/ (81177)
53 placebo.tw. (87662)
54 random.tw. (66739)
55 exp methodology/ (978777)
56 or/45-55 (2838898)
57 44 and 56 (137)
58 (randomized or randomised).tw. (155528)
59 44 and 58 (45)
60 57 or 59 (160)
61 (gemcitabine and breast and advanced).ti,ab. (100)
62 (gemcitabine and breast and metast$).ti,ab. (154)
63 61 or 62 (190)
64 or/45-55,58 (2871634)
65 63 and 64 (99)
66 60 or 65 (200)
67 limit 66 to (human and english language) (199)
68 from 67 keep 1-199 (199)

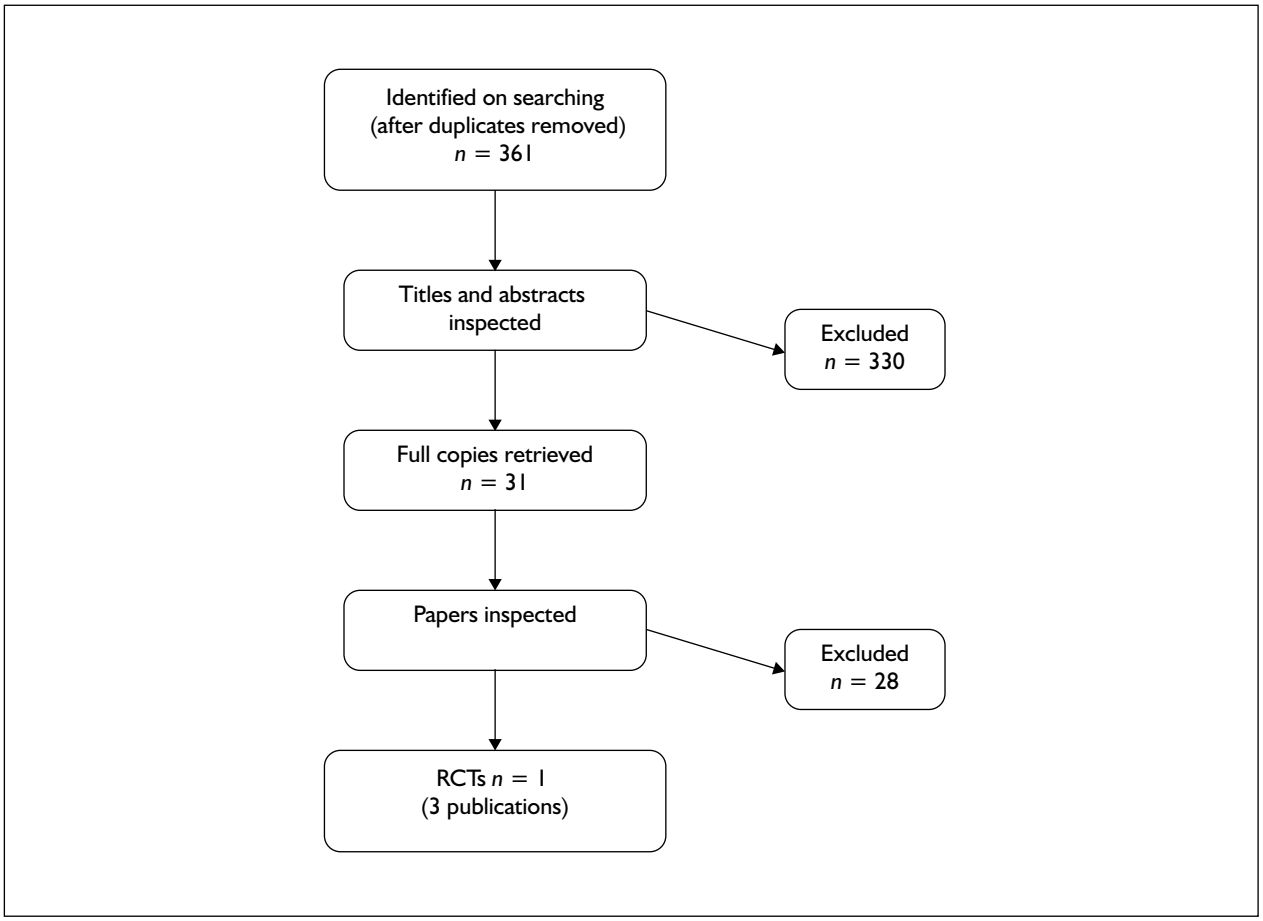
Health economics search strategy for Medline (OVID)

1 (breast adj25 neoplasm$).ti,ab. (2511)
2 adj25 cancer$).ti,ab. (94865)
3 (breast adj25 tumo?r$).ti,ab. (37695)
4 (breast adj25 carcinoma$).ti,ab. (29249)
5 (breast adj25 adenocarcinoma$).ti,ab. (2720)
6 (breast adj25 sarcoma$).ti,ab. (1506)
7 (breast adj25 dcis).ti,ab. (1014)
8 (breast adj25 ductal).ti,ab. (4669)
9 (breast adj25 infiltrating).ti,ab. (1648)
10 (breast adj25 intraductal).ti,ab. (1025)
11 (breast adj lobular).ti,ab. (27)
12 (breast adj medullary).ti,ab. (9)
13 (mammary adj25 neoplasm$).ti,ab. (629)
14 (mammary adj25 cancer).ti,ab. (5742)
15 (mammary adj25 tumo?r$).ti,ab. (15793)
16 (mammary adj25 adenocarcinoma$).ti,ab. (2625)
17 (mammary adj25 dcis).ti,ab. (72)
18 (mammary adj25 ductal).ti,ab. (1163)
19 (mammary adj25 infiltrating).ti,ab. (257)
20 (mammary adj25 sarcoma).ti,ab. (339)

21 (mammary adj25 intraductal).ti,ab. (221)
22 (mammary adj25 lobular).ti,ab. (284)
23 (mammary adj25 medullary).ti,ab. (60)
24 (mammary adj25 carcinoma$).ti,ab. (7649)
25 (metasta$ or stage IV or stage 4).mp. (219955)
26 (stage III or stage3 or advanc$).mp. (227217)
27 exp breast neoplasms/ (126904)
28 or/1-24 (131930)
29 exp breast/ (20010)
30 breast.tw. (150108)
31 exp neoplasms/ (1630884)
32 31 and (29 or 30) (118618)
33 exp economics/ (341932)
34 exp economics hospital/ (13578)
35 exp economics pharmaceutical/ (1540)
36 exp economics nursing/ (3669)
37 exp economics medical/ (9720)
38 value of life/ (4580)
39 exp models economic/ (4463)
40 exp fees/ and charges/ (6774)
41 exp "costs and cost analysis"/ (118900)
42 exp budgets/ (8937)
43 (economic$ or price$ or pricing or pharmacoeconomic$ or pharma economic$).tw. (76079)
44 (cost$ or costly or costing$ or costed).tw. (167889)
45 (cost adj2 (benefit$ or utilit$ or minim$)).tw. (8757)
46 (expenditure$ not energy).tw. (9274)
47 (value adj2 (money or monetary)).tw. (544)
48 budget$.tw. (9527)
49 (economic adj2 burden).tw. (1181)
50 "resource use".ti,ab. (22418)
51 or/33-50 (504736)
52 28 or 32 (141652)
53 52 and (25 or 26) (37752)
54 51 and 53 (893)
55 28 and 51 (3841)
56 55 and (25 or 26) (867)
57 (breast and (metast$ or advanced)).ti. (9963)
58 51 and 57 (168)
59 (mammary and (metast$ or advanced)).ti. (705)
60 51 and 59 (2)
61 58 or 60 (170)
62 limit 61 to (humans and english language) (157)
63 "advanced breast cancer".ab. (3117)
64 (metast$ adj breast adj cancer).ab. (4479)
65 51 and (63 or 64) (178)
66 61 or 65 (263)
67 limit 66 to (humans and english language) (240)
68 (detect$ or diagnos$).ti. (417443)
69 67 not 68 (232)
70 from 69 keep 1-232 (232)

Appendix 4

Flow chart of inclusion process for clinical effectiveness



Appendix 5

Excluded studies

A total of 31 titles were retrieved for further inspection as part of the review of clinical effectiveness. The 28 excluded titles are listed below, with reasons for exclusion.

Excluded on: study design and participants

Colomer R, Llombart-Cussac A, Lluch A, Barnadas A, Ojeda B, Caranana V, *et al*. Biweekly paclitaxel plus gemcitabine in advanced breast cancer: phase II trial and predictive value of HER2 extracellular domain. *Ann Oncology* 2004;**15**:201–6.

Colomer R, Llombart A, Lluch A, Ojeda B, Barnadas A, Caranana V, *et al*. Paclitaxel/gemcitabine administered every two weeks in advanced breast cancer: preliminary results of a phase II trial. *Semin Oncol* 2000;**27**(1 Suppl 2): 20–24.

Delfino C, Caccia G, Gonzales LR, Mickiewicz E, Rodger J, Balbiani L, *et al*. Gemcitabine plus paclitaxel as first-line chemotherapy for patients with advanced breast cancer. *Oncology* 2004;**66**:18–23.

Delfino C, Caccia G, Riva GL, Mickiewicz E, Rodger J, Balbiani L, *et al*. Gemcitabine/paclitaxel as first-line treatment of advanced breast cancer. *Oncology (Huntingt)* 2003;**17**(12 Suppl 14):22–25.

Iaffaioli RV, Tortoriello A, Santangelo M, Turitto G, Libutti M, Benassai G, *et al*. Phase I dose escalation study of gemcitabine and paclitaxel plus colony-stimulating factors in previously treated patients with advanced breast and ovarian cancer. *Clin Oncol (Royal College of Radiologists)* 2000;**12**:251–5.

Llombart A, Colomer R, Lluch A, Ojeda B, Barnadas A, Caranana V, *et al*. Biweekly gemcitabine and paclitaxel in advanced breast cancer. Phase II trial and predictive value of HER2 extracellular domain (ECD). *Euro J Cancer* 2000;**36**(Suppl. 5):S121–2.

Murad AM, Guimaraes RC, Aragao BC, Scalabrini'Neto AO, Rodrigues VH, Garcia R. Gemcitabine and paclitaxel as salvage therapy in metastatic breast cancer. *Oncology (Huntingt)* 2001;**15** (2 Suppl 3):25–7.

Murad AM, Guimaraes RC, Aragao BC, Scalabrini-Neto AO, Rodrigues VH, Garcia R. Phase II trial of the use of paclitaxel and gemcitabine as a salvage treatment in metastatic breast cancer. *Am J Clin Oncol* 2001;**24**:264–8.

Sanchez-Rovira P, Gonzalez E, Medina MB, Mohedano N, Jaen A, Porras I, *et al*. Results from a phase II study of gemcitabine in combination with paclitaxel in metastatic breast cancer (MBC). *Breast Cancer Res Treat* 1999;**57**:87.

Sanchez P, Medina MB, Mohedano N, Jaen A, Porras I, Gonzalez E, *et al.* Results from a phase II study of gemcitabine in combination with paclitaxel in metastatic breast cancer. *Ann Oncol* 1998;**9**:16.

SanchezRovira P, Mohedano N, Moreno MA, Gonzalez E, Jaen A, Medina B, *et al*. Preliminary results from an early phase II combination of gemcitabine and taxol in metastatic breast cancer. *Euro J Cancer* 1997;**33**:685.

Excluded on: study design

Alexopoulos A, Karamouzis MV, Ioannidis G, Stavrinides H, Ardavanis A, Stavrakakis J, *et al*. Salvage treatment with biweekly administration of paclitaxel (P) and gemcitabine (G) in patients (pts) with metastatic breast cancer (MBC) heavily pretreated with anthracycline and docetaxel containing regimens. *J Clin Oncol* 2005;**23**:86S.

Demiray M, Kurt E, Evrensel T, Kanat O, Arslan M, Saraydaroglu O, *et al*. Phase II study of gemcitabine plus paclitaxel in metastatic breast cancer patients with prior anthracycline exposure. *Cancer Invest* 2005;**23**:386–91.

Llombart-Cussac A, Moreno-Bueno G, Ruiz A, Albanell J, Mayordomo JI, Carnana V, *et al*. Gene expression profiling (GEP) for the prediction of response to neoadjuvant paclitaxel and gemcitabine in breast cancer (BC). Preliminary results from a Phase II trial. *J Clin Oncol* 2004;**22**:580.

Lluch A, Llombart A, Colomer R, Ojeda B, Barnadas A, Alberola V, *et al*. Paclitaxel and gemcitabine administered every two weeks: a phase II trial in untreated advanced breast cancer. *Breast Cancer Res Treat* 1999;**57**:88.

Murad AM. Paclitaxel and gemcitabine as salvage treatment in metastatic breast cancer. *Oncology (Huntingt)* 2003;**17**(12 Suppl 14):26–32.

Excluded on: study design and intervention

Schueller JJS, Czejka MMC, Ostermann EEO, Muric LLM, Heinz DDH. Influence of Herceptin (HER) on pharmacokinetics (PK) of taxanes (paclitaxel and

docetaxel) or gemcitabine (GEM) in breast cancer patients. *Breast Cancer Res Treat* 2004;**88**:S129.

Sledge GW Jr. Gemcitabine, paclitaxel, and trastuzumab in metastatic breast cancer. *Oncology (Huntingt)* 2003; **17**(12 Suppl 14):33–5.

Excluded as unavailable

Yardley DA. Gemcitabine plus paclitaxel in breast cancer. *Semin Oncol* 2005;**32**(4, Suppl 6):S14–21.

Yunus F. Phase III randomized study of paclitaxel with or without gemcitabine in women with unresectable, locally recurrent, or metastatic breast cancer. The Cochrane Central Register of Controlled Trials (CENTRAL). 2007; Issue 1.

Retrieved for background information only

Carlson RW. Quality of life issues in the treatment of metastatic breast cancer. *Oncology (Huntingt)* 1998;**12** (3 Suppl 4):27–31.

Colomer R. Gemcitabine and paclitaxel in metastatic breast cancer: a review. *Oncology (Huntingt)* 2004;**18** (14 Suppl 12):8–12.

Conte P, Salvadori B, Donati S, Landucci E, Gennari A. Gemcitabine, epirubicin, and paclitaxel combinations in advanced breast cancer. *Semin Oncol* 2001;**28**(2 Suppl 7): 15–17.

Friedman DT, Sparano JA. Treatment of anthracycline-resistant breast cancer. *Am J Cancer* 2004;**3**:151–62.

Giordano SH, Buzdar AU, Smith TL, Kau S-W, Yang Y, Hortobagyi GN. Is breast cancer survival improving? Trends in survival for patients with recurrent breast cancer diagnosed from 1974 through 2000. *Cancer* 2004;**100**:44–52.

Heinemann V. Gemcitabine in metastatic breast cancer. *Expert Rev Anticancer Ther* 2005;**5**:429–43.

Silvestris N, D'Aprile M, Andreola G, Locopo N, Marini L, Crucitta E, *et al*. Rationale for the use of gemcitabine in breast cancer (review). *Int J Oncol* 2004;**24**:389–98.

Sledge GW Jr. Gemcitabine combined with paclitaxel or paclitaxel/trastuzumab in metastatic breast cancer. *Semin Oncol* 2003;**30**(2 Suppl 3):19–21.

Appendix 6

Quality assessment criteria

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

Drummond 10-point check-list for assessing economic evaluations

Drummond M *et al*. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford University Press; 1997.

1. **Was a well-defined question posed in answerable form?**
   - 1.1. Did the study examine both costs and effects of the service(s) or programme(s)?
   - 1.2. Did the study involve a comparison of alternatives?
   - 1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. **Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?**
   - 2.1. Were there any important alternatives omitted?
   - 2.2. Was (should) a do-nothing alternative be considered?

3. **Was the effectiveness of the programme or services established?**
   - 3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?
   - 3.2. Was effectiveness established through an overview of clinical studies?
   - 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. **Were all the important and relevant costs and consequences for each alternative identified?**
   - 4.1. Was the range wide enough for the research question at hand?
   - 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
   - 4.3. Were the capital costs, as well as operating costs, included?

5. **Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)?**
   5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
   5.2. Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. **Were the cost and consequences valued credibly?**
   6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)
   6.2. Were market values employed for changes involving resources gained or depleted?
   6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
   6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost–benefit, cost–utility – been selected)?

7. **Were costs and consequences adjusted for differential timing?**
   7.1. Were costs and consequences that occur in the future 'discounted' to their present values?
   7.2. Was there any justification given for the discount rate used?

8. **Was an incremental analysis of costs and consequences of alternatives performed?**
   8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?

9. **Was allowance made for uncertainty in the estimates of costs and consequences?**
   9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?
   9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?
   9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10. **Did the presentation and discussion of study results include all issues of concern to users?**
    10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
    10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?
    10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?
    10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?
    10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

Appendix 7

Data extraction form for included study

Reviewers: EL/ALT.

Reference and design	Intervention	Participants	Outcome measures
Ref ID: 459, 566, 567 Authors: O'Shaughnessy *et al.*;[42] Albain *et al.*;[43] Moinpour *et al.*[44] Additional information from conference PowerPoint presentations Year: 2003; 2004; 2004 Country: multinational, 19 countries Study design: RCT Number of centres: 98 Funding: Eli Lilly	*Group A: GEM/PAC* *n* = 267 Drug 1: GEM Dose: 1250 mg/m^2 days 1 and 8 Drug 2: PAC Dose: 175 mg/m^2 day 1 Median cycles: 6 Median dose delivered: 1134.0 mg/m^2 GEM and 175.0 mg/m^2 PAC Omitted doses: 7% GEM and <1% PAC Reduced doses: 8% GEM and 5% PAC *Group B: PAC* *n* = 262 Drug 1: PAC Dose: 175 mg/m^2 day 1 Median cycles: 5 Median dose delivered: 175.0 mg/m^2 Omitted doses: <1% Reduced doses 2% States drugs given q21 (where q is taken to mean every) days until progression – 38% group A and 55% group B stopped therapy due to progression. Other interventions used: none	No. of participants: 529 Sample attrition/drop-out: 1 patient off study for overall survival analysis Sample crossovers: none reported. One abstract states that second-line therapy was nearly identical in both arms, except for a 4-fold greater use of GEM in the PAC arm. These second-line treatments were administered after completion of the randomised treatments but may influence longer term outcomes. 521 patients randomised and received treatment for the safety analysis, 529 for effectiveness analysis Inclusion/exclusion criteria for study entry: histologically confirmed, measurable unresectable, locally recurrent or MBC previously treated with adjuvant/neoadjuvant anthracyclines (or non-anthracyclines if clinically contraindicated) but no prior CT for MBC, Karnofsky Performance Status (KPS) ⩾70 (Albain presentation: KPS 70–100). Females aged ⩾18 years. Prior hormonal therapy permitted. At least one bidimensionally measurable lesion Characteristics of participants: reported in published abstracts for total group only and states the arms were balanced. Median age 53 years. >70% had visceral metastases, 75% had ⩾2 sites of metastatic disease, one-third had receptor-positive disease and 96% had prior anthracyclines Eli Lilly website has following patient characteristics: median age (range) in years: group A (GEM/PAC) 53 (26–83), group B (PAC) 52 (26–75) Metastatic disease: GEM/PAC 97.0%, PAC 96.9% Baseline KPS ⩾90: GEM/PAC 70.4%, PAC 74.4% Number of tumour sites: 1–2: GEM/PAC 56.6%, PAC 58.8%; ⩾3: GEM/PAC 43.4%, PAC 41.2% Visceral disease: GEM/PAC 73.4%, PAC 72.9% Prior anthracycline therapy: GEM/PAC 96.6%, PAC 95.8% Additional information in PowerPoint presentations: Ethnicity, *n* (%) Group A (GEM/PAC)/Group B (PAC): Caucasian 157 (59)/159 (61) Asian 52 (20)/51 (20) Hispanic 47 (17)/43 (16) Other 11 (4)/9 (3) Stage at entry, *N* (%) Unresectable, local 8 (3)/8(3) Metastatic 259 (97)/254 (97)	Primary outcomes: overall survival Secondary outcomes: time to documented progression from disease, progression-free survival, overall response, QoL (RSCL), palliation of pain (BPI), toxicity, time to progressive disease, analgesic use Methods of assessing outcomes: states trial was monitored by independent data safety and monitoring board and imaging was independently reviewed. Only data from validated translations of the RSCL and BPI were included Length of follow-up: median follow-up 15.6 months for overall survival outcome Analgesic level (investigator-rated) – 5-point scale

continued

Reference and design	Intervention	Participants	Outcome measures
		Sites of metastases, *n* (%): Visceral 196 (73)/191 (73) Non-visceral 71(27)/71 (27) No. of disease sites: 1 65 (24)/63 (24) 2 86 (32)/91(35) ⩾3 116 (43)/108 (41) ER/PR status, *n* (%): ER and/or PR+ 102(38)/103(39) ER and PR– 67 (25)/81 (31) Unknown 88 (33)/76 (29) Prior therapy, *n* (%): Prior adjuvant CT 267(100)/260 (99) Anthracycline 258 (97)/251 (96) Prior hormonal therapy 138 (52)/130 (50) Prior trastuzumab 1(<1)/2(<1) Prior radiotherapy 177 (66)/184 (70) KPS ⩾90 70.4%/74.4%	

Results

Outcomes	GEM/PAC (*n* = 267)	PAC (*n* = 262)	*p*-Value
Survival			
Median overall survival	18.5 months (95% CI 16.5 to 21.2)	15.8 months (95% CI 14.4 to 17.4)	
One-year survival	70.7% (95% CI 65.1 to 76.3%)	60.9% (95% CI 54.8 to 66.9%)	0.019
Overall survival hazard ratio	0.775 (95% CI 0.627 to 0.959) in favour of GEM/PAC, $p = 0.018$. The HR persisted in favour of GEM/PAC in Cox regression after adjusting for baseline covariates: 0.740 (95% CI 0.598 to 0.915), $p = 0.006$		
Comments: First overall survival analysis by Kaplan–Meier and Cox regression conducted at approximately 75% (343) of the deaths needed (440) for the planned final overall survival report. Albain PowerPoint presentation *interim* survival analysis at 78% of required deaths: interim overall survival log-rank $p = 0.018$, hazard ratio 0.78 (95% CI 0.63 to 0.96).			
JHQG Cox multivariate analysis for *interim* overall survival	Covariate GEM/PAC vs PAC KPS ⩾90 No. of tumour sites Time from diagnosis	Hazard ratio (95% CI) 0.74 (0.60 to 0.92) 0.57 (0.45 to 0.72) 1.25 (1.16 to 1.35) 0.86 (0.82 to 0.90)	 0.006 <0.0001 <0.0001 <0.0001
Comments: visceral disease, prior therapy (surgery, hormonal, anthracycline, radiotherapy), receptor status and age were not significant at interim analysis			
JHQG *interim* overall survival:			
Deaths	160	183	
Censored	40.1%	30.2%	
Median overall survival (months) (95% CI)	18.5% (16.5 to 21.2)	15.8 (14.4 to 17.4)	
12-month survival	70.7%	60.9%	
18-month survival	50.7%	41.9%	
Comments: none			
Events, *n*	207	217	

continued

Outcomes	GEM/PAC (n = 267)	PAC (n = 262)	p-Value
Median time to progressive disease (months)	5.4 (95% CI 4.6 to 6.1)	3.5 (95% CI 2.9 to 4.0)	0.0013
JHQG median TTP (months)	5.2 (4.2 to 8.6)	2.9 (2.6 to 3.7)	<0.001
Hazard ratio	0.734 (95% CI, 0.607 to 0.889), p = 0.0015 with an increased probability of approximately 50% for the GEM/PAC group of being progression free at 6 months		
Overall response rate	39.3% (95% CI 33.5 to 45.2%)	25.6% (95% CI 20.3 to 30.9%)	0.0007
JHQG planned *interim* analysis – response rate	40.8% (95% CI 34.9 to 46.7)	22.1% (95% CI 17.2 to 27.2)	<0.0001
Comments: progression-free survival was significantly better with GEM/PAC (p = 0.0021)			
JHQG time to documented progressive disease	Log rank p < 0.0001 in favour of GEM/PAC. HR 0.650 (95% CI 0.524 to 0.805)		
Progression-free at 6 months (95% CI) – (O'Shaughnessy PowerPoint)	44 (38 to 50)	30 (24 to 35)	
JHQG 6-month progression free (Albain PowerPoint)	37%	23%	0.0027
Median response duration (months) (95% CI)	8.8 (7.4 to 10.2)	7.2 (6.8 to 8.6)	0.4158
QoL			
Global QoL (in O'Shaughnessy abstract[42])	No data presented	No data presented	States not significant
BPI, n = 291	N = 141 Unable to estimate data from graph No data presented	N = 150 Unable to estimate data from graph No data presented	
Comments: states mean changes in pain intensity and interference were similar across treatment arms. BPI assesses impact of chronic pain. Items scored 0–10. Patient-reported outcome. No significant difference averaged across time between treatment arms in ITT or symptomatic populations for prespecified outcomes. No indication that GEM/PAC arm reported worse pain scores			
RSCL, n = 350 (n = 370 in Moinpour PowerPoint)	N = 172	N = 178	States significantly
Global QoL	No data presented	No data presented	better for Group A than Group B
Other scales	No data presented	No data presented	States no consistent differences
Comments: States 85% of expected questionnaires were completed. Also reports that difference in global QoL as measured by the RSCL was clinically significant RSCL: 4 scales to assess QoL, scored 0–100: physical symptom distress; psychological distress; activity level; and overall valuation of life (global QoL). Patient-reported outcome Moinpour PowerPoint presentation states there was no significant difference averaged across time between treatment arms for any scale. A greater improvement was reported by GEM/PAC patients at later cycles for overall valuation of life Significant treatment-by-time interaction reported in mixed ANOVA; cycle-specific comparison showed significant improvement for GEM/PAC over PAC by cycles 5 and 6 with adjusted mean differences between GEM/PAC and PAC being 7.6 and 6.5 (p = 0.005 and 0.036), respectively RSCL overall valuation of life term (GEM/PAC n = 152, PAC n = 162): cycles 5 and 6 were significantly better for GEM/PAC than baseline and between arms using mixed-effects ANOVA			
Comments: states that data from sensitivity analyses consistently support the findings on the BPI and RSCL.			
Of patients requiring baseline (n = 216), proportion able to decrease for >1 cycle	25% N = 110 (24.5% Moinpour PowerPoint)	15% N = 106 (15.1% Moinpour PowerPoint)	Not reported
Comments: Analgesic level was investigator-rated on a 5-point scale.			

continued

Outcomes	GEM/PAC (n = 267)	PAC (n = 262)	p-Value
Adverse effects			
Neutropenia	17.2%	6.6%	
Anaemia	1.1%	0.4%	
Thrombocytopenia	0.4%	0%	
Febrile neutropenia	0.4%	0%	
Toxic death	1	1	
NCCI Grade 3 or 4 non-haematological toxicity (% patients) (O'Shaughnessy PowerPoint):			
Peripheral neuropathy	6	4	
Dyspnoea	2	<1	
Hypersensitivity	0	<1	
Nausea/vomiting	3	3	
Fatigue	7	2	
Diarrhoea	3	2	
AST/ALT	5/2	<1/<1	

JHQG Grade 3 or 4 non-haematological toxicity (% patients) (Albain PowerPoint)	GEM/PAC (n = 262)		PAC (n = 259)	
	Grade 3	Grade 4	Grade 3	Grade 4
Sensory neuropathy	5	<1	4	0
Motor neuropathy	2	<1	<1	0
Emesis	2	0	2	0
Fatigue	6	<1	1	<1
Diarrhoea	3	0	2	0
Dyspnoea	2	<1	0	0

Comments: Dyspnoea appears to be different in the O'Sullivan PowerPoint figure and the Albain PowerPoint – probably means the same thing.

NCI–CTC Grade 3 or 4 haematological toxicity and transfusions (% patients)	GEM/PAC (n = 262)		PAC (n = 259)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	6	1	2	<1
Haemoglobin	6	1	2	<1
Leucocytes	10	1	2	0
Neutrophilis	31	17	4	7
Platelets	5	<1	0	0
Febrile neutropenia or sepsis	5		2 (1 in Albain PowerPoint)	
Transfusions:				
RBC	10		4	
Platelets	<1		<1	
All deaths (including not drug-related)	4.6%		3.1%	
Therapy ended due to AEs	6.7%		5.0%	
Therapy discontinued due to AEs (drug-related)	6%		3%	
Therapy discontinued due to disease progression	38%		55%	

Comments: there were 2 drug-related deaths, 1 per arm. Patterns of missing data for patient-rated outcomes were analysed. Patients dropping out early for negative reasons (e.g. related to disease progression or toxicity) had worse scores. Patients who dropped out late or who had positive reasons (e.g. satisfactory response to treatment) had better scores. More patients in the paclitaxel-only group dropped out early and for negative reasons. No numbers given. Sensitivity analysis results presented, but not data extracted for clinical effectiveness.

ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase; RBC, red blood cell.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Inadequate
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention-to-treat analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Inadequate

Appendix 8

Model fitting for overall survival and disease progression data

Suppose that a Weibull distribution or exponential distribution for the overall survival data of the PAC group estimated from the trial publication is contemplated. Then

$$OS_p(t) = \exp(-\lambda t^{\gamma})$$

Taking the logarithm of $OS_p(t)$, multiplying by –1 and taking logarithms a second time gives

$$\log[-\log OS_p(t)] = \log\lambda + \gamma^{*}\log t$$

The overall survival data estimated from trial publication were then substituted for $OS_p(t)$ in the equation above and $\log[-\log OS_p(t)]$ was regressed against $\log t$.

An estimate of γ that is close to unity indicates the survival times could have an exponential distribution. In other circumstances, a Weibull distribution is assumed with the estimation of parameter γ and λ.

Upon fitting the data with an appropriate parametric survival model, the transition probability of death at cycle n for the PAC group was given by

$$tpOS_p(t_n) = 1 - \frac{OS_p(t_n)}{OS_p(t_{n-1})}$$

and

$$tpOS_{gp}(t_n) = 1 - \frac{OS_{gp}(t_n)}{OS_{gp}(t_{n-1})}$$

where $OS_{gp}(t) = \exp(-HR \cdot \lambda t^{\gamma})$ and HR = hazard ratio, for GEM/PAC group versus the PAC group.

The above was repeated for the time-to-progression data.

Appendix 9

Equations

Converting ORR to response per cycle:

$$tp(ORR) = 1 - (1 - ORR)^{\frac{1}{j}}$$

where:

$tp(ORR)$	is the transition probability
ORR	is the reported overall response rate
j	is number of follow-up cycles.

The expected utility for disease state z is estimated as

$$E(U)z = toP_{\text{tox}} \cdot U_{\text{tox}}{}^{z} + (1 - toP_{\text{tox}}) \cdot U_{\text{no}}{}^{z}$$

where

$U_{\text{tox}}{}^{z}$	is the health state utility for state z with toxicity
$U_{\text{no}}{}^{z}$	is the health state utility for state z without toxicity.
toP_{tox}	is the probability of developing any toxicity, defined formally as $\sum_{\text{tox} = a}^{g} = P_{tox}$, where $a, b, c, \ldots, g$ are toxicities listed in Appendix 10

The equation for calculating expected total treatment cost in 'stable' or 'responsive' state is

$$E(C)s, r = C_{\text{chemo}} (1 - tP_{\text{discount}}) + \sum_{\text{tox} = a}^{g} P_{\text{tox}} \cdot \text{C}_{\text{tox}}$$

where

s, r	refer to the stable and responsive health states, respectively
C_{chemo}	is the cost per cycle of chemotherapy (including drug, consultation and administration)
tP_{discount}	is the probability of discontinuing treatment
P_{tox}	is the probability of developing toxicity a
$C_{\text{tox} = a}$	is the cost for treating toxicity a.

Appendix 10

Summaries of parameter inputs

Parameter	GEM/PAC		PAC		Distribution assigned
	Mean	SE	Mean	SE	
Overall response rate	0.393	0.03	0.256	0.03	Beta
Proportion of patients discontinued chemotherapy	0.07	0.02	0.05	0.01	Beta
Drug cost (£)	1,766.84	–	985.60	–	–
Overall survival:					
λ	–	–	0.0073	0.07	Log-normal
γ			1.4187	0.02	Log-normal
Time to progression:					
λ	–	–	0.0323	0.22	Log-normal
γ	–	–	1.6739	0.10	Log-normal
Note for λ and γ: derived from regression analysis on trial data. Correlation between λ and γ is assumed to be –1.0 in both OS and TTP and was handled through Cholesky decomposition					
Proportion of patients who developed toxicities:					
Anaemia	0.07	0.02	0.025	0.01	Beta
Neutropenia	0.48	0.03	0.11	0.02	Beta
Febrile neutropenia	0.05	0.01	0.02	0.01	
Leucopenia	0.11	0.02	0.02	0.01	Beta
Thrombocytopenia	0.055	0.01	0	-	Beta
Neuropathy	0.08	0.02	0.045	0.01	Beta
Emesis	0.02	0.01	0.02	0.01	Beta
Fatigue	0.065	0.02	0.015	0.01	Beta
Diarrhoea	0.03	0.01	0.02	0.01	Beta
Dyspnoea	0.025	0.01	0	–	Beta
Elevated liver enzymes	0.07	0.02	0.01	0.01	Beta
Note: the inputs for means were obtained from trial data and the SEs were estimated using a standard formula.					

Parameter	Mean	SE	Distribution assigned
Body surface area (m^2)	1.6	0.16	–
Consultation cost (£)	61.24	6.12	Gamma
Administration cost (£)	84.81	8.48	Gamma
Utility score before cycle 3	0.64	0.15	Gamma with transformation
Hazard ratio:			
Overall survival	0.78	0.11	Log-normal
Time to progression	0.65	0.11	Log-normal
Adjustment rates for mortality risk:			
Responsive	0.2	0.04	Log-normal
Stable	0.5	0.01	Log-normal
Progressive	1.0	0.2	Log-normal
Adjustment rates for risk of disease progression:			
Responsive	1.0	0.2	Log-normal
Stable	1.5	0.3	Log-normal
Costs of treating toxicities:			
Anaemia	611.35	61.13	Gamma
Febrile neutropenia	1,111.97	111.20	Gamma
Thrombocytopenia	184.39	18.44	Gamma
Neuropathy	151.87	15.19	Gamma
Emesis	433.48	43.35	Gamma
Diarrhoea	154.31	15.43	Gamma
Note: the SEs for adjustment rates were estimated at 20% of the mean values. The SEs for costs for treating toxicities were estimated at 10% of the mean values			
Utility scores with toxicities			
Responsive	0.67	0.06	Gamma with transformation
Stable	0.54	0.01	Gamma with transformation
Progressive	0.45	0.12	Gamma with transformation
Utility scores without toxicities:			
Responsive	0.81	0.02	Gamma with transformation
Stable	0.65	0.07	Gamma with transformation
Progressive	0.45	0.12	Gamma with transformation

SE, standard error.

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We look forward to hearing from you.

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