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Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer

L Jones, N Hawkins, M Westwood,
K Wright, G Richardson and R Riemsma

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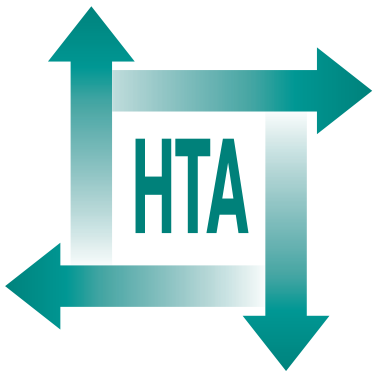

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Abstract

Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer

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Objective: To examine the clinical effectiveness and cost-effectiveness of oral capecitabine for locally advanced and metastatic breast cancer in relation to its licensed indications.

Data sources: Twenty-three electronic databases and other databases of ongoing research and Internet resources, bibliographies of retrieved articles and industry submissions.

Review methods: Two reviewers independently screened and assessed all titles and/or abstracts including economic evaluations. Randomised controlled trials (RCTs) and observational studies that investigated capecitabine monotherapy, in patients pretreated with an anthracycline-containing regimen or a taxane, or capecitabine in combination with docetaxel, in patients pretreated with an anthracycline-containing regimen, were included. The economic evaluation was based on data reported in the manufacturer's submission.

Results: For capecitabine monotherapy, 12 uncontrolled observational studies were identified. The methodological quality of the studies was low. Capecitabine demonstrated antitumour activity, but was associated with a particular risk of hand–foot syndrome and diarrhoea. Economic evaluation was hampered by the poor quality of the published studies, but compared indirectly with vinorelbine, capecitabine was associated with lower costs and improved patient outcomes. For capecitabine in combination with docetaxel, one RCT was identified. Combination therapy was superior to single-agent docetaxel in terms of survival, time to disease progression and overall response. Adverse events occurred more frequently with combination therapy. The economic evaluation demonstrated an overall improved QALY score for combination therapy with a slight reduction in costs.

Conclusions: No conclusions could be drawn regarding the therapeutic benefit of capecitabine monotherapy; RCTs are required. Capecitabine appeared cost-effective compared with vinorelbine, but serious doubts remain; the poor quality of the trials may invalidate this conclusion. Based on limited evidence, combination therapy was more effective than single-agent docetaxel and likely to be cost-effective, but was associated with higher incidences of hand–foot syndrome, nausea, diarrhoea and stomatitis.

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Glossary and list of abbreviations

Glossary

Absolute risk reduction The decreased chance of having an outcome from the treatment compared with the comparator, or the increased chance of not having an outcome from the comparator compared with the treatment. In oncology, this can be considered as, for example, the reduction in the risk of not responding to treatment.

Adjuvant treatment This usually refers to systemic chemotherapy or hormonal treatment or both, taken by patients after removal of a primary tumour (in this case, surgery for early breast cancer), with the aim of killing any remaining micrometastatic tumour cells and thus preventing recurrence.

Advanced disease Locally advanced (stage III) and metastatic (stage IV) disease (see also Appendix 2, Staging of breast cancer).

Anthracycline refractory Never responded to anthracycline therapy.

Anthracycline resistance The development of resistance to anthracyclines after initial response to first-line treatment with combinations containing anthracycline.

Ascites An accumulation of fluid in the abdominal (peritoneal) cavity.

Carcinoma A cancerous growth.

Case series In this report the term case series has been used to denote Phase II studies which are uncontrolled prospective studies.

Chemotherapy The use of drugs that kill cancer cells, or prevent or slow their growth.

Clinical oncologist A doctor who specialises in the treatment of cancer patients, particularly through the use of *radiotherapy*, but who may also use *chemotherapy*.

Combination chemotherapy regimen The use of more than one drug to kill cancer cells.

Complete response Total disappearance of all detectable malignant disease for at least 4 weeks (must state measurement device/ technology).

Cost–utility analysis Analysis in which the additional cost per quality-adjusted life-year (QALY) saved or gained is estimated.

Cycle Chemotherapy is usually administered at regular (normally monthly) intervals. A cycle is a course of chemotherapy followed by a period in which the patient's body recovers.

Cytology The study of the appearance of individual cells under a microscope.

Cytotoxic Toxic to cells. This term is used to describe drugs that kill cancer cells or slow their growth.

Differentiation The degree of morphological resemblance between cancer tissue and the tissue from which the cancer developed.

Disease-free interval Time between surgery for early breast cancer and developing metastatic breast cancer.

Duration of response The time from initial complete tumour response or partial tumour response to documented disease progression or death.

Early breast cancer Operable disease (stage I or II), restricted to the breast and sometimes to local lymph nodes.

EORTC QLQ-BR32 A breast cancer specific questionnaire designed to be used in conjunction with the EORTC QLQ-C30.

continued

Glossary *continued*

EORTC QLQ-C30 A self-administered questionnaire designed to measure health-related quality of life. The questionnaire consists of 15 domains: one global health domain, five function domains (physical, role, emotional, cognitive and social) and nine symptom domains (fatigue, pain, nausea/vomiting, dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact).

First-line treatment Initial treatment for a particular condition that has previously not been treated. For example, first-line treatment for metastatic breast cancer may include chemotherapy or hormonal therapy, or both. Used in advanced disease where the treatment intent may be curative (e.g. in some cases of locally advanced disease) but is usually palliative. The main treatment modality is systemic therapy.

Global Health Status Functional domain on the EORTC QLQ-C30.

Grading of breast cancer Grading refers to the appearance of the cancer cells under the microscope. The grade gives an idea of how quickly the cancer may develop. There are three grades: grade 1 (low grade), grade 2 (moderate grade) and grade 3 (high grade).

Heterogeneous Of differing origins or different types.

Histological grade Degree of malignancy of a tumour, usually judged from its histological features.

Histological type The type of tissue found in a tumour.

Histology An examination of the cellular characteristics of a tissue.

Incremental cost-effectiveness analysis Estimates of the additional cost per specific clinical outcome.

Kaplan–Meier method A statistical technique used in the analysis of survival data which allows data to be censored.

Karnofsky scale A subjective measure of patient performance of activities of daily living.

Localised disease Tumour confined to a small part of an organ.

Locally advanced disease (breast) Disease that has infiltrated the skin or chest wall, or disease that has involved axillary nodes.

Lymph nodes Small organs that act as filters in the lymphatic system. Lymph nodes close to the primary tumour are often the first sites to which cancer spreads.

Marginal or minor response Less than 50% but greater than 25% tumour regression for all measurable tumours for at least 4 weeks with no new lesions appearing (measurement technique must be stated).

Measurable lesion A lesion that could be unidimensionally or bidimensionally measured by physical examination, echography, X-rays or computed tomographic scan.

Medical oncologist A doctor who specialises in the treatment of cancer through the use of *chemotherapy*.

Meta-analysis The statistical analysis of the results of a collection of individual studies to synthesise their findings.

Metastatic breast cancer Stage IV breast cancer (see also Appendix 2, Staging of breast cancer).

Metastasis Spread of cancer cells from the original site to other parts of the body via the blood circulation or lymphatic system.

Neoadjuvant treatment Treatment given before the main treatment; usually *chemotherapy* or *radiotherapy* given before surgery.

Non-measurable lesion No exact measurements could be obtained, e.g. pleural effusions, ascites.

Objective or overall response A complete or partial response.

continued

Glossary *continued*

Oestrogen receptor A protein on breast cancer cells that binds oestrogens. It indicates that the tumour may respond to hormonal therapies. Patients with tumours rich in oestrogen receptors have a better prognosis than those with tumours that are not.

Palliative Anything that serves to alleviate symptoms due to the underlying cancer but is not expected to cure it. Hence palliative care, palliative *chemotherapy*.

Partial response At least 50% decrease in tumour size for > 4 weeks without an increase in the size of any area of known malignant disease or the appearance of new lesions (definitions vary between trials; the technique used for measurement must be stated).

Performance status A measure of how the disease affects the daily living abilities of the patient.

Primary anthracycline resistance Failure to respond to a first- or second-line anthracycline (disease progression) or relapse.

Progressive disease The tumour continues to grow or the patient develops more metastatic sites.

Prophylaxis An intervention used to prevent an unwanted outcome.

Protocol A policy or strategy that defines appropriate action.

Quality-adjusted life-years Index of survival that is weighted or adjusted by the patient's quality of life during the survival period.

Quality of life The individual's overall appraisal of her situation and subjective sense of well-being.

Radiotherapy The use of radiation, usually X-rays or gamma rays, to kill tumour cells.

Randomised controlled trial An experimental study in which subjects are randomised to receive either an experimental or a control treatment or intervention. The relative effectiveness of the intervention is assessed by comparing event rates and outcome measures in the two groups.

Recurrence/disease-free survival The time from the primary treatment of the breast cancer to the first evidence of cancer recurrence.

Refractory disease Disease that has never responded to first-line therapy.

Remission A period when cancer has responded to treatment and there are no signs of tumour or tumour-related symptoms.

Secondary anthracycline resistance Disease progression after an initial objective response to first- or second-line therapy or disease progression during treatment with an anthracycline.

Salvage therapy Any therapy given in the hope of achieving a response when the 'standard' therapy has failed. This may overlap with second-line therapy, but could also include therapy given for patients with refractory disease, i.e. disease that has never responded to first-line therapy.

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. Depending on the circumstances patients may be treated with the same regimen again or a different regimen. In either case this is defined as second-line therapy.

Stable disease No change or less than 25% change in measurable lesions for at least 4–8 weeks with no new lesions appearing.

Staging The allocation of categories (stage I–IV) to tumours defined by internationally agreed criteria. Stage I tumours are localised, while stages II–IV refer to increasing degrees of spread through the body from the primary site. Tumour stage is an important determinant of treatment and prognosis.

continued

Glossary *continued*

Stomatitis Inflammatory disease of the mouth.

Time to disease progression The length of time from the start of treatment (or time from randomisation within the context of a clinical trial) until tumour progression.

Time to treatment failure The length of time from start of treatment (or time from randomisation within the context of a clinical trial) to disease progression, death, or treatment discontinuation for any other reason or for initiation of new antitumour therapy.

Uncontrolled study A study that has no control group.

Utilities A measure of value of an outcome that reflects the attitude towards the probability of that outcome occurring.

Utility approach Assigns numerical values on a scale from 0 (death) to 1 (optimal health). It provides a single number that summarises all of health-related quality of life: a global measure of health-related life quality.

Utility scores Strength of a patient's preference for a given health state or outcome.

Values Preferences without risk or uncertainty.

List of abbreviations

ABC	advanced breast cancer
AIDS	acquired immunodeficiency syndrome
ASAT	aspartate aminotransferase
BNF	British National Formulary
CAP/DOC	capecitabine/docetaxel combination
CBR	clinical benefit response
CCTR	Cochrane Controlled Trials Register
CI	confidence interval
CIPFA	Chartered Institute of Public Finance and Accounting
CMF	cyclophosphamide, methotrexate and 5-fluorouracil
CR	complete response
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effectiveness
5′-DFUR	5′-deoxy-5-fluorouridine
DOC	single-agent docetaxel
DPD	dihydropyrimidine dehydrogenase
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
5-FU	5-fluorouracil
GCSF	granulocyte colony-stimulating factor
HDC-ASCS	high-dose chemotherapy plus autologous stem cell support
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
INR	international normalised ratio
IRC	independent review committee

List of abbreviations *continued*

ISTP	Index to Scientific and Technical Proceedings
ITT	intention-to-treat (analysis)
iv	intravenous
KPS	Karnofsky performance scale
LOCF	last observation carried forward
LOS	length of stay
MBC	metastatic breast cancer
NA	not applicable
NCIC-CTC	National Institute of Canada common toxicity criteria
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NR	not reported
ns	not significant
NS	not stated
OHE HEED	Office of Health Economics Health Economic Evaluations Database
OR	overall or objective response, complete response plus partial response
PD	disease progression
PPE	palmar–plantar erythrodysthaesia
PR	partial response
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-years
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SCI	Science Citation Index
SD	stable disease
TNM	tumour, node, metastases
UICC	International Union Against Cancer (Union Internationale Contre le Cancer)
UKCCCR	United Kingdom Co-ordinating Committee on Cancer Research
WHO	World Health Organization

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

Executive summary

Background

Breast cancer is the most common cancer affecting women in the UK, accounting for nearly 30% of all cancers in women. It is the second leading cause of cancer deaths in women; in 1998 there were over 13,000 deaths from breast cancer in the UK. Around 50% of women diagnosed with primary breast cancer will eventually relapse and develop metastatic or advanced disease. In addition, around 10% of patients present with metastatic disease at first diagnosis. Metastatic breast cancer is currently considered incurable and most women will die of the disease. Prognosis of patients with metastatic disease depends on age, extent of disease and oestrogen receptor status. First-line chemotherapy regimens available for advanced or metastatic breast cancer include CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and anthracycline-containing regimens. Almost all patients who have received first-line chemotherapy for their metastatic progression will relapse or progress and require subsequent treatment. For these patients requiring second- and subsequent-line therapy, the goals of treatment are to maintain a good quality of life (QoL) and to prolong survival. Current guidance from the National Institute for Clinical Excellence (NICE) recommends the taxanes (paclitaxel and docetaxel) "as an option for the treatment of advanced breast cancer where initial cytotoxic chemotherapy has failed or is inappropriate". In addition, vinorelbine, a third-generation vinca alkaloid, has demonstrated some activity in advanced breast cancer in patients with anthracycline-resistant or -refractory disease. Capecitabine has recently been licensed for use as monotherapy for patients who have failed anthracycline-containing and taxane chemotherapy and in combination with docetaxel for patients who have failed anthracycline-containing chemotherapy.

Objective

To examine the clinical effectiveness and cost-effectiveness of oral capecitabine (Xeloda®; Roche) for locally advanced and metastatic breast cancer in relation to its licensed indications.

Methods

Search strategy

Twenty-three electronic databases and other databases of ongoing research and Internet resources were searched from inception to May 2002. The bibliographies of retrieved articles and submissions received from the drug company were also examined.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of capecitabine monotherapy, uncontrolled Phase II and observational studies were included which only recruited patients reported to have received previous treatment with an anthracycline and/or a taxane. For the assessment of capecitabine in combination with docetaxel, randomised controlled trials (RCTs) and uncontrolled studies were included which investigated only patients who had received previous treatment with an anthracycline. The outcomes were: survival, response, symptom relief, QoL, adverse events and costs.

Data extraction strategy

Data were extracted into an Access database by one reviewer and checked for accuracy by a second. Any disagreements were resolved by discussion.

Quality assessment strategy

The quality of each clinical study was assessed by one reviewer and checked by a second. Any disagreements were resolved by discussion. The same quality checklist was used regardless of study design to give a continuous measure of quality. The quality of the cost-effectiveness studies was assessed using a checklist updated from that developed by Drummond and colleagues in 1997. This checklist reflected the criteria for economic evaluation detailed in the methodological guidance developed by NICE. This information is presented in table form.

Methods of analysis

Owing to the small number of studies included in the review and the heterogeneity between the studies, statistical pooling was inappropriate, so statistical chi-squared tests of heterogeneity were not performed. Studies were grouped according to whether capecitabine was used alone or in combination with docetaxel. For the time to event data, where reported, hazard ratios (HR) with 95% confidence intervals (CI) were presented. For the remaining outcomes (tumour response, QoL and adverse events) relative risk (RR) estimates were calculated where appropriate, with 95% CI. RR data were also presented in the form of Forest plots without pooled estimates.

Details of each published economic evaluation, with an assessment of study quality, were presented in structured tables and as a narrative summary. Economic data were presented in the form of a summary and critique of the evidence. Additional analysis was undertaken to explore cost-effectiveness more fully. This included a careful assessment of assumptions underlying the submitted economic analyses using relevant experts, the estimation of differential mean survival duration, the use of Monte Carlo simulation to generate cost-effectiveness acceptability curves and the impact of differences in health-related QoL on cost-effectiveness.

Results

Included studies

In total, 347 titles and abstracts were screened for inclusion in the review. Full paper manuscripts of 233 citations were assessed for inclusion.

Capecitabine monotherapy

Twenty-three published reports of 12 uncontrolled studies of clinical effectiveness were identified for inclusion. One economic evaluation was also identified.

Capecitabine in combination with docetaxel

Five published reports of one RCT investigating capecitabine in combination with docetaxel compared with single-agent docetaxel were identified. Two uncontrolled studies were identified which investigated an alternative, low-dose docetaxel regimen. One economic evaluation based on the RCT comparing capecitabine in combination with docetaxel to single-agent docetaxel was identified.

Quality of the clinical effectiveness data

Capecitabine monotherapy

The methodological quality of the studies investigating capecitabine monotherapy was low. All studies suffered from a number of design flaws making them vulnerable to bias, most notably the lack of a control group. In addition, it was difficult to assess the potential effects of confounding factors on treatment outcomes. Concerns about specific studies and differences between the studies in terms of dose regimens and baseline population differences mean that data from these studies should be treated with caution.

Capecitabine in combination with docetaxel

The RCT by O'Shaughnessy and colleagues was of good quality. The other two studies were uncontrolled and used an alternative treatment regimen, so only a limited discussion of their findings was included. Therefore, the assessment of clinical effectiveness is based mainly on the evidence presented in the RCT by O'Shaughnessy.

Quality of economic evaluations

Capecitabine monotherapy

The poor quality of the clinical studies has implications for the economic analysis. As the comparisons of uncontrolled studies used to demonstrate the clinical superiority of capecitabine were open to bias, the results of the economic evaluation based on these results should also be treated with caution. In addition, the choice of vinorelbine as the only comparator is questionable as there is little evidence of the cost-effectiveness of vinorelbine in this setting.

Capecitabine in combination with docetaxel

The economic evaluation of capecitabine in combination with docetaxel compared with docetaxel monotherapy was assessed using an RCT. Some aspects of the methodology of the economic analysis may be questioned, but it was felt that these would not alter the overall conclusions.

Assessment of clinical effectiveness

Capecitabine monotherapy

The assessment of clinical effectiveness of capecitabine monotherapy included 12 non-comparative studies of capecitabine. In the absence of controlled trials, these studies represent the best currently available evidence. The outcomes assessed by the studies included survival time, time to disease progression, duration of response, time to treatment failure, tumour response rates, QoL and adverse event rates. The

findings of the clinical effectiveness studies appear to indicate that capecitabine monotherapy has some effects in terms of survival time (median survival, range 8.1–15.2 months), time to progression (median time to progression, range 2.8–6.2 months) and time to treatment failure. In terms of response, duration of response ranged from 5.0 to 8.3 months, and overall response rate from 15 to 28%. QoL was not adequately addressed by the included studies. Hand–foot syndrome and diarrhoea were the most commonly reported adverse events. The percentage of patients experiencing grade 3 hand–foot syndrome ranged from 5 to 22% (any grade, 35–62%) and the percentage of patients experiencing grade 3/4 diarrhoea ranged from 5 to 19% (any grade, 27–57%). In light of the quality issues relating to uncontrolled studies in general and the particular methodological flaws identified in the studies, these findings should be treated with extreme caution.

Capecitabine in combination with docetaxel

One RCT was identified which investigated a regimen of capecitabine in combination with docetaxel. The trial included 511 patients and compared capecitabine in combination with docetaxel to single-agent docetaxel. In addition, two uncontrolled studies investigated a regimen of weekly low-dose docetaxel plus capecitabine; however, these studies provided limited, poor quality evidence and used an alternative low-dose docetaxel regimen. Hence, this section of the report focused on the admittedly limited, but higher quality evidence, from the RCT. The RCT provided some evidence that capecitabine–docetaxel combination therapy was superior to single-agent docetaxel in patients previously treated with anthracyclines: statistically significant increases in survival time (median survival, HR 0.775, 95% CI 0.634 to 0.947), time to disease progression (median time to progression, HR 0.652, 95% CI 0.545 to 0.780) and time to treatment failure (median time to treatment failure, HR not reported) were reported. Overall tumour response rates (complete response plus partial response) were also significantly increased in the combination therapy group compared with the single-therapy group (overall response, RR 1.40, 95% CI 1.10 to 1.78), although there were no significant differences in complete response rates between the two groups. Measures of QoL recorded no clinically meaningful change from baseline on the global health status domain in either group during treatment. Treatment-related adverse events occurred more frequently in the combination therapy group. The incidence of severe or life-threatening (grade 3/4) hand–foot syndrome (RR 20.66, 95% CI 6.57 to 64.97), nausea (RR 3.26, 95% CI 1.21 to 8.77), diarrhoea (RR 2.37, 95% CI 1.33 to 4.23) and stomatitis were all significantly greater in patients receiving capecitabine in combination with docetaxel.

Assessment of cost-effectiveness

Capecitabine monotherapy

For capecitabine monotherapy indirectly compared with vinorelbine, based on the limited data and poor quality data available, capecitabine was a dominant case in that it was associated with lower costs and improved patient outcomes as measured by QALYs. However, the improved QALY profile is based on the extended survival seen in the comparison of single-arm studies, in which no allowance for case mix was made. This comparison is likely to be subject to bias and while sensitivity analysis consistently favoured capecitabine monotherapy, the weakness of the comparisons made and the questionable status of vinorelbine as sole comparator require that any results be treated with caution.

Capecitabine in combination with docetaxel

The assessment of cost-effectiveness of capecitabine in combination with docetaxel compared with single-agent docetaxel was based on an RCT. The results of the economic evaluation demonstrated an improved QALY score for combination therapy together with a very small reduction in costs. In the base case estimate, therefore, combination therapy was a dominant case. This is reflected in the cost-effectiveness acceptability curve which shows that for all reasonable values of decision-makers' willingness to pay for a QALY, combination therapy is likely to be cost-effective; indeed, the probability of combination therapy being cost-effective exceeds 90% at a willingness to pay for a QALY of £2000. However, QoL was assessed by applying constant utilities to disease states. This methodology fails to address the possibility that adverse events, specific to the individual treatments, may differentially affect QoL and hence produce quite different QALY gains and therefore influence the cost-effectiveness results. Nevertheless, on the available evidence, combination therapy is likely to be cost-effective compared with docetaxel monotherapy.

Conclusions

Capecitabine monotherapy

The evidence base for the assessment of the effectiveness of capecitabine monotherapy was

particularly poor. All of the studies identified for inclusion in the review lacked a control group, leaving them vulnerable to biases and confounding factors.

The evidence from these uncontrolled studies appears to indicate that capecitabine has antitumour activity when used as monotherapy in patients who have received previous treatment with anthracycline-containing regimens and taxanes. The toxicity profile appeared to indicate an increased risk of patients particularly experiencing hand–foot syndrome and diarrhoea. QoL was inadequately assessed; only one study included an assessment as part of the evaluation of capecitabine monotherapy.

In terms of cost-effectiveness, based on the available data, treatment with capecitabine, compared indirectly with treatment with vinorelbine, appears to be cost-effective. No comparative trials of these treatments were reported. Given the diverse patient population, in terms of disease and treatment history, it is likely that an RCT, comparing survival from point of randomisation for both treatments in a comparative trial, could provide different information on relative survival times.

In conclusion, good quality RCTs are urgently needed to compare the effectiveness of capecitabine monotherapy with the alternative third- and subsequent-line therapies currently available, as well as with best supportive care. These data should be collected in a form that facilitates cost-effectiveness analysis. The quality of the economic assessment reflects the poor level of clinical evidence. On the available evidence, capecitabine monotherapy is cost-effective, but there remain serious doubts about whether the quality of the clinical trials invalidates this conclusion. For a more complete picture, systematic reviews of vinorelbine, best supportive care and other relevant comparators in this setting need to be undertaken.

Capecitabine in combination with docetaxel

This review suggests that there is limited evidence in the form of RCTs on which to base an assessment of the effectiveness of capecitabine in combination with docetaxel in comparison to existing and new chemotherapy agents for the second-line treatment of advanced breast cancer. Only one RCT was identified for inclusion in the review comparing capecitabine in combination with docetaxel to treatment with single-agent docetaxel.

From the evidence available from the single trial, capecitabine in combination with docetaxel appears to be more effective than single-agent docetaxel in terms of overall survival, time to disease progression, time to treatment failure and overall tumour response (complete response plus partial response). There was no statistically significant difference between the two groups in any of the QoL domains. Statistically significant differences between combination and single-agent therapy were identified in terms of reported grade 3/4 treatment-related side-effects. Treatment with capecitabine–docetaxel was associated with higher incidences of hand–foot syndrome, nausea, diarrhoea and stomatitis.

In terms of costs, combination therapy seems to be cost-effective; however, the cost-effectiveness analysis did not directly consider the impact on QoL associated with the combination and monotherapy treatments themselves.

In conclusion, further RCTs investigating capecitabine in combination with docetaxel compared to alternative second-line therapies are required. From the limited evidence it would appear that capecitabine in combination with docetaxel is more effective in terms of median survival time, time to disease progression, time to treatment failure and overall response than single-agent docetaxel. The economic analysis indicates that combination therapy is very likely to be cost-effective. However, the method of calculation of QALYs ignores the potential for differences in adverse events between treatments to alter QoL estimates.

Chapter 1

Aim of the review

The aim of the review was to examine the clinical effectiveness and cost-effectiveness of oral capecitabine (Xeloda®; Roche) for locally advanced and metastatic breast cancer in relation to its licensed indications.

Chapter 2
Background

Description of underlying health problem

Breast cancer is the most common cancer affecting women in the UK, accounting for nearly 30% of all cancers in women.[1] It is the second leading cause of cancer deaths in women;[1] in 1998 there were over 13,000 deaths from breast cancer in the UK.[2]

Although the aetiology of breast cancer is largely unknown, several risk factors have been identified. These factors include early menarche, late first pregnancy, low parity and late menopause.[3] The endogenous hormones, both oestrogen and androgens, may also play an important role.[4]

Screening and early diagnosis in addition to systemic adjuvant therapy have increased disease-free overall survival of patients with localised breast cancer.[5] Locally advanced breast cancer (stage III; see Appendix 2) includes tumours larger than 5 cm, tumours of any size with direct invasion of the skin of the breast or the chest wall, and any tumour that has spread to the lymph nodes. Local control can be achieved in 80–90% of women, and about 30% of women with stage IIIb tumours (see Appendix 2) remain cancer free after 10 years.[6] Nevertheless, around 50% of women diagnosed with primary breast cancer will eventually relapse and develop metastatic disease.[7] In addition, around 10% of patients present with metastatic disease at first diagnosis.[5] Metastatic breast cancer is defined by the presence of disease at distant sites such as the bone, liver or lung. The risk of metastatic disease relates to known prognostic factors in the original primary tumour. These factors include oestrogen receptor status negative disease, primary tumour greater than 3 cm and axillary node involvement. Metastatic breast cancer is currently considered incurable and ultimately most women will die of the disease. Prognosis of patients with metastatic disease depends on age, extent of disease and oestrogen receptor status.[4]

Current service provision

The choice of first-line treatment for metastatic breast cancer, whether hormonal therapy or chemotherapy, is based on a variety of clinical factors. The choice of a specific drug or regimen is based on what drugs have already been given as adjuvant treatment, together with the likelihood of benefit balanced against a given drug's adverse effects and tolerability profile.[4,8] There is strong evidence to suggest that polychemotherapy decreases mortality compared with single agents, but otherwise there appears to be no evidence that any particular treatment regimen is more effective than any other.[9]

First-line chemotherapy regimens available for advanced or metastatic breast cancer include CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and anthracycline-containing regimens.[10] A short disease-free interval (less than 1 year) between surgery for early breast cancer and developing metastases suggests that the recurrent disease is likely to be resistant to the drug used for adjuvant therapy.[4,5] Almost all patients who have received first-line chemotherapy for their metastatic progression will relapse or progress and require subsequent treatment.[5] For these patients requiring second- and subsequent-line therapy, the duration of response and survival are shorter than those for initial chemotherapy. The goals of treatment are to maintain a good quality of life (QoL) and to prolong survival.[11]

The taxanes (paclitaxel and docetaxel) are being used increasingly, either alone or in combination with other agents, in first- and second-line therapy.[8] Current guidance from the National Institute for Clinical Excellence (NICE) recommends the taxanes (paclitaxel and docetaxel) "as an option for the treatment of advanced breast cancer where initial cytotoxic chemotherapy has failed or is inappropriate".[12] In addition, vinorelbine, a third-generation vinca alkaloid, has demonstrated some activity in advanced breast cancer in patients with anthracycline-resistant or -refractory disease.[8] NICE guidance states that vinorelbine on its own should be one option for patients when treatment with anthracyclines has failed.

New agents which provide an alternative to the taxanes and anthracyclines are needed as the trend towards more aggressive treatment of the

breast cancer in the earlier stages has led to an increase in the number of patients presenting with advanced or metastatic disease that is resistant to, or has failed, taxane and anthracycline therapy.[7]

Description of new intervention

Capecitabine (Xeloda) is a non-cytotoxic fluoropyrimidine carbamate, which functions as a precursor of 5-fluorouracil (5-FU). Capecitabine is an antimetabolite and is activated via several enzymic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase, is found in tumour tissues at higher levels than in normal tissue. The metabolism of 5-FU is thought to interfere with the synthesis of DNA. The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. This effect of 5-FU is thought to promote cell death.[13]

Current indications for treatment

Capecitabine in combination with docetaxel (Taxotere®) is indicated for the treatment of patients with locally advanced and/or metastatic breast cancer who have failed anthracycline-containing regimens. Capecitabine monotherapy is indicated for the treatment of patients with locally advanced and/or metastatic breast cancer who have failed taxanes and anthracycline-containing chemotherapy or for whom further anthracycline therapy is not indicated.

Summary of drug information

Capecitabine is available in 150 mg and 500 mg film-coated tablets.

The recommended dose of capecitabine is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. Tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

In combination with docetaxel, the recommended dose of capecitabine is 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. Premedication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started before docetaxel administration for patients receiving capecitabine plus docetaxel combination.

Contraindications

- History of severe and unexpected reactions to fluropyrimidine therapy
- known hypersensitivity to capecitabine, fluorouracil or any of the excipients
- patients with known dihydropyrimidine dehydrogenase (DPD) deficiency
- during pregnancy and lactation
- patients with severe leucopenia, neutropenia or thrombocytopenia
- patients with severe hepatic impairment
- patients with severe renal impairment (creatinine clearance below 30 ml/min)
- treatment with sorivudine or its chemically related analogues, such as brivudine
- contraindications for docetaxel also apply to the capecitabine plus docetaxel combination.

Special warnings and special precautions for use

- **Dose-limiting toxicities**: these include diarrhoea, abdominal pain, nausea, stomatitis and hand–foot syndrome. Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.
- **Cardiotoxicity**: cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, caridogenic shock, sudden death and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with a history of significant cardiac disease.
- **Hypocalcaemia or hypercalcaemia**: this has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypocalcaemia or hypercalcaemia.
- **Central or nervous system disease**: caution must be exercised in patients with central or peripheral nervous system disease, such as brain metastasis or neuropathy.
- **Diabetes mellitus or electrolyte disturbances**: caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.
- **Coumarin-derivative anticoagulation**: patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulation therapy should have their anticoagulant response [international normalised ratio (INR) or

prothrombin time] monitored closely and the anticoagulant dose adjusted accordingly.
- **Hepatic impairment**: capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence of liver metastasis.
- **Renal impairment**: the incidence of grade 3 or 4 adverse events in patients with moderate renal impairment (creatinine clearance 30–50 ml/minute) is increased compared with the overall population.

Chapter 3
Methods

Search strategy

The following databases were searched for relevant published literature. Full details of the search strategy are reported in Appendix 1:

- BIOSIS
- CANCERLIT
- Cochrane Controlled Trials Register (CCTR)
- CINAHL
- Conference Papers Index
- Database of Abstracts of Reviews of Effectiveness (DARE)
- EMBASE
- Health Technology Assessment (HTA) database
- HealthStar
- Index to Scientific & Technical Proceedings (ISTP)
- MEDLINE
- NHS Economic Evaluation Database (NHS EED)
- Science Citation Index (SCI)
- Office of Health Economics (OHE) Health Economic Evaluations Database (HEED).

In addition, the bibliographies of retrieved articles and industry submissions made to NICE were searched for further studies.

Inclusion and exclusion criteria

Two authors independently screened titles and abstracts (where available) of the studies identified from all searches and sources. A full paper copy of any study judged to be relevant by either reviewer was obtained. The full paper copy of the study was assessed for inclusion by one reviewer and checked for accuracy by a second, using the criteria outlined below. Studies that did not meet the inclusion criteria were excluded. The bibliographic details of the excluded studies with reasons for exclusion are presented in tables in Appendix 7. Any discrepancies were resolved by discussion and if necessary through consultation with the Reviews Manager.

Study design

For the evaluation of clinical effectiveness the gold standard is the randomised, controlled, Phase III clinical trial. The authors did not identify any randomised, controlled trials (RCTs) to evaluate capecitabine monotherapy, and so uncontrolled Phase II studies and other observational studies were included. For the evaluation of capecitabine in combination with docetaxel, a randomised controlled Phase III trial was identified. Uncontrolled Phase II studies were also included.

Following submission of the report to NICE, an appendix (see Appendix 6) was added in response to comments that some consultees did not appreciate the limitations of using uncontrolled trials as a source of data to assess the effectiveness of clinical interventions.

Interventions

Oral capecitabine (Xeloda) was used alone or in combination with docetaxel versus taxane monotherapy (paclitaxel or docetaxel), vinorelbine or best supportive care, as part of the following stages of treatment for locally advanced and/or metastatic breast cancer:

- as second or subsequent line therapy in combination with docetaxel for patients who have failed anthracycline-containing chemotherapy regimens
- as third or subsequent line monotherapy for patients who have failed taxanes and anthracycline-containing regimens, or who have failed taxanes and for whom further anthracycline therapy is not indicated.

Participants

Women with locally advanced or metastatic breast cancer were included. According to the International Union Against Cancer (UICC) staging system, locally advanced cancer refers to stages IIIa and IIIb, and metastatic cancer to stage IV (see Appendix 2).

Outcome measures

The following outcomes measures were included in the review:

- overall survival
- progression-free survival
- tumour response (complete and partial)
- time to treatment failure

- adverse events/toxicity [diarrhoea, abdominal pain, nausea, vomiting, stomatitis, hand–foot syndrome (also known as hand–foot skin reaction or palmar–plantar erythrodysesthaesia (PPE), hyperbilirubinaemia, fatigue, anaemia, thrombocytopenia, dermatitis and any other adverse effects judged to be appropriate]
- QoL
- costs from all reported perspectives.

For capecitabine monotherapy patient preference for oral therapy was also considered as an additional outcome.

Data extraction strategy

One reviewer, using predefined data extraction forms, extracted data from studies meeting the inclusion criteria into an Access database. The forms were checked for accuracy by a second reviewer and any disagreements were resolved by discussion, or if necessary through consultation with the Reviews Manager.

Quality assessment strategy

Clinical effectiveness studies meeting the inclusion criteria for the review were assessed for quality by one reviewer, and checked for accuracy by a second. The quality of clinical effectiveness studies was assessed according to criteria based on NHS Centre for Reviews and Dissemination (CRD) Report No. 4.[14] The same checklist was used to evaluate all of the effectiveness studies regardless of design in order to give a consistent summary of quality.

Economic evaluations were assessed for quality by one reviewer, and checked for accuracy by a second, using a checklist updated from that developed by Drummond and colleagues;[15] additional commentary was provided where appropriate. Any disagreements were resolved by consensus or, if necessary, through consultation with a third reviewer. This checklist reflects the criteria for economic evaluations detailed in the methodological guidance developed by NICE.[16]

Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study of clinical effectiveness were presented in structured tables and as a narrative summary. The possible effects of study quality on the findings of the review were discussed within the text. Owing to the small number of studies included in the review and the heterogeneity among the studies, statistical pooling was not deemed appropriate. Consequently, statistical chi-squared tests of heterogeneity were not performed. Studies were grouped according to whether capecitabine was used alone or in combination with docetaxel.

Details of each economic evaluation, together with a summary of study quality, were presented in structured tables and as a narrative summary. Details of economic evaluations included in the company submission were assessed. These included, as far as was possible, a detailed analysis of the appropriateness of the parametric and structural assumptions involved and an assessment of how robust the conclusions were to changes in key assumptions. Clarification on specific aspects of the evaluation was sought from the drug manufacturer.

Confidentiality

Some information that was submitted to NICE by Roche, the manufacturer of capecitabine, was marked commercial in confidence in the report. This information was initially included in the report that was made available to the NICE appraisal committee. However, this information has now been excluded from this document, making it available for wider publication. It has been noted within the text where this information has been removed.

Chapter 4
Results

Quantity of research available

In total, 347 titles and abstracts were screened for inclusion in the review. Of these, 233 studies were ordered as full papers and assessed in detail. A summary of the process of study identification is presented in *Figure 1*.

Excluded studies

Of the excluded studies, the majority were non-systematic reviews and news articles (see Appendix 7). Sixteen papers reported studies of capecitabine in combination with agents other than docetaxel, including vinorelbine,[17–22] paclitaxel,[23–28] epirubicin/docetaxel[29–31] and carboplatin/vinorelbine.[32] Five excluded studies[33–37] compared capecitabine monotherapy to paclitaxel monotherapy and were, therefore, not in accordance with the licensed indication. Six studies that examined capecitabine monotherapy[38–43] were excluded because the number of patients pretreated with taxanes and/or anthracycline-containing regimens was not reported, or patients had not received more than two chemotherapy regimens. A study that compared capecitabine as first-line monotherapy to CMF[44] was also excluded. Five other excluded papers[28,45–48] were Phase I studies investigating

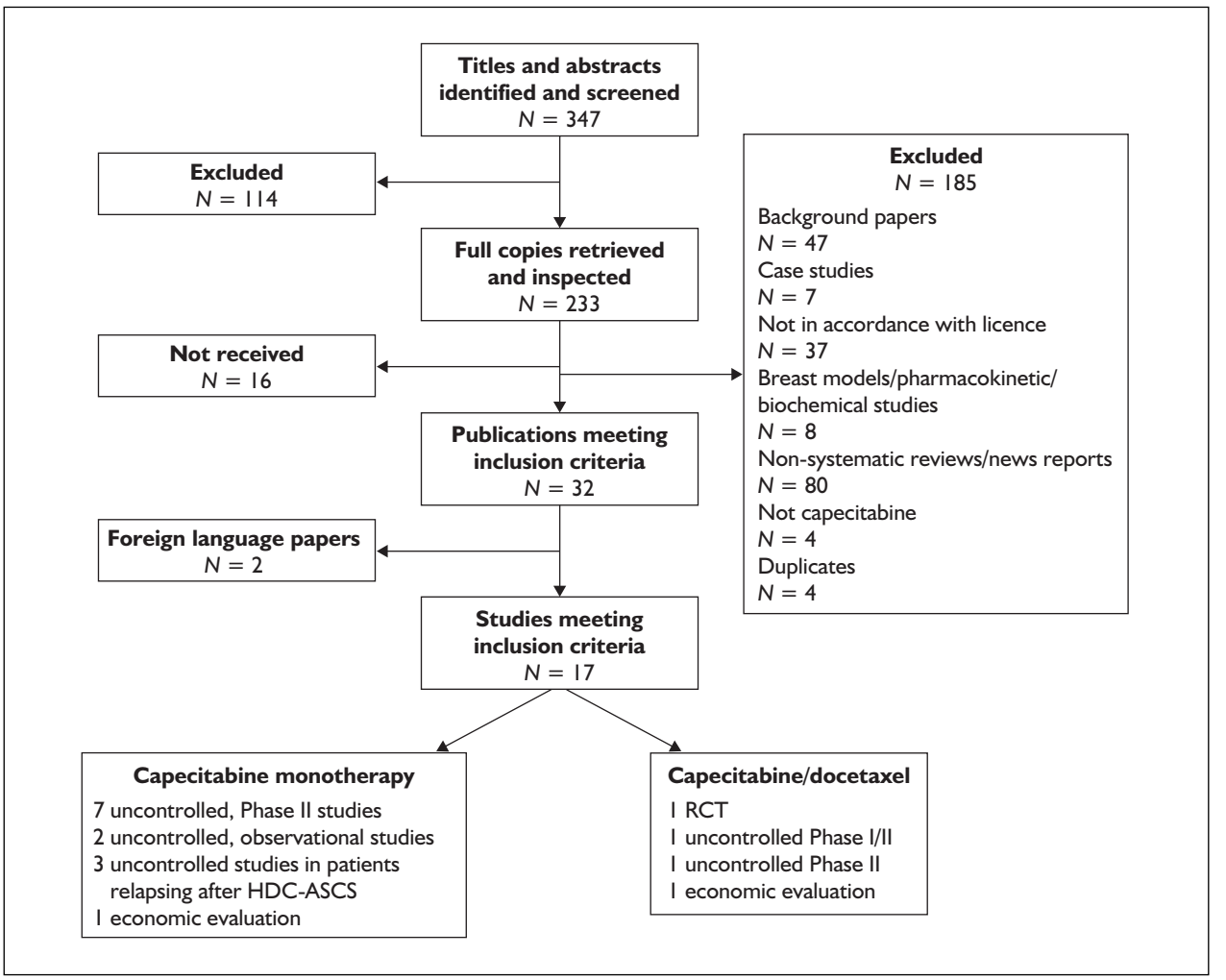

FIGURE 1 *Summary of study identification, retrieval and inclusion/exclusion. HDC-ASCS: high-dose chemotherapy plus autologous stem cell support.*

capecitabine in mixed groups of patients with solid tumours. One paper,[49] which was a Phase I, pharmacokinetic study of capecitabine in combination with docetaxel in a mixed group of patients, was excluded. Seven case reports[50–56] were identified and excluded from the review. Two economic evaluations were excluded; in the first study[57] patients had not been pretreated with anthracyclines, and the second[58] was not an evaluation of capecitabine.

Ongoing studies

One ongoing randomised Phase II study of capecitabine monotherapy in women with advanced or metastatic breast cancer was identified. The main objective of the study was to compare the objective response rate in women treated with two dose levels of capecitabine.

Summary of included studies

Full details of the included studies may be found in Appendix 9. Twenty-three reports of 13 studies for the evaluation of capecitabine monotherapy in patients who were reported to be anthracycline and/or taxane refractory were identified. In addition, seven papers investigating capecitabine in combination with docetaxel were identified. Five were reports of results from one randomised, controlled Phase III trial.[59] The two additional studies were a Phase I/II dose-finding study[60] and an ongoing, Phase II study[61] of weekly docetaxel plus intermittent capecitabine. A summary of the available evidence for the assessment of clinical effectiveness is shown in *Table 1*.

Two foreign language studies,[87,88] one each in Chinese and in Russian, investigating capecitabine

TABLE 1 *Summary of currently available evidence for the assessment of clinical effectiveness*

Study	Full paper available	Published as abstract only
Capecitabine monotherapy		
Blum (1999)[62] Interim results published as Blum (1998)[63] and Blum (2001)[64]	✓	
Blum (2001)[65] Interim results published as Blum (1999)[66]	✓	
Cervantes (2000)[67]		✓
Fumoleau (2002)[68] Also reported as Fumoleau (2001)[69]		✓[a]
Reichardt (2001)[70] Interim results published as Reichardt (2000)[71] and Thuss-Patience (2001)[72]		✓[a]
Semiglazov (2002)[73]		✓
Watanabe (2001)[74]		✓
Leonard (2001)[75] Also published as Leonard (2000)[76] and Anderson (1999)[77] (Scottish subgroup)		✓
Wong (2000)[78]		✓
Capecitabine monotherapy in patients relapsing after HDC-ASCS		
Bashey (2001)[79]	✓	
Jakob (2002)[80] Interim results published as Jakob (2001)[81]	✓	
Sundaram (2000)[82]		✓
Capecitabine/docetaxel combination therapy		
O'Shaughnessy (2002)[59] Interim findings published as Leonard (2001)[83] and Vukelja (2001);[84] additional QoL data published as Twelves (2001);[85] post-hoc analysis of post-study therapy published as Miles (2001)[86]	✓	
Tonkin (2001)[60]		✓
Scarfe (2002)[61]		✓

[a] Extra data available.

monotherapy appeared to meet the criteria for inclusion in the review. Time restraints precluded translation of these papers. The bibliographic details of these two studies are listed in Appendix 8. An English conference abstract[73] was identified by the authors of the Russian study. The number of participants differed, so it was unclear whether it referred to the same study.

Two economic evaluations were identified for inclusion in the review. The first economic evaluation investigated capecitabine monotherapy[89] and the other was based on the RCT[59] investigating capecitabine in combination with docetaxel compared with single-agent docetaxel.[90]

Clinical effectiveness

Capecitabine (Xeloda) monotherapy

Twenty-one[62–82] published reports (not including the two foreign language reports) of 12 studies were included which investigated the use of capecitabine monotherapy in patients who were reported to have failed anthracycline and/or taxane therapy. Four studies[79–82] investigated the use of capecitabine in patients who had relapsed following high-dose chemotherapy and autologous stem cell support (HDC-ASCS). Nine publications[67,68,70,72–75,78,82] had only been published as conference abstracts (see *Table 1*). The drug manufacturer (Roche) provided extra data for two abstracts.[68,70]

Description of included studies

Uncontrolled Phase II studies

Thirteen reports[62–74] were identified of seven Phase II studies. None of the included Phase II studies investigating capecitabine monotherapy included a comparison group. The number of participants recruited to the studies ranged from 32 to 163. The doses of capecitabine investigated were 1250 mg/m^2 twice daily, 1255 mg/m^2 twice daily and 1657 mg/m^2 daily. All studies, except for one, used a dosage schedule of capecitabine for 14 days out of a 21-day cycle. The exception was the study by Watanabe (2001),[74] which used a dosage schedule in which capecitabine 1657 mg/m^2 per day was given for 21 days out of a 28-day cycle. All the patients recruited into the studies had received previous chemotherapeutic regimens for their advanced disease. The percentage of patients who had been pretreated with taxanes was 100% in seven of the eight included studies; the percentage of patients pretreated with anthracyclines ranged from 61 to 100% and was not reported in two studies. The length of follow-up was not reported in the majority of studies and one study was ongoing.[72]

Other uncontrolled observational studies

Of the two other uncontrolled studies included in the review, one was a case series by Wong (2000)[78] and one was an analysis of a UK-based named patient programme by Leonard (2001).[75–77] The capecitabine dose regimens used in these studies were 1275 mg/m^2 twice daily and 1250 mg/m^2 twice daily, respectively. Both administered capecitabine for 14 days out of a 21-day cycle. The study by Leonard (2001)[75] included 102 patients with advanced breast cancer and the study by Wong (2000)[78] included 22 patients. A summary of the details of the included Phase II and other uncontrolled studies are shown in *Tables 2* and *3*, respectively.

Uncontrolled studies in patients relapsing after HDC-ASCS

At present, multicentre, randomised studies have failed to confirm the efficacy of high-dose chemotherapy regimens over standard-dose chemotherapy. The use of HDC-ASCS is therefore still considered experimental.[11]

Four reports[79–82] of three studies were found which investigated the use of capecitabine monotherapy following relapse after HDC-ASCS. The dose of capecitabine administered to patients was 1250 mg/m^2 twice daily for 14 days out of a 21-day cycle, in all studies. The number of participants included in the studies ranged from eight to 14. A summary of the details of these studies is shown in *Table 4*.

Quality of included studies

The quality of the uncontrolled studies was assessed using the same checklist as applied to RCTs. This avoided the potential for the contradictory classification of uncontrolled studies as good quality and RCTs as poor quality, and gave a continuous measure of quality across all of the included studies. In addition, it was felt that the review question should dictate which quality checklist to use, not the design of the included studies. As the review question addressed effectiveness and the gold standard for the assessment of effectiveness is the RCT, all studies were assessed using an RCT checklist. A full report of these data is presented in *Tables 5*–*7*. All of the studies that investigated capecitabine monotherapy were uncontrolled. These trials, therefore, only investigated patients treated with capecitabine and did not use a 'no treatment', or alternative treatment, control group.

TABLE 2 *Capecitabine monotherapy: summary of Phase II studies*

Study	No. of participants	Age (years) (range)	*n/N* (%) pretreated with			Capecitabine			Length of follow-up (range)
			Taxane	Anthracycline	Both	Dosage	No. of cycles (range)	Length per cycle	
Blum (1999)[62] Interim findings published as Blum (1998)[63] and Blum (2001)[64]	163	Mean 55.8 (26–78)	163/163 (100)	148/163 (91)	148/163 (91)	2510 mg/m^2 daily in two divided doses	Unclear	21 days (14 days + 7 days' rest)	At least 48 weeks
Blum (2001)[65] Interim findings published as Blum (1999)[66]	74[a]	Mean 52.4 SD 11.4 (29–77)	75/75 (100)	71/75 (96)	71/75 (96)	1255 mg/m^2 twice daily	≤ 16	21 days (14 days + 7 days' rest)	At least 48 weeks
Cervantes (2000)[67]	32	Mean 51 (39–66)	32/32 (100)	NR	Unclear	2500 mg/m^2 daily in two divided doses	Mean 2.8 (2–15)	21 days (14 days + 7 days' rest)	Unclear
Fumoleau (2002)[68] Interim results published as Fumoleau (2001)[69]	126	Median 54 (30–80)	126/126 (100)	126/126 (100)	126/126 (100)	1250 mg/m^2 twice daily	Median 6 (1–15)	21 days (14 days + 7 days' rest)	Unclear
Reichardt (2001)[70] Interim results published as Reichardt (2000)[71] and Thuss-Patience (2001)[72]	136	Median 56 (32–77)	136/136 (100)	128/136 (94)	128/136 (94)	1250 mg/m^2 twice daily	Median 3 (1–21)	21 days (14 days + 7 days' rest)	Median 7.4 (0.4–24.0) months
Semiglazov (2002)[73]	80	NR	NR	80/80 (100)	31/80 (39)	2510 mg/m^2 daily in two divided doses	NR	21 days (14 days + 7 days' rest)	NR
Watanabe (2001)[74]	60	NR	60/60 (100)	NR	Unclear	1657 mg/m^2 per day	NR	28 days (21 days + 7 days' rest)	NR

[a]Seventy-five patients were recruited to the trial but one subsequently refused treatment
NR, not reported.

TABLE 3 *Capecitabine monotherapy: summary of other uncontrolled observational studies*

Study	No. of participants	Age (years) (range)	*n/N* (%) pretreated with			Capecitabine			Length of follow-up (range)
			Taxane	Anthracycline	Both	Dosage	No. of cycles (range)	Length per cycle	
Leonard (2001)[75] Interim results published as Leonard (2000),[76] Scottish subgroup published as Anderson (1999)[77]	102	Median 53.2 (30–95)	26/102 (26)	62/102 (61)	NR	1250 mg/m^2 twice daily	Median 5 (NR)	21 days (14 days + 7 days' rest)	NR
Wong (2000)[78]	22	Median 49 (33–70)	Previous treatment with anthracycline and taxanes used in 14/22 (63%)			2550 mg/m^2 daily in two divided doses	NR	21 days (14 days + 7 days' rest)	NR

TABLE 4 *Capecitabine monotherapy: summary of uncontrolled studies investigating treatment following relapse after HDC-ASCS*

Study	No. of participants	Age (years) (range)	*n/N* (%) pretreated with			Capecitabine			Length of follow-up (range)
			Taxane	Anthracycline	Both	Dosage	No. of cycles (range)	Length per cycle	
Bashey (2001)[79]	10	(36–58)	10/10 (100)	8/10 (80)	8/10 (80)	1250 mg/m^2 twice daily	Median 8 (4–24)	21 days (14 days + 7 days' rest)	Median 183 (97–540) days
Jakob (2002)[80] Interim results published as Jakob (2001)[81]	14	Median 45.5 (35–60)	–	6/14 (43)	8/14 (57)	2500 mg/m^2 daily in two divided doses (12 h apart)	Median 5 (1–19)	21 days (14 days + 7 days' rest)	NR
Sundaram (2000)[82]	8	Median 42 (36–56)	8/8 (100)	6/8 (75)	6/8 (75)	2500 mg/m^2 daily in two divided doses	Median 6 (2–16)	21 days (14 days + 7 days' rest)	Median 21 (3–48) weeks

TABLE 5 *Capecitabine monotherapy: quality of uncontrolled Phase II studies*

Quality criteria	Blum (1999)[62]	Blum (2001)[65]	Cervantes (2000)[67]	Fumoleau (2002)[68]	Reichardt (2001)[70]	Semiglazov (2002)[73]	Watanabe (2001)[74]
Was the method used to assign participants to the treatment groups really random?	×	×	×	×	×	×	×
Method of random assignment	None	None	None	None	None	None	None
Was the allocation of treatment concealed?	×	×	×	×	×	×	×
Method of treatment allocation	×	×	×	×	×	×	×
Was the number of participants who were randomised stated?	×	×	×	×	×	×	×
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×	×	×	×	×	×
Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×	×	×	×	×	×
Were the eligibility criteria for study entry specified?	✓	✓	✓/×	✓/×	✓	✓/×	✓/×
Were any co-interventions identified that may influence the outcomes for each group?	×	×	×	×	×	×	×
Were the outcome assessors blinded to the treatment allocation?	×	×	×	×	×	×	×
Were the individuals who administered the intervention blinded to the treatment allocation?	×	×	×	×	×	×	×
Were the participants who received the intervention blinded to the treatment allocation?	×	×	×	×	×	×	×
Was the success of the blinding procedure assessed?	×	×	×	×	×	×	×
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	×	×	×	×	×	×	×
Were the reasons for any withdrawals stated?	✓	✓	×	✓/×	×	×	×
Was an intention-to-treat analysis included?	✓	✓	NS	✓	✓	NS	NS

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); NS, not stated.

TABLE 6 *Capecitabine monotherapy: quality of other uncontrolled observational studies*

Quality criteria	Leonard (2001)[75]	Wong (2000)[78]
Was the method used to assign participants to the treatment groups really random?	×	×
Method of random assignment	None	None
Was the allocation of treatment concealed?	×	×
Method of treatment allocation	×	×
Was the number of participants who were randomised stated?	×	×
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×
Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×
Were the eligibility criteria for study entry specified?	×	×
Were any co-interventions identified that may influence the outcomes for each group?	×	×
Were the outcome assessors blinded to the treatment allocation?	×	×
Were the individuals who administered the intervention blinded to the treatment allocation?	×	×
Were the participants who received the intervention blinded to the treatment allocation?	×	×
Was the success of the blinding procedure assessed?	×	×
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	×	×
Were the reasons for any withdrawals stated?	×	×
Was an intention-to-treat analysis included?	×	×

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); NS, not stated.

Of the seven Phase II studies, five[67,68,70,73,74] were only published as conference abstracts and therefore provided limited data. Full manuscripts were available for two studies.[62,65] All of the studies clearly reported their aims or primary objective for the study. The primary aims of Phase II cancer studies are to determine whether a drug has antitumour activity and whether it is safe to use. Three studies[62,65,68] clearly reported the eligibility criteria for entry into the study. The number of participants recruited into the studies varied, ranging from 32 to 163. Only one study (Blum, 1999[62]) reported that statistical methods had been used to justify the sample size. The remaining studies failed to report whether their sample sizes were sufficient to show clinically or statistically significant effects.

According to the licensing information, capecitabine monotherapy is indicated for patients who have failed treatment with both a taxane and an anthracycline-containing regimen. However, in a number of the studies investigating capecitabine monotherapy the numbers of patients pretreated with these two agents were inadequately reported. The percentage of patients pretreated with anthracyclines was not reported in two studies[67,74] and ranged from 61 to 100% in those that did report it. The length of follow-up was inadequately reported in a number of studies. It was, therefore, difficult to judge whether patients had been followed up for a sufficiently long period. In the three studies where it was reported, length of follow-up ranged from a median of 7.4 months to 'at least' 48 weeks.

Independent assessment of tumour response is particularly important given that response rates can be a very subjective end-point. Since none of the included studies used a control group, blinding was not possible. Lack of blinding is not so important for outcomes with a clear end-point, such as death, but is particularly important for response outcomes as the assessor may report a biased, more or less favourable outcome compared with the true effect. Only two studies reported that independent assessments had been performed (Blum, 1999;[62] Blum, 2001[65]).

TABLE 7 *Capecitabine monotherapy: quality of uncontrolled studies in patients relapsing after HDC-ASCS*

Quality criteria	Bashey (2001)[79]	Jakob (2002)[80]	Sundaram (2000)[82]
Was the method used to assign participants to the treatment groups really random?	×	×	×
Method of random assignment	None	None	None
Was the allocation of treatment concealed?	×	×	×
Method of treatment allocation	×	×	×
Was the number of participants who were randomised stated?	×	×	×
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×	×
Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×	×
Were the eligibility criteria for study entry specified?	✓/×	✓	✓/×
Were any co-interventions identified that may influence the outcomes for each group?	×	×	×
Were the outcome assessors blinded to the treatment allocation?	×	×	×
Were the individuals who administered the intervention blinded to the treatment allocation?	×	×	×
Were the participants who received the intervention blinded to the treatment allocation?	×	×	×
Was the success of the blinding procedure assessed?	×	×	×
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	×	×	×
Were the reasons for any withdrawals stated?	×	×	×
Was an intention-to-treat analysis included?	?	✓	NS

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); ?, unclear.

Four studies reported that they had carried out an intention-to-treat (ITT) analysis.[62,65,68,70] In three studies, the ITT population included all eligible patients who received at least one dose of medication. In the fourth study,[70] the ITT population was not defined but included all patients recruited into the study. Assessing data using the ITT principle gives a clearer indication of the performance of a treatment in everyday clinical practice. In the remaining three studies,[67,73,74] the method of analysis was not reported.

Both of the uncontrolled observational studies[75,78] were only available as abstracts. In the study by Wong and colleagues[78] the entry criteria for eligibility into the study were not well described. The group of patients appeared to be mixed, as patients at all disease stages were included. Also, not all of the patients had been pretreated with anthracyclines and taxanes. Similarly, in the study by Leonard and colleagues,[75] the patient group appeared to be mixed and was not well described.

Of the three studies investigating capecitabine following relapse after HDC-ACSC, two were available as full papers.[79,80] Only one study[80] reported a full description of the criteria for entry into the study. The percentage of patients who had been pretreated with anthracyclines and/or taxanes was reported in all studies, and in two of the studies[79,82] 100% of patients had been pretreated with a taxane. ITT analysis was only reported to have been undertaken in one study,[80] although in the study by Bashey and colleagues[79] all patients appeared to have been evaluated. Sundaram and colleagues[82] only reported results for those patients evaluable for response.

Overall, the methodological quality of the studies investigating capecitabine monotherapy was low. With regard to the evaluation of effectiveness, all the studies suffered from a number of design flaws making them vulnerable to bias, most notably the lack of a control group. In addition, owing to limited reporting of participant characteristics in some studies, it was difficult to assess the potential effects of confounding factors on treatment outcomes. Issues related to specific studies and differences between the studies in terms of dose regimens and baseline population differences mean that data from these studies should be treated with caution. In terms of the aim of this report and its assessment of the clinical effectiveness of capecitabine, alternative studies using a controlled design (preferably an RCT) are urgently required to make an assessment based on good quality evidence.

Effectiveness of capecitabine monotherapy

The following section describes the clinical effectiveness data from 12 uncontrolled studies. This section of the report, as outlined in the Methods section (Chapter 3), aims to assess the clinical effectiveness of capecitabine using the best quality evidence available. In the absence of any RCTs, or even non-randomised controlled studies, investigating capecitabine monotherapy the reviewers had to focus on lower level evidence from uncontrolled studies. For reasons related to the study quality issues discussed previously (see previous subsection), these results should be treated with great caution.

Overall survival

In all of the studies, except for the Cervantes trial[67] and the Semiglazov trial,[73] the probability of survival was estimated using Kaplan–Meier analysis, and survival curves were presented. Median survival time was reported in five studies[62,65,68,70,73] and ranged from 8.1 to 15.2 months.

Time to disease progression

Time to disease progression was defined as the interval between the initiation of treatment with capecitabine and the first recording of progressive disease or date of death in the ITT population in the Blum (2001) trial.[65] None of the other studies reported a specific definition.

Time to disease progression was reported as median time to disease progression in six studies[62,65,68,73,74,91] and ranged from 2.8 to 6.2 months. Kaplan–Meier curves were presented in four of the six studies.[62,65,68,70]

Duration of response

In their 2001 trial, Blum and colleagues[65] defined the duration of response as the interval between the initiation of treatment with capecitabine and the first observation of progressive disease in patients achieving a confirmed response to therapy. None of the other studies reported a specific definition.

Duration of response was reported as the median duration of response in five studies[62,65,68,70,74] and ranged from 5 to 8.3 months. Kaplan–Meier analyses of duration of response were reported to have been undertaken in four studies.[62,65,68,70]

Time to treatment failure

Median time to treatment failure was reported in one study (Blum, 2001[65]) as 3.2 months [95% confidence interval (CI) 2.2 to 4.4]. The time to treatment failure analysis included all patients withdrawn from treatment because of adverse events or withdrawal of informed consent, as well as those who showed progressive disease.

The results for the individual studies are summarised in *Table 8*. The two uncontrolled, observational studies, by Leonard (2001)[75] and Wong (2000),[78] did not report any time to event data.

Tumour response

Response rates can be a very subjective end-point, particularly when the assessor is not independent or blinded to the intervention. Since none of the included studies used a control group, blinding was not possible, and the results should therefore be treated with caution.

In the study by Blum and colleagues,[62] complete response was defined as the disappearance of all known disease. Partial response was defined as a decrease in the sum of the product of the perpendicular diameters for all lesions by 50%. Progressive disease was defined as a 25% increase in the cross-sectional area of one or more lesions or the appearance of new lesions. All other outcomes were scored as stable disease. In the studies by Blum (2001),[65] Fumoleau[69] and Reichardt,[71] tumour response was assessed according to standard World Health Organisation (WHO) criteria.[92] Tumour response was not defined in the remaining studies.

For capecitabine monotherapy the overall response (OR) rate ranged from 15 to 28% and the complete response (CR) rate ranged from 0 to 6%. For the study using the low-dose capecitabine

TABLE 8 *Capecitabine monotherapy: summary of time to event data*

Study	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Blum (1999)[62]	Patients with measurable disease (*n* = 27): 7.9 months (range 3.2–10.6) (ongoing)	ITT population (*n* = 162): 3.0 months (95% CI 2.8 to 3.5)	NR	ITT population (*n* = 162): 12.6 months (95% CI NR)
Blum (2001)[65]	Patients with partial response (*n* = 17): 8.3 months (95% CI 7.0 to 9.9)	ITT population (*n* = 74): 3.2 months (95% CI 2.3 to 4.3)	(*n* unknown): 3.2 months (95% CI 2.2 to 4.4)	ITT population (*n* = 74): 12.2 months (95% CI 8.0 to 15.3)
Cervantes (2000)[67]		NR		
Fumoleau (2002)[68]	Responders (*n* = 35): 5 months (95% CI 4.2 to 6.2)	ITT population (*n* = 126): 4.6 months (95% CI 4.0 to 6.2)	NR	ITT population (*n* = 126): 15.2 months (95% CI 13.5 to 19.6)
Reichardt (2001)[70]	Responders (*n* = 21): 7.4 months (95% CI 6.0 to 9.0)	ITT population (*n* = 136): 3.3 months (95% CI 2.8 to 4.2)	NR	ITT population (*n* = 136): 10.4 months (95% CI 8.2 to 12.7)
Semiglazov (2002)[73] Anthracycline refractory (*n* = 49)	NR	6.5 months (95% CI NR)	NR	10.0 months (95% CI NR)
Semiglazov (2002)[73] Antracycline- and docetaxel refractory (*n* = 31)	NR	6.2 months (95% CI NR)	NR	8.1 months (95% CI NR)
Watanabe (2001)[74]	Responders (*n* = 11): 7.2 months (221 days)	Eligible patients (*n* = 55): 2.8 months (84 days)	NR	NR

regimen (1657 mg/m^2) the OR and CR rates were 20% and 2%, respectively. The results for the individual studies are presented in *Table 9*.

Subgroup analysis of response rate Blum (1999)[62] reported the response rate for a retrospectively defined subgroup of 42 patients, resistant to both paclitaxel and doxorubicin. The overall response rate (CR + PR) in this group of patients was 29%.

In their 2001 study,[65] Blum and colleagues reported the response rate for a subgroup of 69 patients with measurable disease according to whether they had been pretreated with paclitaxel or docetaxel. The overall response rates were 27% and 20% in the paclitaxel- and docetaxel-pretreated patients, respectively.

It must be borne in mind that subgroup analyses can be very unreliable and misleading, particularly where the groups only contain a small number of participants, as in these instances.

Other outcomes

QoL Only one study (Fumoleau, 2002[68]) assessed QoL in patients receiving capecitabine monotherapy. QoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire,[93] a cancer-specific questionnaire. The questionnaire assessed both functional (including global health status, cognitive functioning and emotional functioning) and symptom-related (including fatigue, nausea and pain) parameters. Based on questionnaires from 46 patients, it was reported that patients showed an improvement in global health status and physical, role, emotional and cognitive functioning at cycle 6. Data for the other domains on the QoL questionnaire were not reported, but the author stated that there was a trend towards improvement on all measured parameters.

Clinical benefit response Two studies (Blum, 1999;[62] Blum, 2001[65]) assessed the clinical benefit response

TABLE 9 *Capecitabine monotherapy: summary of response to treatment (best response)*

Study	Response rate *n/N* (%)				
	OR (CR + PR)	**CR**	**PR**	**SD**	**PD**
Phase II studies					
Blum (1999)[62] Patients with measurable disease	27/135 (20) (95% CI 14 to 28)	3/135 (2)	24/135 (18)	54/135 (40) (95% CI 31.7 to 48.8)	46/135 (34)
Blum (1999)[62] Patients with assessable but not measurable disease	5/27 (19)	NR	NR	NR	NR
Blum (2001)[65]	19/74 (26) (95% CI 15.7 to 35.6)	2/74 (3)	17/74 (23)	23/74 (31) (95% CI 20.5 to 41.6)	NR
Cervantes (2000)[67]	13/32 (41)	2/32 (6)	11/32 (34)	6/32 (19)	13/32 (41)
Fumoleau (2002)[68]	35/126 (28) (95% CI 20 to 34)	5/126 (4)	30/126 (24)	44/126 (35)	47/126 (37)
Reichardt (2001)[70]	21/136 (15)	2/136 (2)	19/136 (13)	63/136 (46)	NR
Semiglazov (2002)[73] Anthracycline refractory	12/49 (24)	3/49 (6)	9/49 (18)	NR	NR
Semiglazov (2002)[73] Anthracycline and docetaxel refractory	(21)[a]	0/31	(21)[a]	NR	NR
Watanabe (2001)[74]	11/55 (20) (95% CI 10.4 to 33.0)	1/55 (2)	10/55 (18)	NR	NR
Other uncontrolled studies					
Leonard (2001)[75]	19/102 (19)	3/102 (3)	17/102 (17)	47/102 (46)	31/102 (30)
Wong (2000)[78]	6/22 (27)	0/22	6/22 (27)	2/22 (9)	NR

[a] *n/N* could not be calculated from the percentage reported.
CR, complete response; PR, partial response; SD, stable disease; PD, disease progression.

(CBR). The CBR was used as an assessment of the effect of treatment on clinically relevant tumour-related symptoms. The definition of a positive CBR was as follows (the parameter had to be maintained for at least 4 weeks):

- pain intensity — ≥ 50% reduction in patients with baseline pain ≥ 20 mm
- analgesic consumption — ≥ 50% reduction in patients with baseline analgesic consumption ≥ 70 mg morphine equivalents
- Karnofsky performance scale (KPS) status — improvement of ≥ 20 points.

Negative responses were defined as a worsening of any parameter maintained for at least 4 weeks. A patient was classified as a responder if they achieved a positive response in at least one of the self-rated parameters and their score was stable in the remaining parameters. Patients with a negative score in one or more of any of the parameters were classified as non-responders; all other patients were classified as having achieved a stable response. The results of the assessment of CBR are reported in *Table 10*.

Adverse events/toxicity The two studies (Blum, 1999;[62] Blum, 2001[65]) that were available as full manuscripts reported adverse event data in full. In the remaining seven studies, which were only published as conference abstracts, it was unclear whether the studies had not reported complete data for adverse events or whether the adverse events had not occurred during the study. In two studies,[68,70] where Roche provided extra data, common adverse event data were reported graphically but were not extractable. One study (Cervantes, 2000[67]) did not report any adverse event or toxicity data.

TABLE 10 *Capecitabine monotherapy: summary of clinical benefit response*

Study	N	Overall score *n*/*N* (%)		
		Positive	Stable	Negative
Blum (1999)[62]	147	29/147 (20)	45/147 (30)	73/147 (50)
Blum (2001)[65]	54	8/54 (15)	22/54 (41)	24/54 (44)

Four studies[62,65,68,71] reported that adverse events, with the exception of hand–foot syndrome, were graded according to the National Cancer Institute of Canada common toxicity criteria (NCIC-CTC). In all four studies, hand–foot syndrome was graded using protocol-specific definitions. The grading scale for hand–foot syndrome is reproduced in Appendix 3.

The most commonly reported adverse event (all grades) in all studies was hand–foot syndrome (also known as PPE), followed by diarrhoea, nausea and vomiting. The most commonly reported severe adverse event (grade 3/4) was hand–foot syndrome. Hand–foot syndrome affects the palms of the hands and the soles of the feet, causing a macular, often painful, reddening of the skin and a tingling sensation. In severe cases the surface of the skin may begin to blister and degrade, impacting significantly on the QoL of the patient. One trial (Fumoleau[68]) reported a high incidence of grade 3/4 granulocytopenia (18/126; 14%). Three of the 18 cases were classified as life-threatening (grade 4), but the authors report that all cases were uncomplicated. *Table 11* shows the number of individual adverse events reported in each of the included studies.

Laboratory adverse events were not fully reported in the majority of the included studies. The most frequently reported change in laboratory parameter during the Blum (1999) study[62] was in total bilirubin. There were 17/162 (10.5%) grade 3/4 bilirubin elevations (nine were concomitant with liver metastases). In their 2001 study,[65] Blum and colleagues reported that the main clinically relevant grade 3/4 shifts in laboratory parameters were neutropenia (6/74; 8.1%), leucocytopenia (5/74; 6.8%) and thrombocytopenia (4/74; 5.4%). Watanabe and colleagues[74] reported that grade 3/4 increases in serum bilirubin and aspartate aminotransferase (ASAT) were observed in 5/60 (8.3%) and 4/60 (6.7%) patients, respectively.

Impact of dose reduction Blum and colleagues reported a retrospective analysis to evaluate the impact of dose modification on treatment efficacy in an update[64] of their 1999 study.[62] The analysis demonstrated that in patients in whom the dose had been reduced to 75% of the starting dose for adverse events, there was no significant increase in the risk of progression [hazard ratio (HR) 1.07, Wald test p = 0.73] compared with those not requiring dose reduction. In 45 patients requiring dose reductions the median time to dose reduction was 1.6 months. Blum and colleagues conducted a similar analysis in their 2001 study[65] and found that, again, dose reduction for adverse events did not appear to have an impact on efficacy. In 37 patients requiring a 75% dose reduction the median time to dose reduction was 1.4 months (range 0.2–9.2 months).

Effectiveness of capecitabine monotherapy following relapse after treatment with HDC-ASCS

Four reports[79–82] of three studies were identified which investigated capecitabine monotherapy in patients who had undergone HDC-ASCS for metastatic breast cancer.

Overall survival

Overall survival was reported in two of the three studies. Bashey and colleagues[79] did not report a method for calculating survival. Total overall survival time from treatment with HDC-ASCS ranged from 196 to 904 days. Jakob and colleagues[80] calculated survival from the start of treatment with capecitabine to the date of death or the last date on which the patient was known to be alive. Probability of survival was estimated using the Kaplan–Meier method. The median survival time according to the Kaplan–Meier method was not reached (range 3.9–36.5 months; eight patients were still alive at the end of follow-up and six patients had died). The remaining study, by Sundaram and colleagues,[82] did not report any measure of overall survival.

Time to disease progression

Jakob and colleagues[80] calculated time to disease progression from first treatment until disease progression or death. The reported median time to disease progression was 2.8 months (range

TABLE 11 *Capecitabine monotherapy: summary of adverse events (all grades)*

Adverse event	References	Severe adverse events (grade 3/4) *n*/*N* (%)	Adverse events (all grades) *n*/*N* (%)
Hand–foot syndrome	Blum (1999)[62]	16/162 (10)	91/162 (56)
	Blum (2001)[65]	16/74 (22)	46/74 (62)
	Fumoleau (2002)[68]	27/126 (21)	Unclear
	Reichardt (2001)[70]	16/134 (12)	70/134 (52)
	Semiglazov (2002)[73a]	3/31 (10)	NR
	Watanabe (2001)[74]	8/60 (13)	NR
	Leonard (2001)[75]	8/102 (8)	36/102 (35)
	Wong (2002)[78]	1/22 (5)	10/22 (45)
Diarrhoea	Blum (1999)[62]	23/162 (14)	88/162 (54)
	Blum (2001)[65]	14/74 (19)	43/74 (57)
	Fumoleau (2002)[68]	13/126 (10)	Unclear
	Reichardt (2001)[70]	7/134 (5)	36/134 (27)
	Leonard (2001)[75]	7/102 (7)	35/102 (34)
Nausea	Blum (1999)[62]	7/162 (4)	84/162 (52)
	Blum (2001)[65]	7/74 (9)	41/74 (55)
	Fumoleau (2002)[68]	5/126 (4)	Unclear
	Reichardt (2001)[70]	5/134 (4)[c]	63/134 (47)[c]
	Leonard (2001)[75]	1/102 (1)	31/102 (30)
Vomiting	Blum (1999)[62]	6/162 (4)	60/162 (37)
	Blum (2001)[65]	4/74 (5)	27/74 (36)
	Fumoleau (2002)[68]	4/126 (3)	Unclear
	Leonard (2001)[75]	2/102 (2)	17/102 (17)
Fatigue/lethargy	Blum (1999)[62]	12/162 (7)	59/162 (36)
	Blum (2001)[65]	6/74 (8)	17/74 (23)
	Reichardt (2001)[70]	–	21/134 (16)
	Leonard (2001)[75]	4/102 (4)	21/102 (20)
Constipation	Blum (1999)[62]	2/162 (1)	25/162 (15)
Dermatitis/rash	Blum (1999)[62]	2/162 (1)	25/162 (15)
Abdominal pain	Blum (1999)[62]	5/162 (3)	24/162 (15)
Decreased appetite	Blum (1999)[62]	1/162 (1)	18/162 (11)
Anorexia	Blum (2001)[65]	–	10/74 (14)
Pyrexia	Blum (1999)[62]	1/162 (1)	18/162 (11)
Erythematous rash	Blum (1999)[62]	–	17/162 (11)
Paraesthesia	Blum (1999)[62]	–	16/162 (10)
Stomatitis	Blum (1999)[62]	4/162 (3)	15/162 (9)
	Blum (2001)[65]	9/74 (12)	25/74 (34)
Mucosal inflammation/mucositis	Blum (1999)[62]	7/162 (4)	15/162 (9)
	Leonard (2001)[75]	2/102 (2)	6/102 (6)
	Wong (2000)[78]	–	3/22 (14)
Dehydration	Blum (1999)[62]	6/162 (4)	11/162 (7)
	Blum (2001)[65]	5/74 (7)	11/74 (15)
Coagulation disorder	Blum (1999)[62]	1/162 (1)	1/162 (1)
Haemorrhagic diarrhoea	Blum (2001)[65]	1/74 (1)	NR
Sepsis	Blum (2001)[65]	1/74 (1)	NR
Neutropenia	Blum (2001)[65]	1/74 (1)	NR
	Leonard (2001)[75]	3/102 (3)	6/102 (6)
	Reichardt (2001)[70b]	2/136 (2)	NR
Granulocytopenia	Fumoleau (2002)[68]	18/126 (14)	Unclear
Thrombocytopenia	Blum (2001)[65]	2/74 (3)	NR
	Reichardt (2001)[70b]	1/136 (1)	NR
	Leonard (2001)[75]	1/102 (1)	7/102 (7)
	Wong (2000)[78]	–	1/22 (5)
Leucopenia	Reichardt (2001)[70b]	1/136 (1)	NR
Anaemia	Reichardt (2001)[70b]	1/136 (1)	NR

Some values are approximated from percentages reported in the studies.
[a] 31 patients both anthracycline and taxane refractory.
[b] Two patients were not evaluable.
[c] Nausea and vomiting combined.

TABLE 12 *Capecitabine monotherapy following HDC-ASCS: summary of time to event data*

Study	Median duration of response	Median time to progression	Survival
Bashey (2001)[79]	8.3 (range 2.1–15.4) months	Length of progression-free survival: 2.2–17.7 months	Overall survival: range 6.4–29.6 months
Jakob (2002)[80]	7.2 (range 0.7–12.0) months	2.8 (range 0.4–13.3) months	No median reached (range 3.9–36.5 months)
Sundaram (2000)[82]	NR	NR	NR

TABLE 13 *Capecitabine monotherapy following HDC-ASCS: summary of response to treatment*

Study	Response *n/N* (%)				
	OR	CR	PR	SD	PD
Bashey (2001)[79]	7/10 (70)	3/10 (30)	4/10 (40)	3/10 (30)	0/10
Jakob (2002)[80]	6/14 (43) (95% CI 17.7 to 71.1)	1/14 (7)	5/14 (36)	2/14 (14)	NR
Sundaram (2000)[82]	5/7 (71)	1/7 (14)	4/7 (57)	2/7 (27)	0/7

OR, overall response (CR+PR).

0.4–13.3 months). They also presented a Kaplan–Meier curve. Bashey and colleagues[79] used Kaplan–Meier analysis to estimate the probability of progression-free survival. The length of progression-free survival ranged from 2.2 to 17.7 months. Sundaram and colleagues[82] did not report any measure of time to disease progression.

Duration of response

Two studies (Bashey;[79] Jakob[80]) determined duration of response from the first documentation of response until disease progression. Duration of response was 8.3 and 7.2 months in each of the two studies. Sundaram and colleagues[82] did not report any measure of duration of response. A summary of the time to event data is shown in *Table 12*.

Tumour response

One study, by Jakob and colleagues,[80] based tumour assessment on the WHO criteria for response.[92] Bashey and colleagues[79] defined a complete response as the disappearance of measurable and evaluable disease and normalisation of the CA27.29 tumour marker level (over at least three cycles). A partial response was defined as a ≥ 50% reduction in the sum of measurable lesions or, in the absence of measurable disease, a ≥ 50% reduction in CA27.29 level (at least three cycles). Stable disease was defined as a < 25% change in the size of the measurable lesions and the appearance of no new metastatic lesions (over three cycles) or a < 25% change in CA27.29 levels (over three cycles). Disease progression was defined as a > 25% increase in the volume of measurable disease, the occurrence of new metastatic lesions, or a > 50% increase in serum CA27.29 level. Sundaram and colleagues[82] did not report a definition for any measure of tumour response.

The overall response (CR + PR) rate ranged from 43 to 71% and the CR rate ranged from 7 to 30%. One study[80] did not report the number of patients who developed progressive disease. A summary of the response to treatment for the individual studies is shown in *Table 13*.

Other outcomes

Quality of life One study (Jakob, 2002[80]) assessed QoL in 12 patients using the EORTC QLQ-C30. The questionnaire was completed before each second treatment course (6-weekly intervals). Six patients showed an improvement in their QoL score of at least 20% and one further patient showed an improvement of more than 10% (the authors do not report the period in which QoL was measured). The other two studies did not assess QoL.

Adverse events/toxicity Bashey and colleagues[79] and Jakob and colleagues[80] both used the NCIC-CTC

grading system for adverse events. The method of grading was not reported in the study by Sundaram and colleagues.[82]

In all three studies the most frequently reported adverse event of any grade was hand–foot syndrome. Reported grade 3 adverse events were hand–foot syndrome, dizziness, nausea, diarrhoea and fever. Reported grade 3 haematological toxicities were leucopenia, myelosuppression and neutropenia.

Patient preference for oral therapy

No studies were found that addressed patient preference for oral therapy in direct relation to capecitabine. Liu and colleagues[94] assessed patient preference for oral versus intravenous (i.v.) palliative chemotherapy in patients with incurable cancer. They used a scenario-based trade-off technique to assess the strength and preference for oral and intravenous therapy as a function of treatment efficacy. The large majority of patients expressed a preference for oral therapy but were not willing to sacrifice efficacy for their preference.

Summary of effectiveness data for capecitabine monotherapy

Twelve uncontrolled studies were identified which investigated capecitabine monotherapy. As discussed previously, the methodological quality of these studies was low. All of the studies suffered from the lack of a control group, making them particularly vulnerable to bias. In order to make an assessment based on good quality evidence, at the very least controlled trials are urgently required.

Uncontrolled Phase II and other observational studies

The findings of these studies would appear to show that capecitabine monotherapy has some effects in patients previously treated with anthracyclines and taxanes. However, owing to the methodological problems outlined these results should be treated with extreme caution. In the studies where it was reported, median survival ranged from 8.1 to 15.2 months, time to disease progression ranged from 2.8 to 6.2 months, time to treatment failure was reported as 3.2 months in one trial, and duration of response ranged from 5 to 8.3 months. In terms of response to treatment, the overall response rate ranged from 15 to 28%, complete response ranged from 0 to 6%, and partial response ranged from 15 to 34%. The large range in effect sizes implies that heterogeneity exists between the included studies and reflects the fact that the evidence from such uncontrolled studies is extremely weak. In addition, the lack of a control group does not allow any inferences to be drawn as to the 'additional' survival that patients may experience from capecitabine monotherapy.

Two studies (Blum, 1999;[62] Blum, 2001[65]) assessed the CBR, an assessment of the effect of treatment on clinically relevant tumour-related symptoms. The percentage of patients who achieved a positive response was 20% and 15% in each of these two studies.

Only one of the ten studies assessed QoL. Although it was reported that patients showed an improvement from baseline scores, in global health status and other domains on the EORTC QLQ-C30 questionnaire, the number of patients involved in the analysis was very small.

Hand–foot syndrome was the most commonly reported adverse event. The percentage of patients experiencing grade 3 or 4 hand–foot syndrome ranged from 5 to 22%, and the percentage of patients experiencing any grade of hand–foot syndrome ranged from 35 to 62%.

Uncontrolled studies in patients relapsing following HDC-ACSC

The findings from uncontrolled studies investigating capecitabine monotherapy in patients relapsing following HDC-ACSC were inconclusive. All of the included studies suffered from small sample sizes and lack of a control group, which affects the precision of the analyses.

Capecitabine (Xeloda) in combination with docetaxel (Taxotere)

Five reports[59,83–86] of a single Phase III, RCT[59] were identified which investigated the use of capecitabine in combination with docetaxel in patients who had received previous anthracycline therapy and/or were anthracycline resistant or refractory. In addition, Roche provided a full clinical study report on Xeloda (unpublished). The publication by Miles (2001)[86] was a post hoc analysis of post-study therapy, and the publication by Twelves (2001)[85] reported supplementary QoL data. In addition to the RCT, a Phase I/II dose-finding study[60] and an abstract of an ongoing, uncontrolled study by Scarfe and colleagues[61] were identified, both of which investigated a schedule of weekly low-dose docetaxel plus intermittent capecitabine.

Description of included studies

Randomised controlled trial

The RCT by O'Shaughnessy (2002)[59] evaluated

capecitabine in combination with docetaxel compared with single-agent docetaxel. All patients had to have advanced breast cancer that had recurred after anthracycline treatment. Failure of anthracycline treatment was defined as: (1) progression while receiving anthracycline-based chemotherapy without experiencing any transient improvement; (2) no response after administration of four or more cycles of anthracycline-based chemotherapy; (3) relapsing within 2 years of completing (neo)adjuvant anthracycline-based chemotherapy; or (4) a brief objective response to anthracycline-based chemotherapy with subsequent progression while receiving the same therapy or within 12 months after the last dose. The study included 511 patients: 255 were randomised to the capecitabine plus docetaxel group and 256 to the single-agent docetaxel group. In the combination therapy group, patients were randomised to receive capecitabine (1250 mg/m^2 twice daily) for 14 days out of a 21-day cycle, in addition to docetaxel (75 mg/m^2 1 hour i.v. infusion) on the first day of each 21-day cycle. Patients randomised to the single-agent docetaxel group received 100 mg/m^2 one hour i.v. infusion docetaxel on the first day of each 21-day cycle. The median ages of both groups were similar (52 years in the combination therapy group versus 51 years in the single-agent therapy group). Relevant patient characteristics, including the dominant site of metastatic disease, were balanced between the two groups. Only patients whose cancer had recurred after anthracycline-based chemotherapy were eligible for inclusion in the study. Ten per cent and 9% of patients in the combination therapy and single-agent therapy groups, respectively, had received previous treatment with paclitaxel. The primary outcome of interest for the study was time to disease progression or death. Study details are summarised in *Table 14* and full details are reported in Appendix 9.

Uncontrolled studies

The two additional studies by Tonkin and colleagues[60] and Scarfe and colleagues[61] both investigated an alternative regimen of capecitabine in combination with docetaxel. Patients received weekly low-dose docetaxel (30 mg/m^2 i.v.) combined with capecitabine at 900 mg/m^2 twice daily for 14 days of a 21-day cycle. The study by Scarfe and colleagues was a follow-on study from that by Tonkin and colleagues, which established the feasibility of the regimen. The study by Tonkin and colleagues[60] was a Phase I dose-finding study with an additional Phase II portion which continued with 12 patients on the lower dose regimen. Scarfe and colleagues[61] enrolled 19 patients, but only 14 patients were evaluable for efficacy and toxicity. A summary of the study details is shown in *Table 15* and full details are reported in Appendix 9.

Quality of included studies

Randomised controlled trial

The study (SO14999) by O'Shaughnessy and colleagues[59] was available as a final report and as a full trial report provided by the drug manufacturer (Roche, unpublished).

Patients were randomised using a centralised randomisation service by country in blocks of four. In addition, patients were stratified according to whether or not they had received previous treatment with paclitaxel. This method of randomisation means that allocation of patients was highly likely to have been concealed. The number of patients randomised was stated and the two groups achieved baseline comparability on factors likely to influence response to treatment; patients were comparable in terms of dominant site of metastatic disease, number of tumour sites and hormone receptor status. The eligibility criteria for entry into the study were well described and were judged to be suitably comprehensive.

Owing to the nature of the treatment regimens and method of administration, it would have been difficult to blind patients to their intervention assignment. As discussed in the section assessing the quality of the capecitabine monotherapy studies, the absence of blinding, in particular for assessment of tumour response, may introduce bias. O'Shaughnessy and colleagues reported that X-rays and computed tomographic scans were reviewed by an independent review committee (IRC). The IRC was blinded to the study treatment, clinical condition of the patient and the investigators' response.

A minimum follow-up period of 15 months had been reached in all patients at the time of publication. All of the patients enrolled in the study were accounted for and an ITT analysis was undertaken for the efficacy data. The safety population included patients randomised to treatment who received at least one dose of study medication and for whom follow-up safety information was available. Analysis of results using the ITT method may give a clearer picture of actual clinical practice. Overall, the trial would seem to be of good quality. A summary of the quality of the RCT is reported in *Table 16*.

TABLE 14 *Capecitabine/docetaxel: summary of RCT*

Study	No. of participants	Age and range	Capecitabine/docetaxel			Docetaxel			Length of follow-up
			Dosage	No. of cycles	Length per cycle	Dosage	No. of cycles	Length per cycle	
O'Shaughnessy (2002)[59]	Total: 511 CAP/DOC: 255 DOC: 256	CAP/DOC: median 52 (range 26–79) years DOC: median 51 (range 25–75) years	Capecitabine 1250 mg/m^2 twice daily plus docetaxel 75 mg/m^2 i.v. infusion	≥ 2	Capecitabine for 14 days followed by 7 days' rest plus docetaxel on first day of each 21-day cycle	100 mg/m^2 1 hour i.v. infusion	≥ 2	First day of each 21-day cycle	≥ 15 months

CAP/DOC, capecitabine/docetaxel combination group; DOC, single-agent docetaxel group.

TABLE 15 *Capecitabine/docetaxel: summary of uncontrolled studies*

Study	No. of participants	Age and range	Capecitabine/docetaxel			Length of follow-up
			Dosage	Number of cycles	Length per cycle	
Tonkin (2001)[60]	Phase I: 9 Phase II: 12	NR	**Phase I** Dose level 0: docetaxel 30 mg/m^2 i.v. weekly plus capecitabine 1800 mg/m^2 daily Dose level 1: docetaxel 36 mg/m^2 i.v. weekly plus capecitabine 1,800 mg/m^2 daily *Phase II* Continued at dose level 0	NR	21 days (capecitabine for 14 days followed by 7 days' rest)	NR
Scarfe (2002)[61]	19 (14 patients were evaluable for response)	NR	Docetaxel 30 mg/m^2 i.v. weekly plus capecitabine 900 mg/m^2 p.o. daily in two divided doses	Maximum 8 cycles	21 days (capecitabine for 14 days followed by 7 days' rest)	Ongoing study; final results are not yet published

TABLE 16 *Capecitabine/docetaxel: quality checklist for RCT*

Quality criteria	O'Shaughnessy (2002)[59]
Was the method used to assign participants to the treatment groups really random?	✓
Method of random assignment	Computer-generated
Was the allocation of treatment concealed?	✓
Method of treatment allocation	Centralised service
Was the number of participants who were randomised stated?	✓
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	✓
Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	✓
Were the eligibility criteria for study entry specified?	✓
Were any co-interventions identified that may influence the outcomes for each group?	×
Were the outcome assessors blinded to the treatment allocation?	×
Were the individuals who administered the intervention blinded to the treatment allocation?	×
Were the participants who received the intervention blinded to the treatment allocation?	×
Was the success of the blinding procedure assessed?	×
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	✓
Were the reasons for any withdrawals stated?	✓/×
Was an intention-to-treat analysis included?	✓

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed).

TABLE 17 *Capecitabine/docetaxel: quality checklist for uncontrolled studies*

Quality criteria	Tonkin (2001)[60]	Scarfe (2002)[61]
Was the method used to assign participants to the treatment groups really random?	×	×
Method of random assignment	None	None
Was the allocation of treatment concealed?	×	×
Method of treatment allocation	None	None
Was the number of participants who were randomised stated?	×	×
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×
Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	×	×
Were the eligibility criteria for study entry specified?	✓/×	✓/×
Were any co-interventions identified that may influence the outcomes for each group?	×	×
Were the outcome assessors blinded to the treatment allocation?	×	×
Were the individuals who administered the intervention blinded to the treatment allocation?	×	×
Were the participants who received the intervention blinded to the treatment allocation?	×	×
Was the success of the blinding procedure assessed?	×	×
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	×	×
Were the reasons for any withdrawals stated?	×	×
Was an intention-to-treat analysis included?	×	×

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed).

TABLE 18 *Capecitabine/docetaxel RCT: overall survival*

Outcome	Capecitabine/docetaxel	Docetaxel	HR
Median survival	14.5 months (95% CI 12.3 to 16.3)	11.5 months (95% CI 9.8 to 12.7)	0.775 (95% CI 0.634 to 0.947; log-rank $p = 0.0126$)

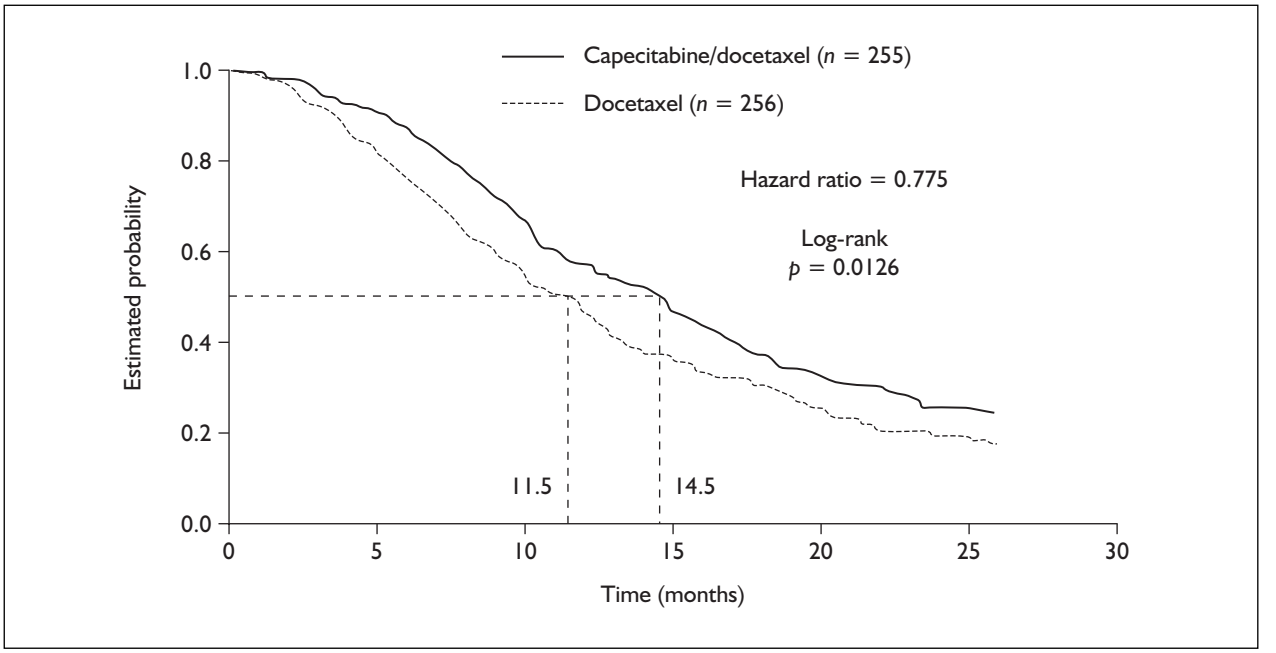

FIGURE 2 *Capecitabine/docetaxel RCT: Kaplan–Meier survival curve for capecitabine/docetaxel versus docetaxel. Reproduced from the Roche submission to NICE [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished], by kind permission of Roche.*

Uncontrolled studies

The two uncontrolled studies were only available as abstracts and, therefore, patient eligibility and characteristics were not described in detail. Data from these studies should be treated with great caution. Consequently, only a limited discussion of the findings of these studies has been included in the report. In light of this, the assessment of the clinical effectiveness of capecitabine in combination with docetaxel is based on the higher quality evidence presented in the RCT by O'Shaughnessy and colleagues. A summary of trial quality is reported in *Table 17*.

Effectiveness of capecitabine in combination with docetaxel

Randomised controlled trial

The following section of the report summarises the findings of the trial SO14999 by O'Shaughnessy and colleagues[59] and the Xeloda clinical study report provided by Roche (unpublished).

Overall survival Survival was defined as the time from randomisation to the date of death or the last date on which the patient was known to be alive.

Overall survival in the combination arm was 14.5 months (95% CI 12.3 to 16.3), compared with 11.5 months (95% CI 9.8 to 12.7) in the single-agent docetaxel arm. The corresponding HR was 0.775 (95% CI 0.634 to 0.947; log-rank $p = 0.0126$). The 12-month survival rate in the combination therapy group was 57% (95% CI 51 to 63), compared with 47% (95% CI 41 to 53) in the single-agent docetaxel group. Overall survival with Kaplan–Meier estimates is summarised in *Table 18*. *Figure 2* presents the Kaplan–Meier survival curve for capecitabine/docetaxel compared with single-agent docetaxel.

Time to disease progression Time to disease progression was defined as the time from randomisation to the first recording of disease

TABLE 19 *Capecitabine/docetaxel RCT: time to disease progression*

Outcome	Capecitabine/docetaxel	Docetaxel	HR
Median time to progression	6.1 months (95% CI 5.4 to 6.5)	4.2 months (95% CI 3.4 to 4.5)	0.652 (95% CI 0.545 to 0.780; log-rank $p = 0.0001$)

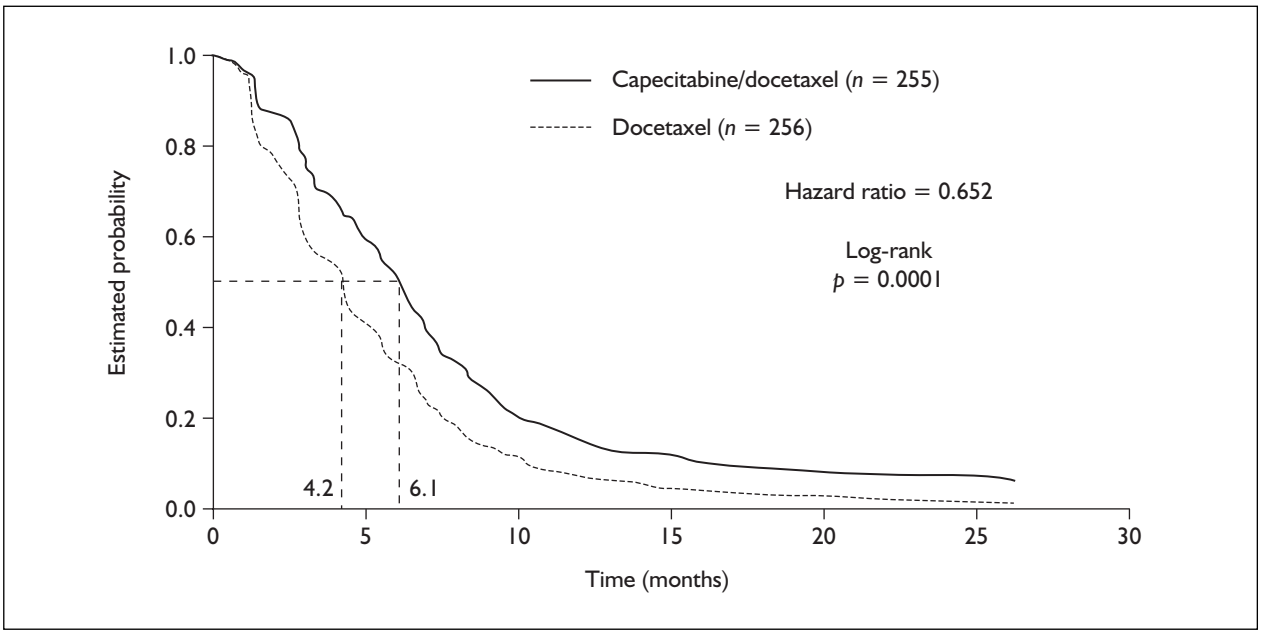

FIGURE 3 *Capecitabine/docetaxel RCT: Kaplan–Meier curve showing time to disease progression for capecitabine/docetaxel versus docetaxel. Reproduced from the Roche submission to NICE [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished], by kind permission of Roche.*

progression or the date of death in patients with no evidence of disease progression.

The median time to disease progression in the combination therapy group and the single-agent docetaxel group was 6.1 and 4.2 months, respectively. The corresponding HR was 0.652 (95% CI 0.545 to 0.780; log-rank $p = 0.0001$). Time to disease progression with Kaplan–Meier estimates is summarised in *Table 19*.

Figure 3 presents the Kaplan–Meier curve for time to disease progression for capecitabine/docetaxel compared with single-agent docetaxel.

Duration of response The calculation of duration of response was based on WHO criteria. For complete responders, duration of response was defined as the interval between the first recording of a CR and the time of disease progression or death. For partial responders, duration of response was measured from randomisation. Patients whose disease did not progress were censored using the date at which they were last known to have not progressed.

The median duration of response was reported to be 7.3 months in the capecitabine/docetaxel combination group compared with 7.0 months in the single-agent docetaxel group. This difference was not significant (HR not reported). Duration of response with Kaplan–Meier estimates is summarised in *Table 20*.

Time to treatment failure O'Shaughnessy and colleagues[59] carried out an analysis of time to treatment failure. This was a composite of safety and efficacy end-points, in which withdrawals of patients because of progressive disease or death, adverse events, treatment refusal or loss to follow-up were included as events.

Median time to treatment failure was 4.0 months (95% CI 3.3 to 4.3) in the capecitabine/docetaxel group and 2.8 months (95% CI 2.4 to 3.5) in the single-agent docetaxel group ($p = 0.0002$). Data

TABLE 20 *Capecitabine/docetaxel RCT: duration of response*

Outcome	Capecitabine/docetaxel (*n* = 106)	Docetaxel (*n* = 76)	HR
Median duration of response	7.3 months (95% CI 6.9 to 8.4)	7.0 months (95% CI 5.8 to 8.0)	NR

TABLE 21 *Capecitabine/docetaxel RCT: time to treatment failure*

Outcome	Capecitabine/docetaxel	Docetaxel	HR
Median time to treatment failure	4.0 months (95% CI 3.3 to 4.3)	2.8 months (95% CI 2.4 to 3.5)	NR

on time to treatment failure with Kaplan–Meier estimates are summarised in *Table 21*.

Tumour response The objective response of measurable disease was based on the WHO criteria. The best overall response achieved was reported. Patients were classified as achieving stable disease if at the first tumour assessment after study treatment administration there was neither disease progression nor a response. The IRC independently assessed tumour response.

The overall response rate to treatment, as determined by the study investigators, was 42% in the capecitabine/docetaxel combination group and 30% in the docetaxel single-agent group ($p = 0.006$). The IRC assessment confirmed the statistical significance of the investigators' findings (32% vs 23% in the combination therapy and single-agent docetaxel groups, respectively, $p = 0.025$). The rate of complete response to treatment was 5% in the combination therapy group and 4% in the single-agent group. This difference was not significant. The percentage of patients without post-baseline tumour response data was 10% in the combination therapy group and 6% in the single-agent docetaxel group. The most common reason for missing data was due to patients discontinuing study treatment before the first tumour assessment ($n = 11$ in the combination therapy group and $n = 7$ in the single-agent docetaxel group). Data on best response to treatment with calculated relative risks are summarised in *Table 22* and *Figure 4*.

Quality of life QoL was assessed in the safety population using the EORTC QLQ-C30 (version 2.0) with the disease-specific, breast cancer module QLQ-BR23.[93] The EORTC QLQ-C30 is a self-administered questionnaire, designed to measure health-related quality of life (HRQoL). The questionnaire consists of 15 domains: one global health domain, five function domains (physical, role, emotional, cognitive and social) and nine symptom domains (fatigue, pain, nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The QLQ-BR32 is administered in addition to the QLQ-C30 and consists of eight domains specific to breast cancer: four function domains (body image, sexual functioning, sexual enjoyment and future perspective) and four symptom domains (systemic therapy side-effects, breast symptoms, arm symptoms and upset by hair loss). Higher scores in the function domains indicate better functioning and QoL, whereas higher scores in the symptom domains indicate the increased presence of symptoms.

Patients completed questionnaires before treatment administration on the first day of therapy, every 6 weeks at the start of each treatment cycle (until week 48), and when going off study. Patients without a post-baseline measurement of QoL were excluded from the analysis. A total of 454 patients (224 in the combination therapy group and 230 in the single-agent docetaxel group) completed a QoL questionnaire at least once at baseline or during the treatment phase.

The global health score on the EORTC QLQ-C30 at week 18 (i.e. after six treatment cycles) was selected as the primary parameter for statistical testing. Based on the last observation carried forward (LOCF) method there was no significant difference between the two treatment groups at week 18. A summary of the scores and change from baseline for global health status using the LOCF method is presented in *Table 23*.

TABLE 22 *Capecitabine/docetaxel RCT: response to treatment (best response)*

Outcome	Capecitabine/docetaxel *n*/*N* (%) (*N* = 255)	Docetaxel *n*/*N* (%) (*N* = 256)	Relative risk (RR)[a]
Overall response (CR + PR)	106/255 (42) (95% CI 36 to 48)	76/256 (30) (95% CI 24 to 36)	1.40 (95% CI 1.10 to 1.78)
CR	12/255 (5) (95% CI 2 to 8)	9/256 (4) (95% CI 2 to 7)	1.34 (95% CI 0.57 to 3.12)
PR	94/255 (37)	67/256 (26)	1.41 (95% CI 1.08 to 1.83)
SD	96/255 (38%) (95% CI 32 to 44)	113/256 (44) (95% CI 38 to 50)	0.84 (95% CI 0.68 to 1.04)
PD	28/255 (11) (95% CI 7 to 15)	51/256 (20) (95% CI 15 to 25)	0.55 (95% CI 0.36 to 0.84)[b]
Missing postbaseline	25/255 (10) (95% CI 6 to 14)	16/256 (6) (95% CI 4 to 10)	–

[a] RR > 1 favours combination therapy, except for
[b] In the case of progressive disease a RR < 1 favours combination therapy.

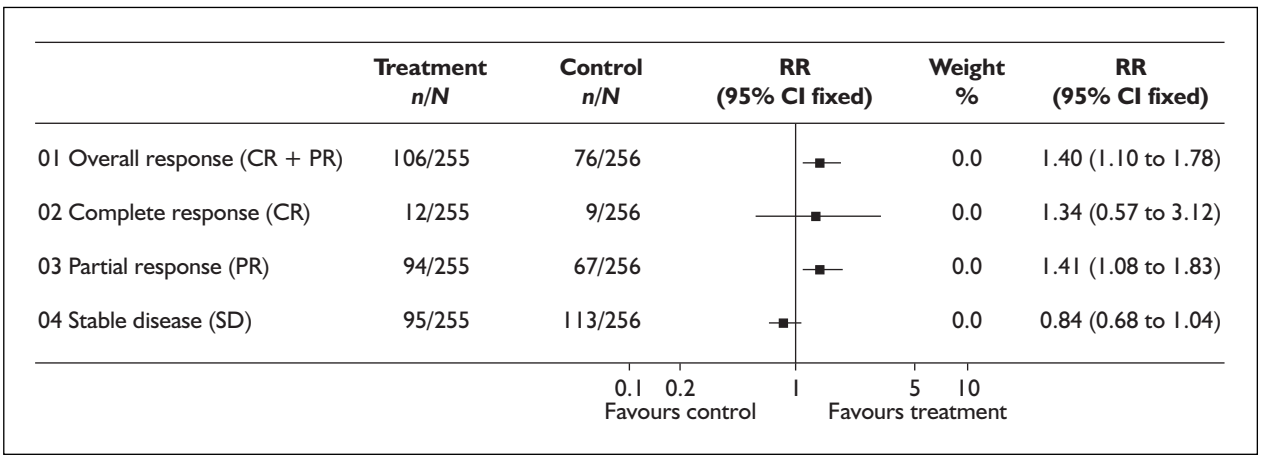

FIGURE 4 *Relative risks for response rates for capecitabine/docetaxel versus docetaxel*

Figure 5 shows change from baseline in global health status without LOCF (i.e. actual scores).

Global health score on the QLQ-C30 is a fairly insensitive end-point for the measurement of QoL. More detailed data were presented for each of the quality of life domains in the industry submission data. These data were marked commercial in confidence.

Adverse events/toxicity All adverse events encountered during the clinical study (from first dose to 28 days after last dose) were to be reported. An adverse event was defined as any adverse change from the patient's baseline condition, including intercurrent illness, whether considered related to treatment or not. Adverse events were graded according to NCIC-CTC, with the exception of hand–foot syndrome. Adverse events not listed in the NCIC-CTC were graded as mild, moderate, severe or life threatening. Hand–foot syndrome was graded on a three-point scale, as in the capecitabine monotherapy trials (see Appendix 3).

Four patients in the capecitabine/docetaxel combination therapy group and one patient in the single-agent docetaxel group did not receive study medication after randomisation. Therefore, the safety population included 251 patients in the capecitabine/docetaxel combination therapy group and 255 patients in the docetaxel monotherapy group.

The number of patients experiencing at least one treatment-related adverse event of any grade was

TABLE 23 *Capecitabine/docetaxel RCT: global health status (QLQ-C30) – summary of scores and change from baseline (LOCF)*

	Treatment group		*p*
	Capecitabine/docetaxel (*n* = 224)	**Docetaxel (*n* = 230)**	
Baseline	55.3 ± 23.8	52.7 ± 24.1	–
Week 18	–3.7 ± 25.8	–4.0 ± 25.1	0.8303
Week 30	–3.4 ± 24.6	–4.4 ± 25.4	ns

Data are shown as mean ± SD change from baseline.
ns, not significant.

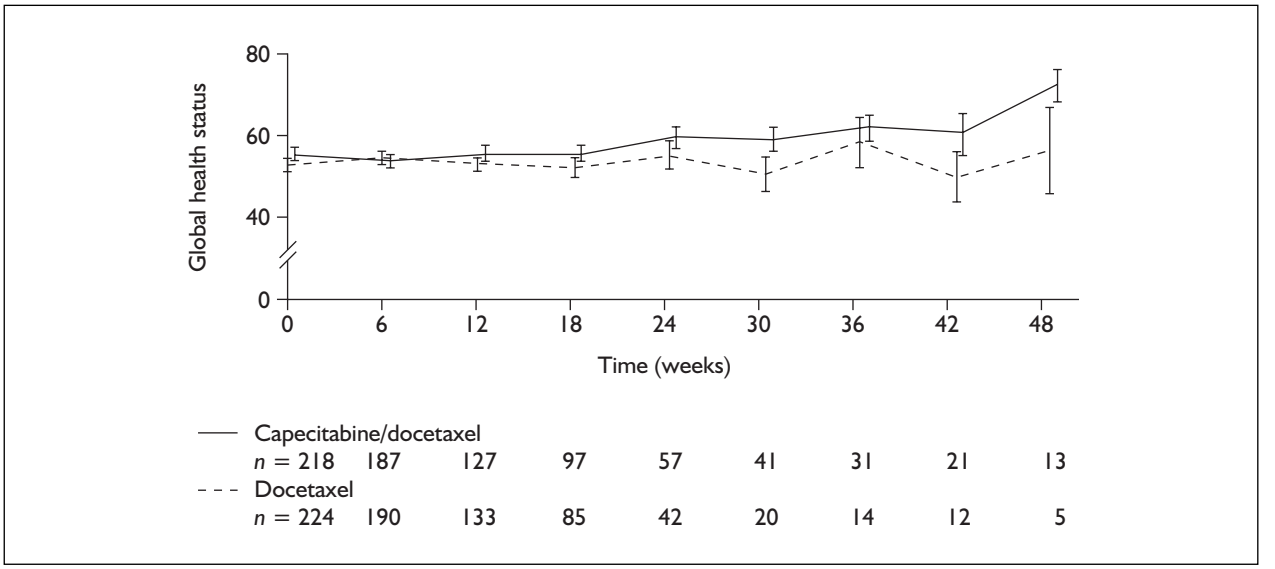

FIGURE 5 *Capecitabine/docetaxel RCT: global health status (QLQ-C30) – change from baseline (actual values). Reproduced from the Roche submission to NICE [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished], by kind permission of Roche.*

246/251 (98.0%) in the combination therapy group and 239/255 (93.7%) in the single-agent docetaxel group. Significantly higher incidences of decreased appetite [relative risk (RR = 2.44, 95% CI 0.74 to 2.01)], diarrhoea (RR = 1.43, 95% CI 1.21 to 1.68), dyspepsia (RR = 2.34, 95% CI 1.25 to 4.39), hand–foot syndrome (RR = 8.50, 95% CI 5.46 to 13.24), increased lacrimation (RR = 2.27, 95% CI 1.46 to 4.26), stomatitis (RR = 1.57, 95% CI 1.33 to 1.86) and vomiting (RR = 1.51, 95% CI 1.13 to 2.03) occurred in the capecitabine/docetaxel combination therapy group than in the single-agent docetaxel group. Significantly higher incidences of myalgia (RR = 0.57, 95% CI 0.39 to 0.83), peripheral neuropathy (RR = 0.49, 95% CI 0.25 to 0.95) and pyrexia (RR = 0.72, 95% CI 0.53 to 0.99) occurred in the single-agent docetaxel group. Treatment-related adverse events of all grades reported in more than 10% of patients are summarised in *Table 24*. Calculated relative risks are presented in *Figure 6*.

The number of patients experiencing at least one treatment-related grade 3 or 4 adverse event was 196/251 (78.1%) in the combination therapy group and 163/255 (63.9%) in the single-agent docetaxel group. The most commonly reported grade 3/4 treatment-related adverse event in the combination therapy group was hand–foot syndrome, which was reported in 61/251 (24.3%) patients. In comparison, in the single-agent docetaxel group, hand–foot syndrome was reported in just 3/255 (1.2%) patients (RR = 20.66, 95% CI 6.57 to 64.97). In addition, the incidences of grade 3 or 4 diarrhoea (13.9% vs 5.8%; RR = 2.37, 95% CI 1.33 to 4.23), nausea (6.4% vs 2.0%; RR = 3.25, 95% CI 1.21 to 8.74) and stomatitis (17.5% vs 4.7%; RR = 3.73, 95% CI

TABLE 24 *Capecitabine/docetaxel RCT: summary of treatment-related adverse events (all grades)*

Adverse event	Capecitabine/docetaxel *n*/*N* (%) (*N* = 251)	Docetaxel *n*/*N* (%) (*N* = 255)
Abdominal pain	34/251 (14)	22/255 (9)
Alopecia	102/251 (41)	106/255 (42)
Anaemia	32/251 (13)	27/255 (11)
Anorexia	30/251 (12)	25/255 (10)
Appetite decreased	24/251 (10)	10/255 (4)
Arthralgia	28/251 (11)	45/255 (18)
Constipation	34/251 (14)	30/255 (12)
Diarrhoea	160/251 (64)	114/255 (45)
Dyspepsia	30/251 (12)	13/255 (5)
Fatigue/asthenia	109/251 (44)	119/255 (47)
Hand–foot syndrome	159/251 (63)	19/255 (7)
Lacrimation increased	29/251 (12)	13/255 (5)
Myalgia	34/251 (14)	61/255 (24)
Nail disorder	34/251 (14)	37/255 (15)
Nausea	109/251 (43)	89/255 (35)
Neutropenia	43/251 (17)	42/255 (16)
Neutropenic fever	40/251 (16)	53/255 (21)
Oedema lower limb	34/251 (14)	30/255 (12)
Paraesthesia	28/251 (11)	37/255 (15)
Peripheral neuropathy	12/251 (5)	25/255 (10)
Pyrexia	52/251 (21)	73/255 (29)
Sore throat	27/251 (11)	19/255 (7)
Stomatitis	167/251 (67)	108/255 (42)
Taste disturbance	37/251 (15)	35/255 (14)
Vomiting	82/251 (33)	55/255 (22)
Weakness	32/251 (13)	22/255 (9)

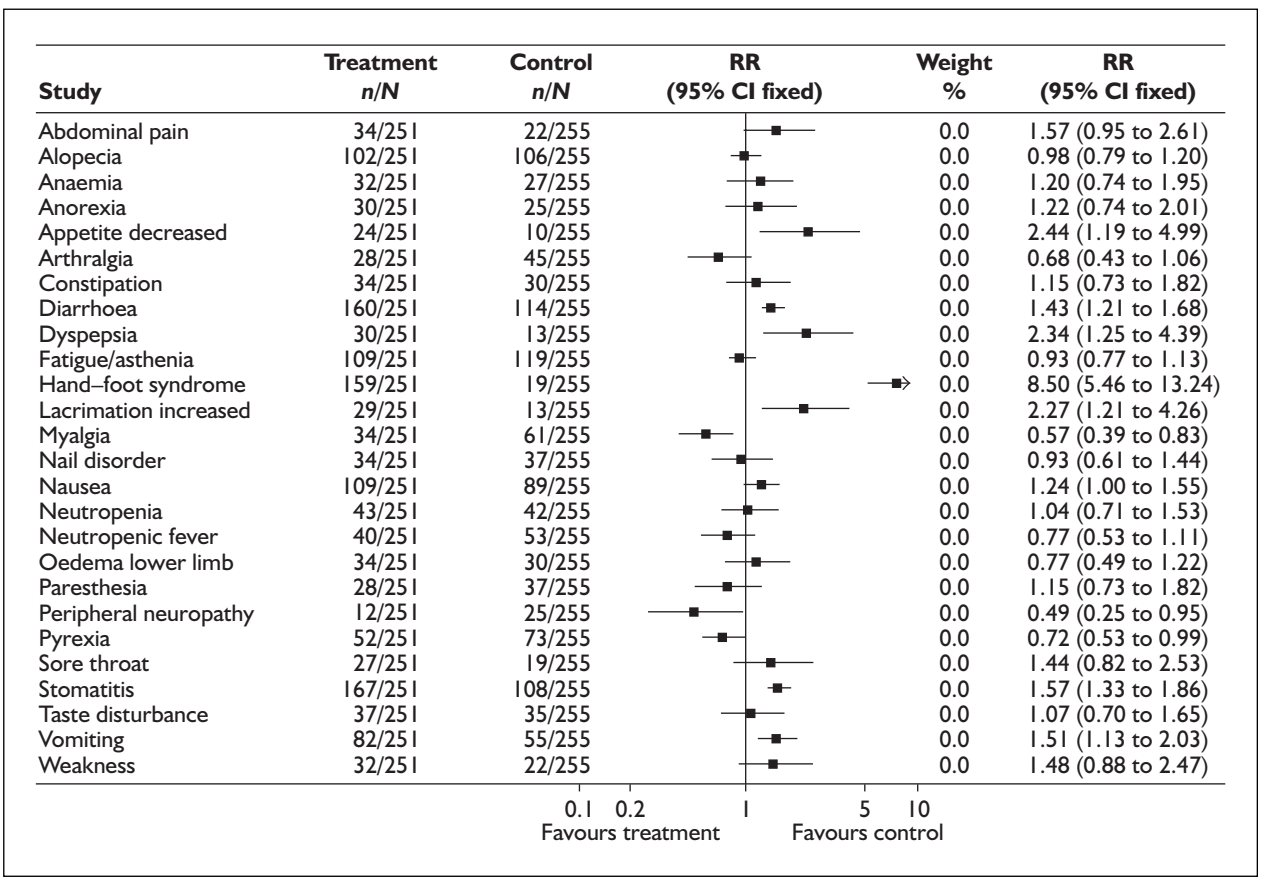

FIGURE 6 *Relative risks of treatment-related adverse events (all grades) for capecitabine/docetaxel versus docetaxel*

TABLE 25 *Capecitabine/docetaxel RCT: summary of treatment-related adverse events (severe or life-threatening)*

Adverse event	Capecitabine/docetaxel *n*/*N* (%) (*N* = 251)		Docetaxel *n*/*N* (%) (*N* = 255)		Relative risk (grade 3 or 4)[a]
	Grade 3	Grade 4	Grade 3	Grade 4	
Alopecia	15/251 (6.0)	0	17/255 (6.7)	0	0.90 (95% CI 0.46 to 1.76)
Diarrhoea	34/251 (13.5)	1/251 (0.4)	14/255 (5.4)	1/255 (0.4)	2.37 (95% CI 1.33 to 4.23)
Fatigue/asthenia	19/251 (7.6)	1/251 (0.4)	27/255 (10.6)	0	0.75 (95% CI 0.43 to 1.31)
Hand-foot syndrome	61/251 (24.3)	NA	3/255 (1.2)	NA	20.66 (95% CI 6.57 to 64.97)
Nausea	16/251 (6.4)	0	5/255 (2.0)	0	3.26 (95% CI 1.21 to 8.77)
Neutropenia[b]	12/251 (4.8)	27/251 (10.8)	7/255 (2.7)	29/255 (11.4)	1.10 (95% CI 0.72 to 1.67)
Neutropenic fever	7/251 (2.8)	33/251 (13.1)	12/255 (4.7)	41/255 (16.1)	0.77 (95% CI 0.53 to 1.11)
Stomatitis	43/251 (17.1)	1/251 (0.4)	12/255 (4.7)	0	3.73 (95% CI 2.02 to 6.88)

[a] RR < 1 favours combination therapy.
[b] Requiring medical intervention (e.g. antibiotic therapy, granulocyte colony-stimulating factor).
NA: not applicable.

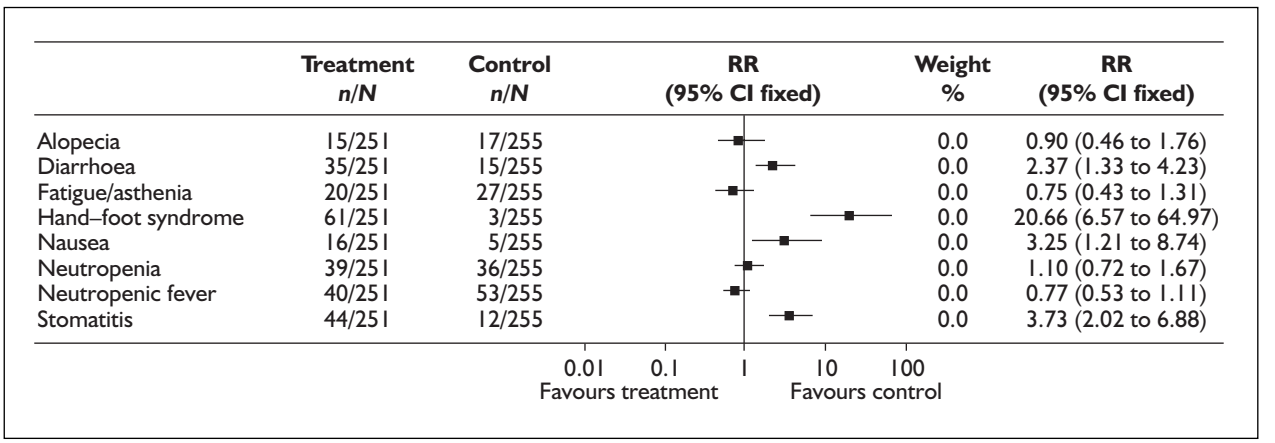

FIGURE 7 *Relative risks of treatment-related adverse events (grade 3/4) for capecitabine/docetaxel versus docetaxel*

2.02 to 6.88) were significantly higher in the capecitabine/docetaxel combination therapy group. Grade 3 and 4 treatment-related adverse events reported in more than 5% of patients with calculated relative risks are summarised in *Table 25* and *Figure 7*.

Laboratory abnormalities The most frequently reported grade 3/4 adverse laboratory event was neutropenia/granulocytopenia in both the combination therapy group and the single-agent docetaxel group. The incidence of grade 3/4 neutropenia was lower in the combination therapy group than in the single-agent docetaxel group (68% vs 77%; RR = 0.89, 95% CI 0.89 to 0.99). Grade 3/4 laboratory abnormalities are summarised in *Table 26* and relative risks are presented in *Figure 8*.

Impact of dose reduction The percentage of patients requiring a dose reduction of capecitabine alone, docetaxel alone or both for adverse events was 65% in the combination arm compared with 36% in the single-agent docetaxel arm.

O'Shaughnessy and colleagues[59] assessed the impact of dose reduction on efficacy by using a proportional hazards regression model of time to

TABLE 26 *Capecitabine/docetaxel: grade 3/4 laboratory abnormalities*

Laboratory parameter	Capecitabine/docetaxel *n/N* (%) (*N* = 251)		Docetaxel *n/N* (%) (*N* = 255)		Relative risk (grade 3 or 4)[a]
	Grade 3	Grade 4	Grade 3	Grade 4	
Neutropenia/ granulocytopenia	48/251 (19)	123/251 (49)	28/255 (11)	168/255 (66)	0.89 (95% CI 0.89 to 0.99)
Hyperbilirubinaemia	17/251 (6.8)	5/251 (2.0)	5/255 (2.0)	4/255 (1.6)	2.48 (95% CI 1.17 to 5.29)
Hyperglycaemia	33/251 (13)	3/251 (1)	18/255 (7)	2/255 (1)	1.78 (95% CI 1.06 to 2.99)

[a] RR < 1 favours combination therapy.

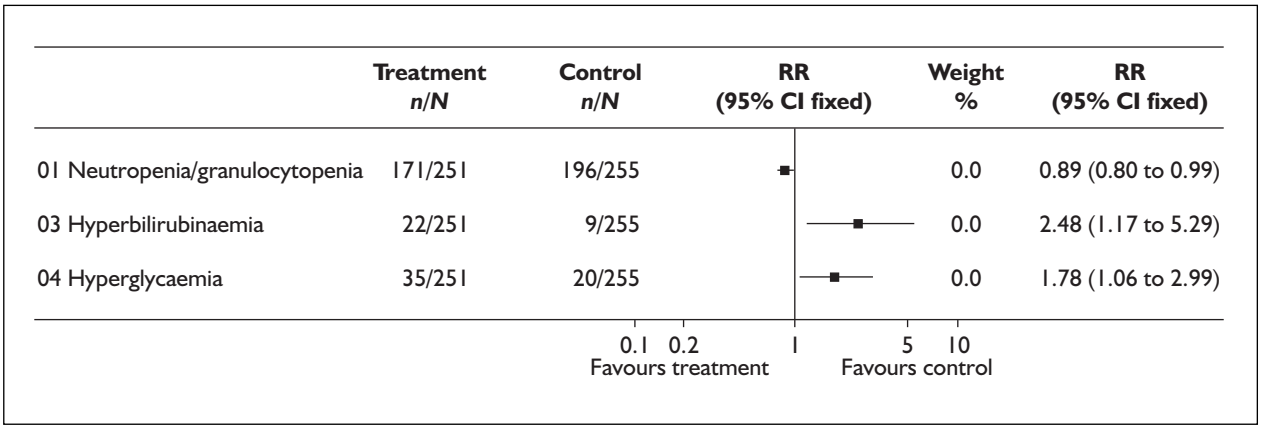

FIGURE 8 *Capecitabine/docetaxel: relative risks for grade 3/4 laboratory abnormalities*

TABLE 27 *Capecitabine/docetaxel uncontrolled studies: summary of survival*

Outcome	Tonkin (2001)[60]	Scarfe (2002)[61]
Progression-free survival (6 months)	NR	56%
Overall survival (6 months)	NR	76%

disease progression. They reported that for the combination therapy arm there was no evidence that dose modification had a negative impact on efficacy.

Uncontrolled studies

The following section of the report briefly summarises the data from the uncontrolled Phase II study by Scarfe and colleagues[61] and data from the Phase II portion of the study by Tonkin and colleagues.[60] For reasons related to the study quality issues that have previously been discussed (see 'Quality of included studies' p. 24) these results should be treated with great caution.

Overall survival Tonkin and colleagues[60] did not report any data for duration of response or survival. In the study by Scarfe and colleagues,[61] of the 14 patients evaluable for response, 56% had survived for 6 months without progression of their disease. The overall survival rate was 76%. Survival is summarised in *Table 27*.

Response to treatment Neither of the studies reported a specific definition for response to treatment. The overall response rates reported by Tonkin and colleagues[60] and by Scarfe and colleagues[61] were 50% and 14%, respectively. Two patients in the Tonkin study and none in the Scarfe study were

TABLE 28 *Capecitabine/docetaxel uncontrolled studies: summary of response to treatment*

Outcome	Tonkin (2001)[60] *n/N* (%)	Scarfe (2002)[61] *n/N* (%)
OR (CR + PR)	6/12 (50)	2/14 (14)
CR	2/12 (17)	0/14
PR	4/12 (33)	2/14 (14)
SS	2/12 (17)	7/14 (50)
PD	3/12 (25)	5/14 (36)

reported to have had a complete response to treatment. Response to treatment is summarised in *Table 28*.

Summary of effectiveness data for capecitabine in combination with docetaxel

Only one RCT was identified which investigated a regimen of capecitabine in combination with docetaxel. The trial included 511 patients and compared capecitabine in combination with docetaxel to single-agent docetaxel. In addition, two uncontrolled studies, were found, which investigated a regimen of weekly low-dose docetaxel plus capecitabine. However, these two studies only provided limited poor quality evidence and used an alternative low-dose docetaxel regimen. Hence, this section of the report has focused on the admittedly limited, but higher quality evidence, from the RCT by O'Shaughnessy and colleagues.[59] The results from the effectiveness data are summarised in *Table 29*.

There was evidence from the RCT by O'Shaughnessy and colleagues[59] that treatment with capecitabine/docetaxel combination therapy was superior to treatment with single-agent docetaxel. Median survival was significantly longer in the capecitabine/docetaxel group than in the single-agent docetaxel group (14.5 vs 11.5 months; HR = 0.775, 95% CI 0.634 to 0.947). The corresponding HR translated into a 23% reduction in the risk of death in the combination therapy group. Median time to disease progression also favoured capecitabine/docetaxel combination therapy over single-agent docetaxel (6.1 vs 4.2 months; HR = 0.652, 95% CI 0.545 to 0.780). The corresponding HR translated into a 35% decrease in the risk of disease progression in patients receiving combination therapy. Time to treatment failure was also statistically significantly

TABLE 29 *Capecitabine/docetaxel: summary of effectiveness data from RCT*

Outcome	Result
Survival	Favoured capecitabine/docetaxel over docetaxel 14.5 vs 11.5 months (HR = 0.775; 95% CI 0.634 to 0.947; $p = 0.0126$)
Time to progression	Favoured capecitabine/docetaxel over single-agent docetaxel 6.1 vs 4.2 months (HR = 0.652; 95% CI 0.545 to 0.780; $p = 0.0001$)
Time to treatment failure	Favoured capecitabine/docetaxel over single-agent docetaxel 4.0 vs 2.8 months ($p = 0.0002$)
Tumour response	Overall response favoured capecitabine/docetaxel over docetaxel 42% vs 30% (RR = 1.40; 95% CI 1.10 to 1.78)
QoL	No statistically significant differences between the two groups
Treatment-related adverse events and laboratory abnormalities (grade 3/4)	Incidence of hand–foot syndrome favoured docetaxel over capecitabine/docetaxel 24.3% vs 1.2% (RR = 20.66; 95% CI 6.57 to 64.97)
	Incidence of nausea favoured docetaxel over capecitabine/docetaxel 6.4% vs 2.0% (RR = 3.26; 95% CI 1.21 to 8.77)
	Incidence of diarrhoea favoured docetaxel over capecitabine/docetaxel 14.4% vs 5.4% (RR = 2.37; 95% CI 1.33 to 4.23)
	Incidence of stomatitis favoured docetaxel over capecitabine/docetaxel 17.4% vs 5.0% (RR = 3.73; 95% CI 2.02 to 6.88)
	Incidence of neutropenia/granulocytopenia favoured capecitabine/docetaxel over docetaxel 68.0% vs 77.0% (RR = 0.89; 95% CI 0.89 to 0.99)
	Incidence of hyperbilirubinaemia favoured docetaxel over capecitabine/docetaxel 8.8% vs 3.6% (RR = 2.48; 95% CI 1.17 to 5.29)
	Incidence of hyperglycaemia favoured docetaxel over capecitabine/docetaxel 14.0% vs 8.0% (RR = 1.78; 95% CI 1.06 to 2.99)

longer in the combination therapy group than in the single-agent docetaxel group (4.0 vs 2.8 months; $p = 0.0002$).

In terms of response to treatment, overall response (complete response plus partial response) was statistically significantly in favour of the capecitabine/docetaxel combination group compared with single-agent docetaxel (42% vs 30%; RR = 1.40, 95% CI 1.10 to 1.78). This effect was dominated by the higher proportion of patients achieving a partial response in the combination therapy group than in the single-agent docetaxel group (37% vs 26%; RR = 1.41, 95% CI 1.08 to 1.83). The difference between the two groups for patients achieving a complete response was not statistically significant.

There was no statistically significant difference between the two groups on any of the QoL domains.

The incidences of hand–foot syndrome, diarrhoea, nausea and stomatitis were significantly higher in the combination therapy group than in the single-agent docetaxel group.

Chapter 5
Economic analysis

Economic evaluation of capecitabine monotherapy

The systematic literature review identified one abstract[89] referring to an economic evaluation of the cost-effectiveness of capecitabine monotherapy. There were insufficient details of the study methodology within the abstract to draw any conclusions regarding the validity of the reported results. During the course of the assessment of clinical effectiveness no relevant comparative trials of capecitabine monotherapy were identified. There were insufficient data identified during the course of this review to allow an independent economic model to be developed. The economic evaluation of capecitabine monotherapy in this report was, therefore, based on the data reported in the Roche submission to NICE [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished].

The economic evaluation included in the company submission was assessed. This included, as far as was possible, a detailed analysis of the appropriateness of the parametric and structural assumptions involved and an assessment of how robust the conclusions were to changes in key assumptions. Clarification on specific aspects of the evaluation was sought from the drug manufacturer.

Review of Roche submission

Overview

The economic evaluation of capecitabine monotherapy included in the Roche submission evaluated the cost-effectiveness of the treatment of advanced breast cancer with capecitabine compared with treatment with vinorelbine in patients previously treated with anthracyclines and a taxane. The analysis was based on a simple comparison of estimates of the costs and effects of treatment with vinorelbine and capecitabine. The evaluation utilised data from a number of non-comparative studies of vinorelbine. Data relating to other potential comparators were not considered in the submission. Precise details of the inclusion criteria and search methods used were not stated in the submission. Although a preliminary search of the MEDLINE database did not identify any extra studies that should have been included in the Roche submission, it is not possible to exclude bias in the selection of data. A systematic, comprehensive search for publications relating to uncontrolled studies of vinorelbine or other potential comparators in this setting, such as best supportive care, was not undertaken as part of this rapid review because of resource and time constraints.

Choice of comparator

The scope for this review, as defined by NICE, stated that the appropriate comparators were vinorelbine and best supportive care.

It appears in the industry submission that the choice of appropriate comparator is problematic. It is argued in Section 4 of the Roche submission to NICE [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished], 'Demonstrating the clinical effectiveness of capecitabine', that vinorelbine is unsuitable for use as a comparator in clinical trials:

> "Vinorelbine is widely used in anthracycline and taxane pretreated breast cancer. However, evidence of its efficacy and tolerability in this situation is weak. Better characterised treatments are needed" (p. 20).

> "The regimens used in this situation are varied, though vinorelbine is, probably, the most widely used. This is a rational choice given the limited information available, but vinorelbine cannot be described as a gold-standard treatment in this setting and, until there are more reliable and comprehensive data available on its activity in this situation, it is unsuitable for use as the control treatment in comparative trials" (p. 20).

All of the capecitabine trials referenced in the industry submission were single arm. No comparative trials of capecitabine for the treatment of breast cancer following previous treatment with anthracyclines and taxanes were identified during the systematic review. However, a survey of 105 UK oncologists included in the Roche submission did identify a number of potential comparators for such clinical trials, including gemcitabine, liposomal doxorubicin, 5-FU/mitomycin, CMF and best supportive care.

As a result of the absence of comparative trials, the validity of any assessment of clinical effectiveness, and hence any economic evaluation, is questionable.

Later in the Roche submission it is argued that vinorelbine is the appropriate comparator for the economic evaluation of capecitabine monotherapy:

> "As described in the clinical section, drug treatments are still a preferred option for this patient population and vinorelbine seems to be the first drug of choice by most UK oncologists. Vinorelbine was also accepted by NICE as the most appropriate comparator. Vinorelbine has evidence of its cost-effectiveness in earlier treatment lines for metastatic breast cancer (Leung and colleagues, 1999), but none in later stages of treatment" (p. 51).

The Roche submission also reported the results of a study of post-trial treatment received by a group of 256 patients from the docetaxel arm of a comparative trial.[86] In these patients, who had previously been treated with both a taxane and an anthracycline, 166 patients received further chemotherapy, 71 of whom received vinorelbine. For patients receiving vinorelbine as their first post-study treatment, the HR was 1.0 versus those receiving any other chemotherapy, suggesting that vinorelbine does not reduce the risk of death compared with other, possibly cheaper, chemotherapeutic agents.

The validity of the economic evaluation included in the Roche submission is contingent upon vinorelbine being a cost-effective treatment for the treatment of breast cancer following prior treatment with an anthracycline and a taxane. As was highlighted in the Roche submission, there is little evidence of the effectiveness, and hence cost-effectiveness, of vinorelbine in this setting compared with other possible therapies (of which a number were identified in the Roche submission). The validity of an economic evaluation of capecitabine with vinorelbine as the sole comparator should be questioned. In addition, the economic evaluation section of the Roche submission did not explicitly consider best supportive care.

Unfortunately, there is insufficient evidence available at the time of this review to conduct a more comprehensive evaluation.

Evaluation of effectiveness

The estimates of effectiveness in the submission for vinorelbine and capecitabine treatment were based on estimates of the median time to progression and the median survival time from a number of clinical trials by Livingstone[95] and Zelek[96] for vinorelbine, and Blum (1999),[62] Blum (2001),[65] Cervantes,[67] Reichardt[70] and Fumoleau[68] for capecitabine. All of these trials were non-comparative, single-arm trials. It is not possible to exclude the possibility of bias in the comparison of treatment arms from different studies. Differences, both observed and unobserved, in the patient characteristics and treatment between studies may lead to biased estimates of treatment effect.[97]

Quality-adjusted life-years (QALYs) were used as the measure of effectiveness for the economic evaluation. They were calculated as follows:

$$\text{QALYs} = \begin{array}{l}\text{median\_ttp*util\_sd} + \\ \text{(median\_surv} - \text{median\_ttp)*util\_pd}\end{array}$$

where median_ttp = median time to progression (years), median_surv = median survival time (years), util_sd = estimated utility index for stable disease, and util_pd = estimated utility index for progressive disease.

The estimated utility indexes for stable (0.81) and progressive (0.39) disease were estimated based on interviews of 25–30 oncology nurses from each of Germany, Italy, The Netherlands, Spain, the UK and the USA using standard gamble methodology.[98] In the combination therapy section of the Roche report two alternative estimates for these indexes are referenced. Launois[99] estimated utility indexes for stable (0.75) and progressive disease (0.65) based on a survey of 20 French nurses using a standard gamble methodology. Hutton and colleagues[98] estimated the utility indexes to be 0.62 for stable disease and 0.41 for progressive disease based on a survey of 20 UK nurses using a standard gamble methodology. It should be noted that these utility indexes were not derived from patients.

The use of median times in the calculation of total QALYs is not consistent with the 'QALY' paradigm; for example, 1 year of life with a utility index of 0.2 is regarded as equivalent to 0.2 years of life with a utility index of 1. Calculations using mean times would be consistent in this respect. An important issue in the economic analysis is the use of 'generic' utility indices for stable and progressive disease that are common to both treatments being considered. This means that any variation in QoL associated with the specific treatments under consideration will not be accounted for in the analysis. The effects of any toxicities associated with the specific treatments,

TABLE 30 *Estimates of effectiveness in the Roche evaluation*

Study	Capecitabine				Vinorelbine		
	Blum (1999)[62]	Blum (2001)[65]	Reichardt (2001)[70]	Fumoleau (2002)[68]	Livingstone (1997)[95]	Udom (2000)[100]	Zelek (2001)[96]
QALYs	0.56	0.51	0.45	0.66	0.38	NA	0.41

NA, not applicable.

such as a PPE for capecitabine and peripheral neuropathy for vinorelbine, on patient QoL will not be accounted for in this analysis. As treatment in this setting is generally seen as palliative rather than curative, it is particularly important to consider patient QoL.

Both median survival times and time to progression were only reported in two of the vinorelbine trials (Livingstone;[95] Zelek[96]). [It is noted on page 30 of the Roche submission that "The exception was the report Zelek *et al*. (2001) who reported a 6 month median time to disease progression. However, this figure must be regarded with some skepticism since median survival in this study was also 6 months". The 6-month median time to disease progression reported in the Zelek study was only for those patients who responded to the vinorelbine (10/40), and as such does seem consistent. The calculation of QALYs for this study in the Roche submission for this study was incorrect as it did not account for this.] It is noted in the Roche submission that the Livingstone trial[95] can be discounted as irrelevant to UK practice, since it used very high doses of vinorelbine that required continuous support with the haematopoietic growth factor, granulocyte colony-stimulating factor (GCSF), in an attempt to prevent life-threatening haematological toxicity.

The lack of any comparative trial involving capecitabine in this setting, and hence the reliance on effectiveness estimates from single-arm non-comparative studies, makes any economic evaluation subject to a high level of uncertainty owing to the difficulty of assessing the incremental efficacy of capecitabine compared with other treatments. Although survival may be considered an objective end-point and should not be subject to observation bias, there may be systematic differences between trials and centres in the case-mix of enrolled subjects and their ancillary treatment, which could lead to differences in the observed survival times of subjects. This patient population is diverse in terms of disease and treatment history. It is possible that there may be differences in the patient populations recruited, which could cause systematic differences in the observed survival times between trials. For example, the Zelek trial[96] recruited patients at a French oncology centre, the Livingstone trial[95] recruited patients at a US oncology centre, the Blum (1999) trial[62] recruited patients from the USA and Canada, and the Blum (2001) trial[65] recruited patients from the USA and France.

Further to this, if one accepts the assertion that the Livingstone trial[95] is not representative of UK practice, the quantitative assessment of the effectiveness of vinorelbine rests on the results of a single, 40 patient trial. The absence of comparative data, and the paucity of effectiveness data of any type for vinorelbine – as highlighted in the Roche submission – means that the validity of this analysis is uncertain, and may also cause the appropriateness of vinorelbine as the sole comparator for this evaluation to be questioned. Unfortunately, there is insufficient evidence available at the time of this review to conduct a more comprehensive evaluation.

The estimates of effectiveness made in the Roche evaluation are shown in *Table 30*.

Evaluation of costs

Costs were estimated based on the studies used for the evaluation of effectiveness, with the addition of Udom and colleagues.[100] Only estimates of the costs of the cytotoxic drugs themselves were included in the economic evaluation; no other costs were included. The actual quantities, and hence costs, of drug used in the trials were not available. The costs were estimated as follows:

$$\text{p\_resp} \times \text{median\_ttp} \times \text{cst\_per\_cycle} + (1 - \text{p\_resp}) \times \text{cst\_per\_cycle}$$

where p_resp = orobability of a treatment response, median_ttp = median time to progression (months), median_surv = median survival time (months), and cst_per_cycle = cost per 3-week cycle.

TABLE 31 *Treatment costs as estimated by Roche*

	Capecitabine				Vinorelbine		
	Blum (1999)[62]	Blum (2001)[65]	Reichardt (2001)[70]	Fumoleau (2002)[68]	Livingstone (1997)[95]	Udom (2000)[100]	Zelek (2001)[96]
Cost per patient	£432	£466	£398	£605	£689	£904	£993

Assuming that the substitution of medians for means is valid, it is probably not appropriate to multiply the median time to progression by the response rate, as the quoted medians, with the exception of Zelek and colleagues,[96] are for the whole population and are not restricted to the responders. Including this factor may lead to the drug costs being underestimated.

The treatment of costs in this evaluation was extremely limited, as only the cost of the cytotoxic drugs was included. If there are important differences in the use of other resources between the treatments this may lead to the evaluation being invalid.

The treatment costs were estimated in the Roche submission as shown in *Table 31*.

Perspective

The evaluation was conducted from the point of view of the NHS, although again it should be noted that a very narrow range of cost items was explicitly considered and there may be potential costs to the NHS that were not assessed.

Discounting

No discounting was undertaken owing to the limited expected lifespan of patients in this setting. This was appropriate.

Summary of assumptions

The following were felt to be key assumptions made in the evaluation.

- Vinorelbine is the appropriate sole comparator for this evaluation.
- Treatment toxicities do not have a significant differential effect on patient QoL. The calculation of QALYs used in the evaluation does not directly account for the effect of toxicities specific to the drugs used, such as hand–foot syndrome and neuropathy.
- Costs, other than the cost of vinorelbine and capecitabine, were not significantly different between the two groups.
- The estimation of drug costs assumes that treatment is discontinued as soon as the disease progresses.
- The results of the various uncontrolled trials referred to may be directly and meaningfully compared.

As far as possible, these assumptions were tested through further analysis and by consultation with the expert panel.

Further analysis

The following further analyses were undertaken.

Estimated effects

The total QALYs for each study were recalculated using means and standard errors for time to progression and survival time calculated assuming an exponential survival curve (see Appendix 12). This derivation of mean survival is theoretically valid assuming an exponential survival curve is appropriate.

Total QALYs were calculated as follows:

$$\text{QALYs} = \begin{array}{l}\text{mean\_ttp*util\_sd} + \\ (\text{mean\_surv} - \text{mean\_ttp})*\text{util\_pd}\end{array}$$

where mean_ttp = mean time to progression (years), mean_surv = mean survival time (years), util_sd = estimated utility index for stable disease, and = util_pd = estimated utility index for progressive disease. [For the Zelek study,[96] the mean time to progression for those patients who responded was multiplied by the overall response rate to obtain a mean for the whole population.]

The estimated utilities, presented as mean and standard error (SE), for each of the studies in combination with each of the utility estimates are shown in *Table 32*. It should be noted that covariance between the estimated mean time to progression and estimated mean survival time could not be taken into account when calculating the standard error of the QALY estimate.

TABLE 32 *Capecitabine monotherapy: summary of estimated QALYs*

	Capecitabine		Vinorelbine	
	Blum (1999)[62a]	**Blum (2001)[65]**	**Livingstone (1997)[95]**	**Zelek (2001)[96]**
Median time to progression (months)	3.1	3.2	3.25	6[b]
Estimated time to progression	4.47 ± 0.50	4.62 ± 0.76	4.69 ± 1.05	2.16 ± 0.48
Median survival time (months)	12.6	12.2	8.25	6
Estimated survival time	18.18 ± 2.02	17.6 ± 2.89	11.90 ± 2.66	8.66 ± 1.94
QALYs based on Launois utility indexes (0.75, 0.65)	1.02 ± 0.11	0.99 ± 0.16	0.68 ± 0.15	0.49 ± 0.11
QALYS based on Brown & Hutton utility indexes (0.81, 0.39)	0.75 ± 0.08	0.73 ± 0.12	0.55 ± 0.12	0.36 ± 0.08
QALYs based on Hutton *et al*. utility indexes (0.62, 0.04)	0.73 ± 0.12	0.67 ± 0.11	0.48 ± 0.11	0.33 ± 0.07

Data are shown as median or mean ± SE.
[a] The median survival times were taken from the Roche Final Study Report for SO14697 (unpublished).
[b] For patients who responded to treatment.

TABLE 33 *Capecitabine monotherapy: summary of per-patient costs*

	Capecitabine		Vinorelbine	
	Blum (1999)[62]	**Blum (2001)[65]**	**Livingstone (1997)[95]**	**Zelek (2001)[96]**
Mean total dose (mg) per patient	253,392	246,701	744	446
Mean cost per patient	£1252	£1218	£2328	£1396

The estimates of QALYs made using estimates of the mean time to progression and mean survival were, with the exception of the Zelek study,[96] greater than those presented in the Roche submission. However, QALYs were estimated by applying a constant utility to stable and progressive disease; this calculation ignores the impact of specific toxicities associated with the individual treatments on QoL.

Estimated costs

The treatment costs for the capecitabine studies were based on the actual drug consumption as reported in the final study reports. Although this may not account for total treatment costs for the patients in these studies as further chemotherapy may have been administered after the studies ended, and the dosages used in the trials differed from those recommended in the Summary of product characteristics (SmPC), actual drug consumption was felt to provide the best available estimate of treatment cost. The treatment costs for the Zelek trial[96] were calculated based on the reported median dose of vinorelbine (22.5 mg/m^2 per week), an assumed mean body surface area of 1.7 m^2 and assuming that patients who responded received the drug until the estimated mean time disease progressed and that those who did not respond received treatment for 4 weeks. The treatment costs for the Livingstone trial[95] were calculated based on the reported mean number of treatment cycles (15.8), the reported mean dose (27.7 mg/m^2 per week) and an assumed mean body surface area of 1.7 m^2. The cost of GCSF was not included. The unit costs for vinorelbine (£3.13/mg) and capecitabine (£0.00494/mg) were obtained from the British National Formulary (BNF) March 2002, and the per-patient costs are summarised in *Table 33*. The cost estimates for vinorelbine and capecitabine patients calculated in this way were greater than those presented in the Roche submission.

As capecitabine monotherapy is both lower in cost and associated with improved patient outcomes, it is a dominant case. However, this dominance is based on the extended survival period in uncontrolled studies and is therefore questionable. In addition, it is unclear whether it is appropriate in this instance to consider only the costs of the

TABLE 34

Treatment	QALYs	Cost
Capecitabine	0.73	£1268
Vinorelbine	0.55	£1513

QALYs, quality adjusted life years.

drug; other costs falling on the NHS could be considered.

Sensitivity analysis

Owing to the uncertainty regarding the comparability of the capecitabine and vinorelbine trials, a threshold analysis was undertaken. Using the most favourable vinorelbine trial (Livingstone[95]), the least favourable capecitabine trial (Blum, 2001[65]) and the least favourable utility estimates for capecitabine (Brown & Hutton[98]), the effects and costs would be as shown in *Table 34*.

These results suggest a gain of 0.18 QALYs with an associated cost saving of £245. These estimates ignore any change associated with moving from an intravenous to an oral medication. This result is consistent with the base case estimate that capecitabine is dominant when compared with vinorelbine.

Assuming that 1 QALY has a monetary value of £30,000, treatment with capecitabine would have to have extra associated costs of £5400 before vinorelbine became cost-effective. Alternatively, taking an extreme case, assuming that the QALYs associated with vinorelbine treatment could be achieved with supportive care common to both treatments (i.e. vinorelbine is no better than best supportive care), the incremental cost of capecitabine treatment would be £1286 and the incremental QALY gain would need to drop to 0.04 before capecitabine failed to be cost-effective. This would represent a 19% decrease in the QALYs achieved by capecitabine therapy or a 25% increase in the QALYs achieved with the alternative treatment.

Comments made by the expert panel

In general, it was felt that vinorelbine was an appropriate comparator, that neither treatment was associated with toxicities that would have an important impact on either patient quality of life or costs, and that the comparison between separate single-arm trials was valid given the limited available evidence and the difficulty in conducting an RCT in this setting.

Conclusions

Based on the limited data available, the studies considered suggest that capecitabine monotherapy is less costly and more effective than vinorelbine. The poor quality and paucity of data, together with questions over the suitability of the comparator and the costing methodology, require that these results be treated with caution.

Economic evaluation of capecitabine in combination with docetaxel

The systematic literature review identified one abstract[90] referring to an economic evaluation of the cost-effectiveness of capecitabine combination therapy. There were insufficient details of the study methodology within the abstract to draw any conclusions regarding the validity of the reported results. In the absence of any suitable published literature, the economic evaluation of capecitabine in this report was based on data reported in the Roche submission to NICE. Insufficient data were available to allow an independent economic model to be developed.

The economic evaluation included in the company submission was assessed. This included, as far as was possible, a detailed analysis of the appropriateness of the parametric and structural assumptions involved, and an assessment of how robust the conclusions were to changes in key assumptions. Clarification on specific aspects of the evaluation was sought from the drug manufacturer.

Review of Roche submission

Overview

The economic evaluation of capecitabine combination therapy included in the Roche submission evaluated the cost-effectiveness of the treatment of advanced breast cancer with docetaxel in combination with capecitabine compared to treatment with docetaxel monotherapy. The analysis was based on a simple comparison of estimates of the costs and effects of treatment with combination and monotherapy.

Choice of comparator

Docetaxel monotherapy was an appropriate choice as a comparator. Paclitaxel monotherapy would have been an alternative, appropriate comparator but was not considered in this evaluation. As the available evidence suggests that docetaxel is more effective and is considered cost-effective, this seems a suitable choice of comparator.

Evaluation of effectiveness

Comparative effectiveness was determined from a single 511 patient RCT, SO149999,[59] comparing docetaxel in combination with capecitabine with docetaxel monotherapy. The trial included patients from the USA, the UK, Russia, France, Canada, Mexico and Australia. The trial was open label and, therefore, bias arising from an awareness of the treatment that the patient received cannot be discounted. There was an increased mean time to progression and mean survival time associated with the combination treatment. A preference (utility)-based QoL instrument was not used in the trial. A measure of QALYs was derived from these measures using published estimates of utility associated with stable and progressive disease. The QALYs were calculated as the product of mean time to progression and an estimated utility score for stable disease plus the product of the mean survival time minus the mean time to progression and an estimated utility score for progressive disease. The utility measures used in the Roche submission were the mean of the relevant utility measures from three publications (Launois,[99] Hutton and colleagues[101] and Brown & Hutton[98]). The use of common utility indices for both treatment arms will not capture any differences in QoL resulting from the specific interventions; for example, impairments in QoL associated with toxicities such as PPE, diarrhoea and neutropenia. The mean number of QALYs for patients in the combination arm was estimated as 0.82 and in the monotherapy arm was estimated as 0.67 in the Roche NICE submission. These estimates were obtained by using the mean of the estimated utility indices for progressive and stable disease.

Evaluation of costs

The following direct costs were considered in the analysis: drug acquisition costs, hospitalisation for adverse events, drug acquisition costs for adverse events and consultations with physicians for adverse events. The drug acquisition cost was found to be lower for the combination arm by £154 (2.3% of monotherapy cost); the additional cost of the capecitabine was offset by the reduced cost of a lower dose of docetaxel. The drug acquisition cost was based on a nominal average body surface area of 1.7 m^2.

Hospitalisation costs were found to be lower in the combination arm than in the monotherapy arm by £247 (1.3% of monotherapy cost). This was based on a hospitalisation cost of £334 (Personal Social Services Research Unit (PSSRU), 2000, cost of medical oncology visit). As these hospitalisation costs include drug and treatment costs, which are already included in this evaluation, the use of this will cause these treatment costs to be double counted. An appropriate cost to use would be the 'hotel' cost, the cost of accommodating a patient in hospital excluding any treatment cost.

Drug treatment costs for adverse events were less for monotherapy than for combination therapy by £39 (12% of combination cost). Only the ten most common treatments, in terms of number of patients receiving treatment, were included.

Consultation costs were found to be lower for the combination therapy arm by £206 (39% of the cost for monotherapy). Specialist consultations were all assumed to last for 60 minutes and to take place in a hospital based on the PSSRU unit price (an alternative cost for the various specialities could have been obtained from the Chartered Institute of Public Finance and Accounting (CIPFA)).

No costs beyond 1 year were included. This will favour the treatment, in this case combination therapy, with the greater mean survival time as a greater fraction of the total cost will be excluded. The magnitude of this effect cannot be quantified from the data included in the manufacturer's submission. In addition, no account was made for censoring when calculating treatment costs, although the effect of this omission will probably be less than the effect of truncating costs at 1 year.

The costs in the two treatment arms estimated by Roche are summarised in *Tables 35–38*.

Summary of assumptions

The following were felt to be the key assumptions made during the evaluation.

- Docetaxel was the appropriate comparator.
- The toxicities associated with the specific therapies did not have a significant effect on the QoL of the patients.
- The cost items considered would capture all the significant differences in the cost of treatment for the two groups.
- The trial produced valid results despite being open label.

As far as possible, these assumptions were tested through further analysis and by consultation with the expert panel.

Further analysis

The following further analyses were undertaken.

Effect of altering hospital unit cost

The estimated daily cost of an inpatient stay associated with adverse events used in the report

TABLE 35 *Cost of hospital admissions*

	Cost of hospital day (£)	*N* of hospitalisations (all hospitalisations)	Mean length of stay	Cost of hospitalisation (£)	*N* of hospitalisations (all hospitalisations)	Mean length of stay	Cost of hospitalisation (£)
All hospital admissions	334	143	9	429,858	136	11	499,664
Neutropenic fever	334	35	7	81,830	44	7	102,872
Neutropenia	334	9	8	24,048	11	6	22,044
Neutropenic sepsis	334	4	7	9,352	8	10	26,720
Diarrhoea	334	6	7	14,028	3	12	12,024
Pyrexia	334	6	7	14,028	3	3	3,006
Pleural effusion	334	1	8	2,672	7	24	56,112
Vomiting	334	6	6	12,024	1	3	1,002
Asthenia	334	4	7	9,352	2	11	7,348
Pneumonia	334	1	15	5,010	5	11	18,370
Stomatitis all	334	4	10	13,360	1	14	4,676
Dyspnoea	334	0	0	0	5	9	15,030
Dehydration	334	3	8	8,016	1	15	5,010
Sepsis	334	3	12	12,024	1	5	1,670
Total for hospitalisations > 1% (£)				205,744			275,884
Total for remaining hospitalisations (£)				224,114			223,780
Overall total (£)				429,858			499,664
Cost per patient in trial (£)				1,712.58			1,959.47
Average duration of hospitalisation per patient in trial (days)				5.13			5.87

TABLE 36 *Cost of consultations*

	Consultation type	Cost of visit (£)	No. of visits	Total cost (£)	No. of visits	Total cost (£)
GP	All visits		87	2,803	138	4,309
	Day-care unit visits	70	10	700	12	840
	Emergency unit visit	70	6	420	7	490
	Home visits	45	15	675	31	1,395
	Office visits	18	56	1,008	88	1,584
Nurse/other	All visits		409	6,924	384	6,461
	Day-care unit visits	17	184	3,067	91	1,517
	Emergency unit visit	17	22	367	33	550
	Home visits	19	46	874	26	494
	Office visits	17	157	2,617	234	3,900
Specialist	All visits		1090	124,260	639	72,846
	Day-care unit visits	114	330	37,620	143	16,302
	Emergency unit visit	114	104	11,856	148	16,872
	Home visits	114	5	570	4	456
	Office visits	114	651	74,214	344	39,216
All visits, all providers			1586	133,987	1161	83,617
Consultations per patient			6.32		4.55	
Cost per patient				534		328

TABLE 37 *Drug treatment costs for adverse events*

					Combination therapy		Monotherapy	
Treatment preferred term	**Assumed dose**	**Manufacturer**	**Cost per dose**	**Cost per day**	**Total days use**	**Total cost**	**Total days use**	**Total cost**
Paracetamol	500 mg tablets (1 tablet 3 times daily)	Generic	£0.01	£0.02	1583	£28.49	1051	£18.92
Panadeine co	500 mg tablets (1 tablet 3 times daily)	Cheshire 500 mg tablets, $2.7 for 20 tablets	$0.08	$0.23	192	£44.36	213	£49.21
Ciprofloxacin	400 mg i.v. every 8 hours	Ciproxin Bayer	£1.20	£86.44	467	£40,367.48	431	£37,255.64
Ciprofloxacin hydrochloride	500 mg every 12 hours	Ciproxin Bayer 100 mg, 6 for £2.18	£2.33	£4.67	133	£620.67	172	£802.67
Sodium chloride	2000 ml once daily	Generic 50 ml = £1.95	£78.00	£27.62	265	£7,319.30	301	£8,313.62
Fluid replacement	The classic fluid replacement regimen is 1 bag normal saline at 125 ml/hour then 2 consecutive bags D5-1/2N at 125 ml/hour (3 × 1000 ml per day). However, assume 2 litres of fluids as not all patients will receive 3 litres	Generic sodium chloride 2 litres	£20.00	£20.00	201	£4,020.00	107	£2,140.00
Loperamide	2 mg caplet (max. 4 caplets/day)	Imodium Janssen-Cilag	£0.04	£0.16	404	£65.72	227	£36.93
Loperamide hydrochloride	2 mg caplet (max. 4 caplets/day)	Generic	£0.04	£0.17	1428	£239.90	99	£16.63
Metoclopramide	1 mg/kg prior to infusion	Faulding Pharm 5 mg/ml 20 ml 10s $141.76	$3.15	$3.15	346	£1,089.90	318	£1,001.70
Metoclopramide hydrochloride	1 mg/kg prior to infusion	Maxolon injection (Shire)	£1.87	£1.87	119	£222.83	282	£528.05
Nystatin	Lozenges, 200,000 IU/lozenge (max. 5/day)	Nystan (BMS)	£0.14	£0.68	1001	£684.02	420	£287.00
Furosemide	40 mg once daily	Generic	£0.08	£0.08	1170	£92.35	922	£72.77
Morphine	30 mg P.O. every 3 hours	MST continuous (Napp)	£0.29	£2.30	99	£227.30	773	£1,774.81
Morphine sulfate	30 mg P.O. every 3 hours	MXL (Napp)	£0.42	£3.35	70	£234.60	556	£1,863.39
Filgrastim	5 μg/kg per day	Amgen Neupogen 0.5 ml at 600 μg/ml. Assume 350 μg for a 70 kg patient	£85.92	£85.92	170	£14,606.40	105	£9,021.60
GCSF	5 μg/kg per day	Amgen Neupogen 0.5 ml at 600 μg/ml. Assume 350 μg for a 70 kg patient	$85.82	$85.82	92	£7,895.44	66	£5,664.12
Dexamethasone	4 mg/day	Dexsol, Rosemont	£3.00	£3.00	338	£1,014.00	381	£1,143.00
					8,078	£78,772.76	6,424	£69,990.05
					32.18		25.19	
						£313.84		£274.47

TABLE 38 *Total treatment costs as estimated by Roche*

Medical resource	Combination therapy (*n* = 251)			Monotherapy (*n* = 255)		
	Mean	SD	SE	Mean	SD	SE
Hospitalisations for adverse events	£1,713	£143	£9	£1,959	£168	£11
Drugs						
Docetaxel	£5,163	£3,787	£239	£6,685	£5,235	£328
Capecitabine	£1,363	£1,053	£66			
Consultations	£534	£15	£1	£328	£11	£1
Treatments for adverse events	£314	£10	£1	£274	£9	£1
Total[a]	£9,086	£3,933	£248	£9,246	£5,238	£328

[a] These are costs per patient.

TABLE 39 *Capecitabine/docetaxel: summary of QALY estimates*

	Utility index		
	Launois[99]	Brown & Hutton[98]	Hutton *et al.*[101]
Combination therapy QALYs	0.98 ± 0.04	0.81 ± 0.03	0.71 ± 0.03
Monotherapy QALYs	0.82 ± 0.04	0.65 ± 0.03	0.58 ± 0.03

was £334 (PSSRU, 2000, cost of medical oncology visit). As the cost of chemotherapeutic treatment and costs of drugs for the treatment of adverse events are accounted for elsewhere in the analysis, this may well be an overestimate of the hospitalisation costs. Arbitrarily reducing the hospitalisation cost to £167 reduced the cost difference between the two arms of the trial from £246 less for combination therapy to £123 less for combination therapy. This suggests that the outcome of the analysis is not sensitive to the estimated daily cost for an inpatient stay.

Estimates of cost-effectiveness

The estimates of effects were derived from the reported means and standard errors for survival time and time to progression quoted in the Roche NICE submission. There were calculated according to the following formula:

$$\text{QALYs} = \begin{array}{l}\text{mean\_ttp*(util\_sd} - \text{util\_pd)} + \\ \text{mean\_surv*util\_pd}\end{array}$$

where mean_ttp = mean time to progression (years), mean_surv = mean survival time (years), util_sd = estimated utility index for stable disease, and util_pd = estimated utility index for progressive disease.

QALY estimates for each trial arm were calculated for each of the available utility indices shown in *Table 39*.

Roche supplied the estimates of total costs and standard used in these further analyses. Taking the least favourable QALY estimates, obtained using the Hutton utility estimates,[101] a Monte Carlo simulation was developed. Mean costs and effects were modelled using log-normal distributions based on the means and standard errors observed in the trial. Covariance was assumed to be zero; as the costs and effects were likely to be positively correlated owing to the correlation between survival and treatment duration this was felt to be a conservative assumption. A graphical representation of uncertainty in incremental costs and effects observed in the simulation is shown in a cost-effectiveness plane in *Figure 9*.

This indicates that whereas there is a great deal of uncertainty as to whether combination therapy is cheaper or more expensive than monotherapy, it is very likely that there is a gain in QALYs associated with combination therapy, based on the results of the SO149999 study.[59]

The probability that combination therapy is cost-effective compared with monotherapy is shown in *Figure 10* for a range of maximum values that the NHS might be willing to pay for an additional QALY in this patient population.

The simulation suggests that combination therapy is likely to be cost-effective above a very modest

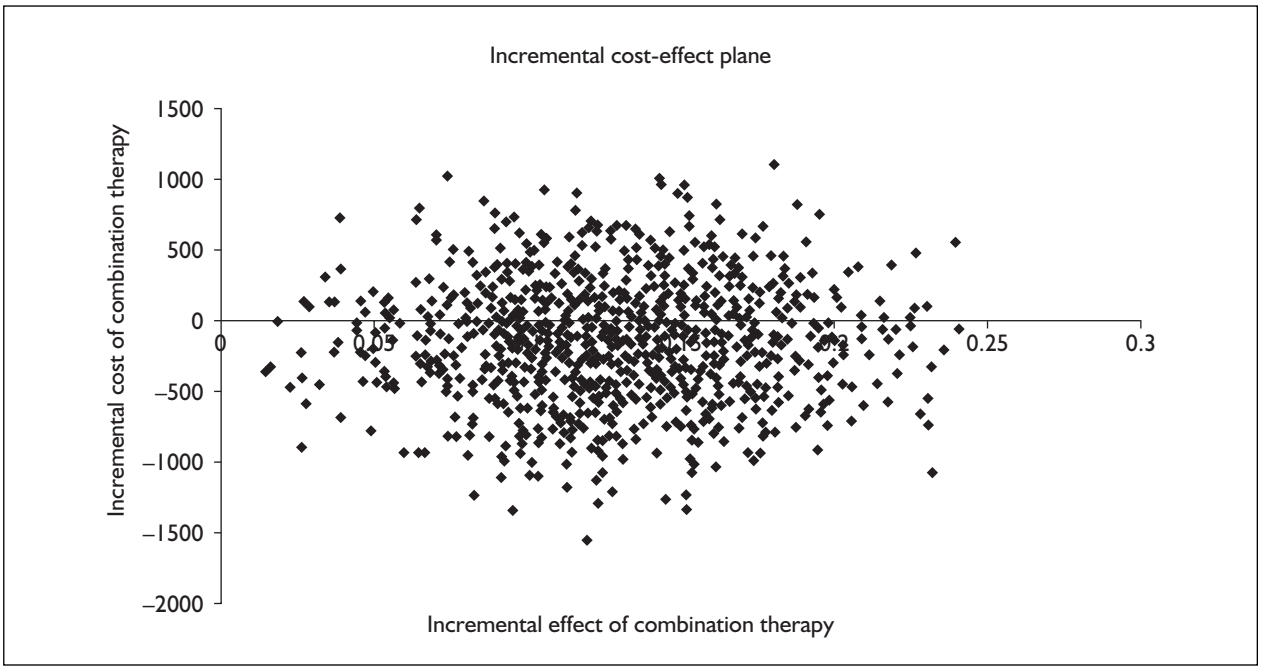

FIGURE 9 *Incremental cost-effectiveness plane for capecitabine/docetaxel combination therapy compared with docetaxel monotherapy*

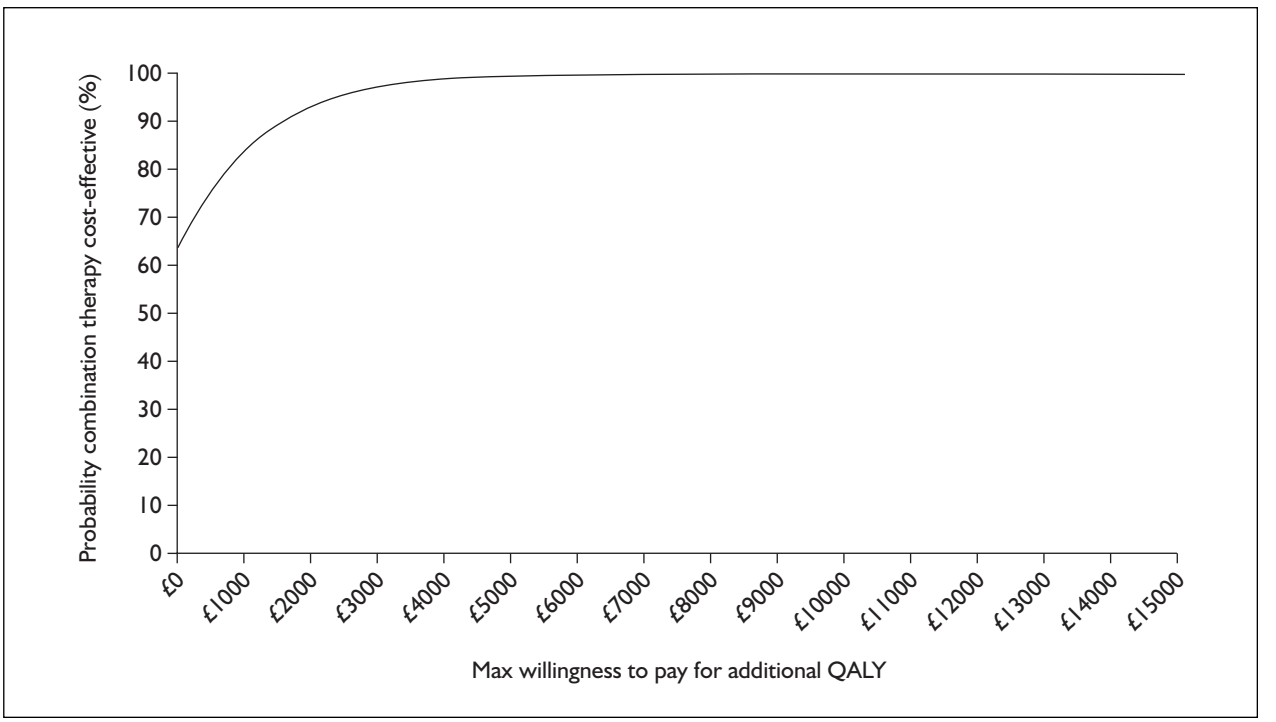

FIGURE 10 *Cost-effectiveness acceptability curve for capecitabine/docetaxel combination therapy compared with docetaxel monotherapy*

estimate of the NHS maximum willingness to pay for an additional QALY.

If one assumes that the maximum NHS willingness to pay for an additional life-year is £30,000, this simulation suggests that combination therapy would have to incur additional costs of at least £4000 above the estimates made based on the SO149999 trial[59] before the probability of the combination therapy being cost-effective declined to 50%. This suggests that the assumption of cost-effectiveness is robust to changes in the cost estimates made based on the trial.

Comments made by the expert panel

It was felt that docetaxel was an appropriate comparator. There was some disagreement as to whether combination therapy was associated with important toxicities. One clinician felt that combination therapy was quite 'toxic', being myelosuppressive, and may not be appropriate for this patient population. Another clinician highlighted that the adverse event profile and available QoL data from the Roche SO149999 study did not indicate that the combination therapy was poorly tolerated.

Estimate of NHS budgetary impact

These estimates are based on the prevalence figures presented in the Roche submission to NICE. It is assumed that 36,000 breast cancer patients are identified each year; of these, 18,000 progress to metastatic disease. Sixty per cent (10,800) of these will be treated with an anthracycline, and 20% (3600) will be treated with taxane plus trastuzumab or capecitabine according to their human epidermal growth factor receptor-2 status. The remaining 20% (3600) will receive other treatment. It was assumed that 700 patients still requiring treatment after trastuzumab would receive capecitabine monotherapy and 7500 patients would receive combination therapy following anthracycline treatment.

The net cost of capecitabine monotherapy compared with vinorelbine treatment, assuming that all patients who receive capecitabine would have previously received vinorelbine, is estimated to be a cost saving of £171,500 based on an assumed per-patient cost for capecitabine of £1268 and for vinorelbine of £1513. The gross cost of capecitabine itself in monotherapy is estimated to be £888,600.

The net cost of capecitabine combination therapy compared with docetaxel monotherapy, assuming that all patients who receive combination therapy would have received docetaxel monotherapy, is a cost saving of £1,200,000, assuming a total cost of treatment (including all items considered in the evaluation) of £9086 for combination therapy and £9246 for monotherapy. The gross cost of the capecitabine and docetaxel in the combination therapy is £49,000,000.

Conclusions

Based on the results of the SO149999 trial, as a result of the increased survival and time to progression observed in the combination arm in the absence of a significant increase in costs, combination therapy appears to be cost-effective. It should be noted that the cost-effectiveness analysis did not directly consider the impact on QoL associated with the combination and monotherapy.

Chapter 6
Discussion

Capecitabine monotherapy

The assessment of clinical effectiveness identified 13 non-comparative studies of capecitabine monotherapy. In the absence of controlled trials, these studies represent the best currently available evidence.

The assessment of cost-effectiveness identified one abstract referring to an economic evaluation of the cost-effectiveness of capecitabine monotherapy. There were insufficient details of the study methodology within the abstract to draw any conclusions regarding the validity of the reported results. The economic evaluation of capecitabine monotherapy is, therefore, based on the data reported in the Roche submission to NICE.

Issues about the quality of the clinical effectiveness evidence

The intrinsic weakness of non-comparative study designs means that all of the included studies suffered from a number of methodological flaws, which could bias their findings. When investigating the effectiveness of an intervention it is important to be aware that the observed effects may be due not to the therapeutic intervention itself but to other confounding factors. Potential confounding factors include the natural progression of the disease (i.e. variability in disease status or the influence of different prognostic factors), extraneous factors (e.g. lifestyle, the use of other medication, placebo effect) and information errors (incorrect assessment or reporting of the outcome measure). Undertaking a well-designed RCT means that these confounding factors and biases, which may influence the estimate of the effect, can be controlled for.

A full discussion of the limitations of using uncontrolled trials as a source of data to assess the effectiveness of clinical interventions is presented in Appendix 6.

Summary of the clinical effectiveness data

The outcomes assessed by the studies included survival time, time to disease progression, duration of response, time to treatment failure, tumour response rates, QoL and adverse event rates. The findings of the clinical effectiveness studies appear to indicate that capecitabine monotherapy has some effects, in terms of survival time, time to progression and time to treatment failure, duration of response and overall response rate in patients progressing after treatment with a taxane- and anthracycline-containing regimen. However, the lack of a control group does not allow any inferences to be made as to the 'additional' survival that patients may experience from capecitabine monotherapy. In the light of the quality issues relating to uncontrolled studies in general and the particular methodological flaws identified in the studies, these findings should be treated with extreme caution.

The outcome measures used in the studies were largely undefined, representing a potential source of bias. Tumour response rates, in particular, are a highly subjective measure of outcome. This issue is of particular concern in uncontrolled trials where the assessor is, by default, not blinded to the intervention. Median survival times were reported by some studies. However, in the absence of any comparator group these results have limited meaning. In general, time to event data should be analysed using Kaplan–Meier methods and hazard ratios to take into account the fact that the outcome of interest may not be observed over the period of follow-up, as well as the loss to analysis of individuals throughout the period of follow-up.

Assessment of QoL is particularly important for third-line treatment of advanced breast cancer, where the aim of treatment is palliative rather than curative. Outcome measures such as tumour response and duration of survival do not take into account the patient's subjective assessment of the impact of the disease or chemotherapy on their lifestyle.[102] It may be the case that the treatment causes greater morbidity than the disease process itself. It is, therefore, essential that QoL is assessed in patients receiving third-line treatment for advanced breast cancer. Of the 13 effectiveness studies, only one assessed QoL, using the EORTC QLQ-C30. Capecitabine appeared to have a positive influence on a number of QoL domains; however, the number of patients involved in the analysis was very small. Given that the goal of

third- and subsequent-line treatment is to maintain a good QoL and prolong survival,[11] it is unacceptable that the vast majority of studies failed to address this outcome.

The studies have established an increased adverse event profile for capecitabine monotherapy, in particular, with respect to the incidence of hand–foot syndrome. Hand–foot syndrome affects the palms of the hands and the soles of the feet, causing a macular, often painful, reddening of the skin and a tingling sensation. In severe cases the surface of the skin may begin to blister and degrade, impacting significantly on the QoL of the patient. In the manufacturer's summary of drug information, capecitabine is associated with cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy. However, none of these events was reported in any of the monotherapy trials. This may have been because in many of the trials, data were only reported for common adverse events (i.e. those affecting at least 5–10% of patients) and because the trials were underpowered to detect rare adverse events such as these, where the associated morbidity has a high impact on QoL.

Quality and summary of cost-effectiveness data

Based on the limited and poor quality data available, treatment with capecitabine, indirectly compared to treatment with vinorelbine, appears to be cost-effective. The estimates of cost and effectiveness in the Roche submission showed capecitabine both to be lower in cost and to have improved patient outcome compared with vinorelbine. The scale of these differences depends on which trials are compared. However, the economic evaluation was based on several assumptions. First, vinorelbine is the appropriate sole comparator for this evaluation; there was no information available regarding patient survival under best supportive care, and it should also be noted that the survival estimates for vinorelbine were based on those studies identified in the Roche NICE submission. Second, the results of the various uncontrolled trials referred to may be directly and meaningfully compared; no comparative trials of capecitabine and vinorelbine were reported. Given that the groups in the various trials are likely to differ in their prognosis it is unlikely that an unbiased comparison will result.[97] The validity of the comparison should be questioned. Third, the treatment toxicities do not have a significant differential effect on patient QoL between the two treatments. The impact of toxicities on QoL associated with the specific treatments was not directly assessed. Because of the assumptions made, the economic analysis may not accurately represent all relevant aspects of the clinical situation and this must be borne in mind when interpreting the results of the analysis.

In summary, the quality of the studies used in the economic analysis was poor. The strength of inference associated with indirect comparisons is limited and the results of this cost-effectiveness analysis should be questioned.

Capecitabine in combination with docetaxel

Only one RCT was identified which investigated a regimen of capecitabine in combination with docetaxel, compared with single-agent docetaxel. Two additional uncontrolled studies were identified. However, these studies were only available as abstracts, used an alternative treatment regimen and provided limited, poor quality evidence. The evidence regarding the effectiveness of capecitabine in combination with docetaxel is therefore derived primarily from a single RCT (trial SO14999).

The assessment of cost-effectiveness identified one abstract referring to an economic evaluation of the cost-effectiveness of capecitabine in combination with docetaxel based on trial SO14999. There were insufficient details of the study methodology within the abstract to draw any conclusions regarding the validity of the reported results. The economic evaluation of capecitabine in combination with docetaxel is, therefore, based on the data reported in the Roche submission to NICE.

Issues about the quality of the clinical effectiveness evidence

In terms of the assessment of clinical effectiveness the single RCT was of good quality. The main area of concern is that the evidence is limited to data from a single randomised trial. Combining data from several different trials, as a result of the larger sample size, usually provides a more powerful test for treatment differences and an increased precision of the estimated treatment effect.[103]

Summary of the clinical effectiveness data

The RCT provided some evidence that capecitabine/docetaxel combination therapy was superior to single-agent docetaxel in patients previously treated with anthracyclines; statistically

significant increases in survival time, time to disease progression and time to treatment failure were reported. Overall tumour response rates (complete response plus partial response) were also significantly increased in the combination therapy group compared with the single-therapy group, although there were no significant differences in complete response rates between the two groups. Measures of QoL recorded no clinically meaningful change from baseline on the global health status domain in either group during treatment. However, the global health score on the EORTC QLQ-C30 is a fairly insensitive measure of QoL. [Data removed as marked commercial in confidence.] In addition, data were reported using the LOCF method. Given that patients experiencing a negative response to treatment are more likely to be missing from the analysis, this method may have overestimated QoL.

Treatment-related adverse events occurred more frequently in the combination therapy group. The incidences of severe or life-threatening (grade 3/4) hand–foot syndrome, nausea, diarrhoea and stomatitis were all significantly greater in patients receiving capecitabine in combination with docetaxel. As reported for capecitabine monotherapy, in severe cases hand–foot syndrome may affect the patients' ability to perform activities of daily living.

Quality and summary of cost-effectiveness data

Based on the results of the SO149999 trial, which indicated increased survival and time to progression in the combination arm in the absence of a significant increase in costs, combination therapy appears to be cost-effective. Combination therapy was associated with a lower cost (£9086 vs £9246) than monotherapy with docetaxel and also had a positive effect on patient QoL (the exact level of improved effectiveness depends on the trials being compared). It should be noted that the cost-effectiveness analysis did not directly consider the impact on QoL of the combination and monotherapy treatments themselves. Thus, there remains a degree of uncertainty around the measure of effectiveness.

Limitations of the review

Capecitabine monotherapy

No head-to-head comparisons of capecitabine monotherapy and other third-line chemotherapies (including no treatment) were identified. Suitable comparators in this setting include vinorelbine, CMF, cisplatin, infusional 5-FU and best supportive care. Indirect comparisons of capecitabine and other third-line therapies were not undertaken as part of this review owing to the inherent limitations of this method. Simple comparisons of different single-arm trials are vulnerable to numerous biases.[99] Given the clinical diversity of this patient population and the unknown natural history of the disease it is highly unlikely that patients from the different trials could be matched in terms of prognosis. Any observed differences between treatments may simply be due to different patient characteristics and other prognostic factors in the different trials.

A full discussion of the limitations of using uncontrolled trials as a source of data to assess the effectiveness of clinical interventions is presented in Appendix 6.

Capecitabine in combination with docetaxel

Evidence for the effectiveness of capecitabine was limited to data from a single randomised trial. Increased precision of the estimated treatment effect between capecitabine/docetaxel combination therapy and single-agent docetaxel would have resulted from combining data from several different trials.

Comparison with other systematic reviews

The Cancer Care Ontario Practice Guidelines Initiative carried out a systematic review of the use of capecitabine in stage IV breast cancer.[104] The review was updated in August 2002. The review team considered that capecitabine monotherapy as second-, third- or fourth-line chemotherapy appeared to be a reasonable treatment option and compared favourably with data available for other single agents used in these patients. They concluded that the superiority of one drug over another remains to be established through well-designed randomised trials. The review considered that in selected patients, the combination of docetaxel and capecitabine may represent an appropriate treatment option.

Implications for future research

In view of the limited evidence available, there is an urgent need for basic research into the effectiveness of new second-, third- and

subsequent-line chemotherapy agents for the treatment of advanced breast cancer. In particular, good quality RCTs are needed to compare the effectiveness of capecitabine monotherapy with the alternative third- and subsequent-line therapies currently available, as well as with best supportive care. Future trials should ensure that data are collected on a range of outcomes, with particular emphasis on QoL and patient preferences. These data should be collected in a form that facilitates cost-effectiveness analysis. In addition, further RCTs investigating capecitabine in combination with docetaxel and alternative second-line therapies are required.

Future trials should be adequately randomised so as to avoid selection bias. In addition, it is particularly important for the avoidance of bias in effect sizes, given the difficulties of allocation concealment associated with therapies involving different modes of delivery, that data be analysed on an ITT basis and that those assessing the outcome measure are blinded to treatment allocation. With respect to time to event data, it is important that data are presented in the form of Kaplan–Meier survival curves and compared using an HR with 95% CI. The presentation of dichotomous data in terms of RR with 95% CI, as well as absolute event rates, is also preferable.

Chapter 7
Conclusions

Capecitabine monotherapy

The evidence base for the assessment of the effectiveness of capecitabine monotherapy was particularly poor. All of the studies identified for inclusion in the review lacked a control group, leaving them vulnerable to biases and confounding factors.

The evidence from these uncontrolled studies appears to indicate that capecitabine has antitumour activity when used as monotherapy in patients who have received previous treatment with anthracyclines and/or taxanes. The toxicity profile appeared to indicate an increased risk of patients developing hand–foot syndrome and diarrhoea. QoL was inadequately addressed; only one study included an assessment as part of the evaluation of capecitabine monotherapy.

In terms of cost-effectiveness, based on the available data, which are not based on a systematic review, treatment with capecitabine compared indirectly with treatment with vinorelbine appears to be cost-effective. No comparative trials of these treatments were reported. Given the diverse patient population, in terms of disease and treatment history, it is likely that an RCT, comparing survival from point of randomisation, for both treatments, could provide quite different information on relative survival times.

For a more complete picture, systematic reviews of vinorelbine, best supportive care and other relevant comparators in this setting need to be undertaken. However, given the available studies, comparing these treatments in a controlled trial might be a better use of scarce resources.

Capecitabine in combination with docetaxel

This review suggests that there is limited evidence in the form of RCTs on which to base an assessment of the effectiveness of capecitabine in combination with docetaxel in comparison to existing and new chemotherapy agents for the second-line treatment of advanced breast cancer. Only one RCT was identified for inclusion in the review comparing capecitabine in combination with docetaxel to treatment with single-agent docetaxel.

From the limited evidence available, capecitabine in combination with docetaxel appears to be more effective than single-agent docetaxel in terms of overall survival, time to disease progression, time to treatment failure and overall tumour response (complete response plus partial response). There was no statistically significant difference between the two groups in any of the QoL domains. Statistically significant differences between combination and single-agent therapy were identified in terms of reported grade 3/4 treatment-related side-effects. Treatment with capecitabine in combination with docetaxel was associated with higher incidences of grade 3/4 hand–foot syndrome, nausea, diarrhoea and stomatitis.

Combination therapy appears likely to be cost-effective; however, it should be noted that the cost-effectiveness analysis did not directly consider the impact on QoL associated with the combination and monotherapy treatments themselves.

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Contributions of authors

Lisa Jones	Lead reviewer responsible for writing the protocol and the final report; primary role in study selection and involved in data extraction, checking data entry and synthesis of data.
Marie Westwood	Assisted with study selection, data extraction and synthesis of data. Read and commented on draft copies of the protocol and final report.
Kath Wright	Devised the search strategy and carried out literature searches. Responsible for writing the search methodology section of the report.
Neil Hawkins	Responsible for the cost-effectiveness section of the report; involved in study selection, data extraction and report writing.
Gerry Richardson	Managed the cost-effectiveness section of the report. Provided input at all stages and commented on various drafts of the report.
Rob Riemsma	Review manager responsible for the overall management of the project. Commented on the protocol and various versions of the report.

Reviewers' declaration of interests

Other members of the team undertaking Technology Assessment Reviews within the Centre for Health Economics have received consultancy and/or research funding from Roche, but these individuals were not involved in this report and have not worked on capecitabine.

Members of the expert peer review panel

The following individuals have provided comments on draft versions of both the protocol and final report, in addition to providing advice on clinical and methodological issues.

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References

1. Cancer Research UK. About cancer: specific cancers. Breast cancer. URL: http://www.cancerresearchuk.org/aboutcancer/specificcancers/9365. Accessed 14 June 2002.
2. Office of National Statistics. Cancer trends in England and Wales, 1950–1999. London: The Stationery Office; 2001.
3. Williams C. Cancer biology and management: an introduction. Chichester: Wiley; 1990.
4. Clinical evidence. The international source of the best available evidence for effective health care. London: BMJ Publishing; 2001.
5. Marty M, Espie M, Cottu PH, Cuvier C, Lerebours F. Optimizing chemotherapy for patients with advanced breast cancer. *Oncology* 1999; **57** Suppl 1:21–6.
6. Hortobagyi GN. Treatment of breast cancer. *N Engl J Med* 1998;**339**:974–84.
7. Blum JL. The role of capecitabine, an oral, enzymatically activated fluoropyrimidine, in the treatment of metastatic breast cancer. *Oncologist* 2001;**6**:56–64.
8. Leonard RC. Oral fluoropyrimidines among the new drugs for patients with metastatic breast cancer. *Br J Cancer* 2001;**84**:1437–42.
9. NHS Executive. Improving outcomes in breast cancer. The research evidence. London: NHS Executive, Health Services Directorate; 1996.
10. Cancerbacup. Understanding secondary breast cancer. Chemotherapy. URL: http://www.cancerbacup.org.uk/info/sbrest/sbrest12.htm. Accessed 14 June 2002.
11. Esteva FJ, Valero V, Pusztai L, Boehnke Michaud L, Buzdar AU, Hortobagyi GN. Chemotherapy of metastatic breast cancer: what to expect in 2001 and beyond. *Oncologist* 2001;**6**:133–46.
12. National Institute for Clinical Excellence. Guidance on the use of taxanes for the treatment of breast cancer. NICE; 2001. URL: http://www.nice.org.uk/pdf/taxanesreviewguidance.pdf. Accessed 14 June 2002.
13. Xeloda. Summary of product characteristics. URL: http://www.rocheuk.com/productDB/Documents/rx/spc/Xeloda_SPC.pdf. Accessed 14 June 2002.
14. Khan K, Ter Riet G, Glanville J, Sowden AJ, Kleijnen J. Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews. 2nd ed. York: NHS Centre for Reviews and Dissemination, University of York; 2001.
15. Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford Medical Publications; 1997.
16. National Institute for Clinical Excellence. National Institute for Clinical Excellence methodological guidence: economic evaluations. London: NICE.
17. Welt A, Borquez D, Oberhoff C, Tewes M, Flömer F, Mohrbacher R, *et al*. Phase I study of capecitabine and vinorelbine in pretreated patients with metastatic breast cancer. 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/1979.htm. Accessed 14 May 2002.
18. Nole F, Catania C, Mandala M, Munzone E, Rocca A, Zampino G, *et al*. Phase I study of vinorelbine (V) and capecitabine (C) in advanced breast cancer (ABC). 2000. URL: http://www.asco.org/prof/me/html/00abstracts/bc/m_428.htm. Accessed May 2002.
19. Domenech G, Perez A, Vogel C. Vinorelbine/Capecitabine (VINOCAP) combination remission induction therapy for metastatic breast cancer (MBC). 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/1939.htm. Accessed 14 May 2002.
20. Hess D, Thuerlimann B, Pagani O, Aebi S, Rauch D, Ballabeni P, *et al*. Phase I–II trial of capecitabine and vinorelbine in elderly patients (pts: > 65 y) with metastatic breast cancer (MBC): SAKK 25/99 for the Swiss Group of Clinical CancerResearch, Berne, Switzerland [abstract 2915]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.
21. Ahn Sr J, Kim S-B, Lee J-S, Kim W. Phase II study of a combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: preliminary results [abstract 2030]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.
22. Ghosn M, Farhat F, Kattan J. Vinorelbine (navelbine) IV and capecitabine (vinocap) as front line chemotherapy in metastatic breast cancer (MBC) [abstract 1978]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.

23. Khoury P, Villalona Calero M, Blum J, Diab S, Elledge R, Kraynak M, *et al*. Phase I study of capecitabine in combination with paclitaxel in patients with previously treated metastatic breast cancer [meeting abstract 793]. *Proc Annu Meet Am Soc Clin Oncol* 1998;**17**:206a. URL: http://www.asco.org/prof/me/html/98abstracts/cp/m_793.htm

24. Perez-Manga G, Batista N, Constenla M, Guillem V, Carabantes F, Ahlgren J, *et al*. Efficacy and safety profile of capecitabine (Xeloda®) in combination with paclitaxel (P) in patients with locally advanced or metastatic breast cancer: preliminary results of a phase II study [meeting abstract]. *Breast Cancer Res Treat* 2000;**64**:124.

25. Villalona-Calero M, Blum J, Diab S, Elledge R, Khoury P, Kraynak M, *et al*. Phase I study of capecitabine in combination with paclitaxel in patients with previously treated metastatic breast cancer. *Ann Oncol* 1998;**9**:97, abstract 370.

26. Villalona-Calero MA. Capecitabine and paclitaxel: synergistic combination? [meeting abstract]. *Cancer Invest* 1998;**17**:37–9.

27. Villalona Calero MA, Blum JL, Jones SE, Diab S, Elledge R, Khoury P, *et al*. A phase I and pharmacologic study of capecitabine and paclitaxel in breast cancer patients. *Ann Oncol* 2001;**12**:605–14.

28. Villalona-Calero MA, Weiss GR, Burris HA, Kraynak M, Rodrigues G, Drengler RL, *et al*. Phase I and pharmacokinetic study of the oral fluoropyrimidine capecitabine in combination with paclitaxel in patients with advanced solid malignancies. *J Clin Oncol* 1999;**17**:1915–25.

29. Venturini M, Del Mastro L, Garrone O, Angiolini C, Merlano M, Bergaglio M, *et al*. Phase I, dose-finding study of capecitabine in combination with docetaxel and epirubicin as first-line chemotherapy for advanced breast cancer. *Ann Oncol* 2002;**13**:546–52.

30. Angiolini C, Venturini M, Del Mastre L, Bergaglio M, Garrone O, Merlano M, *et al*. A phase I dose-finding study of capecitabine in combination with epirubicin and docetaxel as first-line chemotherapy in advanced breast cancer patients. *Ann Oncol* 2000;**11**:36.

31. Venturini M, Del Mastro L, Merlano M, Angiolini C, Straneo M, Tolino G, *et al*. Dose finding study of capecitabine in combination with docetaxel and epirubicin in prior untreated advanced breast cancer patients. 2000. URL: http://www.asco.org/prof/me/html/00abstracts/bc/m_419.htm. Accessed 14 May 2002.

32. Donaldson L, Jennings C, Lee F-C, Mangalik A. A phase I/II study of carboplatin, vinorelbine and capecitabine in patients with metastatic breast cancer [abstract 1960]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.

33. Talbot DC, Moiseyenko V, Van Belle S, O'Reilly SM, Alba Conejo E, Ackland S, *et al*. Randomised, phase II trial comparing oral capecitabine (Xeloda®) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. *Br J Cancer* 2002;**86**:1367–72.

34. Moiseyenko V, O'Reilly SM, Talbot DC, Gordon RJ, Griffin T, Osterwalder B. A randomized phase II study of Xeloda™ (capecitabine) vs paclitaxel in breast cancer patients failing previous anthracycline therapy. *Ann Oncol* 1998;**9**:13.

35. O'Reilly SM, Moiseyenko V, Talbot DC, Gordon RJ, Griffin T, Osterwalder B. A randomized phase II study of Xeloda (capecitabine) vs paclitaxel in breast cancer patients failing previous anthracycline therapy [meeting abstract 627]. *Proc Annu Meet Am Soc Clin Oncol* 1998;**17**:163a.

36. Moiseenko VM, O'Reilly SM, Dalbot DC, Van Belle S, Gordon RJ, Griffin T, *et al*. Sravnitel'noe randomizirovannoe issledovanie po II faze kselody (kapetsitabina) i paklitaksela u bol'nykh rakom molochnoi zhelezy, progressiruiushchikh posle antratsiklinovykh antibiotikov [A comparative randomized phase-II study of Xeloda (capecitabine) and paclitaxel in patients with breast cancer progressing after anthracycline antibiotics]. *Vopr Onkol* 2000; **46**:285–9.

37. Moiseyenko V. Randomized phase II study of Xeloda (capecitabine) vs paclitaxel in breast cancer patients failing previous anthracycline therapy. In 23rd European Society for Medical Oncology (ESMO) Annual Meeting, Athens, Greece; 1998. Lugano, Switzerland: ESMO Congress Secretariat. Abstract No. 62.

38. Guthrie TH, Agaliotis DP, Gaddis TG. Capecitabine (C) has activity in breast cancer patients (BCP) progressing after autologous peripheral stem cell transplant (AuPSCT) [meeting abstract]. *Breast Cancer Res Treat* 1999; **57**:90.

39. Kusama M, Sano M, Ikeda T, Sonoo H, Takashima S. A phase II study of xeloda (capecitabine) in patients with advanced/metastatic breast carcinoma: the Cooperative Study Group of Capecitabine for Breast Carcinoma. 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/1924.htm. Accessed 14 May 2002.

40. Saeki T, Takashima S, Terashima M, Tabei T, Enomoto K, Tominaga T, *et al*. An early phase 2 study with Xeloda™ (capecitabine) in patients with metastatic breast cancer. *Ann Oncol* 1998;**9**:155.

41. Procopio G, Bajetta E, Catena L, Ferrari L, Alù M, Longarini R, *et al*. A phase II study of capecitabine in elderly patients with advanced breast cancer.

2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/3134.htm. Accessed 14 May 2002.

42. Ilersich A, Jandciu S, Verma S, Tomiak A. Capecitabine (C) in metastatic breast cancer (MBC) post-marketing surveillance of multiple outcomes in a universal health care system. 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0025/991.htm. Accessed 14 May 2002.

43. Michaud L, Gauthier M, Wojdylo J, Valero V, Theriault R, Ibrahim N, *et al*. Improved therapeutic index with lower dose capecitabine in metastatic breast cancer (MBC) patients (Pts). 2000. URL: http://www.asco.org/prof/me/html/00abstracts/bc/m_402.htm. Accessed 14 May 2002.

44. O'Shaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, *et al*. Randomized, open-label, phase II trial of oral capecitabine (Xeloda®) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. *Ann Oncol* 2001;**12**:1247–54.

45. Pronk L, Vasey AP, Sparreboom A, Gordon RJ, Osterwalder B, Twelves C. A matrix-designed phase I dose-finding and pharmacokinetic study of the combination of Xeloda plus taxoteres [meeting abstract 816]. *Proc Annu Meet Am Soc Clin Oncol* 1998;**17**:212a. URL: http://www.asco.org/prof/me/html/98abstracts/cp/m_816.htm

46. Pronk LC, Vasey P, Sparreboom A, Reigner B, Planting AST, Gordon RJ, *et al*. A phase I and pharmacokinetic study of the combination of capecitabine and docetaxel in patients with advanced solid tumours. *Br J Cancer* 2000;**83**:22–9.

47. Villalona-Calero M, Shapiro C, Otterson G, Hauger M, Kraut E, Clinton S, *et al*. Phase I study of weekly docetaxel in combination with capecitaine in patients with solid malignancies [meeting abstract 537]. In 23rd Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA. 2002; p. 125.

48. Budman DR, Meropol NJ, Reigner B, Creaven PJ, Lichtman SM, Berghorn E, *et al*. Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. *J Clin Oncol* 1998; **16**:1795–802.

49. Vasey P. Phase I and pharmacologic study of Xeloda™ (capecitabine) in combination with docetaxel. *Eur J Cancer* 1997;**33**:S246.

50. Bell KA, Perna AG, Hsu S. Mucositis as a treatment-limiting side effect in the use of capecitabine for the treatment of metastatic breast cancer. *J Am Acad Dermatol* 2001;**45**:790–1.

51. Bertolini A, Flumano M, Fusco O, Muffatti A, Scarinci A, Pontiggia G, *et al*. Acute cardiotoxicity during capecitabine treatment: a case report. *Tumori* 2001;**87**:200–6.

52. Chen GY, Chen YH, Hsu MM, Tsao CJ, Chen WC. Onychomadesis and onycholysis associated with capecitabine. *Br J Dermatol* 2001;**145**:521–2.

53. Schmid Wendtner MH, Wendtner CM, Volkenandt M, Heinemann V. Clinical picture: leopard-like vitiligo with capecitabine. *Lancet* 2001;**358**:1575.

54. Walkhom B, Fraunfelder FT, Henner WD. Severe ocular irritation and corneal deposits associated with capecitabine use. *N Engl J Med* 2000; **343**:740–1.

55. Wang ML, Yung WK, Royce ME, Schomer DF, Theriault RL. Capecitabine for 5-fluorouracil-resistant brain metastases from breast cancer. *Am J Clin Oncol* 2001;**24**:421–4.

56. Schnetzler B, Popova N, Collao Lamb C, Sappino AP. Coronary spasm induced by capecitabine. *Ann Oncol* 2001;**12**:723–4.

57. Baran R, Dupere W, Miao S, Taylor K. Clinical and economic outcomes associated with metastatic breast cancer in managed care populations: capecitabine (xeloda) versus comparison therapies [abstract 1942]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.

58. Beltz SE, Yee GC. Pharmacoeconomics of cancer therapy. *Cancer Control* 1998;**5**:415–24.

59. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub J-P, Cervantes G, *et al*. Superior survival with capecitabine plus doxetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;**20**:2812–23.

60. Tonkin K, Scarfe A, Koski S, Bodnar D, Smylie M, Au H-J, *et al*. Preliminary results of a phase I/II study of weekly docetaxel (Taxotere®) combined with intermittent capecitabine (Xeloda®) for patients with anthracycline pre-treated metastatic breast cancer. 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/2016.htm. Accessed 14 May 2002.

61. Scarfe A, Bodnar D, Tonkin K, Koski S, Au H, Smylie M, *et al*. Interim results of a phase II study of weekly docetaxel (Taxotere®) combined with intermittent capecitabine (Xeloda®) for patients with anthracycline pre-treated metastatic breast cancer [abstract 1984]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.

62. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, *et al*. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999;**17**:485–93.

63. Blum JL, Buzdar AU, LoRusso PM, Kuter I, Vogel C, Burger HU, *et al*. A multicenter phase II

trial of Xeloda (capecitabine) in paclitaxel-refractory metastatic breast cancer (MBC) [meeting abstract 476]. *Proc Annu Meet Am Soc Clin Oncol* 1998;**17**:125a.

64. Blum J, Jones SE, Buzdar A. Capecitabine (Xeloda) in 162 patients with paclitaxel-treated MBC: updated results and analysis of dose modification. *Eur J Cancer* 2001;**37**:190.

65. Blum JL, Dieras V, Lo Russo PM, Horton J, Rutman O, Buzdar A, *et al*. Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. *Cancer* 2001;**92**:1759–68.

66. Blum J, Buzdar A, Dieras V, LoRusso P, Rutman O, Curtiss K, *et al*. A multicenter phase II trial of Xeloda™ (capecitabine) in taxane-refractory metastatic breast cancer. 1999. URL: http://www.asco.org/prof/me/html/99abstracts/bc/m_403.htm. Accessed 14 May 2002.

67. Cervantes G, Torrecillas L, Erazo A, Delgadillo F, Suarez T, Leoner C, *et al*. Capecitabine (Xeloda) as treatment after failure to taxanes for metastatic breast cancer. 2000. URL: http://www.asco.org/prof/me/html/00abstracts/bc/m_469.htm. Accessed 14 May 2002.

68. Fumoleau P, Largriller R, Trillet-Lenoir V, Orfeuvre H, Extra J, Dieras V, *et al*. Capecitabine (Xeloda) in patients with advanced breast cancer (ABC), previously treated with anthracyclines and taxanes: results of a large phase II study [abstract 247]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.

69. Fumoleau P, Largillier R, Trillet-Lenoir V, Orfeuvre H, Extra JM, Lesimple T, *et al*. Phase II study of capecitabine (xeloda®) in pts with advanced breast cancer (ABC), previously treated with anthracyclines and taxanes. *Breast Cancer Res Treat* 2001;**69**:435.

70. Reichardt P, von Minckwitz G, Luck H, Thuss-Patience P, Jonat W, Kolbl H, *et al*. Capecitabine: the new standard in metastatic breast cancer failing anthracylcine and taxane-conatining chemotherapy? Mature results of a large multicenter phase II trial. *Eur J Cancer* 2001;**37**:191.

71. Reichardt P, von Minckwitz G, Lueck HJ, Thuss-Patience PC, Jonat W, Koelbl H, *et al*. Capecitabine: an active and well tolerated treatment option for patients with metastatic breast cancer recurring after taxane-containing chemotherapy. Results of a multicenter phase II trial. *Breast Cancer Res Treat* 2000;**64**:83.

72. Thuss-Patience P, von Minckwitz G, Lück H, Jonat W, Kölbl H, Kieback D, *et al*. Capecitabine: a new standard in metastatic breast cancer recurring after anthracycline and taxane-containing chemotherapy? Results of a multicenter phase II trial. 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/2012.htm. Accessed 14 May 2002.

73. Semiglazov T, Geshanovich M, Semigalvoz V. Oral capecitabine (Xeloda) in the treatment of anthracycline-refractory, anthracycline and docetaxel-refractory metastatic breast cancer (MBC) [abstract 2061]. Proc Am Soc Clin Oncol, 2002. URL: http://www.asco.org/. Accessed 18 June 2002.

74. Watanabe T, Katsumata N, Sasaki Y, Saeki T, Aogi K, Toi M, *et al*. A multicenter phase II trial of Xeloda™ (capecitabine) in patients with docetaxel-refractory advanced/metastatic breast cancer. 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/1991.htm. Accessed 14 May 2002.

75. Leonard RCF, Anderson A, Salazar R, Twelves C, Hutcheon A, Bissett D, *et al*. Capecitabine named patient program for patients with advanced breast cancer: the UK experience [meeting abstract]. *Br J Cancer* 2001;**85**:21.

76. Leonard R, Anderson A, Twelves C, Hutcheon A, Bissett D, Chaturvedi A, *et al*. Capecitabine named patient programme for patients with advanced breast cancer: the UK experience [meeting abstract 334]. In 23rd Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA. 2000. p. 84.

77. Anderson A, Cameron DA, Douglas S, Gourley C, Hayward L, Leonard RCF. Capecitabine named patient programme for patients with advanced breast cancer: the Edinburgh experience. *Br J Cancer* 1999;**80**:101.

78. Wong Z, Wong K, Chew L, Low J, Ang P, Sc Au E, *et al*. Capecitabine as an oral chemotherapeutic agent in the treatment of refractory metastatic breast carcinoma (MBC). URL: http://www.asco.org/prof/me/html/00abstracts/bc/m_466.htm. Accessed 14 May 2002.

79. Bashey A, Sundaram S, Corringham S, Jones V, Lancaster D, Silva Gietzen J, *et al*. Use of capecitabine as first-line therapy in patients with metastatic breast cancer relapsing after high-dose chemotherapy and autologous stem cell support. *Clin Oncol* 2001;**13**:434–7.

80. Jakob A, Bokemeyer C, Knop S, Schupp M, Mayer F, Kanz L. Capecitabine in patients with breast cancer relapsing after high-dose chemotherapy plus autologous peripheral stem cell transplantation: a phase II study. *Anti-cancer Drugs* 2002;**13**:405–10.

81. Jakob A, Schupp M, Knop S, Frings S, Floemer F, Kanz L. A phase II study of capecitabine in patients, who relapsed after high dose chemotherapy followed by peripheral blood stem cell transplantation for metastatic breast cancer.

2001. URL: http://www.asco.org/prof/me/html/01abstracts/0011/1966.htm. Accessed 14 May 2002.

82. Sundaram S, Lancaster D, Silva J, Corringham S, Law P, Ball E, *et al*. Oral capecitabine is an active and well tolerated primary palliative treatment in patients with metastatic breast cancer who progress after high dose chemotherapy and autologous stem cell support. 2000. URL: http://www.asco.org/prof/me/html/00abstracts/bmt/m_223.htm. Accessed 14 May 2002.

83. Leonard R, Cervantes G, Lui W, Mauriac L, Miles D, Moiseyenko V, *et al*. Survival update of SO14999: a large phase III trial of capecitaibe/docetaxel combination therapy vs docetaxel monotherapy in patients with locally advanced (LABC) or metastatic breast cancer (MBC). *Eur J Cancer* 2001;**37**:151.

84. Vukelja SJ, Moiseyenko V, Leonard R, Conte PF, Garin A, McKendrick J, *et al*. Xeloda (capecitabine) plus docetaxel combination therapy in locally advanced/metastatic breast cancer: latest results. *Breast Cancer Res Treat* 2001;**69**:352.

85. Twelves C, Fumoleau P, Jones SE, Cherubini R, Foimtchuk MJ, Kroener JF, *et al*. Adding Xeloda (capecitabine) to docetaxel significantly improves survival and does not compromise quality of life in patients with metastatic breast cancer. *Breast Cancer Res Treat* 2001;**69**:542.

86. Miles D, Ayoub J, O'Shaughnessy J, Cervantes G, Erikstein F, Findlay M, *et al*. Survival benefit with Xeloda (capecitabine)/doxetaxel vs docetaxel: analysis of post-study therapy [meeting abstract 442]. In 24th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA. 2001. p. 287.

87. Liu X, Song S, Guan Z, Wu S, Duan Y, Yu J, *et al*. [Capecitabine (Xeloda) in the treatment of relapsed and metastatic breast cancer]. *Zhonghua Zhong Liu Za Zhi* 2002;**24**:71–3.

88. Semiglazov TI, Gershanovich ML. Kseloda (kapetsitabin) v lechenii disseminirovannogo raka molochnoi zhelezy posle ischerpannogo effekta antratsiklinov i taksanov [Xeloda (capecetabine) in the treatment of disseminated breast cancer after failure with anthracyclines and taxanes]. *Vopr Onkol* 2001;**47**:298–302.

89. Silberman G, Gupta S, Berkowitz N, Leyland Jones B. Cost-effectiveness of capecitabine, continuous infusion 5-FU, gemcitabine and vinorelbine in the treatment of metastatic breast cancer [meeting abstract 1629]. *Proc Annu Meet Am Soc Clin Oncol* 1999;**18**:422a. URL: http://www.asco.org/prof/me/html/99abstracts/hsr/m_1629.htm

90. O'Shaughnessy JA, Jones SE, Vukelja SJ, Kaywin PR, Kroener JF, Maraninchi D, *et al*. Pharmacoeconomic analysis of Xeloda (capecitabine) in combination with docetaxel for the treatment of advanced breast cancer pretreated with anthracyclines. *Breast Cancer Res Treat* 2001; **69**:264.

91. Smorenburg CH, Bontenbal M, Verweij J. Capecitabine in breast cancer: current status. *Clin Breast Cancer* 2001;**1**:288–93.

92. World Health Organisation handbook for reporting results of cancer treatment. Geneva: World Health Organisation; 1979.

93. EORTC QLQ-C30 scoring manual. 2nd ed. Brussels: Quality of Life Unit, EORTC Data Center; 1999.

94. Liu G, Franssen E, Fitch M, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997;**15**:110–15.

95. Livingstone RB, Ellis GK, Gralow JR, Williams MA, White R, McGuirt C, *et al*. Dose-intensive vinorelbine with concurrent granulocyte colony-stimulating factor support in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1997; **15**:1395–400.

96. Zelek L, Barthier S, Riofrio M, Fizazi K, Rixe O, Delord JP, *et al*. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. *Cancer* 2001;**92**:2267–72.

97. Bucher H, Guyatt G, Griffith L, Walter S. The results of direct and indirect treatment comparisons in meta-analysis of randomised controlled trials. *J Clin Epidemiol* 1997;**50**:683–91.

98. Brown R, Hutton J. Cost utility model comparing docetaxel and paclitaxel in advanced breast cancer patients. *Anti-cancer Drugs* 1998;**9**:899–907.

99. Launois R. A cost–utility analysis of second-line chemotherapy in metastatic breast cancer docetaxel versus paclitaxel versus vinorelbine. *Pharmacoeconomics* 1996;**10**:504–21.

100. Udom DI, Vigushin DM, Linardou H, Graham H, Palmieri C, Coombes RC. Two weekly vinorelbine: administration in patients who have received at least two prior chemotherapy regimes for advanced breast cancer. *Eur J Cancer* 2000;**36**:177–82.

101. Hutton J, Brown R, Borowitz M, Abrams K, Rothman M, Shakespeare A. A new decision model for cost–utility comparisons of chemotherapy in recurrent metastatic breast cancer. *Pharmacoeconomics* 1996;**9**:8–22.

102. Payne S. A study of quality of life in cancer patients receiving palliative chemotherapy. *Soc Sci Med* 1992;**35**:1505–9.

103. Sylvester R, Collette L, Duchateau L. The role of meta-analyses in assessing cancer treatments. *Eur J Cancer* 2000;**36**:1351–8.

104. Tomiak E, Verma S, Levine M, Prichard K, Sawka C, Breast Cancer Disease Site Group. Use of capecitabine in stage IV breast cancer (Evidence summary report no. 1-16). Cancer Care Ontario; 2002. URL: http://www.ccopebc.ca/guidelines/bre/es1_16f.html. Accessed 2 September 2002.

105. Harris J, Lippman M, Veronesi U, Willet W. Medical progress. Breast cancer. *N Engl J Med* 1992;**6**:390–8.

106. Egger M, Davey Smith G, Altman D. Systematic reviews in health care: meta-analysis in context. London: BMJ Books; 2000.

107. De Craen A, Kaptchuk T, Tijssen J, Kleijnen J. Placebos and placebo effects in medicine: historical overview. *J R Soc Med* 1999;**92**:511–15.

108. Koopmans P. Registration of drugs for treating cancer and HIV infection: a plea to carry out phase 3 trials before admission to the market. *BMJ* 1995;**310**:1305–6.

109. Byar D, Schoenfield D, Green S, Amato D, Davis R, De Gruttola V, *et al*. Design considerations for AIDS trials. *N Engl J Med* 1990;**323**:1343–8.

110. Capecitabin – neues orales tumoraktiviertes fluoropyrimidin. *Dtsch Apoth Ztg* 1997;**137**:34.

111. Xeloda: oral agent for metastatic breast cancer resistant to standard chemotherapy. *Formulary* 1998;**33**:621.

112. Capecitabin zur oralen Behandlung von Brustkrebs. *Dtsch Apoth Ztg* 1998;**138**:47–8.

113. Breast cancer drug eyed for fast approval. *Drug Topics* 1998;**142**:30.

114. Capecitabine studies show flexible dose effective, recurrent breast cancer responsive. *Oncology (Huntingt)* 2000;**14**:1003.

115. Capecitabine and breast cancer. *Eur J Cancer Care* 2000;**9**:131.

116. Capecitabine gives new life to fluorouracil in treatment of breast cancer. *Drugs Ther Perspect* 2000;**16**:1–5.

117. Fragen zum thema: neue substanzen und neue wirkprinzipien in der onkologie. *Onkologe* 2000; **6**:458–9.

118. Cytotoxic agent – capecitabine. *Manuf Chem* 2000;**71**:22.

119. Combination treatment better for breast cancer. *Pharm J* 2001;**267**:636.

120. Capecitabin/Docetaxel-kombinationstherapie bei Metastasierendem Brustkrebs. *Dtsch Apoth Ztg* 2001;**141**:32.

121. Capecitabin in Kombination mit docetaxel. *Dtsch Apoth Ztg* 2001;**141**:34.

122. Capecitabine–docetaxol combination may improve breast cancer survival. *Pharm J* 2001;**266**:45.

123. Drug combination approved for treatment of breast cancer. *J Gender Specif Med* 2001;**4**:5.

124. Kombination von Capecitabin mit Docetaxel verbessert Lebneserwartung bei fortgeschrittenem Brustkrebs. *Dtsch Apoth Ztg* 2001;**141**:46.

125. Drug combination approved for advanced breast cancer. *FDA Consum* 2002;**36**:5.

126. Awada A, Di Leo A, Piccart MJ. Actualites therapeutiques dans le cancer du sein. *Bull Cancer* 2000;**87**:49–62.

127. Borquez D, Seeber S. Therapiestrategien bei der behandlung des metastasierten mammakarzinoms. *Onkologie* 1999;**22**:16–17.

128. Brito RA, Medgyesy D, Zukowski TH, Royce ME, Ravandi Kashani F, Hoff PM, *et al*. Fluoropyrimidines: a critical evaluation. *Oncology* 1999;**57** Suppl 1:2–8.

129. Bunnell CA, Winer EP. Oral 5-FU analogues in the treatment of breast cancer. *Oncology (Huntingt)* 1998;**12**:39–43.

130. Carbone PP. Advances in the systemic treatment of cancers in the elderly. *Crit Rev Oncol Hematol* 2000; **35**:201–18.

131. Cassata A, Procopio G, Alu M, Ferrari L, Ferrario E, Beretta E, *et al*. Capecitabine: indications and future perspectives in the treatment of metastatic colorectal and breast cancer. *Tumori* 2001; **87**:364–71.

132. Chernin T. War on cancer reaches turning point. *Am Drug* 1999;**216**:36–41.

133. Cole C, Foster AJ, Freeman S, Jaffar M, Murray PE, Stratford IJ. The role of thymidine phosphorylase/PD-ECGF in cancer chemotherapy: a chemical perspective. *Anticancer Drug Des* 1999; **14**:383–92.

134. Crown J. Nonanthracycline containing docetaxel-based combinations in metastatic breast cancer. *Oncologist* 2001;**6** Suppl 3:17–21.

135. Danova M, Porta C, Ferrari S, Riccardi A. Strategies of medical treatment for metastatic breast cancer [review]. *Int J Oncol* 2001;**19**:733–9.

136. Dees EC, Kennedy MJ. Recent advances in systemic therapy for breast cancer. *Curr Opin Oncol* 1998;**10**:517–22.

137. Del Vecchio M, Procopio G, Cassata A, Pozzi P, Busto G, Celio L, *et al*. Fluoropyrimidines in the treatment of advanced neoplastic diseases: role and advantages of UFT. *Tumori* 1999;**85**:6–11.

138. Diasio RB. Improving fluorouracil chemotherapy with novel orally administered fluoropyrimidines. *Drugs* 1999;**58**:119–26.

139. Diasio RB. An evolving role for oral fluoropyrimidine drugs. *J Clin Oncol* 2002; **20**:894–6.

140. Frings S. Capecitabine: a novel oral tumor-activated fluoropyrimidine. *Onkologie* 1998;**21**:451–8.

141. Fujimoto Ouchi K, Tanaka Y, Tominaga T. Schedule dependency of antitumor activity in combination therapy with capecitabine/5′-deoxy-5-fluorouridine and docetaxel in breast cancer models. *Clin Cancer Res* 2001;**7**:1079–86.

142. Galligioni E. Docetaxel (Taxotere®) combined with anthracycline, Xeloda® and new pharmaceuticals. *Tumori* 2001;**87**:S1–9.

143. Gieschke R, Reigner B, Steimer Jean L. Capecitabine population pharmacokinetics of combined sparse data from phase II breast cancer patients and extensive data from a bioequivalence study [meeting abstract 666]. *Proc Annu Meet Am Soc Clin Oncol* 1999;**18**:174a. URL: http://www.asco.org/prof/me/html/99abstracts/cp/m_666.htm

144. Gradishar WJ. Clinical status of capecitabine in the treatment of breast cancer. *Oncology (Huntingt)* 2001;**15**:69–71.

145. Harstrick A. Future treatment options with capecitabine. *Semin Oncol* 2000;**27**:149–52.

146. Hori T, Kodama H, Nishimura S, Taniguchi R, Hatano T, Okamura R, *et al*. A randomized controlled study of oral combination chemotherapy in advanced/recurrent breast cancer. 2000. URL: http://www.asco.org/prof/me/html/00abstracts/bc/m_429.htm. Accessed 14 May 2002.

147. Hoshi A, Castaner J. Capecitabine. Antineoplastic. *Drugs Future* 1996;**21**:358–60.

148. Ignoffo RJ. Capecitabine: a new oral fluoropyrimidine. *Cancer Pract* 1998;**6**:302–4.

149. Ignoffo RJ. Novel oral fluoropyrimidines in the treatment of metastatic colorectal cancer. *Am J Health Syst Pharm* 1999;**56**:2417–28.

150. Johnston PG, Kaye S. Capecitabine: a novel agent for the treatment of solid tumors. *Anti-cancer Drugs* 2001;**12**:639–46.

151. Kaye SB. New antimetabolites in cancer chemotherapy and their clinical impact. *Br J Cancer* 1998;**78** Suppl 3:1–7.

152. Kaye S. New paradigms in the treatment of breast and colorectal cancer – an introduction. *Eur J Cancer* 2002;**38**:S1–2.

153. Levin J, Hohneker J. Clinical development of eniluracil/fluorouracil: an oral treatment for patients with solid tumors. *Invest New Drugs* 2000; **18**:383–90.

154. Lewis NL, Meropol NJ. Oral fluoropyrimidines in cancer treatment. *Cancer Invest* 2000;**18**:747–60.

155. Mader RM, Schrolnberger C, Rizovski B, Brunner M, Wenzel C, Locker G, *et al*. Penetration of capecitabine and its metabolites into malignant and healthy tissue from patients with advanced breast cancer [meeting abstract]. *Eur J Cancer* 2001;**37**:S18.

156. McVie JG. Are European cancer patients getting a fair deal? *Ann Oncol* 2001;**12**:1033–5.

157. Mevissen G. Eine therapie im umbruch. *Pharm Ztg* 2000;**145**:36, 39.

158. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, *et al*. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998;**34**:1274–81.

159. Mlineritsch B, Mayer P, Moik M, Rass C, Reiter E, Russ G, *et al*. Phase II study of pegylated liposomal doxorubicin (caeylx)-monotherapy in previous treated metastatic breast cancer [meeting abstract]. *Breast Cancer Res Treat* 2001;**69**:287.

160. Moiseenko VM, Semenova AI, Orlova RV. Vozmozhnosti kapetsitabina (kselody) v lechenii bol'nykh rasprostranennym formami solidnykh opukholei [The potential of capecitabine (xeloda) in the treatment of disseminated solid tumors]. *Vopr Onkol* 2001;**47**:112–19.

161. Mokbel K. The Twenty-third Annual San Antonio Breast Cancer Symposium. *Curr Med Res Opin* 2001;**16**:276–84.

162. Mross K, Semsek D. Neue antitumorale wirkstoffe. *Klinikarzt* 1998;**27**:150–4.

163. Nelson NJ. Trial data lacking for elderly patients with breast cancer. *J Natl Cancer Inst* 2000; **92**:1968–9.

164. Olencki T, Pratt S, Budd GT, Peereboom DM, McClain D, Bukowski RM. Phase I trial of capecitabine and subcutaneous interferon-alpha in renal cell carcinoma (RCC) [meeting abstract 855]. *Proc Annu Meet Am Soc Clin Oncol* 1999;**18**:222a.

165. Paridaens R, Clement P. Nieuwe ontwikkelingen bij de behandeling van borkstkanker. *Tijdschr Geneeskd* 2001;**57**:801–8.

166. Park JW, Tripathy D, Campbell MJ, Esserman LJ. Biological therapy of breast cancer. *BioDrugs* 2000; **14**:221–46.

167. Pazdur R. Investigational New Drugs: the Journal of New Anticancer Agents: introduction. *Invest New Drugs* 2000;**18**:297–8.

168. Piccart M, Rubens R, Howell A, Martin C, Foster H, Robertson J. New cytotoxic agents. *Cancer Treat Rev* 1997;**23**:S59–67.

169. Piccart MJ, Awada A. State-of-the-art chemotherapy for advanced breast cancer. *Semin Oncol* 2000;**27**:3–12.

170. Piccart Gebhart MJ. Introduction. *Anti-cancer Drugs* 2001;**12**:S1–2.

171. Portyansky E. Targeted breast cancer drug offers better tolerability profile. *Drug Topics* 1998;**142**:25.

172. Portyansky E. Flood of new research brings hope to many cancer patients. *Drug Topics* 1998;**142**:37.

173. Possinger K, Schmid P. Neue substanzen zur therapie des mammakarzinoms. Standards auf dem prufstand. *Onkologe* 2000;**6**:392–409.

174. Pusztai L, Tanyi J, Hortobagyi GN. Current status of the cytotoxic treatment of breast cancer. *CME J Gynecol Oncol* 2000;**5**:373–81.

175. Rochlitz C. Adjuvante systemtherapie des mammakarzinoms-prognostische und pradiktive faktoren. *Swiss Surg* 1999;**5**:222–7.

176. Saeki T, Takashima S. [Mechanism and possible biochemical modulation of capecitabine (Xeloda), a newly generated oral fluoropyrimidine]. *Gan To Kagaku Ryoho* 1999;**26**:447–55.

177. Salvini P, Ripa C, Ginanni V. Il carcinoma metastatico della mammella: quali obiettivi? *Tumori* 2000;**86**:S22–8.

178. Sasaki T, Maeda Y. [Capecitabine – a review of its antitumor activity and toxicity in clinical studies]. *Gan To Kagaku Ryoho* 2000;**27**:1307–13.

179. Schilsky RL. Recent advances in oral fluoropyrimidine therapies: introduction. *Oncology (Huntingt)* 1998;**12**:9–11.

180. Schilsky RL. Pharmacology and clinical status of capecitabine. *Oncology (Huntingt)* 2000; **14**:1297–306.

181. Schmid P, Possinger K. Neue therapiestrategien beim fortgeschrittenen mammakarzinom. Palliativmassnahmen werden immer vertraglicher [Advanced breast cancer. Palliative measures are becoming ever more tolerable]. *MMW Fortschr Med* 2000;**142**:22–4.

182. Schmid P, Fritz J, Possinger K. Behandlungsoptionen beim metastasierten Mammakarzinom. *Internist Prax* 2001;**41**:319–32.

183. Schmoll HJ. Vorwort. *Onkologie* 2000;**23**:V–VI.

184. Slater S. Non-curative chemotherapy for cancer: is it worth it? *Clin Med* 2001;**1**:220–2.

185. Slezak M. Xeloda, herceptin offer breast cancer hope. *Am Drug* 1998;**215**:20–1.

186. Smorenburg CH, Sparreboom A, Bontenbal M, Verweij J. Combination chemotherapy of the taxanes and antimetabolites: its use and limitations. *Eur J Cancer* 2001;**37**:2310–23.

187. Sulkes A. From 5 fluorouracil to the new oral fluoropyrimidines: a brief overview of four decades of clinical investigations. *Isr Med Assoc J* 2001; **3**:278–81.

188. Takahashi H, Maeda Y, Watanabe K, Taguchi K, Sasaki F, Todo S. Correlation between elevated intratumoral thymidine phosphorylase and prognosis of node-positive breast carcinoma undergoing adjuvant doxifluridine treatment. *Int J Oncol* 2000;**17**:1205–11.

189. Tanaka C, Toi M. [Capecitabine for treatment of advanced breast cancers]. *Nippon Rinsho* 2000; **58** Suppl:279–83.

190. Timmerman D. Positive results achieved with new oral chemotherapy agent. *Oncol Nurs Forum* 1999; **26**:675.

191. Toi M, Tominaga T, Abe O, Ohashi Y, Uchino J, Hayasaka H, *et al*. Role of thymidine phosphorylase for predicting the prognosis and therapeutic effects of 5′-deoxy-5-fluorouridine, an intermediate form of capecitabine, in early breast cancer patients; findings from a randomized controlled trial. 2001. URL: http://www.asco.org/prof/me/html/01abstracts/0009/120.htm. Accessed 14 May 2002.

192. Tominaga T. [Progress in breast cancer treatment over a quarter of a century]. *Gan To Kagaku Ryoho* 1999;**26** Suppl 1:99–109.

193. Tominaga T, Ouchi K, Tanaka Y. Schedule-dependency of antitumor activity in combination therapy with capecitabine/doxifluridine and docetaxel in breast cancer models [meeting abstract]. *Breast Cancer Res Treat* 2000;**64**:86.

194. Twelves C, Glynne Jones R, Cassidy J, Schuller J, Goggin T, Roos B, *et al*. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. *Clin Cancer Res* 1999;**5**:1696–702.

195. Valgus JM. Emerging therapies for breast cancer. *Cancer Pract* 1999;**7**:100–3.

196. Vardy J. Capecitabine (Xeloda®). *Cancer Forum* 2001;**25**:156–7.

197. Wagner U. Hallelujaubung und hochdosis-chemotherapie. *Pharm Ztg* 1998;**143**:41–2.

198. Wenzel C, Schmidinger M, Huber H. Gibt es fortschritte in der medikamentosen therapie von patientinnen mit mammakarzinom [A review of the current breast cancer trials]. *Wien Klin Wochenschr* 2001;**113**:306–20.

199. Wilke H. Future treatment options with capecitabine in solid tumours. *Eur J Cancer* 2002;**38**:S21–5.

200. Wolf E. Capecitabin zur peroralen tumortherapie. *Pharm Ztg* 2001;**146**:25.

201. Yoshimoto M, Takahashi K, Saito M, Tada T, Makita M, Kasumi F. Oral combination chemotherapy of 5′-deoxy-5-fluorouridine (5′-DFUR, furtulon) and cyclophosphamide (CPA) for metastatic breast cancer (MBC) [meeting abstract 401]. *Proc Annu Meet Am Soc Clin Oncol* 1999;**18**:106a. URL: http://www.asco.org/prof/me/html/99abstracts/bc/m_401.htm

Appendix 1

Search strategy

The core search strategy used for this review was as follows:

capecitabine
xeloda
#1 or #2
explode "Breast-Neoplasms"/ all subheadings
breast* near4 (cancer* or tum?r or malignanc*)
breast* near4 (oncolog* or carcinoma* or neoplas*)
#4 or #5 or #6
#3 and #7

This strategy was designed for searching the MEDLINE electronic database (on Silverplatter), and was adapted as appropriate for all other databases searched, taking into account differences in indexing terms and search syntax for each database. Search strategies were not designed to restrict the retrieved results by study type. In total, 336 references were retrieved.

Full details of all databases searched and search strategies used are provided below.

BIOSIS

Via Edina 1985 to May 2002. Searched 13 May 2002:

(capecitabine or xeloda)
and
((breast* neoplasm*) or (breast* cancer*) or (breast* tumour*) or (breast* tumor*) or (breast* oncolog*) or (breast* carcinoma*) or (breast* malign*))

CancerLit

Via Silverplatter 1996 to May 2002. Searched 13 May 2002:

capecitabine
xeloda
#1 or #2
explode "Breast-Neoplasms"/ all subheadings
breast* near4 (cancer* or tum?r or malignanc*)
breast* near4 (oncolog* or carcinoma* or neoplas*)
#4 or #5 or #6
#3 and #7

CCTR

Via Cochrane Library, 2002, Issue 2. Searched 13 May 2002:

capecitabine
xeloda
#1 or #2
explode "breast-cancer"/ all subheadings
breast* near4 (cancer* or tum?r or malignanc*)
breast* near4 (oncolog* or carcinoma* or neoplas*)
#4 or #5 or #6
#3 and #7

CINAHL

Via Silverplatter, 1982–2002/03. Searched 13 May 2002:

capecitabine
xeloda
#1 or #2
explode “Breast-Neoplasms”/ all topical subheadings / all age subheadings
breast* near4 (cancer* or tum?r* or malignanc*)
breast* near4 (oncolog* or carcinoma* or neoplasm*)
#4 or #5 or #6
#3 and #7

Conference Papers Index

Via Dialog, 1973 to May 2002. Searched 14 May 2002:

s capecitabine
s xeloda
s s1 or s2
s breast?(4w)(cancer? Or tumor? Or tumour? Or malignanc?)
s breast?(4w)(oncolog? Or carcinoma? Or neoplasm?)
s s4 or s5
s s3 and s6

DARE

The administrative version, rather than the public version, of this database was searched. Searched 13 May 2002:

Capecitabine
Xeloda
1 or 2
breast*(w)cancer*
breast*(w)tumor*
breast*(w)tumour*
breast*(w)malignanc*
breast*(w)oncolog*
breast*(w)carcinoma*
breast*(w)neoplasm*
4 or 5 or 6 or 7 or 8 or 9 or 10
3 and 11

EMBASE

Via Silverplatter 1988 to 2002/03. Searched 13 May 2002:

capecitabine
xeloda
#1 or #2
explode "breast-cancer"/ all subheadings
breast* near4 (cancer* or tum?r or malignanc*)
breast* near4 (oncolog* or carcinoma* or neoplas*)
#4 or #5 or #6
#3 and #7

HTA database

The administrative version, rather than the public version, of this database was searched. Searched 13 May 2002:

Capecitabine
Xeloda
1 or 2
breast*(w)cancer*
breast*(w)tumor*
breast*(w)tumour*
breast*(w)malignanc*
breast*(w)oncolog*
breast*(w)carcinoma*
breast*(w)neoplasm*
4 or 5 or 6 or 7 or 8 or 9 or 10
3 and 11

HealthStar

Via http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?, 1966 to May 2002. Searched 13 May 2002:

Capecitabine or xeloda
(breast* cancer*) or (breast* tumor*) or (breast tumour*) or (breast malignanc*) or (breast* oncolog*) or (breast* carcinoma*) or (breast* neoplasm*)
"breast neoplasms"[MESH]
#2 OR #3
#1 AND #4

ISTP

Via MIMAS, 1990 to May 2002. Searched 13 May 2002:

(capecitabine or xeloda)
and
((breast* cancer*) or (breast* neoplasm*) or (breast tum?r*) or breast* oncolog*) or (breast* carcinoma*) or (breast* malignanc*))

MEDLINE

Via Silverplatter 1966 to May 2002 April week 4. Searched 13 May 2002:

capecitabine
xeloda
#1 or #2
explode "breast-cancer"/ all subheadings
breast* near4 (cancer* or tum?r or malignanc*)
breast* near4 (oncolog* or carcinoma* or neoplas*)
#4 or #5 or #6
#3 and #7

NHS EED

The administrative version, rather than the public version, of this database was searched. Searched 13 May 2002:

Capecitabine
Xeloda
1 or 2
breast*(w)cancer*
breast*(w)tumor*
breast*(w)tumour*
breast*(w)malignanc*
breast*(w)oncolog*
breast*(w)carcinoma*
breast*(w)neoplasm*
4 or 5 or 6 or 7 or 8 or 9 or 10
3 and 11

SCI

Via MIMAS 1981 to May 2002. Searched 13 May 2002:

(capecitabine or xeloda)
and
((breast* cancer*) or (breast* neoplasm*) or (breast* tum?r*) or (breast* oncolog*) or (breast* carcinoma*) or (breast* malignanc*)

OHE HEED

CD-ROM produced by the Office of Health Economics, May 2002 issue. Searched 13 May 2002:

(capecitabine or xeloda)

Searches for ongoing trials

Searches of the trials registers listed below were carried out for information about ongoing trials.

National Research Register

CD-ROM 2001 Issue 1. Searched 13 May 2002:

capecitabine
xeloda
#1 or #2
explode "breast-cancer"/ all subheadings
breast* near4 (cancer* or tum?r or malignanc*)
breast* near4 (oncolog* or carcinoma* or neoplas*)
#4 or #5 or #6
#3 and #7

UKCCCR Register

(http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html)
Searched 14 May 2002.

National Cancer Institute

(http://cancernet.nci.nih.gov/trialsrch.shtml)
Searched 14 May 2002.

National Institutes of Health

(http://clinicaltrials.gov/ct/gui/c/r)
Searched 14 May 2002.

CenterWatch Clinical Trials Listing Service

(http://www.centerwatch.com/main.htm)
Searched 14 May 2002

Current Controlled Trials

(http://www.controlled-trials.com/)
Searched 14 May 2002.

American Society of Clinical Oncology

(http://www.asco.org/)
Searched 14 May 2002.

NCIC

(http://www.ctg.queensu.ca/)
Searched 14 May 2002.

EORTC

(http://www.eortc.be/)
Searched 14 May 2002.

Appendix 2

Staging of breast cancer (adapted from Harris and colleagues, 1992[105])

The tumour, node, metastases TNM system is an internationally recognised staging system for cancer of the breast. The system is based on the extent of the tumour, the involvement of the lymph nodes and the presence of metastases.

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 fixed or to other structures
	N3	Metastases to ipsilateral internal mammary lymph nodes
M	M0	No evidence of distant metastasis
	M1	Distant metastases

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 3

Hand–foot syndrome grading scale

The following scale applies only for grading hand–foot syndrome and not for describing any other skin event and/or cutaneous area (taken from Blum, 1999[62]).

Grade	Clinical domain[a]	Functional domain
1	Numbness, dysaesthesia/paraesthesia, tingling, painless swelling or erythema	Discomfort that does not disrupt normal activities
2	Painful erythema, with swelling	Discomfort that affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

[a] In case of a discrepancy between the clinical and functional domains, the assigned grade should correspond to the most important intensity from one or the other domain.

Appendix 4

Details of data extraction

Clinical effectiveness data

Clinical effectiveness data will be extracted and entered into an Access database under the following headings:

[ ] indicates a list of options included in a pull-down box
( ) indicates a click on/off button, where on represents 'yes' and off 'no'
{ } indicates free text entered in a box.

Study details

- Name of trial {trial name, I.D. or 'not stated'}
- Endnote reference {endnote reference number}
- Primary source [database, handsearching, company submission]
- Author {i.e. Jones et al}
- Date {i.e. year of publication or date of interim data collection}
- Type of report [abstract, full manuscript, interim report]
- Type of study phase [phase II, phase III …, not stated)
- Comparison group included [placebo, alternative drug, unclear, not stated]
- Intervention 1 {i.e. drug(s) name(s)}
- Dose of intervention 1 {dose}
- Number of cycles of intervention 1 {number}
- Length per cycle of intervention 1 {length}
- Intervention 2 {i.e. drug(s) name(s)}
- Dose of intervention 2 {dose}
- Number of cycles of intervention 2 {number}
- Length per cycle of intervention 2 {length}
- Comments about interventions {summary of comments or 'none'}

Participants

- Inclusion/exclusion criteria {summary of trial inclusion/exclusion criteria}
- Previous treatment {summary of drugs or other treatments such as debulking, radiotherapy etc …}
- Refractory disease present after first treatment [yes, no, unclear, not stated, not applicable]
- Dominant site of metastatic disease {state whether visceral or non-visceral, summary of numbers and specific site such as lung, liver etc …}
- Age or age range of participants {age(s)}
- Other participant characteristics {summary of characteristics including: treatment-free interval, disease bulk, number of previous regimens, histology and performance status}
- Comments about participants {summary of comments or 'none'}

Numbers in conditions

- Number recruited or accrued {summary or 'not stated'}
- Length of follow-up after treatment finishes {summary or 'not stated'}
- Number and times of follow-up measurements {summary or 'not stated'}
- Attrition intervention 1 {summary of number involved and reasons for loss}
- Attrition intervention 2 {summary of number involved and reasons for loss}
- Per protocol analysis performed [yes, no, not stated, unclear]
- Comments {summary of comments or state 'none'}

Results (data for all outcomes specified in the protocol were entered in the following format)

- Outcome 1 {description of outcome measure}
- Intervention 1 baseline data {data for outcome 1}
- Intervention 2 baseline data { data for outcome 1}
- Intervention 1 follow-up data {data for outcome 1}
- Intervention 2 follow-up data {data for outcome 1}
- Comments on outcome 1 {summary of comments}
- Overall comments {summary of comments}

Economic evaluation data

Economic evaluation data will be extracted and entered into an Access form under the following headings:

[ ] indicates a list of options included in a pull-down box

( ) indicates a click on/off button, where on represents 'yes' and off 'no'
{ } indicates free text entered in a box.

- Endnote reference {in the form of xyz, no '#'}
- Primary source [database, handsearching, company submission]
- Author {i.e. Jones et al}
- Date {i.e. year of publication or date of interim data collection}
- Type of economic evaluation [cost effectiveness analysis, cost utility analysis, cost benefit analysis]
- Currency used [$US, $AS, £Sterling …, not stated]
- Year to which costs apply {enter year or not stated}
- Perspective used [health service, societal, hospital, third party payer, patient, unclear]
- Study population {describe the population characteristics}
- Intervention 1 {description of intervention 1}
- Intervention 2 {description of intervention 2}
- Source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of unit cost data [literature, data from actual source, not stated]
- Link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected …]
- Clinical outcomes measured and methods of valuation used {summary of outcomes and valuation methods used}
- Cost data handled appropriately {summary of methods used to e.g. discount, inflate}
- Modelling {summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs}
- Outcome measures used in economic evaluations {summary of outcome measures used in economic evaluations e.g. incremental cost-effectiveness ratio, net benefit, cost-effectiveness acceptability curve}
- Direction of result with appropriate quadrant location
- Statistical analysis for patient-level stochastic data {summary of analyses used}
- Appropriateness of statistical analysis {comment on appropriateness}
- Uncertainty around cost-effectiveness expressed
- Appropriateness of method of dealing with uncertainty around cost-effectiveness
- Sensitivity analysis {list summary of analysis}
- Appropriateness of sensitivity analysis {comment on appropriateness}
- Modelling inputs and techniques appropriate
- Author's conclusions {list as in publication}
- Implications for practice {summary of implications}
- Comments {summary of comments}

Appendix 5

Details of quality assessment

Clinical effectiveness

Studies of clinical effectiveness were assessed using the following criteria, based on CRD Report No.4[14]:

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

Items were graded in terms of: ✓: yes (item properly addressed); ×: no (item not properly addressed); ✓/×: partially (item partially addressed); ?: unclear or not enough information; or NA: not applicable.

Cost-effectiveness

Studies of cost-effectiveness were assessed using the following criteria, based on an updated version of the checklist developed by Drummond and colleagues[15]:

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 any important alternatives omitted?
   - 2.2 Was (should) a *do-nothing* alternative (be) considered?

3. Was the effectiveness of the programmes 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 established 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 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 costs 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 which occur in the future 'discounted' to their present values?
   - 7.2 Was 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 or consequences were stochastic, were appropriate statistical analyses performed?
   - 9.2 If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?
   - 9.3 Were 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 6

Limitations of uncontrolled trials as a source of data to assess the effectiveness of clinical interventions

For the assessment of the clinical effectiveness of capecitabine monotherapy, no RCTs comparing capecitabine with vinorelbine or best supportive care were identified. All of the studies identified were uncontrolled, that is they did not use a 'no treatment' or alternative treatment group for comparison. The intrinsic weakness of this study design means that all of the included studies suffered from a number of methodological flaws, which could bias their findings.

When investigating the effectiveness of an intervention it is important to be aware that the observed effect may be due actually not to the therapeutic intervention itself but to confounding factors and other sources of bias. The RCT is the principal research design in the evaluation of medical interventions.[106] Bias either exaggerates or underestimates the 'true' effect of an intervention.[14] Undertaking a well-designed RCT minimises bias. With regard to systematic reviews, Egger and colleagues comment that "based on a group of sensibly combined and representative randomised trials (a systematic review) will provide an essentially unbiased estimate of the treatment effect, with an increase in the precision of this estimate".[106]

Confounding and bias

The validity of uncontrolled trials may be affected by confounding and other biases, including selection bias, measurement bias and attrition bias.

Without a control group it is difficult to ascertain whether the observed effect was due to the intervention under investigation. The observed effect may be influenced by the natural progression of the disease, extraneous factors including lifestyle, the use of other medications, or even a placebo effect.[107] Furthermore, deciding who will receive treatment in an uncontrolled trial is influenced by many factors, including prognosis. The effect of selection bias and confounding is difficult to assess, particularly when the selection of patients in the trials is not clear. In an uncontrolled study it may be possible to take into account confounders that are known, but only randomisation of patients to treatment and an appropriate control can take account of confounders that are not known or cannot be measured.

Outcome assessment cannot be blinded in uncontrolled studies; therefore, there is the potential for measurement bias, particularly in the measurement of subjective outcomes such as response. Biased assessment may lead to the researchers reporting a more or less favourable outcome then the true effect.

Attrition bias occurs when not all of the patients included in the trial are accounted for in the analyses. This applies to controlled as well as uncontrolled trials; however, uncontrolled studies allow no comparison of the extent of dropout or exclusion, or the reasons for it, between the treatment under investigation and an appropriate control.

All of the trials investigating capecitabine monotherapy were vulnerable to these biases. In particular, the lack of a control group meant that the observed effects on survival, response and the other outcomes reported in the trials could not confidently be attributed solely to treatment with capecitabine. In addition, the measurement of tumour response was subjective, with the potential for measurement bias. The majority of the included studies were only published as conference abstracts and therefore how patients were selected for the trials, and whether all patients had been included in the analyses, was often unclear.

Circumstances where uncontrolled studies may be used as an alternative to RCTs

Capecitabine monotherapy was licensed on the basis of results from uncontrolled, Phase II studies.

The primary aim of Phase II studies is to determine whether a drug is efficacious and whether it is safe to use. Assessing the benefit–risk balance with Phase II cancer trials may be difficult for the following reasons: the effect of the drug is usually temporary, the correlation between response or improvement in clinical measurements and patient well-being is often poor, and the side-effects of drugs are often serious.[108] However, there may be circumstances where it is not feasible to conduct an RCT and, therefore, uncontrolled studies that evaluate the efficacy of a new drug may be considered as an alternative. Researchers involved in trials on the acquired immunodeficiency syndrome (AIDS) in the early 1990s proposed a list of criteria that should be met before uncontrolled studies are considered as an alternative to RCTs:[109]

1. There must be no other treatment appropriate to use as a control.
2. There must be sufficient experience to ensure that the patients not receiving therapy will have a uniformly poor prognosis.
3. The therapy must not be expected to have substantial side-effects that would compromise the potential benefit to the patients.
4. There must be a justifiable expectation that the potential benefits to the patients will be sufficiently large to make interpretation of the results of a non-randomised trial unambiguous.
5. The scientific rationale for the treatments must be sufficiently strong that a positive result would be widely accepted.

With regards to capecitabine, criteria 2 and 5 apply, but whether the rest of the criteria are met is debatable. Criterion 1 may possibly be met as there is currently no established therapy in this group of heavily pretreated patients, although vinorelbine and best supportive care were accepted as suitable comparators for this assessment. However, some researchers are critical of the use of best supportive care or placebo as a control treatment in this population, seeing it as unethical. Criteria 3 and 4 are not met. Capecitabine therapy is associated with substantial side-effects, particularly hand–foot syndrome, and in a population of heavily pretreated patients the benefits are not expected to be large.

Conclusions

Owing to the limitations of using uncontrolled studies for assessing effectiveness, conclusions about the therapeutic benefit of capecitabine monotherapy based on uncontrolled trials should be approached with extreme caution. This type of study design is extremely vulnerable to various sources of bias, none of which is easy to account for and all of which have the potential to distort the true effect of capecitabine monotherapy.

RCTs remain the gold-standard for the assessment of effectiveness. The justification for not conducting RCTs in this advanced cancer population is questionable.

Appendix 7

List of excluded studies and reason for exclusion

Study details	Reason for exclusion
Ahn Sr (2002)[21]	Capecitabine in combination with vinorelbine
Angiolini (2000)[30]	Capecitabine in combination with epirubicin and docetaxel
Anon (1997)[110]	Not a clinical study, short report on the structure and action of capecitabine. In German
Anon (1998)[111]	Short report on FDA approval of capecitabine
Anon (1998)[112]	News report on FDA approval of oral capecitabine
Anon (1998)[113]	News report on capecitabine
Anon (2000)[114]	Research report on capecitabine
Anon (2000)[115]	News report on capecitabine and breast cancer
Anon (2000)[116]	Non-systematic review of capecitabine in breast cancer
Anon (2000)[117]	Article about new therapies in oncology
Anon (2000)[118]	Short overview on capecitabine
Anon (2001)[119]	Short news report of study results
Anon (2001)[120]	News report on capecitabine/docetaxel combination therapy. In German
Anon (2001)[121]	News article about capecitabine/docetaxel combination. In German
Anon (2001)[122]	Short news report of study results
Anon (2001)[123]	Product update on capecitabine
Anon (2001)[124]	News report on capecitabine/docetaxel combination. In German
Anon (2002)[125]	News report on FDA approval of capecitabine/docetaxel combination
Awada (2000)[126]	Non-systematic review of current therapies for breast cancer. In French
Baran (2002)[57]	Economic evaluation. Patients had not been pretreated with anthracyclines
Bell (2001)[50]	Case study: report of treatment-limiting side-effect
Beltz (1998)[58]	Economic evaluation: was not an evaluation of capecitabine
Bertolini (2001)[51]	Case study
Borquez (1999)[127]	Non-systematic review of therapies for metastatic breast cancer. In German
Brito (1999)[128]	Non-systematic review of the fluoropyrimidines
Budman (1998)[48]	Mixed group of patients. Phase I dose-finding study
Bunnell (1998)[129]	Overview of 5-FU analogues in breast cancer
Carbone (2000)[130]	Non-systematic review of systemic cancer treatment in the elderly
Cassata (2001)[131]	Non-systematic review of indications and future perspectives for capecitabine
Chen (2001)[52]	Case study: report of onychomadesis and onycholysis
Chernin (1999)[132]	Non-systematic review of combination therapies
Cole (1999)[133]	Not a clinical study. Describes the role of thymidine phosphorylase in cancer chemotherapy
Crown (2001)[134]	Overview of non-anthracycline containing docetaxel-based regimens
Danova (2001)[135]	Non-systematic review of medical strategies for MBC
Dees (1998)[136]	Overview of recent advances in systemic therapy for breast cancer
Del Vecchio (1999)[137]	Non-systematic review of the role of UFT (a combination of tegafur and uracil)
Diasio (1999)[138]	Non-systematic review of the novel orally administered fluoropyrimidines
Diasio (2002)[139]	Editorial about oral fluropyrimidine drugs
Domenech (2001)[19]	Study evaluated capecitabine in combination with vinorelbine
Donaldson (2002)[32]	Capecitabine in combination with carboplatin and vinorelbine

continued

Study details	Reason for exclusion
Frings (1998)[140]	Non-systematic review of capecitabine
Fujimoto Ouchi (2001)[141]	Study to identify the optimal administration schedule in combination therapy with capecitabine/docetaxel in human cancer xenograft models
Galligioni (2001)[142]	Not an original trial; article reports results of three docetaxel combination trials, including docetaxel/capecitabine (O'Shaughnessy *et al*.). In Italian
Ghosn (2002)[22]	Capecitabine in combination with vinorelbine
Gieschke (1999)[143]	Population pharmacokinetic for capecitabine based on a Phase II study
Gradishar (2001)[144]	Non-systematic review of clinical status of capecitabine in the treatment of breast cancer
Guthrie (1999)[38]	High dose chemotherapy and autologous peripheral stem cell therapy. Does not report how many patients had been pretreated with taxanes and/or anthracyclines
Harstrick (2000)[145]	Non-systematic review of treatment options for capecitabine
Hess (2002)[20]	Capecitabine in combination with vinorelbine
Hori (2000)[146]	Randomised controlled study comparing a combination of doxifluradine, medroxyprogesterone acetate, and cyclophosphamide DMpC therapy with a standard regimen
Hoshi (1996)[147]	Short report on the chemical make-up of capecitabine
Ignoffo (1998)[148]	Non-systematic review/update on capecitabine
Ignoffo (1999)[149]	Update on treatment of colorectal cancer
Ilersich (2001)[42]	Postmarketing surveillance of capecitabine. Does not report how many patients were pretreated with taxanes or anthracyclines
Johnston (2001)[150]	Non-systematic review of capecitabine treatment of solid tumours
Kaye (1998)[151]	Non-systematic review of new antimetabolites for cancer
Kaye (2002)[152]	Short article on new paradigms in the treatment of colorectal and breast cancer
Khoury (1998)[23]	Capecitabine used in combination with paclitaxel, i.e. it is not used in accordance with its licensed indication
Kusama (2001)[39]	Patients had not failed taxane and anthracycline therapy, i.e. study is not in accordance with licensed indication
Levin (2000)[153]	Article about the clinical development of eniuracil/fluorouracil
Lewis (2000)[154]	Non-systematic review of oral fluoropyrimidines in cancer treatment
Mader (2001)[155]	Study of the penetration of capecitabine and its metabolites into malignant and healthy tissue
McVie (2001)[156]	Report on the European Medicines Evaluation Agency (EMEA) approval of cancer drugs
Mevissen (2000)[157]	News article about therapies for breast cancer. In German
Michaud (2000)[43]	Postmarketing investigation of capecitabine use. Does not report how many patients were pretreated with taxanes and/or anthracyclines
Miwa (1998)[158]	Study investigated tissue localisation of three enzymes required for capecitabine activation
Mlineritsch (2001)[159]	Short report about capecitabine
Moiseenko (2000)[36]	Patients had not failed taxane therapy, i.e. not in accordance with licensed indication for cap monotherapy
Moiseenko (2001)[160]	Non-systematic review about capecitabine. In Russian
Moiseyenko (1998)[34]	Regimen does not fit into licensed indication. Patients were given capecitabine monotherapy but had not failed taxane therapy
Moiseyenko (1998)[37]	Phase II study of capecitabine vs paclitaxel
Mokbel (2001)[161]	Review paper summarising the topics at the 23rd Annual San Antonio Breast Cancer Symposium
Mross (1998)[162]	Non-systematic review of antitumour drugs. In German
Nelson (2000)[163]	News article: reports future cancer trials in elderly patients
Nole (2000)[18]	Study evaluated capecitabine in combination with vinorelbine
Olencki (1999)[164]	Phase I study of capecitabine in renal cell carcinoma
O'Reilly (1998)[35]	Patients had not failed taxane-containing therapy, i.e. study is not in accordance with licensed indication

Appendix 7 cont'd *List of excluded studies and reason for exclusion*

Study details	Reason for exclusion
O'Shaughnessy (2001)[44]	Capecitabine is used as first-line therapy versus CMF, and hence not in accordance with the licensed indication
Paridaens (2001)[165]	Non-systematic review of new developments in the treatment of breast cancer
Park (2000)[166]	Review of biological therapies for breast cancer
Pazdur (2000)[167]	Introduction to series of articles about anticancer drugs
Perez-Manga (2000)[24]	Capecitabine is used in combination with paclitaxel, i.e. it is not used in accordance with its licensed indication
Piccart (1997)[168]	Overview of new cytotoxic cancer agents
Piccart (2000)[169]	Non-systematic review chemotherapy for advanced breast cancer
Piccart Gebhart (2001)[170]	Introduction to symposium
Portyansky (1998)[171]	News report on capecitabine
Portyansky (1998)[172]	News article on new cancer drugs
Possinger (2000)[173]	Non-systematic review about new therapies for breast cancer. In German
Procopio (2001)[41]	Patients were not reported to have failed previous taxane therapy or anthracyclines
Pronk (1998)[45]	Mixed group of patients. Dose-finding and pharmacokinetic study
Pronk (2000)[46]	Mixed group of patients. Dose-finding and pharmacokinetic study
Pusztai (2000)[174]	Non-systematic review of cytotoxic agents for breast cancer
Rochlitz (1999)[175]	Non-systematic review of adjuvant systemic therapies for breast cancer. In German
Saeki (1998)[40]	Patients were not reported to be taxane resistant or refractory
Saeki (1999)[176]	Article about the mechanism and biomodulation of capecitabine. In Japanese
Salvini (2000)[177]	Non-systematic review of therapies for metastatic breast cancer. In Italian (English abstract)
Sasaki (2000)[178]	Review of the antitumour activity of capecitabine in colorectal cancer. In Japanese
Schilsky (1998)[179]	Overview of recent advances in oral fluoropyrimidine therapies
Schilsky (2000)[180]	Non-systematic review of the pharmacology and clinical status of capecitabine
Schmid (2000)[181]	Short article about new therapies for ABC. In German
Schmid (2001)[182]	Non-systematic review of treatment options for metastatic breast cancer. In German
Schmid Wendtner (2001)[53]	Case study: report of leopard-like vitiligo
Schmoll (2000)[183]	Foreword to series of articles in *Onkologie*. In German
Scnetzler (2001)[56]	Case study: report of a coronary spasm
Slater (2001)[184]	Conference report of discussion of non-curative chemotherapy
Slezak (1998)[185]	News report on capecitabine and herceptin
Smorenburg (2001)[186]	Non-systematic review of taxane combination therapies
Sulkes (2001)[187]	Brief overview of advances in fluoropyrimidine therapy
Takahashi (2000)[188]	Study about correlation of thymidine phosphorylase and prognosis of breast cancer
Talbot (2002)[33]	Patients in capecitabine group had not failed taxane-containing therapy, i.e. study is not in accordance with licensed indication
Tanaka (2000)[189]	Non-systematic review of capecitabine therapy. In Japanese
Timmerman (1999)[190]	News report
Toi (2001)[191]	Open-label multicentre randomised trial comparing 5′-DFUR and surgery alone
Tominaga (1999)[192]	Non-systematic review of progress in breast cancer therapy. In Japanese
Tominaga (2000)[193]	Study of capecitabine/doxifluridine and docetaxel in breast cancer models
Twelves (1999)[194]	Study to investigate the effect of hepatic dysfunction on pharmacokinetics of capecitabine
Valgus (1999)[195]	Non-systematic review of new therapies for breast cancer
Vardy (2001)[196]	Non-systematic review of capecitabine
Vasey (1997)[49]	Phase I and pharmacokinetic study. Mixed group of patients
Venturini (2000)[31]	Dose-finding study of docetaxel and epirubicin combined with capecitabine

Appendix 7 cont'd *List of excluded studies and reason for exclusion*

Study details	Reason for exclusion
Venturini (2002)[29]	Study evaluated the addition of capecitabine to epirubicin/docetaxel combination therapy as first-line treatment for ABC
Villalona-Calero (2001)[27]	Phase I study of capecitabine and paclitaxel
Villalona-Calero (2000)[47]	Phase I study of patients with mixed solid malignancies
Villalona-Calero (1998)[26]	Phase I study of capecitabine in combination with paclitaxel
Villalona-Calero (1998)[25]	Capecitabine in combination with paclitaxel
Villalona-Calero (1999)[28]	Phase I study of capecitabine in combination with paclitaxel. Mixed group of patients
Wagner (1998)[197]	Article about high-dose chemotherapy and alternative medicine. In German
Walkhom (2000)[54]	Case report: ocular irritation and corneal deposits
Wang (2001)[55]	Case study
Welt (2001)[17]	Phase I study of capecitabine combined with vinorelbine
Wenzel (2001)[198]	Non-systematic review of current breast cancer trials. In German
Wilke (2002)[199]	Non-systematic review of future treatment options with capecitabine
Wolf (2001)[200]	News report on capecitabine
Yoshimoto (1999)[201]	Combination of 5′-DFUR and cyclophosphamide for MBC

FDA, US Food and Drug Administration; MBC, metastatic breast cancer; ABC, advanced breast cancer; 5′-DFUR, 5′-deoxy-5-fluorouridine.

Appendix 8

Studies awaiting assessment

Author (year)	Title
Liu (2002)[87]	[Capecitabine (Xeloda) in the treatment of relapsed and metastatic breast cancer] (English abstract)
Semiglazov (2001)[88]	Kseloda (kapetsitabin) v lechenii disseminirovannogo raka molochnoi zhelezy [Xeloda (capecitabine) and disseminated breast cancer treatment] (English abstract)

Appendix 9

Data extraction tables for clinical effectiveness studies

Capecitabine monotherapy

Uncontrolled Phase II studies

Study details	Participant details	Intervention details	Withdrawals/adverse events
Blum (1999)[62] Interim results published as Blum (1998).[63] Updated results published as Blum (2001)[64] were used to supplement the full paper **Length of follow-up** ≥ 48 weeks **No. and times of follow-up measurements** Tumour assessments were undertaken at weeks 7, 13 and 19. During the maintenance period, tumour assessments were made every 12 weeks and at withdrawal	**No. of participants** 163 patients were enrolled (162 patients received treatment) **Age range** Mean 55.8 (range 26–78) years **Inclusion/exclusion criteria** *Inclusion criteria*: female patients, age 18 or older, who were ambulatory, KPS status of 70% or higher, and had bidimensionally measurable or assessable, histologically or cytologically confirmed MBC. Histological confirmation of a single metastatic site was required. Patients with prior radiotherapy were eligible, provided that the indicator lesion(s) was outside the radiation field or represented recurrent lesions appearing in the radiation field. Patients were to have received at least two but not more than three previous chemotherapy regimens, one of which had to have contained paclitaxel as treatment for metastatic disease. Patients must have shown either primary resistance to paclitaxel (disease progression while receiving paclitaxel therapy) or response followed by progression while still on therapy (paclitaxel failure). Patients withdrawn from paclitaxel because of toxicities before an adequate trial were not eligible for this study. For patients who had received paclitaxel as a single agent, the initial dose of paclitaxel was required to be at least 175 mg/m^2 repeated every 3 weeks. Patients who had received high-dose chemotherapy with	**Intervention** Capecitabine *Dosage* 2510 mg/m^2 per day No. of cycles See below *Length per cycle* 3-week cycles (2 weeks, followed by 1 week rest) **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** Dose was calculated according to body surface area at baseline (not recalculated for weight change). Total daily dose was split into equal morning and evening doses. Administered orally in two divided doses, 12 hours (± 2 hours) apart, within 30 minutes after a meal, with approximately 200 ml water Duration of treatment was based on tumour response. Patients with objective responses or stable disease	**Attrition** *Intervention* One patient was withdrawn because of rapidly progressive disease during screening and 8 patients had incomplete data for response to treatment *Comparator* NA **Adverse events/toxicity** *Summary of frequently reported treatment-related adverse events n (%)* **Adverse event** / **Grade**: **Total** / **1** / **2** / **3** / **4** Hand–foot syndrome: 91 (56.2) / 23 (14.2) / 52 (32.1) / 16 (9.9) / 0 Diarrhoea: 88 (54.3) / 35 (21.6) / 30 (18.5) / 18 (11.1) / 5 (3.1) Nausea: 84 (51.9) / 40 (24.7) / 37 (22.8) / 7 (4.3) / 0 Vomiting: 60 (37.0) / 29 (17.9) / 25 (15.4) / 6 (3.7) / 0 Fatigue: 59 (36.4) / 19 (11.7) / 28 (17.3) / 12 (7.4) / 0 Constipation: 25 (15.4) / 15 (9.3) / 8 (4.9) / 2 (1.2) / 0 Dermatitis: 25 (15.4) / 17 (10.5) / 6 (3.7) / 2 (1.2) / 0 Abdominal pain: 24 (14.8) / 6 (3.7) / 13 (8.0) / 5 (3.1) / 0 Decreased appetite: 18 (11.1) / 10 (6.2) / 7 (4.3) / 1 (0.6) / 0

continued

Study details	Participant details	Intervention details	Withdrawals/adverse events

autologous bone marrow or peripheral blood stem-cell rescue were eligible. Patients were to have a life expectancy of at least 3 months. Patients had to be willing and able to complete the Pain Assessment Questionnaire.

Exclusion criteria: pregnant or lactating patients, women of childbearing potential with a positive or no pregnancy test at baseline or who lacked a reliable contraceptive method, patients with rapidly progressing visceral (liver, lymphangitic, lung) involvement or with CNS metastatic disease at the time of enrolment, and patients with a history of dementia, seizures, CNS disorders, or psychiatric disability thought to be clinically significant in the opinion of the investigator and adversely affecting patient compliance with drug intake. Also excluded were patients who had experienced a prior severe and unexpected reaction to fluoropyrimidine therapy or had known sensitivity to 5-FU. Prior history of other malignancy with 5 years of study entry, aside from basal cell carcinoma of the skin or carcinoma *in situ* of the uterine cervix, precluded participation in the trial. Patients with organ allografts or with clinically significant cardiac disease as defined by symptomatic ventricular arrhythmias, history of congestive heart failure, or history of previous myocardial infarction within 12 months of study entry were excluded. Patients with lack of physical integrity of the upper gastrointestinal tract or known malabsorption were excluded. Significant stomach, small intestine, liver or kidney disease which may have affected the

(at study day 43) could continue to receive treatment in courses of 3 weeks, up to a total of 18 weeks (treatment period). Patients who maintained tumour response or stable disease beyond 18 weeks were allowed an additional 30 weeks (maintenance period). Patients who had not progressed at 48 weeks could continue treatment until disease progression (continuation period)

Dose modifications

Drug dosage was adjusted at any time during the study on the basis of grade ≥ 2 related adverse events as defined by the NCIC-CTC, Version 1.0. At first occurrence of grade 2 toxicity, treatment was interrupted and then resumed after resolution to grade 1 or better at the same dose, with prophylaxis where possible. Subsequent occurrences of the same grade 2 toxicity were managed by treatment interruption followed by 25% dose reduction. If grade 3 or 4 toxicity occurred, treatment was interrupted and followed by a 25% or 50% dose reduction. If the same grade 2 toxicity occurred for a third time, treatment was interrupted until resolved to grade 0–1 and then continued at 50% of the original dose. At the third occurrence of a given toxicity (grade 3), treatment was discontinued and the patient withdrawn. If recurrent grade 2 toxicity in the last 4 days of a 2-week treatment period resolved to grade

Pyrexia	18 (11.1)	11 (6.8)	6 (3.7)	1 (0.6)	0
Erythematous rash	17 (10.5)	10 (6.2)	7 (4.3)	0	0
Paraesthesia	16 (9.9)	9 (5.6)	7 (4.3)	0	0
Stomatitis	15 (9.3)	6 (3.7)	5 (3.1)	4 (2.5)	0
Mucosal inflammation	15 (9.3)	5 (3.1)	3 (1.9)	7 (4.3)	0
Dehydration	11 (6.8)	0	5 (3.1)	5 (3.1)	1 (0.6)
Coagulation disorder	1 (0.6)	0	0	0	1 (0.6)

No deaths were reported as being related to study treatment. The two most common adverse events leading to withdrawal from the study were abdominal pain (3 patients, 2%) and diarrhoea (3 patients, 2%). 6.8% of patients were withdrawn from the study owing to toxicity

Laboratory parameters were monitored in all 162 patients enrolled. Most laboratory values remained stable, or worsened at most by one or two grades. Grade 3 or 4 neutropenia occurred in 5 patients (3%), 1 patient with bone metastases developed grade 4 thrombocytopenia, and there 17 grade 3 or 4 bilirubin elevations (9 concomitant with liver metastases)

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events
	pharmacokinetics of the study drug was a reason for exclusion. Serious uncontrolled infections precluded participation in the study. Seropositivity for either hepatitis B surface antigen or hepatitis C or HIV type 1 antibodies precluded participation. Patients could not have received chemotherapy or hormonal treatment less than 3 weeks before study entry. Patients were required to have certain haematological values. **Characteristics** 135 patients had measurable disease and 27 had non-bidimensionally measurable but assessable disease **Previous treatment** All patients had received prior paclitaxel, 91% had received an anthracycline, and 82% had received a 5-FU-containing regimen Average number of prior systemic therapies for malignant disease: chemotherapeutic regimens: 2.5 chemotherapeutic agents: 4.7 hormonal therapies: 1.3 **Dominant site of metastatic disease** Majority of patients had widely disseminated metastatic breast cancer with a median of 3 organ/tissue sites (range 1–11 sites) involved with metastatic disease: Bone metastases: 54% liver metastases: 43% lung/pleural metastases: 58% soft-tissue disease: 23% visceral predominant disease: 110 (68%) predominantly soft tissue: 35 (22%) predominantly bony disease: 17 (10%)	0–1 within the rest period, the investigator could decide to continue treatment at same dose	

Study details	Participant details	Intervention details	Withdrawals/adverse events
	Refractory disease present after first treatment Yes **Comments** Patients first entered a 1-week run-in period, during which they were assessed for adequate pain control. Patients with no pain or stable pain intensity were entered into the study. Patients were prospectively stratified according to the presence of bidimensionally measurable versus assessable disease		

Results		
Outcome 1: Response to treatment	**Outcome 2: Stable disease**	**Outcome 3: Progressive disease**
Complete/partial response to treatment: 27/135 (20%) (measurable disease) (95% CI 14 to 28%) (3 CR and 24 PR) during treatment and maintenance periods Mean decrease in tumour size: 81% (median 86%) In patients with assessable and not measurable disease, 5/27 (19%) had a tumour response In a retrospectively defined subgroup of 42 patients with unequivocal clinical resistance to both paclitaxel and doxorubicin, the response rate was 29% (8 patients had incomplete data)	54 (40%) Mean decrease in tumour size: 27% Median survival time: 391 days	Progressive disease within first 6 weeks: 46 (34%)

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Results		
Outcome 4: Duration of response (*n* = 27)	**Outcome 5: Time to disease progression/survival**	**Outcome 6: Relationship between tumour response and survival**
Mean duration of response (*n* = 27 responders): 241 days (range 97–324 days, ongoing) In 11 patients, disease had not progressed at clinical cut-off In 3 patients with CR, PD occurred at days 106 and 109 for 2 patients and the third had CR at clinical cut-off For the majority of responders, onset of response occurred within 6–12 weeks of treatment For 27 patients with assessable and not measurable disease, the durations of response ranged from 161 to 235+ days	There were 135 cases of progressive disease or death Median time to disease progression: 93 days (95% CI 84 to 106 days) (3.0 months) Median overall survival (*n* = 162): 384 days (12.8 months)	In patients with measurable disease (*n* = 135), median survival time for those patients whose disease progressed by time of first tumour assessment was 163 days. Median survival time of patients with stable disease was 391 days
Outcome 7: CBR	**Additional results/comments:**	
Determined in 147 patients Overall CBR was positive in 20% patients (*n* = 29), stable in 30% (*n* = 45) and negative in 50% (*n* = 73)	Responders had the following characteristics: 10 (37%) had failed two prior therapeutic regimens and 17 (63%) had failed three regimens. All responders had been treated with paclitaxel. All had been treated with an anthracycline (doxorubicin 93%, and mitoxantrone 7%) either as neoadjuvant and adjuvant therapy (37%) or for metastatic disease (63%). 17 responders (63%) had been previously treated with 5-FU. Two responders (7%) had failed prior high-dose chemotherapy with bone-marrow rescue A retrospective analysis was conducted to evaluate the impact of dose modification on efficacy.[64] The dose was reduced to 75% of the starting dose after a median of 1.6 months in 45/162 patients (27%). A retrospective analysis demonstrated that patients requiring dose reduction for adverse events experienced no significant increase in risk of progression (HR 1.07, Wald test *p* = 0.73) compared with those not requiring dose reduction	
HIV: human immunodeficiency virus.		

Study details	Participant details	Intervention details	Withdrawals/adverse events
Blum (2001)[65] Interim findings were published as Blum (1999)[66] **Length of follow-up** ≤ 48 weeks **Number and times of follow-up measurements** Assessments were completed 1 and 2 weeks before treatment, and repeated at each cycle during the study period of ≤ 48 weeks Tumour assessment was performed by the investigator and the IRC at week 6 and then at 6-week intervals, and at time of withdrawal from the study	**No. of participants** 75 **Age range** Mean 52.4, SD 11.4 (range 29–77) years **Inclusion/exclusion criteria** *Inclusion*: ambulatory female patients, aged ≥ 18 years, KPS ≥ 70% and life expectancy ≥ 3 months. All patients had bidimensionally measurable or evaluable, histologically or cytologically confirmed advanced and/or MBC. Patients who had received prior radiotherapy were eligible, provided the indicator lesion(s) was outside the radiation field or represented a new or recurring lesion in a previously irradiated area *Exclusion*: pregnant or lactating patients; women of childbearing potential with a positive or no pregnancy test at baseline or who lacked a reliable method of contraception; patients with rapidly progressing visceral involvement or CNS metastases at time of enrolment; and patients with a history of seizures, CNS disorders or psychiatric disability. Any patient who had received >3 previous chemotherapy regimens (adjuvant and for advanced/metastatic disease) were excluded. Patients were also ineligible if they had received <2 courses of docetaxel, owing to toxicities. Patients who had experienced prior severe and unexpected reaction to fluoropyrimidine therapy or known hypersensitivity to 5-FU. Prior history of another malignancy within 5 years, patients with clinically significant cardiac disease (symptomatic ventricular arrhythmias, history of congestive heart	**Intervention** Capecitabine *Dosage* 1255 mg/m^2, twice daily *No. of cycles* ≤ 16 *Length per cycle* 3 weeks (2 weeks followed by 1 week rest) **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** Capecitabine dose was calculated on the basis of body surface area at baseline. Treatment was administered within 30 minutes of a meal with approximately 200 ml of water Patients with objective response or stable disease could continue to receive capecitabine treatment until PD or unacceptable toxicity **Dose modifications** Treatment was continued at the same dose unless patients experienced adverse events with a grade 2, 3 or 4 intensity as defined by the NCIC-CTC. At first occurrence of grade 2	**Attrition** *Intervention* One patient refused treatment at baseline *Comparator* NA **Adverse events/toxicity** The majority of patients (89.2%) experienced at least one adverse event; approximately 25% of all treatment-related adverse events were classified as grade 3 (23%) or grade 4 (2%) 15 patients (20%) were hospitalised for adverse events with a possible, probable or unknown relation to capecitabine. Total number of hospitalisations was 17, with median hospital stay duration of 7 days. No treatment-related deaths were reported. 9.5% of patients were withdrawn from the study owing to toxicity *Most common (≥ 10%), all grades, n (%)* Hand–foot syndrome 46 (62.2) Diarrhoea 43 (58.1) Nausea 41 (55.4) Emesis 27 (36.5) Stomatitis 25 (33.8) Fatigue 17 (23.0) Dehydration 11 (14.9) Anorexia 10 (13.5) *Grades 3 and 4 (≥ 5%), n (%)* **Adverse event** / **Grade 3** / **Grade 4** Hand–foot syndrome 16 (21.6) 0 Diarrhoea 12 (16.2) 2 (2.7) Stomatitis 9 (12.2) 0 Fatigue 6 (8.1) 0 Dehydration 5 (6.8) 0

Study details	Participant details	Intervention details	Withdrawals/Adverse events
	failure, history of previous myocardial infarction within 12 months), patients with a lack of physical integrity of the upper gastrointestinal tract or known malabsorption syndromes, patients with abnormal haematological values, and impaired renal or hepatic function **Characteristics** KPS status (%) Mean 88.3, SD 9.5 (range 70–100) **No. of prior anticancer regimens, n (%)** 1: 2 (2.7) 2: 23 (31.7) 3: 37 (50.0) ≥ 4: 12 (16.2) **Previous treatment** All but 2 patients had received ≥ 2 previous chemotherapy regimens (approx. 67% had received ≥ 3 previous chemotherapy regimens, the majority (85%) had received ≥ 4 cytotoxic drugs), one of which contained a taxane (paclitaxel or docetaxel) as treatment for metastatic disease. Patients had either failed prior taxane therapy (defined as disease recurrence occurring 6–12 months after completion of adjuvant therapy, objective response followed by PD within 12 months of last dose, or SD while receiving therapy for ≥ 4 cycles) or were resistant to taxane therapy (defined as disease recurrence within 6 months of completing adjuvant therapy, objective response followed by PD within 6 weeks of last dose or PD while receiving therapy without improvement). Previous cytotoxic chemotherapy or hormonal therapy had to	toxicity, treatment was interrupted and then resumed at original dose after resolution to grade 1 or 0, with prophylaxis administered whenever possible. Subsequent occurrences of the same toxicity at an intensity of grade 2 were managed by treatment interruption followed by 25% dose reduction. If grade 3 or 4 toxicity occurred, treatment was interrupted and the dose was reduced by 25% or 50%, respectively. At the third appearance of a given grade 3 toxicity, treatment was interrupted until the toxicity resolved to grade 1 or 0 and treatment then continued as 50% of the original dose. At the third occurrence of grade 3 toxicity or second grade 4 toxicity, treatment was discontinued and patient withdrawn from the study	Nausea 7 (9.5) 0 Haemorrhagic diarrhoea 0 1 (1.4) Sepsis 0 1 (1.4) Emesis 3 (4.1) 1 (1.4) Thrombocytopenia 1 (1.4) 1 (1.4) Neutropenia 0 1 (1.4) Capecitabine dose was reduced to 75% for 37 patients (median time to dose reduction 1.4 months, range 0.2–9.2 months) and to 50% for 13 patients (median time to dose reduction 3.0 months) Retrospective analysis demonstrated that dose reduction of capecitabine for adverse events did not appear to have an impact on efficacy as assessed by the HR of time to PD in patients with versus those without dose reductions (risk ratio $p = 0.918$)

Study details	Participant details	Intervention details	Withdrawals/Adverse events
	have been completed >3 weeks or 10 days, respectively, before the initiation of capecitabine therapy All patients had been pretreated with taxanes: 47 (64%) with paclitaxel and 27 (36%) with docetaxel as their predominant taxane treatment. Eight patients had received both Seventy-one patients (95.9%) had prior exposure to anthracyclines, 52 patients (70.2%) had received hormonal therapy, 61 patients (82.4%) had received prior radiotherapy, and all had undergone prior surgical procedures **Dominant site of metastatic disease** visceral: 59 (79.7%) soft tissue: 12 (16.2%) bone: 3 (4.1%) The majority of patients had widely disseminated metastatic disease; approx. 50% had ≥ 3 metastatic sites at baseline **Refractory disease present after first treatment** NS **Comments** 69 patients had measurable disease and 5 had non-bidimensionally measurable but assessable disease		

Results

Outcome 1: Overall response rate (CR + PR) (*n* = 74)	**Outcome 2: Stable disease (*n* = 74)**	**Outcome 3: Median time to PD**
26% (95% CI 15.7 to 35.6%)	31% (95% CI 20.5 to 41.6%)	3.2 months (95% CI 2.3 to 4.3 months)
Outcome 4: Median time to treatment failure	**Outcome 5: Median survival (*n* = 74)**	**Outcome 6: CBR (*n* = 54)**
3.2 months (95% CI 2.2 to 4.4 months) Included all patients withdrawn from treatment because of adverse events or withdrawal of informed consent, plus those who showed PD	12.2 months (95% CI 8.0 to 15.3 months) Patients with SD (*n* = 23): 12.9 months	Overall positive outcome: 8 (14.8%) Stable scores: 22 (40.7%) *Definitions*: Pain intensity: ≥ 50% reduction in patients with baseline pain ≥ 20mm Analgesic consumption: ≥ 50% reduction in patients with baseline consumption ≥ 70mg morphine equivalevent KPS status improvement of: ≥ 20 points A patient was classified as a responder if she achieved a positive response in at least one of the self-rated parameters and the score was stable in the others
Outcome 7	**Additional results/comments**	
NA	*Subgroup analysis of response rate (n = 69 patients with measurable disease)*	

	Response rate (%)		
Subgroup	**CR/PR**	**SD**	**PD**
Paclitaxel pretreated (*n* = 44[a])	27	32	27
failed (*n* = 21)	33	38	24
resistant (*n* = 20)	20	20	35
Docetaxel pretreated (*n* = 25)	20	28	48
failed (*n* = 13)	23	38	38
resistant (*n* = 12)	17	17	58

[a] Three patients did not meet the predefined criteria for paclitaxel failure or resistance.

Of 17 patients who achieved PR, 14 had PD at time of data analysis. Median duration of response was 8.3 months (95% CI 7.0 to 9.9 months)

Study details	Participant details	Intervention details	Withdrawals/adverse events
Cervantes (2000)[67] **Length of follow-up** Unclear (ongoing?) **No. and times of follow-up measurements** Evaluations were performed every two cycles	**No. of participants** 32 **Age range** Mean 51 (range 39–66) years **Inclusion/exclusion criteria** *Inclusion*: MBC, having received at least two but not more than three chemotherapy regimens (one of which must have contained either docetaxel or paclitaxel for metastatic disease), KPS score of at least 70%, normal marrow, liver and renal functions, and life expectancy of ≥ 3 months **Characteristics** NA **Previous treatment** NA **Dominant site of metastatic disease** NA **Refractory disease present after first treatment** NA **Comments** None	**Intervention** Capecitabine *Dosage* 2500 mg divided into two daily doses *No. of cycles* Mean 2.8 (range 2–15) *Length per cycle* 2 weeks out of every 3 weeks **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** None **Dose modifications** NA	**Attrition** *Intervention* NA *Comparator* NA **Adverse events/toxicity** NA

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Results		
Outcome 1: Response	**Outcome 2: Death**	**Outcome 3**
Complete response (CR): 2 Partial response (PR): 11 Stable disease (SD): 6 Disease progression (PD): 13 5 patients still in response at end of follow-up (mean no. of cycles = 5.2 (range 2–15)	15 patients had died from progression, 13 of the initial progression group and 2 from those who reached initial stable disease	
Outcome 4	**Outcome 5**	**Outcome 6**
Outcome 7	**Additional results/comments**	

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events
Fumoleau (2002)[68] Interim results published as Fumoleau (2001)[69] **Length of follow-up** Unclear **No. and times of follow-up measurements** Antitumour efficacy was evaluated every three cycles based on WHO criteria	**No. of participants** 126 **Age range** Median 54 (range 30–80) years **Inclusion/exclusion criteria** *Inclusion*: Female outpatients; 18–75 years; histologically proven locally advanced or MBC; previous treatment with two or three chemotherapies including an anthracycline and a taxane; at least one measurable or evaluable lesion; ECOG performance status 0–2; adequate haematological, liver, renal and cardiac function; estimated life expectancy of at least 3 months; and signed informed consent **Characteristics** ECOG performance at baseline >0: 55 (44%) >1: 61 (48%) >2: 9 (7%) Hormone receptor positive: 77 (61%) Receptor status unknown: 15 (12%) **Previous treatment** Median number of chemotherapy lines for advanced disease was 2 (range 1–5) and median number of cycles delivered was 6 *Prior chemotherapies, n (%)* **Neoadjuvant / Adjuvant / Metastatic** Chemotherapy: 22 (17) / 80 (63) / 122 (97) Anthracycline alone: 19 (15) / 66 (52) / 1 (1) Taxane alone: 1 (1) / 1 (1) / 49 (39) Anthracycline + taxane: 1 (1) / 5 (4) / 71 (56) 5-FU: 17 (14) / 70 (56) / 50 (40)	**Intervention** Capecitabine *Dosage* 1250 mg/m^2 twice daily *No. of cycles* Median 6 (range 1–15) *Length per cycle* 14 days + 1 week rest **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** There were a total of 874 cycles in 126 patients. Median treatment duration was 125 days (range 3–396) or 4.1 months. Median daily dose administered was 1210 mg/m^2 twice daily (range 715–1396) **Dose modifications** NR	**Attrition** *Intervention* NR. 25 patients had protocol violation (reasons not reported) *Comparator* NA **Adverse events/toxicity** The most common grade 3/4 (NCIC-CTC) treatment-related adverse events were: granulocytopenia (11%/3%), hand–foot syndrome (21%), diarrhoea (8%/2%), nausea (4%/0%) and vomiting (3%/0%). Time to first hand–foot syndrome was 53 days (95% CI 44 to 70) Median dose reduction was 25% of the total dose. Dose reduction for adverse events was performed in 46/126 patients (37%) Most adverse events occurred within the first three cycles, with most at cycle 2 (37%, 25 adverse events), only 1–4 adverse events occurred in the later cycles. Most adverse events were graded 2 and 3 The adverse events leading most frequently to dose reduction were hand–foot syndrome (17.5%), neutropenia (7.9%) and diarrhoea (5.6%) Seven patients experienced grade 4 adverse events, of which 3 were uncomplicated granulocytopenia There were no treatment-related deaths

Study details	Participant details	Intervention details	Withdrawals/adverse events
	Dominant site of metastatic disease bone: 71 (56%) liver: 69 (55%) pleura: 34 (27%) lung: 33 (26%) nodes: 29 (23%) skin: 26 (21%) **Refractory disease present after first treatment** Yes **Comments** Progressing patients were discontinued from the study, but included in the final analysis		

Results		
Outcome 1: Time to disease progression	**Outcome 2: Tumour response (ITT *n* = 126)**	**Outcome 3: Response duration (ITT *n* = 126)**
ITT population (*n* = 126) Median 4.6 months (95% CI 4.0 to 6.2) Per protocol population (*n* = 110) Median 5 months (95% CI 4.1 to 6.4)	*Response at third cycle* CR: 1 (1%) PR: 23 (18%) SD: 53 (42%) PD: 49 (39%) OR: 19% (95% CI 12 to 20) *Best response* CR: 5 (4%) PR: 30 (24%) SD: 44 (35%) PD: 47 (37%) ORR rate: 28% (95% CI 20 to 34)	Median response duration in patients responding after three cycles was 5 months (95% CI 4.2 to 6.2)
Outcome 4: Overall survival (ITT *n* = 126)	**Outcome 5: QoL**	**Outcome 6**
Estimated median overall survival: 464 days (95% CI 412 to 598); 15.2 months (95% CI 13.5 to 19.6) One-year survival: 62.3% (Kaplan–Meier method), 6 patients were censored and 46 patients had died	QoL evaluated on the EORTC QLQ-C30 questionnaire showed an improvement in global health status and physical, role, emotional and cognitive functioning at cycle 6. Further data were not extractable	
Outcome 7	**Additional results/comments**	
NR		
ECOG, Eastern Cooperative Oncology Group		

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events
Reichardt (2001)[70] Interim findings were published as abstracts, Reichardt (2000)[71] and Thuss-Patience (2001)[72] **Length of follow-up** Median 7.4 (range 0.4–24.0) months **No. and times of follow-up measurements** Tumour assessments performed during screening, at 6-weekly intervals during the treatment phase and at time of withdrawal from the study	**No. of participants** 136 **Age range** Median 56 (range 32–77) years **Inclusion/exclusion criteria** *Inclusion*: Female, aged 18–80 years; KPS score 60–100%; histologically confirmed, bidimensionally measurable breast cancer that had relapsed after taxane-containing chemotherapy; no prior continuous infusion with 5-FU; no chemotherapy for at least 3 weeks prior to enrolment **Characteristics** Scarfe and Bloom tumour grade: grade 2: 31% grade 3: 54% not available: 14% Oestrogen receptor positive: 53% Progesterone receptor positive: 51% KPS score Median: 90% (range 60–100%) ≤ 70: 11% 80/90: 87% 100: 24% **Previous treatment** Prior adjuvant therapy (%): hormonal/chemotherapy: 74 radiotherapy: 50 Prior therapy for metastatic disease (%): palliative radiotherapy: 46 hormonal therapy: 69 anthracycline-containing therapy: 94	**Intervention** Capecitabine *Dosage* 1250 mg/m^2, twice daily *No. of cycles* Maximum 21 (median 3, range 1–21) *Length per cycle* 21 days (14 days + 7 days' rest) **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** Capecitabine therapy was administered on days 1–14 of 21-day treatment cycle Patients with objective responses or stable disease at the first assessment could continue treatment until disease progression or unacceptable toxicity **Dose modifications** Standard capecitabine dose modification scheme was applied in the event of side-effects classified as grade 2 or higher	**Attrition** *Intervention* Reasons for withdrawal were not reported. Two patients were unavailable for safety analysis *Comparator* NA **Adverse events/toxicity (*n* = 134)** Adverse events were classified according to the NCIC-CTC Most common adverse events (>10% of patients) were cutaneous (hand–foot syndrome 12%[a]) and gastrointestinal side-effects (nausea 2%[a]; diarrhoea 5%[a]; stomatitis 1%[a] and vomiting 2%[a]) (no. presented in graph) Alopecia (grade 1/2 only) occurred in 2 patients (1.5%) Adverse events were generally of mild to moderate in intensity. The only grade 4 clinical adverse event was diarrhoea (1 patient), and the most common grade 3 event was hand–foot syndrome, which occurred in 12% of patients *Haematological abnormalities (grade 3; grade 4)* thrombocytopenia: 1; 0 neutropenia: 1; 1 leucopenia: 1; 0 anaemia: 1; 0

Study details	Participant details	Intervention details	Withdrawals/adverse events
	taxane-containing therapy: paclitaxel: 49 docetaxel: 46 both: 4 **Dominant site of metastatic disease** Median no. of metastatic sites: 2 (range 0–8) liver: 53% lung: 35% bone: 42% skin: 25% lymph nodes: 16% **Refractory disease present after first treatment** Yes **Comments** None		

Results		
Outcome 1: Objective response (CR + PR)	**Outcome 2: Disease stabilisation**	**Outcome 3: Median response duration**
21 patients (15%), CR in 2 patients	63 patients (46%)	7.4 months (95% CI 6.0 to 9.0)
Outcome 4: Median time to disease progression	**Outcome 5: Median overall survival**	**Outcome 6: Rate of disease control**
3.3 months (95% CI 2.8 to 4.2)	10.4 months (95% CI 8.2 to 12.7)	62%
Outcome 7	**Additional results/comments**	
	Ongoing trial. Check industry submission	

[a] Values approximated from graph.

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events
Semiglazov (2002)[73] **Length of follow-up** NR **No. and times of follow-up measurements** NR	**No. of participants** 80 (n = 31 anthracycline and docetaxel refractory) **Age range** NR **Inclusion/exclusion criteria** *Inclusion*: Patients were to have received at least two, but not more than three, prior chemotherapy regimens for MBC **Characteristics** NR **Previous treatment** Anthracycline: 49 Anthracycline + docetaxel: 31 **Dominant site of metastatic disease** NR **Refractory disease present after first treatment** Yes **Comments** Patients were divided into groups A and B: A: anthracycline refractory B: anthracycline and docetaxel refractory	**Intervention** Capecitabine *Dosage* 2510 mg/m^2 per day in two divided doses *No. of cycles* NR *Length per cycle* 2 weeks followed by 1 week rest repeated in 3-week cycles **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** None **Dose modifications** NR	**Attrition** *Intervention* NR *Comparator* NA **Adverse events/toxicity** Most common treatment-related adverse events were hand–foot syndrome, diarrhoea, nausea, vomiting and fatigue. Rates of adverse events were the same in both groups. Hand–foot syndrome and diarrhoea occurred with grade 3 and 4 intensity in 12% of patients in group A and 10% in group B

Results		
Outcome 1: Overall response rate	**Outcome 2: Median time to progression**	**Outcome 3: Survival**
A: 24.5% (3 CR) B: 20.7% (0 CR)	A: 6.5 months B: 6.2 months	A: 10.0 months B: 8.1 months
Outcome 4	**Outcome 5**	**Outcome 6**
Patient preference for oral therapy	**Additional results/comments**	

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events
Watanabe (2001)[74] **Length of follow-up** NR **No. and times of follow-up measurements** NR	**No. of participants** 60 **Age range** NR **Inclusion/exclusion criteria** *Inclusion*: Bidimensionally measurable, histologically/cytologically confirmed ABC/MBC **Characteristics** NR **Previous treatment** All patients had docetaxel-refractory ABC/MBC. Patients were required to have received no more than two prior chemotherapy regimens, one of which contained docetaxel as treatment for metastatic disease **Dominant site of metastatic disease** NR **Refractory disease present after first treatment** Yes **Comments** None	**Intervention** Capecitabine *Dosage* 1657 mg/m^2 per day *No. of cycles* NR *Length per cycle* 4 weeks (3 weeks followed by 1 week rest) **Comparator** None *Dosage* NA *Number of cycles* NA *Length per cycle* NA **Comments** None **Dose modifications** NR	**Attrition** *Intervention* Five patients were not eligible for the effectiveness analysis (reasons not reported) *Comparator* NA **Adverse events/toxicity** Treatment-related adverse events with grade 3–4 that occurred in more than 5% of patients were hand–foot syndrome (13.3%), increased serum bilirubin (8.3%) and increased ASAT (6.7%). No grade 3–4 myelosuppression occurred

Results		
Outcome 1: Tumour response (*n* = 55)	**Outcome 2: Response rate (docetaxel refractory/failure)**	**Outcome 3: Median duration of response**
20.0% (95% CI 10.4 to 33.0%)	21.4%/18.5%	221 days
Outcome 4: Median time to disease progression	**Outcome 5: CR**	**Outcome 6**
84 days	*n* = 1 (duration: 253 days)	
Outcome 7	**Additional results/comments**	

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Other uncontrolled observational studies

Study details	Participants	Intervention	Results
Leonard (2001)[75] Earlier results published as Leonard (2000)[76] and Edinburgh subgroup (n = 22), reported as Anderson (1999)[77] **Study design** UK Open Access Programme	**No. of participants** 102 patients with ABC **Age** Median 53.2 (range 30–95) years **Previous therapy** Patients had received 0–4 prior chemotherapy regimens for advanced disease 60.8% had previously received anthracyclines, 25.5% taxoids and 6.9% infusional 5-FU **Site of disease** 58% of patients had visceral disease and median number of sites of disease was 1	**Intervention** Capecitabine *Dosage* 1250 mg/m^2 twice daily, for 14 days every 21 days Mean dose intensity: 95% *Median no. of cycles* 5 (range NR)	**Efficacy** There were 3 complete responders and 17 partial responders, and the total objective response rate was 19%. Stable disease was achieved in 46% and progression was seen in 30% **Toxicity** Dose reductions occurred in 32.4% of patients (10.2% of cycles)

Event	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	2.0	1.0	2.0	1.0
Thrombocytopenia	3.9	2.0	1.0	0.0
Mucositis	1.0	2.9	2.0	0.0
Fatigue	12.7	3.9	2.9	1.0
PPE	15.7	11.8	7.8	0.0
Diarrhoea	21.6	5.9	4.9	2.0
Nausea	23.5	5.9	1.0	0.0
Vomiting	11.8	2.9	2.0	0.0

Study details	Participants	Intervention	Results
Wong (2000)[78] **Study design** Case series	**No. of participants** 22 patients with breast cancer: 5 (23%) patients presented with stage IV disease, 7 (32%) stage III, 8 (36%) stage II and 2 (9%) stage I **Age** Median 49 (range 33–70) years **Previous therapy** Previous anthracycline and taxanes were used in 14 (63%) Capecitabine was used as second-line treatment in 1 (4.5%) and at least third-line treatment in 21 (95.5%) **Site of disease** 17 (77%) had visceral disease and 13 (59%) had bone and soft-tissue metastases. 18 (81%) patients had more than two sites of disease at the start of treatment	**Intervention** Capecitabine *Dosage* 2550 mg/m^2 in divided doses, daily for 2 weeks, every 3 weeks *Median no. of cycles* NR	**Efficacy** Median relapse-free interval for patients with non-metastatic disease at initial diagnosis was 20.3 (range 4.1–58.8) months. Overall response was 27% (0 CR, 6 PR, 2 SD), all of which were seen after the first two treatment cycles **Toxicity** Main toxicity was PPE, which occurred in 10 (45%) patients, of which 90% were grade 1–2. Dose reduction was required in 4 and 6 patients were given pyridoxine. All other toxicities were grade 1 or 2 (gastrointestinal 9%, mucositis 14%, thrombocytopenia 4.5%). No anaemia or neutropenia was observed, and in no patient was hospitalisation required

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Capecitabine monotherapy in patients relapsing after HDC-ASCS

Study details	Participant details	Intervention details	Withdrawals/adverse events
Bashey (2001)[79] **Length of follow-up** Median 183 days from commencement (range 97–540 days) **No. and times of follow-up measurements** Tumour marker (CA27.29) was measured at the start of each 3-week cycle and a formal assessment of measurable disease was performed with every third cycle administered	**No. of participants** 10 **Age range** Range 36–58 years **Inclusion/exclusion criteria** *Inclusion*: 10 consecutive patients who had undergone HDC-ASCS for MBC **Characteristics** All patients had partial or complete response to previous HDC-ASCS **Previous treatment** 8/10 patients previously treated with anthracycline. All patients had prior exposure to taxane therapy **Dominant site of metastatic disease** liver and bone: 3 pleura and nodes: 1 pleura, lung and bone: 1 skin: 1 skin and bone marrow: 1 liver and lung: 1 bone and peritoneum: 1 liver: 1 **Refractory disease present after first treatment** Yes **Comments** Disease progression after HDC-ASCS was defined as a >25% increase in the volume of measurable disease, the occurrence of new metastatic lesions, or a >50% increase in serum CA27.29 level from the best results obtained after HDC-ASCS. Patients with oestrogen or progesterone receptor-positive disease were maintained on hormonal therapy, starting on haematological recovery from HDC-ASCS. Hormonal therapy was continued when capecitabine was commenced	**Intervention** Capecitabine *Dosage* 1250 mg/m^2 twice daily *No. of cycles* Median 8 (range 4–24) *Length per cycle* 14 days + 1 week rest **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** None **Dose modifications** Capecitabine was discontinued on occurrence of toxicity ≥ grade 2 until this resolved to grade 1 or less, when the drug was then recommenced at the original dose. Dose reduction of 25% was used after recurrence of grade 2 or above toxicity	**Attrition** *Intervention* None *Comparator* NA **Adverse events/toxicity** **Adverse event** / **Grade**: 1 / 2 / 3 Hand–foot syndrome: 3 / 4 / 1 Diarrhoea: 1 / 3 / 0 Nausea: 1 / 1 / 0 Fatigue: 5 / 0 / 0 Myelosuppression: 0 / 0 / 1

Results		
Outcome 1: Response after three cycles	**Outcome 2: Length of progression-free survival**	**Outcome 3: Total overall survival from HDC-ASCS**
CR: 3 patients PR: 4 patients SD: 3 patients Response was defined using the following standard criteria: CR: disappearance of all measurable and evaluable disease and normalisation of CA27.29 level for ≥ 3 cycles PR: ≥ 50% reduction in the sum of measurable lesions or >50% reduction in CA27.29 level, each lasting ≥ 3 cycles SD: <25% change in size of measurable lesions and appearance of no new metastatic lesions over 3 cycles, or <25% change in CA27.29 levels over 3 cycles	Range 66–540 days	196–904 days
Outcome 4: Duration of response	**Outcome 5: Kaplan–Meier probability of progression-free survival**	**Outcome 6**
Median 252 (range 63–470) days Determined from the time of documented disease response to the first date of documented disease progression (defined by using same criteria as used for disease progression after HDC-ASCS)	At 180 days: 64%	
Outcome 7	**Additional results/comments**	
Not reported		

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events
Jakob (2002)[80] Interim results published as Jakob (2001)[81] **Length of follow-up** Unclear **No. and times of follow-up measurements** Laboratory tests were repeated at 3-weekly intervals. QoL was completed before each second treatment course (6-weekly intervals). Target lesions were followed by the same diagnostic method in intervals of 6 weeks	**No. of participants** 14 **Age range** Median 45.5 (range 35–60) years **Inclusion/exclusion criteria** *Inclusion*: Age between 18 and 65; female; histologically confirmed diagnosis of breast cancer; bidimensionally measurable or evaluable metastatic lesions; relapse after treatment with high-dose chemotherapy for breast cancer (adjuvant or metastatic) including induction treatment with an anthracycline and/or a taxane followed by autologous PBSCT;[a] KPS status of 60–100%; life expectancy of at least 3 months; adequate renal and hepatic function *Exclusion*: Abnormal haematological values; impaired hepatic or renal function; clinically significant cardiac disease; known hypersensitivity to 5-FU; previous continuous (>48-hour) infusional 5-FU therapy; hypercalcaemia; serious uncontrolled intercurrent infections; patients known to be positive for either hepatitis B surface antigen, hepatitis C antibodies or HIV type 1 antibodies; previous cytotoxic chemotherapy within last 4 weeks prior to treatment start; initiation of bisphosphonate treatment or hormonal treatment within 3 weeks prior to treatment start; pregnant or lactating women	**Intervention** Capecitabine *Dosage* 2500 mg/m^2, daily in two divided dose 12 hours apart *No. of cycles* Median 5 (range 1–19) *Length per cycle* 14 days followed by 7 days' rest **Comparator** None *Dosage* NA *Number of cycles* NA *Length per cycle* NA **Comments** Dose was to be taken at approximately the same time each day within 30 minutes after a meal with approximately 200 ml water. Patients responding or those with stable disease at the end of two treatment cycles were allowed to continue treatment until disease progression **Dose modifications** Treatment interruptions and dose reductions due to adverse events were handled according to the manufacturer's recommendations	**Attrition** *Intervention* NR *Comparator* NA **Adverse events/toxicity** 105 drug-related events were reported; 13% were classified as severe (grade 3). Hand–foot syndrome was reported most frequently (40 reports in 7 patients), followed by nausea (21 reports in 9 patients) and mucositis (8 reports in 5 patients). Seven of these patients suffered from severe drug-related side-effects: 5 patients had hand-foot syndrome, 1 dizziness, and 1 nausea, diarrhoea and fever *Haematological toxicity, n (%)* **Grade 1** / **Grade 2** / **Grade 3** Anaemia: 8 (57) / 3 (21) / 0 Leucopenia: 2 (14) / 5 (36) / 2 (14) Thrombocytopenia: 4 (29) / 1 (7) / 0

[a] PBSCT, peripheral blood stem cell transplantation.

Study details	Participant details	Intervention details	Withdrawals/adverse events
	Characteristics All patients were female and Caucasian Height: median 164.5 (range 157–173) cm Weight: median 67 (range 53–83) kg **Previous treatment** Chemotherapy: 14 (100%) High-dose chemotherapy (single cycle[a]) with PBSCT: 6 (43%) High-dose chemotherapy (two cycles, tandem[b]) with PBSCT: 8 (57%) Radiotherapy: 13 (93%) Second radiotherapy: 5 (36%) Hormone therapy: 14 (100%) Surgical resection: 14 (100%) Bisphosphonate therapy: 5 (36%) Immunotherapy: 1 (7%) Other therapies: 4 (29%) **Dominant site of metastatic disease** Localisation of metastases at relapse: bone: 9 (64%) liver: 9 (64%) lung: 2 (14%) lymph nodes: 4 (29%) pleural: 2 (14%) skin: 3 (21%) mediastinal mass: 1 (7%) On average, patients had metastatic disease at two organ sites (range 1–4 sites). Most patients had multiple metastases **Refractory disease present after first treatment** Yes **Comments**		

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Results		
Outcome 1: Response to treatment	**Outcome 2: Median duration of response**	**Outcome 3: Median time to progression**
CR: 1 PR: 5 SD (at least 12 weeks): 2 OR rate: 42.9% (95% CI 17.7 to 71.1%) All responses were observed at first observation (6 weeks after initiation of treatment)	7.2 (range 0.7–12.0) months	2.8 (range 0.4–13.3) months
Outcome 4: EORTC QLQ-C30 QoL (*n* = 12)	**Outcome 5**	**Outcome 6**
Six patients (50%) showed improvement in the QoL score of at least 20% and 1 further patient of more than 10%. Total number of patients obtaining at least a 10% increase was 7 (58.3%)		
	Additional results/comments	
	The median survival time according to the Kaplan–Meier curve was not reached (range 3.9–36.5 months)	

[a] Two cycles of VIPE induction therapy (cumulative doses: cisplatin 100 mg/m^2, etoposide 1000 mg/m^2, ifosfamide 8 g/m^2 and epirubicin 100 mg/m^2) followed by one cycle of high-dose VIC therapy (etoposide 1500 mg/m^2, ifosfamide 12 g/m^2, carboplatin 1500 mg/m^2).

[b] Three cycles of AT induction therapy (cumulative doses: adriamycin 150 mg/m^2, docetaxel 225 mg/m^2) followed by one cycle of high-dose VIC chemotherapy and a second (tandem) cycle of high-dose chemotherapy (thiotepa 800 mg/m^2, cyclophosphamide 6000 mg/m^2).

PBSCT: peripheral blood stem-cell t_____.

Study details	Participant details	Intervention details	Withdrawals/adverse events
Sundaram (2000)[82] **Length of follow-up** Median 21 (range 3–48) weeks **No. and times of follow-up measurements** Not reported	**No. of participants** 8 **Age range** Median 42 (range 36–56) years **Inclusion/exclusion criteria** *Inclusion*: Patients with MBC whose disease had progressed after HDC-ASCS **Characteristics** Oestrogen receptor positive: 4 Response to pre-HDC induction chemotherapy: PR, 7; CR 1 Best response following HDC-ASCS: CR, 3; PR, 5 Median time to progression following HDC-ASCS: 246 (range 69–480) days **Previous treatment** Prior exposure to: adriamycin: 6 (75%) taxanes: 8 (100%) **Dominant site of metastatic disease** visceral disease: 6 soft-tissue only disease: 1 **Refractory disease present after first treatment** NS	**Intervention** Capecitabine *Dosage* 2500 mg/m^2 per day divided into two daily doses *No. of cycles* Median 6 (range 2–16) *Length per cycle* 14 days + 7 days' rest **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** Minimum dose 3000 mg/day, maximum dose 5600 mg/day **Dose modifications** Treatment interruptions and dose reductions for toxicity were according to the manufacturer's recommendations	**Attrition** *Intervention* NR *Comparator* NA **Adverse events/toxicity** (grade 1; grade 2; grade 3) Hand–foot syndrome: 4; 2; 1 Diarrhoea: 1; 2; 0 Xerophthalmia: 2 (grade ?) One patient had grade 3 neutropenia while receiving concurrent radiotherapy, no other patient had > grade 1 myelotoxicity No patient required inpatient care for toxicity

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Results		
Outcome 1: Response to treatment (*n* = 7)	**Outcome 2: Disease progression**	**Outcome 3**
CR: 1 PR: 4 OR rate: 71% SD: 2	Two patients progressed after remissions that lasted 45 and 18 weeks	
Outcome 4	**Outcome 5**	**Outcome 6**
Patient preference for oral therapy	**Additional results/comments**	
Not reported		

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Capecitabine in combination with docetaxel

Randomised controlled trial

Study details	Participant details	Intervention details	Withdrawals/adverse events
O'Shaughnessy (2002)[59] Interim findings published as Leonard (2001)[83] and Vukelja (2001).[84] Additional QoL data published as Twelves (2001)[85] **Length of follow-up** Minimum of 15 months **No. and times of follow-up measurements** Tumour responses were assessed according to WHO criteria at 6-week intervals until week 48 and then at 12-week intervals until disease progression	**No. of participants** Total: 511 CAP/DOC: 255 DOC: 256 **Age range** CAP/DOC: Median 52 (range 26–79) years DOC: Median 51 (range 25–75) years **Inclusion/exclusion criteria** *Inclusion*: Female, aged ≥ 18 years; histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or metastatic disease. Patients were required to have at least one bidimensionally measurable lesion that had not been irradiated, with minimum size in at least one diameter of ≥ 20 mm for liver lesions and ≥ 10 mm for lung, skin and lymph-node metastases. All patients were to have breast cancer that had recurred after anthracycline treatment, defined as: (1) progression while receiving anthracycline-based chemotherapy without experiencing and transient improvement; (2) no response after administration of four or more cycles of anthracycline-based chemotherapy; (3) relapsing within 2 years of completing (neo)adjuvant anthracycline-based chemotherapy; or (4) a brief objective response to anthracycline-based chemotherapy with subsequent progression while receiving the same therapy or within 12 months after the last dose. All patients had to have a KPS score ≥ 70% and a life expectancy ≥ 3 months, and they had to provide written, informed consent	**Intervention** Capecitabine + docetaxel *Dosage* Capecitabine 1250 mg/m^2 twice daily plus docetaxel 75 mg/m^2 1-hour i.v. infusion on first day of each 3-week cycle *No. of cycles* ≥ 2 *Length per cycle* 14 days followed by 7 days' rest **Comparator** Docetaxel *Dosage* 100 mg/m^2, 1-hour i.v. infusion on first day of each 3-week cycle *No. of cycles* ≥ 2 *Length per cycle* 21 days **Comments** Patients in the combination arm were still regarded as 'on study therapy' if for any reason docetaxel treatment was discontinued before disease progression and the patient continued capecitabine therapy. All patients received docetaxel premedication (e.g. dexamethasone) as per the treatment centre policy. Capecitabine was administered orally	**Attrition** *Intervention* Treatment discontinuation, *n* = 238 (93.3%) *Comparator* Treatment discontinuation, *n* = 250 (97.7%) The main reasons for treatment discontinuation for the capecitabine/docetaxel group and docetaxel group, respectively, included: insufficient therapeutic response (43.1% vs 59.8%) and adverse event (25.9% vs 19.5%) **Adverse events/toxicity** (CAP/DOC, *n* = 251; DOC, *n* = 255) Incidence of treatment-related adverse events was similar in the combination and single arms (98% vs 94%, respectively). The percentage of patients experiencing grade 3 treatment-related adverse events was higher in the combination therapy group (71% vs 49% in the single-agent docetaxel arm) *Treatment-related grade 3/4 adverse events (≥ 5% of patients) (%)* **Adverse event** / **Grade 3** / **Grade 4** *Neutropenic fever* CAP/DOC 3 13 DOC 5 16 *Neutropenia* CAP/DOC 5 11 DOC 3 12 *Stomatitis* CAP/DOC 17 0.4 DOC 5 0 *Diarrhoea* CAP/DOC 14 0.4 DOC 5 0.4

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events

Exclusion: Previous treatment with a docetaxel-containing regimen in either the adjuvant or advanced disease setting (prior paclitaxel was permitted, no minimum interval from prior paclitaxel exposure to study entry was specified), or treatment with three or more chemotherapy regimens for advanced/metastatic disease. Patients with prior radiotherapy to the axial skeleton within 4 weeks of treatment were excluded, as were those who had received hormonal therapy with 10 days of treatment start or chemotherapy within 4 weeks of treatment start. Patients with clinically significant cardiac disease, evidence of CNS metastases, known hypersensitivity to 5-FU, or prior unanticipated, severe reactions to drugs formulated with polysorbate 80, or to fluoropyrimidines were also ineligible. Women with a history of another malignancy (except basal cell skin carcinoma and carcinoma *in situ* of the uterine cervix) within 5 years of study entry were not eligible. The usual exclusion criteria relating to laboratory tests were applied

Characteristics (CAP/DOC; DOC)
Median KPS (%): 90; 90
ER/PR status (%):
- positive: 39; 42
- negative: 32; 28
- unknown: 29; 30

Locally advanced disease (%) (retrospectively defined): 3; 2
No. of tumour sites (% of patients):
- 1: 13; 11
- 2: 22; 21
- ≥ 3: 64; 69

twice daily, within 30 minutes of a meal, approx. 12 hours apart with approx. 200 ml water. Patients achieving a complete or partial response or stable disease after 6 weeks of therapy continued on treatment until disease progression or development of unacceptable toxicity. Patients with documented progressive disease were withdrawn from the study

Dose modifications
In the combination arm, the second occurrence of a given grade 2 toxicity or any grade 3 toxicity resulted in both doses being reduced by 25%. Docetaxel therapy was discontinued if it did not resolve to grade 0 or 1 within 2 weeks, but capecitabine could be resumed at 75% of the starting dose on resolution to grade 0 or 1. On the third occurrence of a given grade 2 toxicity, second occurrence of a given grade 3 toxicity, or any grade 4 toxicity, the dose of capecitabine was reduced by 50% and docetaxel was discontinued. Capecitabine was discontinued if, despite dose reduction, a given toxicity occurred for a fourth time at grade 2, a third time at grade 3, or a second time at grade 4. A similar dose modification scheme was used in patients receiving single-agent docetaxel

Nausea		
CAP/DOC	6	0
DOC	2	0
Hand–foot syndrome		
CAP/DOC	24	n/a
DOC	1	n/a
Alopecia		
CAP/DOC	6	0
DOC	7	0
Fatigue/asthenia		
CAP/DOC	8	0.4
DOC	11	0

In total, 5 patients in the combination arm and 9 patients in the single-agent arm died from any cause (related and unrelated to treatment) within 60 days of initiation of treatment (2.0% vs 3.5%, respectively)

Study details	Participant details	Intervention details	Withdrawals/adverse events
	Previous treatment (%) Surgery: 91; 84 Radiotherapy: 72; 69 Endocrine: metastatic: 47; 54 adjuvant: 32; 32 Anthracyclines: 100; 100 metastatic: 60; 64 neoadjuvant: 22; 18 adjuvant: 31; 31 Anthracycline exposure: 1: 25; 29 2: 16; 16 3: 31; 29 4: 20; 20 None of the above: 7; 7 Alkylating agents: 93; 92 5-FU: 77; 74 Paclitaxel: 10; 9 Setting of study treatment: first-line: 35; 31 second-line: 48; 53 third-line: 17; 16* (*2 patients fourth-line) **Dominant site of metastatic disease** Metastatic sites (% of patients): lymph nodes: 47; 49 liver: 45; 48 bone: 42; 46 lung: 37; 39 skin: 29; 29 **Refractory disease present after first treatment** Yes **Comments** None		

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Results		
Outcome 1: Time to disease progression	**Outcome 2: Overall survival**	**Outcome 3: 12-month survival rate**
CAP/DOC: median 6.1 months (95% CI 5.4 to 6.5) DOC: median 4.2 months (95% CI 3.4 to 4.5) (log-rank $p = 0.0001$; HR, 0.652; 95% CI 0.545 to 0.780) HR translates into a 35% decrease in risk of disease progression with CAP/DOC combination therapy	CAP/DOC: median 14.5 months (95% CI 12.3 to 16.3; 72% of events) DOC: median 11.5 months (95% CI 9.8 to 12.7; 79% of events) (log-rank $p = 0.0126$; HR, 0.775; 95% CI 0.634 to 0.947) HR translates into a 23% reduction in the risk of death in patients receiving CAP/DOC combination therapy	CAP/DOC: 57% (95% CI 51 to 63%) DOC: 47% (95% CI 41 to 53%) Median censoring times were 23.2 months and 22.9 months, respectively
Outcome 4: Objective response rate (best response)	**Outcome 5: Time to response in confirmed responders**	**Outcome 6: Duration of response**
OR *Investigator assessment* CAP/DOC: 42% (95% CI 36 to 48%) DOC: 30% (95% CI 24 to 36%) ($p = 0.006$) **IRC** CAP/DOC: 32% DOC: 23% ($p = 0.025$) **CR** CAP/DOC: 5% (95% CI 2 to 8%) DOC: 4% (95% CI 2 to 7%) **SD** CAP/DOC: 38% (95% CI 32 to 44%) DOC: 44% (95% CI 38 to 50%) **PD** CAP/DOC: 11% (95% CI 7 to 15%) DOC: 20% (95% CI 15 to 25%) **Missing postbaseline** CAP/DOC: 10% (95% CI 6 to 14%) DOC: 6% (95% CI 4 to 10%)	*Days from randomisation to first response (n) (CAP/DOC; DOC)* 1–42: 21; 15 43–84: 59; 43 85–126: 18; 18 127–168: 5; 0 169–210: 2; 0 211–252: 0; 0 253–294: 1; 0 Total: 106; 76	CAP/DOC ($n = 106$): 7.3 months (95% CI 6.9 to 8.4) DOC ($n = 76$): 7.0 months (95% CI 5.8 to 8.0) % patients without disease progression after 6 months: CAP/DOC: 41% (95% CI 35 to 47%) DOC: 29% (95% CI 23 to 34%) ($p = 0.04$)

Outcome 7: Median time to treatment failure	Outcome 8: QoL	Outcome 9: Dose reductions
CAP/DOC: 4.0 months (95% CI 3.3 to 4.3 months; 96% of events) DOC: 2.8 months (95% CI 2.4 to 3.5 months; 98% of events) ($p = 0.0002$) The time to treatment failure was based on a composite measure of safety and efficacy end-points	(CAP/DOC, $n = 224$; DOC, $n = 230$). The EORTC QLQ-C30 (v2.0) global health score was preselected as the primary parameter for statistical testing in the QoL analysis at week 18 Change from baseline scores of the functional scale global health at week 18 and week 30 (CAP/DOC –3.7, –3.4; docetaxel –4.0, –4.4, respectively; $p = 0.8303$ week 18) showed no clinically meaningful change. Analysis of raw (non-imputed) scores showed a trend in favour of CAP/DOC towards a clinically meaningful difference between CAP/DOC and DOC at week 30 (change from baseline –2.3 and –12.1, respectively). There was no difference in other domains, including physical, cognitive, role and social functioning scales, and systemic side-effects	Approximately two-thirds (65%) of patients in the combination arm required dose reduction of capecitabine alone (4%), docetaxel alone (10%) or both (51%) for adverse events. In the single-agent docetaxel arm, 36% patients required dose reduction. The median time to dose reduction was longer in the combination therapy group The impact of dose reduction on efficacy was assessed by including the time to first dose reduction as a time-dependent covariate in a proportional hazards regression model of time to disease progression *Impact of dose reduction on time to disease progression or death, HR (95% CI):* CAP/DOC ($n = 251$) all dose reductions: 0.84 (0.54 to 1.30) 50% of starting dose: 1.14 (0.71 to 1.81) DOC ($n = 255$) all dose reductions: 0.99 (0.70 to 1.40) 50% of starting dose: 1.91 (1.00 to 3.66)

Outcome 10	Additional results/comments

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Study details	Participant details	Intervention details	Withdrawals/adverse events
Miles (2001)[86] **Length of follow-up** Minimum of 15 months **No. and times of follow-up measurements** See O'Shaughnessy (2002)[59]	**No. of participants** Total: 511 Capecitabine/docetaxel: 255 Docetaxel: 256 **Age range** See O'Shaughnessy (2002) **Inclusion/exclusion criteria** See O'Shaughnessy (2002) **Characteristics** See O'Shaughnessy (2002) **Previous treatment (%)** See O'Shaughnessy (2002) **Dominant site of metastatic disease** See O'Shaughnessy (2002) **Refractory disease present after first treatment** Yes **Comments** None	**Intervention** Capecitabine + docetaxel *Dosage* Capecitabine 1250 mg/m^2 twice daily plus docetaxel 75 mg/m^2 1-hour i.v. infusion on first day of each 3-week cycle *No. of cycles* ≥ 2 *Length per cycle* 14 days followed by 7 days' rest **Comparator** Docetaxel *Dosage* 100 mg/m^2, 1-hour i.v. infusion on first day of each 3-week cycle *No. of cycles* ≥ 2 *Length per cycle* 21 days **Comments** **Dose modifications** See O'Shaughnessy (2002)	**Attrition** *Intervention* Premature withdrawal: 26% *Comparator* Premature withdrawal: 20% Insufficient response was the most common reason for withdrawal **Adverse events/toxicity** See O'Shaughnessy (2002)

Results		
Outcome 1: Post-study therapy (min. 23 months follow-up)	**Outcome 2: Post-study chemotherapy**	**Outcome 3: Cytotoxic agents received by patients (CAP/DOC; DOC), *n* (%)**
At least one post-study therapy: CAP/DOC: 218 (85%) DOC: 198 (77%) *Post-study therapies (CAP/DOC; DOC):* surgery: 17 (7%); 12 (5%) radiotherapy: 82 (32%); 81 (32%) systemic therapy: 204 (80%); 185 (72%) hormone therapy: 84 (33%); 77 (30%) trastuzumab: 25 (10%); 24 (9%) chemotherapy: 184 (72%); 166 (65%)	*No. of lines of chemotherapy, % (CAP/DOC; DOC)* 1: 60; 54 2: 29; 28 3: 5; 14 ≥ 4: 7; 4 Combination therapy (any line): 54; 51 Single-agent therapy only (all lines): 46; 49	Capecitabine: 8 (3%); 46 (18%) 5-FU: 52 (20%); 60 (23%) Vinorelbine: 85 (33%); 71 (28%) Anthracyclines: 29 (11%); 28 (11%) Taxanes: 77 (30%); 40 (16%) Paclitaxel: 29 (11%); 24 (9%) Docetaxel: 53* (21%); 18 (7%) Both: 5 (2%); 2 (1%) *68% were patients in whom capecitabine was discontinued prior to disease progression The most commonly administered first-line, post-study combination therapy was vinorelbine plus a second chemotherapeutic agent (predominantly 5-FU): 7% patients in both arms received this treatment
Outcome 4: Impact of first-line, post-study chemotherapy	**Outcome 5: Impact of discontinuing docetaxel versus capecitabine in the combination arm**	**Outcome 6**
Among the patients randomised to single-agent docetaxel, those receiving single-agent capecitabine as their first-line, post-study treatment appeared to have improved outcomes compared with those receiving other chemotherapy agents in this setting. HR for patients receiving single-agent capecitabine versus all other chemotherapy: 0.5 (i.e. 50% decreased risk of dying, ($p = 0.0046$)) Median survival: capecitabine 21.0 months (95% CI 15.6 to 27.6) versus all other chemotherapy 12.3 months (95% CI 10.5 to 14.0)	45 (18%) patients stopped docetaxel prior to disease progression (capecitabine alone) 34 (13%) patients stopped capecitabine prior to disease progression Analysis of these subgroups showed that discontinuation of docetaxel versus capecitabine did not appear to have a negative impact on survival (HR = 0.720; $p = 0.20$) Median survival: capecitabine alone 18.3 months (95% CI 14.5 to 23.4) versus docetaxel alone 15.8 months (95% CI 9.9 to 21.5)	
Outcome 7	**Additional results/comments**	

Appendix 9 cont'd *Data extraction tables for clinical effectiveness studies*

Uncontrolled Phase II studies

Study details	Participant details	Intervention details	Withdrawals/adverse events
Scarfe (2002)[61] **Length of follow-up** Ongoing **Number and times of follow-up measurements** NR	**No. of participants** 19 enrolled, 14 evaluable for response (at least two cycles) **Age range** NR **Inclusion/exclusion criteria** *Inclusion*: Women with capecitabine- and taxane-naive measurable MBC, adequate organ function and functional status, and prior anthracycline exposure **Characteristics** NR **Previous treatment** NR **Dominant site of metastatic disease** NR **Refractory disease present after first treatment** NS **Comments**	**Intervention** Docetaxel plus capecitabine *Dosage* Docetaxel 30 mg/m^2 i.v. weekly + capecitabine 900 mg/m^2 p.o. twice daily *No. of cycles* Maximum 8 *Length per cycle* 21 days (capecitabine was administered for 14 days of 21 days) **Comparator** None *Dosage* NA *No. of cycles* NA *Length per cycle* NA **Comments** **Dose modifications**	**Attrition** *Intervention* 11 patients discontinued treatment prior to eight cycles: 5 due to PD, 5 due to adverse events, and 1 due to withdrawal of consent *Comparator* NA **Adverse events/toxicity** Treatment was discontinued prior to eight cycles due to progressive disease (5/19), hand–foot syndrome (3/19), psoriasis (1/19), asthenia (1/19), and withdrawal of consent (1/19)

Results		
Outcome 1: Response to treatment	**Outcome 2: Survival (6 months)**	**Outcome 3**
PR: 2 SD: 7 PD: 5	Progression-free survival: 56% Overall survival: 76%	
Outcome 4	**Outcome 5**	**Outcome 6**
Outcome 7	**Additional results/comments**	
	Final results yet to be presented	

Appendix 10

Data extraction tables for economic evaluations

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications, comments
Author Silberman (1999)[89] **Type of economic evaluation** Cost-effectiveness analysis **Currency used** $US **Perspective used** Unclear **Study population** Patients with anthracycline- and paclitaxel-resistant MBC **Intervention 1** Capecitabine **Intervention 2** 5-FU or gemcitabine or vinorelbine	**Source of clinical effectiveness data** Expert opinion/study data **Source of cost data** Literature **Modelling** Markov model, no details given	**Clinical effectiveness data** Survival **Economic evaluation** QALYs	**Statistical analysis used** Not reported **Uncertainty** Not expressed **Results** Cannot determine quadrant	Insufficient detail to comment	**Authors' conclusions** Capecitabine cost-effective **Implications** Only abstract available; insufficient detail to comment on validity of analysis **Comments** Only abstract available; insufficient detail to comment on validity of analysis

continued

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications, comments
Author O'Shaughnessy (2001)[90] **Type of economic evaluation** Cost-effectiveness analysis **Currency used** $US **Perspective used** Hospital **Study population** Advanced anthracycline-pretreated breast cancer patients **Intervention 1** Capecitabine and docetaxel combination therapy **Intervention 2** Docetaxel Monotherapy	**Source of clinical effectiveness data** Single study **Source of cost data** Literature **Modelling** Decision tree	**Clinical effectiveness data** Survival **Economic evaluation** Life-years	**Statistical analysis used** Not reported **Uncertainty** Not reported **Results** Cannot determine quadrant	Not reported	**Authors' conclusions** Combination therapy cost-effective **Implications** Only abstract available; insufficient detail to determine validity of analysis **Comments** Only abstract available; insufficient detail to determine validity of analysis

Appendix 11

Details of quality assessment for economics studies

Capecitabine monotherapy

Roche NICE Submission [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished]

1	Was a well-defined question posed in answerable form?	Yes	
1.1	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes	
1.2	Did the study involve a comparison of alternatives?	Yes	The evaluation did include a consideration of an alternative, treatment with vinorelbine
1.3	Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Yes	The viewpoint was defined as that of the NHS
2	Was a comprehensive description of the competing alternatives given? (i.e. can you tell who? did what? to whom? where? and how often?)	Yes	There was a description of alternatives. It was not possible to determine precise details of dosing for the vinorelbine studies. Dosing was simulated for costing purposes
2.1	Were any important alternatives omitted?	Possibly	Best supportive care was not considered, although it was mentioned in the original NICE scope. The appropriateness of a best supportive care comparison may be debated
2.2	Was (should) a do-nothing alternative (be) considered?	No	See above
3	Was the effectiveness of the programmes or services established?	Yes	
3.1	Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	No	Effectiveness was not established through an RCT
3.2	Was effectiveness established through an overview of clinical studies?	Yes	The effectiveness of the programmes was estimated based on a comparison of individual single-arm studies; no comparative trials were undertaken
3.3	Were observational data or assumptions used to established effectiveness? If so, what are the potential biases in results?	Yes	The use of 'observational' data from a series of single-arm studies may have led to biased estimates of effectiveness. The vinorelbine trials used regimens which differed from those currently used in the UK. The vinorelbine data were extremely limited. In addition, QoL was not assessed in the studies
4	Were all the important and relevant costs and consequences for each alternative identified?	Possibly	Only the costs of the interventions themselves were considered. There may have been other important cost items not considered
4.1	Was the range wide enough for the research question at hand?	Possibly	Only the costs of the capecitabine or vinorelbine treatment were considered; no other costs were included. This limited range of items may have led to incorrect estimates of cost, although discussion with clinical expert suggests that there may not be other important cost elements to consider

continued

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.)	Yes	For the purposes of the current review the viewpoint of the NHS was correct
4.3	Were capital costs, as well as operating costs, included?	No	Capital costs were not considered, there were probably no significant capital costs related to these programmes
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)	Possibly	The drugs costs were estimated based on median time to progression and median survival times. The use of medians rather than means may have led to biased estimates. In addition, there appeared to be an error in the calculation of drug costs Consequences were measured as QALYs Disease-free progression and overall survival were used to calculate these. Appropriate QoL instruments with associated utility weightings were not used in the studies considered. QALYs were estimated by using generic utility indices for progressive and stable disease which were common to both treatments. This may have led to important effects of the treatments used on QoL being ignored
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?	No	
5.2	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No	No special circumstances were identified
6	Were costs and consequences valued credibly?	Yes	
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.)	Yes	References for unit costs stated. References for estimated utility indexes stated
6.2	Were market values employed for changes involving resources gained or depleted?	Yes	
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?	NA	
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?)	Yes	The evaluation conducted a cost-effectiveness analysis and found that the new treatment dominated the existing treatment, e.g. had lower costs and greater effectiveness. As effectiveness was measured in terms of QALYs a cost–utility analysis could have been undertaken, but would not have altered the conclusion
7	Were costs and consequences adjusted for differential timing?	No	

Appendix 11 cont'd *Details of quality assessment for economics studies*

7.1	Were costs and consequences which occur in the future 'discounted' to their present values?	No	Short time span involved for the treatment and outcome obviated the need for discounting
7.2	Was any justification given for the discount rate used?	NA	
8	Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
8.1	Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?	Yes	
9	Was allowance made for uncertainty in the estimates of costs and consequences?	No	Only a limited analysis was undertaken. The cost-effectiveness ratio was calculated for every combination obtained by combining the individual cost-effectiveness and utility estimates from the various studies used. This did not adequately account for the uncertainty in the study estimates, especially bearing in mind the non-comparative nature of the studies used
9.1	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	NA	
9.2	If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	No	There was a very limited commentary provided on the sensitivity analysis
9.3	Were 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)?	No	Within the limited sensitivity analysis undertaken the results were robust
10	Did the presentation and discussion of study results include all issues of concern to users?	Yes	The overall report did include a comprehensive discussion of the clinical effectiveness and ancillary aspects of the treatment
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?	Yes	The ratio was interpreted appropriately
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?	No	
10.3	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No	
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)?	Yes	The authors discuss patients' preference for oral medication
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?	Yes	The authors discuss the reduced use of pharmacy resources. Budgetary implication assessed

Appendix 11 cont'd *Details of quality assessment for economics studies*

Silberman and colleagues[89]

1	Was a well-defined question posed in answerable form?	Yes	
1.1	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes	
1.2	Did the study involve a comparison of alternatives?	Yes	The evaluation did include a consideration of alternatives
1.3	Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	No	
2	Was a comprehensive description of the competing alternatives given? (i.e. can you tell who? did what? to whom? where? and how often?)	No	Full details were not given
2.1	Were any important alternatives omitted?	Possibly	Best supportive care was not considered, although it was mentioned in the original NICE scope. The appropriateness of a best supportive care comparison may be debated
2.2	Was (should) a do-nothing alternative (be) considered?	No	See above
3	Was the effectiveness of the programmes or services established?	Yes	
3.1	Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	No	Effectiveness of capecitabine ascertained from registration trial (no details given) and through literature and discussion with experts for other therapies (no details given)
3.2	Was effectiveness established through an overview of clinical studies?	No	Discussion with experts also used. No details of actual studies used provided
3.3	Were observational data or assumptions used to established effectiveness? If so, what are the potential biases in results?	–	Insufficient detail provided to ascertain (only abstract available)
4	Were all the important and relevant costs and consequences for each alternative identified?	–	Insufficient detail provided to ascertain (only abstract available)
4.1	Was the range wide enough for the research question at hand?	–	Insufficient detail provided to ascertain (only abstract available)
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.)	–	Insufficient detail provided to ascertain (only abstract available)
4.3	Were capital costs, as well as operating costs, included?	–	Insufficient detail provided to ascertain (only abstract available)
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)	–	Insufficient detail provided to ascertain (only abstract available)
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?	–	Insufficient detail provided to ascertain (only abstract available)

Appendix 11 cont'd *Details of quality assessment for economics studies*

5.2	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No	No special circumstances were identified
6	Were costs and consequences valued credibly?	–	Insufficient detail provided to ascertain (only abstract available)
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.)	–	Insufficient detail provided to ascertain (only abstract available)
6.2	Were market values employed for changes involving resources gained or depleted?	–	Insufficient detail provided to ascertain (only abstract available)
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?	NA	
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?)	Yes	Insufficient detail provided to ascertain (only abstract available)
7	Were costs and consequences adjusted for differential timing?	–	Insufficient detail provided to ascertain (only abstract available)
7.1	Were costs and consequences which occur in the future 'discounted' to their present values?	–	Insufficient detail provided to ascertain (only abstract available)
7.2	Was any justification given for the discount rate used?	NA	
8	Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
8.1	Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?	Yes	
9	Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	No detail given
9.1	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	–	Insufficient detail provided to ascertain (only abstract available)
9.2	If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	–	Insufficient detail provided to ascertain (only abstract available)
9.3	Were 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)?	-	Insufficient detail provided to ascertain (only abstract available)
10	Did the presentation and discussion of study results include all issues of concern to users?	–	Insufficient detail provided to ascertain (only abstract available)
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?	–	Insufficient detail provided to ascertain (only abstract available)

Appendix 11 cont'd *Details of quality assessment for economics studies*

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?	No	
10.3	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No	
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)?	No	
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?	No	

Capecitabine in combination with docetaxel

Roche NICE Submission [Xeloda (capecitabine): achieving clinical excellence in the treatment of metastatic breast cancer, unpublished]

1	Was a well-defined question posed in answerable form?	Yes	
1.1	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes	
1.2	Did the study involve a comparison of alternatives?	Yes	The evaluation did include a consideration of alternatives, treatment with docetaxel alone
1.3	Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Yes	The viewpoint was defined as that of the NHS
2	Was a comprehensive description of the competing alternatives given? (i.e. can you tell who? did what? to whom? where? and how often?)	Yes	There was a full description of alternatives
2.1	Were any important alternatives omitted?	No	
2.2	Was (should) a do-nothing alternative (be) considered?	No	
3	Was the effectiveness of the programmes or services established?	Yes	
3.1	Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Yes	Effectiveness was established through an RCT
3.2	Was effectiveness established through an overview of clinical studies?	Yes	The effectiveness of the programmes was estimated based on a single clinical trial

Appendix 11 cont'd *Details of quality assessment for economics studies*

3.3	Were observational data or assumptions used to established effectiveness? If so, what are the potential biases in results?	No	
4	Were all the important and relevant costs and consequences for each alternative identified?	Yes	Cost of treatment and costs associated with adverse effects were considered
4.1	Was the range wide enough for the research question at hand?	Yes	
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.)	Yes	For the purposes of the current review the viewpoint of the NHS was correct
4.3	Were capital costs, as well as operating costs, included?	No	Capital costs were not considered, there were probably no significant capital costs related to these programmes
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)	Possibly	Consequences were measured as QALYs Disease-free progression and overall survival were used to calculate these. Appropriate QoL instruments with associated utility weightings were not used in the studies considered. QALYs were estimated by using generic utility indices for progressive and stable disease which were common to both treatments. This may have led to important effects of the treatments used on QoL being ignored Costs were only considered up to 1 year. This would potentially favour the treatment associated with longer survival times
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?	No	
5.2	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No	No special circumstances were identified
6	Were costs and consequences valued credibly?	Yes	The unit cost for hospitalisation may have double counted the treatment costs as these were accounted for separately
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.)	Yes	References for unit costs stated. References for estimated utility indexes stated
6.2	Were market values employed for changes involving resources gained or depleted?	Yes	
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?	NA	
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?)	Yes	The evaluation conducted a cost-effectiveness analysis and found that the new treatment dominated the existing treatment, e.g. had lower costs and greater effectiveness. As effectiveness was measured in terms of QALYs a cost–utility analysis could have been undertaken but would not have altered the conclusion

Appendix 11 cont'd *Details of quality assessment for economics studies*

7	Were costs and consequences adjusted for differential timing?	Partially	Consequences were discounted, costs were not
7.1	Were costs and consequences which occur in the future 'discounted' to their present values?	Partially	Consequences were discounted, costs were not
7.2	Was any justification given for the discount rate used?	Yes	Discount rate advised by NICE
8	Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
8.1	Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?	Yes	
9	Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Sensitivity analysis and Monte-Carlo simulation were undertaken
9.1	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Possibly	The Monte-Carlo simulation was based on individual modelled distributions for each item quantity. This would ignore any covariance between the item quantities. As an alternative, the actual variation in costs observed during the clinical trial could be used.
9.2	If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	Yes	The ranges were based on the 5th and 95th percentiles
9.3	Were 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)?	No	Within the sensitivity analysis undertaken the results were robust
10	Did the presentation and discussion of study results include all issues of concern to users?	Yes	The overall report did include a comprehensive discussion of the clinical effectiveness and ancillary aspects of the treatment
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?	Yes	The ratio was interpreted appropriately
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?	No	
10.3	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No	
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)?	Yes	Budgetary implications considered
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?	Yes	The authors discuss the reduced use of pharmacy resources

Appendix 11 cont'd *Details of quality assessment for economics studies*

O'Shaughnessy and colleagues[90]

1	Was a well-defined question posed in answerable form?	No	The goal of study is stated to be to assess costs associated with therapy, results mention outcome and cost-effectiveness ratios
1.1	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes	
1.2	Did the study involve a comparison of alternatives?	Yes	The evaluation did include a consideration of alternatives
1.3	Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	No	
2	Was a comprehensive description of the competing alternatives given? (i.e. can you tell who? did what? to whom? where? and how often?)	No	Full details were not given
2.1	Were any important alternatives omitted?	No	
2.2	Was (should) a do-nothing alternative (be) considered?	No	
3	Was the effectiveness of the programmes or services established?	–	Insufficient detail provided to ascertain (only abstract available)
3.1	Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Yes	
3.2	Was effectiveness established through an overview of clinical studies?	NA	
3.3	Were observational data or assumptions used to established effectiveness? If so, what are the potential biases in results?	NA	
4	Were all the important and relevant costs and consequences for each alternative identified?	–	Insufficient detail provided to ascertain (only abstract available)
4.1	Was the range wide enough for the research question at hand?	–	Insufficient detail provided to ascertain (only abstract available)
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.)	–	Insufficient detail provided to ascertain (only abstract available)
4.3	Were capital costs, as well as operating costs, included?	–	Insufficient detail provided to ascertain (only abstract available)
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)	–	Insufficient detail provided to ascertain (only abstract available)
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?	–	Insufficient detail provided to ascertain (only abstract available)
5.2	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No	No special circumstances were identified

6	Were costs and consequences valued credibly?	–	Insufficient detail provided to ascertain (only abstract available)
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.)	–	Insufficient detail provided to ascertain (only abstract available)
6.2	Were market values employed for changes involving resources gained or depleted?	–	Insufficient detail provided to ascertain (only abstract available)
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?	NA	
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?)	NA	
7	Were costs and consequences adjusted for differential timing?	–	Insufficient detail provided to ascertain (only abstract available)
7.1	Were costs and consequences which occur in the future 'discounted' to their present values?	–	Insufficient detail provided to ascertain (only abstract available)
7.2	Was any justification given for the discount rate used?	NA	
8	Was an incremental analysis of costs and consequences of alternatives performed?	–	Insufficient detail provided to ascertain (only abstract available)
8.1	Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?	–	Insufficient detail provided to ascertain (only abstract available)
9	Was allowance made for uncertainty in the estimates of costs and consequences?	–	Insufficient detail provided to ascertain (only abstract available)
9.1	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	–	Insufficient detail provided to ascertain (only abstract available)
9.2	If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	–	Insufficient detail provided to ascertain (only abstract available)
9.3	Were 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)?	–	Insufficient detail provided to ascertain (only abstract available)
10	Did the presentation and discussion of study results include all issues of concern to users?	–	Insufficient detail provided to ascertain (only abstract available)
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?	–	Insufficient detail provided to ascertain (only abstract available)

Appendix 11 cont'd *Details of quality assessment for economics studies*

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?	No
10.3	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No
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)?	No
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?	No

Appendix 12

Transforming median survival to mean survival

The data provided in the company submission presented overall median survival for the evaluable population. The economic analysis within the company submission was based on mean costs in the ITT population. For the purposes of this economic review, mean survival is a more useful figure than median survival, and therefore median survival data were converted to mean survival data using the following equations.

Assuming exponential survival curves: the cumulative probability of death at time t,

$$S(t) = 1 - e^{-\lambda t}$$

where λ = hazard ratio.

Therefore, for median survival data:

$$0.5 = 1 - e^{-\lambda t}$$

Rearranging gives:

$$\lambda = \frac{-\ln(0.5)}{t}$$

Mean survival duration (area under curve)

$$= 1/\lambda$$

$$\text{Var}(\lambda) = \lambda^2/r$$

where r = number of deaths per sample.

Using the delta method,

$$\text{Var}(1/\lambda) = \text{var}(\lambda) \times \left(\frac{dA}{d\lambda}\right)^2$$

where $A = \frac{1}{\lambda} = \lambda^{-1}$

$$= \frac{\lambda^2}{r} \times (-\lambda^{-2})^2$$

$$= \frac{1}{r\lambda^2}$$

so standard error $(\lambda) = \frac{1}{\sqrt{r}\lambda}$.

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We look forward to hearing from you.

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