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Contents

Glossary and list of abbreviations

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

Glossary

Absolute risk reduction The decreased chance of having an outcome from the treatment compared to the comparator, or the increased chance of not having an outcome from the comparator compared to the treatment. In oncology, this can be considered as, for example, the reduction of 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.[1]

Advanced disease Locally advanced (stage III) and metastatic (stage IV) disease.

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 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 which 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.[1]

Duration of response Time from initial complete 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.[1]

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,

continued

Glossary *contd*

or both.[1] 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.

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.

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

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

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 Tumour regression of > 25–< 50% for all measurable tumours for ≥ 4 weeks with no new lesions appearing (measurement technique must be stated).

Measurable lesion Lesion which could be unidimensionally or bidimensionally measured by physical examination, echography, X-rays or computed tomography scan.

Medical oncologist 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.

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

Metastatic breast cancer Stage IV breast cancer.

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

Non-measurable lesion No exact measurements could be obtained, for example, pleural effusions or ascites.

Overall response A complete or partial response.

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 which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it. Hence, palliative care or palliative chemotherapy.

Partial response A decrease in tumour size of ≥ 50% 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, and 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.

continued

Glossary *contd*

Prophylaxis An intervention used to prevent an unwanted outcome.

Protocol A policy or strategy which 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 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 getting 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, that is, 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 < 25% change in measurable lesions for ≥ 4–8 weeks with no new lesions appearing.

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

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.

United Kingdom Coordinating Committee on Cancer Research The national committee responsible for coordinating clinical trials for cancer treatment in the UK.

Uncontrolled study A study that has no control group.

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

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

Values Preferences without risk or uncertainty.

List of abbreviations

ABC	advanced breast cancer
b/se(b)	effect size/standard error of the effect size
CBA	cost–benefit analysis
CEA	cost-effectiveness analysis
CER	cost-effectiveness ratio
CI	confidence interval
CMA	cost-minimisation analysis
CNS	central nervous system*
CUA	cost–utility analysis
CMF	cyclophosphamide plus methotrexate plus 5-fluorouracil
df	degrees of freedom*
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FAC	5-fluorouracil plus adriamycin (doxorubicin) plus cyclophosphamide
FAC/FEC	5-fluorouracil plus adriamycin (doxorubicin) plus cyclophosphamide/5-fluorouracil plus epirubicin plus cyclophosphamide
FAN	5-fluorouracil plus doxorubicin plus vinorelbine
FEC	5-fluorouracil plus epirubicin plus cyclophosphamide
FUN	vinorelbine plus 5-fluorouracil
G-CSF	granulocyte colony-stimulating factor
HER2	human epidermal growth factor receptor 2*
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention-to-treat
i.v.	intravenous/intravenously*
MBC	metastatic breast cancer
NA	not applicable*
NICE	National Institute for Clinical Excellence
QoL	quality of life
QALM	quality-adjusted life-month
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
1/se	1/standard error
1/se(b)	1/standard error of the effect size
SUPERFAN	folinic acid plus 5-fluorouracil plus doxorubicin plus vinorelbine

* Used only in tables, figures and appendices

Executive summary

Background

Breast cancer is the leading cause of cancer deaths amongst women in the UK. Figures suggest that about 14% of women initially presenting with breast cancer have advanced disease (stage III or IV) and about 50% presenting with early or localised breast cancer will eventually develop advanced disease.

The prognosis of metastatic breast cancer (MBC) depends on age, extent of disease, oestrogen receptor status and previous chemotherapy treatment. MBC is considered to be incurable and treatment is usually focused on relieving symptoms and improving quality of life (QoL) with as little treatment-related toxicity as possible. The choice between endocrine therapy or chemotherapy and the selection of a specific drug regimen for first-line treatment of MBC is based on a variety of clinical factors, such as what drugs have already been given as adjuvant treatment, the likelihood of benefit balanced against the adverse event profile of the given drug and the given drug's tolerability. Vinorelbine (Navelbine®, Pierre Fabre Ltd, Winchester, UK), an anti-cancer agent used in patients with advanced disease, including MBC, relapsing after anthracycline treatment, may be a useful addition to the drugs available for the treatment of MBC. It can be used in a range of combination chemotherapy regimens in first- or second-line treatment, and may be used as monotherapy for vulnerable groups, such as the elderly.

Objectives

The objectives of the review were to evaluate the clinical effectiveness and cost-effectiveness of vinorelbine in the management of breast cancer.

Methods

Only randomised controlled trials (RCTs) and full economic evaluations were initially considered for inclusion. Included trials had to evaluate vinorelbine alone or in combination with other agents versus systemic therapy without vinorelbine. Only trials that included individuals with breast cancer were included. The National Institute for Clinical Excellence (NICE) subsequently requested that non-comparative Phase II studies of vinorelbine (alone or in combination with other agents) as first-line therapy for advanced breast cancer (ABC) be evaluated for inclusion in the review. These data were added as part of an update of this review.

Several databases were searched using strategies designed specifically for each database. Additional references were identified through reviewing manufacturer and sponsor submissions made to NICE, the bibliographies of retrieved articles, conference proceedings and by searching the Internet.

Data were extracted by one reviewer and checked by a second. Quality assessment was conducted independently by two reviewers. Disagreements were resolved by consensus and, when necessary, by recourse to a third reviewer. The primary outcomes of interest were response, QoL, time to disease progression, overall survival, relief of symptoms and cost. Results of data extraction and quality assessment were presented in structured tables and as a narrative summary. Studies were grouped according to the type of therapy (first- or second-line) and intervention (monotherapy or combination therapy).

Results

Clinical effectiveness data

RCTs

Vinorelbine monotherapy

Two included RCTs investigated the use of vinorelbine monotherapy. One evaluated its use as second-line or salvage therapy for MBC, whilst the other used vinorelbine for either first- (9% of patients) or second-line or subsequent treatment for ABC, compared with melphalan and 5-fluorouracil plus leucovorin with or without mitoxantrone. The overall quality of these two trials was poor.

There were no significant differences between the intervention groups for partial, complete or overall

response, stable disease and disease progression. Time to treatment failure, progression-free survival and median overall survival were significantly longer in participants treated with vinorelbine compared with those treated with melphalan. However, melphalan is not considered to be an appropriate comparator because it is not representative of conventional treatment for MBC, which limits the generalisability of the findings to the clinical setting. When compared to 5-fluorouracil plus leucovorin with or without mitoxantrone, the median survival, duration of response and time to treatment failure appeared to be similar in all three groups. There were no significant differences between the groups in either trial for any of the reported grade 3 or 4 adverse events. One trial assessed QoL and differences between groups were not significant for all dimensions, except physical function.

Vinorelbine combination therapy
Five included RCTs investigated the use of vinorelbine in combination with other chemotherapy agents for MBC. The overall quality of these was moderate to poor.

When vinorelbine plus doxorubicin was compared with doxorubicin alone as mainly first-line therapy, there were no statistically significant differences in any of the parameters of tumour response or survival, adverse events or QoL measures. These data would suggest that the addition of vinorelbine conferred little, if any, treatment benefit above that of doxorubicin alone. However, it is unclear whether the non-significant results are due to a small sample size or the fact that the interventions are similar. In addition, 80% of the participants were treated with a dose (20 mg/m^2) that is lower than that recommended for vinorelbine when used in combination schedules, due to the occurrence of febrile neutropenia.

No statistically significant differences in effectiveness or adverse events were identified when vinorelbine plus doxorubicin was compared with 5-fluorouracil plus doxorubicin plus cyclophosphamide (FAC) for first-line therapy. Similarly, there were no statistically significant differences between vinorelbine plus mitoxantrone and 5-fluorouracil plus doxorubicin or epirubicin plus cyclophosphamide (FAC/FEC) in tumour response or progression-free or overall survival. However, serious febrile neutropenia was more frequent in the vinorelbine/mitoxantrone group, whilst severe nausea and vomiting and alopecia occurred more frequently in the FAC/FEC group.

The comparison of vinorelbine plus docetaxel with docetaxel plus gemcitabine as second-line therapy found no statistically significant differences between the treatments for tumour response. No survival data were reported.

Little data were available for the final trial, which compared vinorelbine plus 5-fluorouracil with docetaxel as first- or second-line therapy (available as an abstract only). Median progression-free survival appeared similar, but there were no statistical comparisons. No tumour response data were reported. The report suggested that toxic deaths in the vinorelbine groups were more frequent, however, the reliability of the reporting is debatable.

The findings of the individual combination therapy RCTs may not be reliable: none of the findings detailed above can be considered definitive. Unfortunately, the use of different combinations and different comparators means that the results of individual trials could not be directly combined in an attempt to derive a more precise estimate of the effectiveness of vinorelbine used as combination therapy. It is also not possible to discern the true effect of vinorelbine itself from that of any interaction that occurs between vinorelbine and other agents when used in the different combinations included in this review.

Uncontrolled Phase II studies
Fourteen uncontrolled studies of vinorelbine monotherapy and 51 of combination therapy were included in the review. These studies were clinically diverse, investigating various vinorelbine-based regimens in a range of populations. Many of the studies were small with limited follow-up times. Only a few subsets of studies, where the diversity appeared to be minimal, were investigated by statistical pooling and even these results must be interpreted with caution.

Overall, for intravenous vinorelbine monotherapy, the complete tumour response rate ranged from 0 to 20% and the overall tumour response rate ranged from 0 to 60%. Median duration of overall tumour response ranged from 1.8 to 9 months, median overall survival ranged from 9.9 to 16.8 months, median time to disease progression ranged from 3 to 6 months and median time to treatment failure ranged from 4.6 to 6 months.

For vinorelbine combination therapy, complete tumour response ranged from 5 to 32% and overall tumour response ranged from 22 to

79%. Studies of vinorelbine plus doxorubicin reported complete and overall tumour response rates ranging from 6 to 32% and 29 to 74%, respectively. For vinorelbine used in combination with epirubicin, reported complete and overall tumour response rates were 6–19% and 50–77%, respectively. Studies of vinorelbine plus paclitaxel reported overall tumour response as 47–67%. Other combinations were investigated in small numbers of clinically diverse studies. For all combination studies, the median duration of overall tumour response ranged from 6 to 16 months, and the median overall survival ranged from 12.3 to 31 months. The median time to disease progression ranged from 3.9 to 15 months, and median time to treatment failure ranged from 7 to 12 months.

Vinorelbine monotherapy may be particularly associated with leukopenia, granulocytopenia, nausea/vomiting and constipation. Vinorelbine combination therapy appeared to be associated with neutropenia, alopecia and nausea/vomiting, although different combinations had differing profiles, the exact nature of which were difficult to discern from the limited data available.

Comparison of effectiveness data from RCTs and uncontrolled Phase II studies

The evidence from uncontrolled Phase II studies appeared to complement the RCT findings. However, Galbraith and funnel plots showed that the findings of the uncontrolled studies did not compensate for the lack of available RCTs. In other words, the data from the uncontrolled studies on their own were inadequate due to clinical diversity, statistical heterogeneity and lack of precision. This was in addition to the fact that uncontrolled studies provide a lower level of evidence due to the biases and lack of rigour that are inherent in such studies.

Economic data

The economic data included in the review were not comparable with the effectiveness data (that is, the same interventions were not assessed). Four economic evaluations were included in the review. Three examined vinorelbine, docetaxel and paclitaxel and one compared capecitabine, vinorelbine, 5-fluorouracil and gemcitabine. The three economic evaluations of vinorelbine, docetaxel and paclitaxel were fairly well conducted. For the remaining economic evaluation, there was insufficient information to properly judge the overall quality of the analysis because it was only available as an abstract.

Only one economic evaluation (based in Canada) comparing vinorelbine, docetaxel and paclitaxel found vinorelbine to be the dominant treatment (more effective and less costly than paclitaxel and docetaxel). The average cost per quality-adjusted progression-free year was Can$31,220 for vinorelbine, Can$59,096 for paclitaxel and Can$110,072 for docetaxel. One economic evaluation (based in the UK) found vinorelbine to be less effective and less expensive than both docetaxel and paclitaxel for the treatment of ABC. Docetaxel was found to be more effective and more expensive than vinorelbine and paclitaxel. The incremental cost per quality-adjusted life-year for docetaxel were £14,500 compared with vinorelbine and £1990 compared with paclitaxel. However, it was noted that the economic evaluation was sponsored by Aventis, who manufacture docetaxel. The third economic evaluation (based in France) found docetaxel to be dominant, and vinorelbine, when compared to docetaxel, was found to have higher costs and poorer outcomes. When generalising these data to the UK, vinorelbine is usually considered as an alternative to taxane therapy for patients who cannot tolerate intensive treatment, rather than a replacement for it.

In the comparison of capecitabine, vinorelbine, 5-fluorouracil and gemcitabine, capecitabine was reported to be the most cost-effective therapy for the treatment of anthracycline-resistant MBC with a cost-effectiveness ratio of Can$1436 and a marginal cost-effectiveness ratio of Can$687 per quality-adjusted life month with 5-fluorouracil as the reference therapy. However, capecitabine is not currently licensed in the UK for MBC, which limits the generalisability of the findings to the NHS.

Conclusions

According to the evidence derived from RCTs, vinorelbine monotherapy as first-line, second-line or subsequent therapy for ABC, may be more effective in terms of progression-free survival and survival than melphalan. However, melphalan is not representative of conventional treatment for MBC, which limits the generalisability of the findings to the clinical setting. Vinorelbine monotherapy was not found to be more effective than other chemotherapy regimens in terms of response rates. In addition, the poor quality of the data on which these findings were based should be borne in mind.

Vinorelbine as combination therapy with doxorubicin, 5-fluorouracil or mitoxantrone did not

appear to be more effective than alternative combinations of chemotherapy in the treatment of MBC. Vinorelbine plus mitoxantrone may be associated with less nausea/vomiting and alopecia than FAC/FEC, but may result in more febrile neutropenia.

The evidence from RCTs show that there were no data to support the use of vinorelbine either as a single agent or in combination over standard first-line chemotherapy with anthracyclines or other non-taxane containing regimens. The efficacy and toxicity profiles were similar, with no suggestion of superiority over existing treatments. Vinorelbine may be one possible option when an alternative agent is required.

The evidence from uncontrolled Phase II studies appeared to indicate that vinorelbine has anti-tumour activity and an acceptable toxicity profile, but may be associated with leukopenia, granulocytopenia, nausea/vomiting and constipation when used as monotherapy and neutropenia, alopecia and nausea/vomiting when used in combination. The data from the uncontrolled studies on their own were inadequate due to the clinical diversity, statistical heterogeneity and lack of precision. This was in addition to the fact that uncontrolled studies are of a lower level of evidence due to the biases and lack of rigour that are inherent in such studies.

The economic studies included in the review tended to compare vinorelbine with taxane therapy. When comparing the cost-effectiveness of vinorelbine, paclitaxel and docetaxel one economic evaluation found vinorelbine to be the most cost-effective intervention, one found vinorelbine to be the least expensive but also the least effective, and another found docetaxel to be the most cost-effective.

Implications for further research

The review identified the following areas for future research.

1. Further large well-conducted RCTs are required to investigate the use of vinorelbine alone or in combination with other chemotherapy agents.
2. Further cost-effectiveness analyses of vinorelbine used in the same combinations as examined in the included trials are required.

Chapter 1

Objectives and background

Objectives of the review

The objectives of the review were to evaluate the clinical effectiveness and cost-effectiveness of vinorelbine (Navelbine®, Pierre Fabre Ltd, Winchester, UK) in the management of breast cancer.

Description of the underlying health problem

Breast cancer is the leading cause of death amongst women aged 35–54 years in the UK.[2] It is the most common cause of death due to malignancy, with over 13,000 deaths reported in 1998.[3] About 35,000 new cases of the disease were reported in 1996.[3]

The aetiology of breast cancer is unclear, although it is likely that hormonal and genetic factors play a role.[4] The incidence of breast cancer increases with age, doubling every year up until menopause.[1] Risk factors include early age of first menarche, later age of first full-term pregnancy, late menopause and a family history of breast cancer.[5]

Figures suggest that about 14% of women initially presenting with breast cancer have advanced disease (stage III or IV, see appendix 1)[6] and approximately 50% of patients presenting with early or localised breast cancer will eventually develop advanced disease.[7,8]

The risk of metastatic breast cancer (MBC), that is, stage IV, relates to known prognostic factors in the original primary tumour. These factors include grade of tumour, oestrogen receptor-negative disease, primary tumours ≥ 3 cm in diameter and axillary node involvement.[1] The findings of a systematic review showed that recurrence occurred within 10 years of adjuvant chemotherapy for early breast cancer in 60–70% of node-positive women and 25–30% of node-negative women.[1]

MBC is considered to be incurable and its prognosis is dependent on age, extent of disease, oestrogen receptor status[1] and previous chemotherapy treatment. Median survival after diagnosis of advanced breast cancer (ABC; stage III or IV) has been reported to be 18–24 months.[9] In women who receive no treatment for metastatic disease, the median survival from diagnosis of metastases is 12 months.[1] For most patients with MBC, treatment provides only temporary control of cancer growth.[10] Treatment is, therefore, usually focused on relieving symptoms and improving quality of life (QoL) with as little treatment-related toxicity as possible.

Current service provision

The choice between endocrine therapy or chemotherapy and the selection of a specific drug regimen for first-line treatment of MBC is based on a variety of clinical factors, such as hormone receptor status, what drugs have already been given as adjuvant treatment, the likelihood of benefit balanced against the adverse event profile of the given drug and the given drug's tolerability.[1]

First-line therapy for MBC usually consists of cyclophosphamide plus methotrexate plus 5-fluorouracil (CMF) or an anthracycline-containing regimen. However, a patient is unlikely to respond well to a drug given previously as adjuvant therapy.[8] A short disease-free interval (e.g. < 1 year) between surgery and adjuvant therapy and the development of metastases suggests that the MBC is likely to be resistant to the adjuvant drug used.[1] This means that other agents need to be considered for first-line treatment of MBC.

In addition, an emerging problem is a subgroup of women with good performance status who have not responded to anthracycline-based combination therapy as first-line treatment for MBC or who have relapsed within a few months of adjuvant chemotherapy.

Vinorelbine is an anti-cancer agent that may be a useful addition to the drugs available for the treatment of locally advanced disease (stage III) or MBC. It is marketed for patients who have failed to respond to anthracycline and taxane regimens, without unacceptable toxicity. The data available regarding this possible clinical use are appraised in this report.

Description of the technology

Identification of patients and criteria for treatment

Vinorelbine is used in patients with ABC/MBC relapsing after anthracycline treatment. It offers a range of combination chemotherapy regimens for use in first- or second-line treatment, and may be used as monotherapy for vulnerable groups, such as the elderly.[11]

Intervention

Vinorelbine (Navelbine) is a semi-synthetic vinca alkaloid with cytostatic activity against a broad range of tumour cell lines including breast cancer.[12] It inhibits tubulin polymerisation, which causes the dissolution of mitotic spindles and the prevention of cell division. Although it has potent activity against mitotic microtubules compared with other vinca alkaloids, *in vitro* studies have found that vinorelbine has a diminished effect on axonal microtubules, the class of microtubule associated with neurotoxic effects.[12] Hence, the drug is believed to have a more favourable profile in terms of side-effects than other currently used vinca alkaloids.

Current indications for vinorelbine

Vinorelbine was launched in the UK for the treatment of ABC in June 1997.[11] However, no recommendations or guidance have been issued in the UK about its role. Vinorelbine is indicated for the treatment of ABC stage III and IV, and ABC relapsing after or refractory to an anthracycline-containing regimen.[13] In this context, vinorelbine may be used as:[11]

- first-line treatment of ABC, either in combination therapy or as a monotherapy, following failure of adjuvant anthracycline therapy
- second-line or later treatment, either in combination therapy or as a monotherapy, following failure of first-line treatment of ABC with an anthracycline-containing regimen.

Vinorelbine is available in 1 and 5 ml vials at a concentration of 10 mg/ml. The net price is £31.25 for a 1 ml vial and £147.06 for a 5 ml vial.[13]

An average patient (body surface area 1.7 m^2) would require between 42.5 and 51 mg vinorelbine per infusion. The maximum single dose is 60 mg. For the average patient, the usual dose can be achieved with one 5 ml vial and the maximum dose with one 5 ml vial plus one 1 ml vial. The usual dose would cost £147 per infusion, with a maximum cost of £178 (£2.96 per mg used). If the average patient receives nine doses, then the median cost per patient at the usual dose would be £1324 for a full course of treatment with vinorelbine.[11]

Summary of current manufacturers information provided for health professionals[13]

Recommended dosage

Vinorelbine is licensed for intravenous administration. An oral form (soft liquid-filled gelatin capsule) is available, but its use is currently limited to clinical trials. Vinorelbine is usually given intravenously at 25–30 mg/m^2 per week. It may be administered by slow bolus (5–10 minutes) after dilution in 20–50 ml of normal saline solution or by a short infusion (20–30 minutes) after dilution in 125 ml of normal saline solution. In these cases, administration should always be followed by a normal saline infusion to flush the vein. The maximum tolerated dose per administration is 35.4 mg/m^2 and the maximum total dose per administration is 60 mg.

Contraindications

- Pregnancy.
- Lactation.
- Severe hepatic insufficiency not related to the disease process.

Special warnings and special precautions for use

- The intra-thecal route should not be used.
- Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver.
- Haematological monitoring (haemoglobin, leukocytes, granulocytes and platelets) should accompany treatment. If patient's neutrophil count is < 2000/mm^3 and/or platelet number is < 75,000/mm^3, treatment should be delayed until the counts have recovered.
- Signs of infection should be promptly investigated.
- The dose should be reduced if there is substantial hepatic impairment.
- All contact with the eye should be avoided due to the risk of severe irritation and possibly corneal ulceration. Immediate liberal washing with saline is recommended.

Adverse effects

The dose-limiting toxicity of vinorelbine is mainly neutropenia. This commonly occurs between days 8–12, but is short-lived and not cumulative. Other adverse effects include neurological problems (peripheral or autonomic neuropathy), gastrointestinal problems (constipation, diarrhoea and nausea/vomiting), allergic reactions and

venous intolerance (local phlebitis and burning at injection site). Patients with neurological toxicity commonly experience peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain and constipation. If neurosymptoms are severe, doses should be reduced. Motor weakness can also occur, which calls for discontinuation of treatment. Generally, recovery of the nervous system is slow but complete. Other undesirable effects include alopecia (generally reversible). In addition, vinca alkaloids can cause severe irritation and care must be taken to avoid extravasation.

Chapter 2
Methods

Objectives

The objectives of the review were to evaluate the clinical effectiveness and cost-effectiveness of vinorelbine (Navelbine) in the management of breast cancer. Only randomised controlled trials (RCTs) of vinorelbine alone or in combination with other agents versus systemic therapy without vinorelbine were initially considered in the assessment of clinical effectiveness. The assessment of cost-effectiveness included only full economic evaluations. The National Institute for Clinical Excellence (NICE) since requested that non-comparative Phase II studies of vinorelbine (alone or in combination with other agents) used as first-line therapy for ABC be evaluated for inclusion in the review. These data have subsequently been added to this review.

Inclusion and exclusion criteria

Titles (and, where possible, abstracts) of studies identified from all searches and sources (see appendix 2) were assessed independently by two reviewers for relevance. If either reviewer considered the paper to be potentially relevant, a full paper copy of the manuscript was obtained. Each full paper copy was reassessed for inclusion using the criteria listed below. Studies that did not meet all of the criteria were excluded and their bibliographic details were listed, along with the reason for exclusion. Information relating to inclusion of trials highlighted by the industry submissions is presented in appendix 3. Any disagreements were discussed in order to obtain a consensus and if no agreement was reached a third reviewer was consulted.

Interventions

Vinorelbine (Navelbine) alone or in combination with other agents versus systemic therapy without vinorelbine were included. When updating the review, vinorelbine was only considered when used as first-line treatment for ABC.

Participants

For the initial review, patients with breast cancer, encompassing all stages of disease, were included. Where possible, the stage of disease was defined using the simplified Union Internationale Contre le Cancer staging system (see appendix 1). When updating the review, only patients with ABC (locally advanced (stage III) or metastatic (stage IV) disease) were included.

Study design

The ultimate standard for the evaluation of medical treatments is the Phase III RCT.[14] For the evaluation of clinical effectiveness, only RCTs were initially included in the review. For the update section of the review that was to include uncontrolled Phase II studies of vinorelbine used as first-line therapy for ABC, non-randomised studies, such as cohort studies, case–control studies and case series, were included. However, the findings of these studies should be interpreted with caution because, in contrast to high-quality RCTs, confounding and selection bias often distorts the findings of such studies.[15] Within the pharmaceutical industry, Phase II studies represent the initial clinical investigation,[16] which are usually single-arm studies involving about 14 to 90 patients.[14] Studies that include less than 14 participants were, therefore, excluded.

To evaluate the cost-effectiveness of vinorelbine, the following economic evaluations were considered:

- cost-effectiveness analyses (CEAs), including cost-minimisation analyses (CMAs) and cost–consequence analyses
- cost–utility analyses (CUAs)
- cost–benefit analyses (CBAs).

Outcome measures

The following outcome measures were included in the review:

- tumour response (including complete and partial response)
- progression-free survival
- overall survival
- symptom relief
- QoL
- adverse effects (haematological toxicity, including neutropenia, thrombocytopenia and anaemia, non-haematological toxicity, including nausea, diarrhoea, constipation,

stomatitis, abdominal pain, fatigue, asthenia, alopecia, anorexia, malaise and hyperbilirubinaemia and any other adverse effects judged to be appropriate)
- cost.

Search strategy

The databases searched for relevant literature were MEDLINE, EMBASE, CANCERLIT, BIOSIS, Index to Scientific and Technical Proceedings (ISTP), Cochrane Controlled Trials Register (CCTR), DARE, NHS EED and National Research Register. More detailed information about the search strategy is presented in appendix 2.

Bibliographies of all included articles were searched for additional references. Manufacturer and sponsor submissions made to NICE were also reviewed to identify additional studies. The Internet was searched for information on ongoing trials.

When updating the review (for the inclusion of non-comparative Phase II studies), the original searches were performed again without the RCT and economic evaluation methodological search filters. Methodological filters were not used in the original searches for the BIOSIS, ISTP, CCTR and National Research Register databases, so the searches remained exactly the same for these databases.

Data extraction strategy

Data extraction was conducted by one reviewer using predefined data extraction forms and checked by a second reviewer. Any disagreement was resolved by consensus, and if this was not reached a third reviewer was consulted. Due to time constraints, only studies reported in English (for both effectiveness and economic data), German, Dutch and French (for effectiveness data only) were included in the report. However, the search strategy included all languages and the bibliographic details of non-English language studies are presented in the tables of excluded studies (appendix 4).

The following types of data were extracted and summarised: specific details about the interventions, the population investigated and the outcome measures used. Studies that have been reported in multiple publications were collated and reported only once.

Where sufficient data were presented, an estimation of the treatment effect along with the 95% confidence interval (CI) was calculated for each individual study. Where possible, this was done on an intention-to-treat (ITT) basis. For dichotomous outcome measures, the relative risk (RR) was calculated. For time to event outcomes (e.g. survival), hazard ratios (HRs) were not reported by included studies. The median values and any measures of variance are, therefore, presented.

In order to assess the economic data in terms of the clinical effectiveness of the intervention (i.e. the direction of the cost-effectiveness data and the magnitude of effectiveness data), each study was given a summary grading (A–I) according to the level and direction of dominance (i.e. whether the intervention of interest should be preferred over the comparator). Extended dominance indicates that both the effectiveness data and the economic data support the use of either the intervention or the comparator and the decision on resource allocation is clear. When only the economic or the effectiveness data supports the intervention/comparator, the dominance is said to be partial or weak and a decision can still be made. However, if there is no dominance indicated then further incremental cost analysis may be required in order to estimate the incremental cost-effectiveness ratio (CER). This is important in helping the decision-making process. The matrix shown in *Figure 1* illustrates all of the possible permutations, and was used to assign each study a summary grading.[17,18]

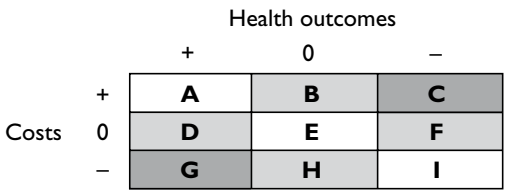
Quality assessment strategy

The methodological quality of each included study was assessed using predefined checklists (see appendix 5). Two reviewers conducted this process independently. Any disagreements were resolved by consensus and a third reviewer was consulted if required.

Methods of analysis/synthesis

Results of data extraction and quality assessment are presented in structured tables (see appendices 6–8) and also as a narrative summary. Studies are grouped according to the type of intervention (monotherapy or combination therapy) and study design used. The results from the uncontrolled studies (identified whilst updating the review) are compared to the overall findings of the RCTs that were included in the initial review.

Both RCTs and uncontrolled (Phase II) studies were assessed for clinical diversity and, where appropriate, statistical heterogeneity. Where there was no significant diversity or statistical heterogeneity, pooled estimates of effects were calculated.



- strong dominance for decision in either direction (i.e. in favour of the intervention or comparator)
- weak dominance for decision
- non-dominance; no obvious decision

Implication of findings

Code	Implication for intervention	Summary of the direction of the cost-effectiveness data and the magnitude of the effectiveness data
A	Trade-off	Higher costs but better outcomes (incremental analysis required)
B	Reject	Higher costs and no difference in outcomes
C	Reject	Higher costs and poorer outcomes
D	Accept	No difference in costs and improved outcomes (partial dominance)
E	Neutral	No difference in costs and no difference in outcomes
F	Reject	No difference in costs and poorer outcomes
G	Accept	Lower costs and improved outcomes (extended dominance)
H	Accept	Lower costs and no difference in outcomes (partial dominance)
I	Trade-off	Lower costs but poorer outcomes (incremental analysis required)

FIGURE 1 *Incremental cost of intervention compared to control*

For the initial review, it was not possible to investigate the extent of publication bias due to the limited number of included studies. Sensitivity analyses were also not undertaken for the same reason. For the update review, publication bias among observational studies is evaluated using funnel plots.

A narrative summary of the cost-effectiveness data is presented considering the methods of analysis used, the sources of effectiveness and cost data, the quality of the economic evaluation and the generalisability of the findings to the UK setting.

The number of excluded studies, along with the reason for exclusion is presented in the results section of the report. The bibliographic details of studies that did not meet the inclusion criteria (including those that included less than 14 participants and Phase II studies of vinorelbine used as second-line therapy for ABC) have been tabulated, along with the reason for exclusion, and presented in appendix 4.

Chapter 3

Results – clinical effectiveness

The evidence base for vinorelbine is shown in *Table 1*.[19–93]

Quantity and quality of included RCTs

Excluded studies

During the initial review process, 82 studies were ordered as full papers and then excluded when the inclusion criteria were applied by two reviewers independently. Details of these studies are presented in appendix 4. Nine were non-systematic reviews,[12,94–100] 60 were vinorelbine trials that did not include a comparison group,[43,49,51,53,66,73–75,101–152] two were case studies or case reports of side-effects,[153,154] three administered vinorelbine in both trial arms,[155–157] two were not vinorelbine trials,[158,159] three were not trials,[116,160,161] one was an abstract for a systematic review,[162] one was a critique of an included economic evaluation[163] and one was a non-RCT.[164]

Whilst updating the review to include data from uncontrolled studies of vinorelbine used as first-line therapy for ABC, 19 studies that were initially excluded were subsequently included.[43,49,51,53,66,73–75,99,115,122,129,132–135,142,148,152] A list of planned and ongoing trials is presented in appendix 9.

Included RCTs

Vinorelbine monotherapy

Two trials investigated the use of vinorelbine monotherapy.[33,38] Their details are summarised in *Table 2*[11,33,38,39–41,92,93,165–176] and appendix 6. Venturino and colleagues[33] evaluated its use as second-line or salvage therapy for MBC, whilst Jones and colleagues[38] used vinorelbine for either first-line (9% of patients), second-line or subsequent treatment (91% of patients) for ABC. The numbers of participants included in the two trials were 183[38] and 99.[33]

The dose of vinorelbine used in both trials was 30 mg/m^2 intravenously once a week. Jones and colleagues reported that the dose had to be reduced in 66% (76/115) of participants and 75% (86/115) required a delay in dosing.[38] The dose intensity actually delivered was 19.3 mg/m^2/week for vinorelbine and 4.8 mg/m^2/week for melphalan. The median number of cycles was nine in one trial[38] and seven (range 2–15) in the second trial.[33]

The type of chemotherapy regimen used as the comparator included melphalan 25 mg/m^2 intravenously every 4 weeks[38] and the L-isomer of leucovorin (100 mg/m^2) followed by 5-fluorouracil (370 mg/m^2) intravenously on days 1–3 or days 1–5 every 28 days, with or without mitoxantrone (12 mg/m^2) intravenously on day 1.[33] The median number of cycles for melphalan was two.[38] The median number of cycles used for leucovorin plus 5-fluorouracil was five (range 2–8) with mitoxantrone and six (range 2–8) without mitoxantrone.[33] The length of follow-up was not reported in either trial. The survival curves reported by Jones and co-workers ran up to 800 days.[38]

Vinorelbine combination therapy

Five RCTs investigated the use of vinorelbine in combination with other chemotherapy drug(s) as either first-[39–41,92] or second-line therapy of ABC or MBC.[92,93] Their details are summarised in *Table 2* and appendix 6. The sample size for the included trials of vinorelbine as combination therapy ranged from 34[93] to 303.[41]

Two trials studied vinorelbine in combination with doxorubicin.[39,41] Both trials initially used 25 mg/m^2 of vinorelbine intravenously on days 1 and 8 and 50 mg/m^2 of doxorubicin intravenously on day 1 every 21 days. However, Norris and co-workers modified the dose regimen 10 months into the trial because 16 of the first 65 participants randomised suffered from febrile neutropenia.[41] Subsequent doses were 20 mg/m^2 for vinorelbine and 40 mg/m^2 for doxorubicin. This subsequent dose is lower than the recommended dose for vinorelbine combination schedules, which is 25–30 mg/m^2. The median number of cycles for the vinorelbine plus doxorubicin treatment group in one trial was four (range 1–10)[39] and the approximate number of cycles given in the second trial was 11.[41]

The comparator drug used in both trials of vinorelbine plus doxorubicin differed. One trial, reported by Blajman and colleagues, used 5-fluorouracil plus adriamycin (doxorubicin) plus cyclophosphamide (FAC) at doses of 500 mg/m^2, 50 mg/m^2 and 500 mg/m^2, respectively,

intravenously on day 1 every 21 days.[39] The second trial, reported by Norris and colleagues, used doxorubicin at 70 mg/m^2 intravenously on day 1 every 21 days.[41] This dose regimen was then modified to 60 mg/m^2 10 months into the trial. The median number of cycles for the FAC treatment group was five (range 1–10) and the approximate number of cycles given to participants treated with doxorubicin was seven.

For the remaining three trials, Monnier and colleagues[92] examined vinorelbine (25 mg/m^2 given on days 1 and 5) in combination with 5-fluorouracil (750 mg/m^2/day on days 1–5 continuously; FUN), Namer and co-workers[40] evaluated the use of vinorelbine (25 mg/m^2 intravenously on days 1 and 8 if the level of neutrophils was ≥ 1000/mm^3) combined with mitoxantrone intravenously every 21 days, and Frasci and colleagues[93] investigated vinorelbine (25 mg/m^2 intravenously on days 1 and 8) in combination with escalating doses of docetaxel (starting from 30 mg/m^2). The median number of cycles for the FUN treatment group was six (range 1–9) and the median number of cycles for participants treated with vinorelbine plus mitoxantrone was six (range 1–18). The total number of cycles of vinorelbine plus docetaxel administered was 53.

The comparator chemotherapy regimen for the above two trials included docetaxel 100 mg/m^2 intravenously every 3 weeks,[92] a combination of 5-fluorouracil (500 mg/m^2 intravenously) and cyclophosphamide (500 mg/m^2 intravenously), with either adriamycin (doxorubicin; 50 mg/m^2 intravenously) or epirubicin (50 mg/m^2 intravenously; FAC/FEC) repeated every 21 days,[40] and gemcitabine (1000 mg/m^2) plus escalating doses of docetaxel (starting from 30 mg/m^2).[93] The median number of cycles for the docetaxel treatment group was six (range 1–12) and the median number of cycles for participants treated with FAC or FEC was five (range 1–12). The total number of cycles administered in the gemcitabine plus docetaxel treatment group was 41.

Two trials (one was published as an abstract by Monnier and colleagues, 1998[92]) did not state the length of follow-up.[92,93] The median length of follow-up for the remaining three trials were 24,[40] 29[41] and 60 months.[39]

Quality of included RCTs

A summary of the quality of the included vinorelbine trials is presented in *Table 3*,[33,38–41,92,93] which relates to the checklist presented in appendix 5.

Randomisation

Proper randomisation with concealment of allocation means that selection bias is avoided. This should include an adequate procedure for generating a random number list, which ensures that all participants have a prespecified (very often equal) chance of being assigned to the experimental or control group,[177] as well as concealed allocation of the interventions by an independent person who is not responsible for determining the eligibility of patients. Foreknowledge of group assignments leaves the allocation sequence subject to manipulation by researchers and participants.[177]

The method of randomisation used was not reported for either trial that investigated vinorelbine monotherapy. It was, therefore, not possible to assess whether the procedure was adequate or if the treatment allocation had been concealed.[33,38] Both trials reported the number of participants that were randomised and the number of evaluable patients.

For trials that evaluated vinorelbine as combination therapy, only one trial reported an adequate method of randomisation. Namer and colleagues reported that participants were randomised using computer-generated numbers.[40] Frasci and co-workers reported that eligible participants were 'alternatively enrolled' in one of two treatment groups.[93] The randomisation procedure for this trial was, therefore, considered to be inadequate. It was not possible to assess the adequacy of the method used to randomise participants in the remaining three trials due to insufficient information.[39,41,92]

Allocation of treatment, to either vinorelbine as combination therapy or control, was considered to have been concealed in two trials. This was reported to have been conducted at a centralised pharmacy point.[40,41] Namer and co-workers investigated vinorelbine in combination with mitoxantrone[40] and Norris and colleagues evaluated the use of vinorelbine in combination with doxorubicin.[41] The remaining three trials of vinorelbine as combination therapy did not report whether allocation had been concealed.[39,92,93] However, due to the method of randomisation used in two trials, it was decided that allocation had not been adequately concealed.[39,93] Blajman and colleagues reported using block randomisation using a block size of four.[39] This means that after the randomisation of two or three participants it may have been possible for trial investigators or clinicians to guess to what intervention the next randomised participant would be allocated, introducing the

possibility of selection bias. Baseline characteristics of participants for this study showed a large discrepancy between groups for prior chemotherapy, possibly indicating that the randomisation procedure may not have been adequate. In other words, the two intervention groups for this trial were not comparable at baseline to an extent that it may have influenced the prognosis of included participants and, therefore, should have been corrected for in the analysis. Frasci and colleagues reported alternating treatment group assignments, which meant that it would have been very easy for the trial investigators to guess what intervention group the next participant would have been allocated to receive.[93]

All five trials of vinorelbine as combination therapy stated the number of participants that were randomised as well as the number of evaluable participants. One trial reported by Monnier and colleagues was published as an abstract and included an interim report, having recruited 178 participants out of the planned 180 participants.[92]

Baseline characteristics

The two trials that evaluated vinorelbine monotherapy reported some baseline characteristics for all groups. Both trials reported on previous therapy. Venturino and co-workers investigated the use of second-line therapy for MBC,[33] and Jones and colleagues used vinorelbine for mainly second-line or subsequent treatment for ABC.[38] Both trials reported how many participants had received previous anthracycline chemotherapy, but only Jones and co-workers reported how many had had previous exposure to vinorelbine.[38] Further baseline characteristics reported by the trials included age,[33,38] Karnofsky performance scale scores above 70,[38] Eastern Cooperative Oncology Group (ECOG) performance status scores,[33] menopausal status,[38] oestrogen receptor status,[33,38] sites of metastases,[33] dominant site of metastases[38,166] and having two or more metastatic sites.[38] Jones and co-workers only reported percentage values for these characteristics (except for age).[38]

Baseline comparability may not have been achieved by either trial of vinorelbine monotherapy. For one trial, the three intervention groups differed at baseline with regard to dominant site of metastases. For the second trial, the percentage of participants ≥ 65 years of age was slightly higher in the melphalan group, and a slightly greater proportion of participants in the vinorelbine group had lymph node metastases.[38] Only controlling for these in the analysis may show their impact.

All five trials that evaluated vinorelbine as combination therapy reported on some baseline characteristics in addition to previous treatment. These included age,[39-41,93] sites of metastases,[39,40,92,93] number of involved metastatic sites,[39–41,92] performance status,[40,41] menopausal status,[39,40] oestrogen receptor status[39,41,93] and disease-free interval.[40,41] However, Monnier and colleagues[92] only reported proportions for each characteristic, and Frasci and co-workers[93] only reported on the characteristics of the sample population as a whole and not separately for the two intervention groups.

Namer and colleagues reported that baseline characteristics were well balanced between the two treatment groups, however, they did not report on histology, stage of disease (women with stage III or IV disease were eligible for inclusion), disease bulk or the number of previous regimens.[40] Monnier and colleagues also reported that the treatment groups were comparable at baseline, but only reported information on three baseline characteristics with the addition of previous therapy.[92] Norris and co-workers reported that both study groups (vinorelbine plus doxorubicin versus doxorubicin alone) were comparable at baseline in terms of all of the characteristics investigated apart from the number of patients with bone metastases (66% in the intervention and 55% in the control group) and pleural effusions (18% in the intervention and 30% in the control group).[41] Participants in the trial reported by Blajman and colleagues were also considered not to be comparable at baseline for one of the reported characteristics (negative hormone receptor status was 21% in the intervention and 11% in the control group).[39] It was not possible to ascertain the baseline comparability of the two treatment groups in the trial reported by Frasci and co-workers due to lack of data.[93]

Although all four trials of combination therapy reported information on how many participants received previous chemotherapy, only Namer and colleagues[40] and Frasci and co-workers[93] reported data on the number of participants who had received previous adjuvant anthracycline therapy. These data were presented for the sample population as a whole and not according to the individual treatment groups for the trial reported by Frasci and colleagues.[93] Monnier and colleagues, who evaluated vinorelbine as first- or second-line therapy, did not report participants' previous

therapy for MBC.[92] Only percentages of participants who had received prior chemotherapy in the four settings (adjuvant/neoadjuvant only, advanced disease only or adjuvant and advanced disease) were presented.

Eligibility criteria

Both trials that evaluated vinorelbine monotherapy reported information on the inclusion and exclusion criteria that were used.[33,38] Four of the included trials that evaluated vinorelbine as combination therapy reported information on the inclusion and exclusion criteria.[39–41,93]

Co-interventions stated

Only one of the included vinorelbine trials reported on whether participants received any other medications, such as those used to alleviate the symptoms of adverse effects (e.g. anti-emetic drugs). Frasci and colleagues reported that oral dexamethasone was used to reduce the incidence of hypersensitivity reactions and fluid retention.[93]

Blinding

Whilst blinding of administrators and patients (the criteria for a double-blind trial) is unlikely in RCTs of intravenous chemotherapy due to the nature of the disease and of the drugs being given, blind outcome assessment is still feasible (e.g. using an independent committee). The reason that blind outcome assessment is important is that it avoids observer bias and is, therefore, essential for any subjective clinician-evaluated outcome measures, such as alleviation of symptoms and QoL.

One vinorelbine monotherapy trial was not blinded.[38] The other did not report information regarding blinding.[33] One of the combination therapy trials (FUN)[92] was unblinded, but no details of blinding were reported in the four other trials.[39–41,93]

Follow-up ≥ 80%

All seven trials were considered to have followed up 80% or more of the participants.[33,38–41,92,93]

Reasons for withdrawals

For trials that evaluated vinorelbine monotherapy, the reasons for withdrawals were not stated by Venturino and colleagues,[33] and Jones and co-workers did not report the number of participants who withdrew prior to receiving treatment according to their allocated treatment group.[38] In the second trial, the reason was not stated for those who withdrew due to adverse events, but the rates were presented by intervention group.[38]

The percentages of withdrawals due to adverse effects reported by Jones and colleagues were 24.4% in the vinorelbine group after course 1 and 82.6% after course 4 and 51.6% in the melphalan group after course 1 and 90.6% after course 4.[38] The same trial reported that survival at 1 year was 35.7% for participants treated with vinorelbine and 21.7% for participants treated with melphalan. The Kaplan–Meier survival curves were presented and ran up to 800 days, at which point < 12% of the randomised participants were included.

For vinorelbine used as combination therapy, the reasons for withdrawal were only reported by Blajman and co-workers[39] and Frasci and colleagues.[93] However, Blajman and co-workers did not report these according to the two intervention groups. Namer and co-workers reported the number of participants who were withdrawn because they did not meet the eligibility criteria but did not give any further details than this.[40] Norris and colleagues reported that three women withdrew post-randomisation and the reasons for withdrawal were presented.[41] However, the same trial also reported that a further 14 participants could not be assessed for response for which reasons were not presented. The reasons for withdrawals in the final vinorelbine combination therapy trial were not stated.[92]

ITT

Using an ITT analysis means that participants are analysed according to the groups to which they were initially randomly allocated, regardless of whether or not they dropped out, fully complied with the treatment or crossed over and received the other treatment. This protects against attrition bias.

An ITT analysis was not undertaken by either trial that evaluated vinorelbine monotherapy.[38,166] However, Venturino and colleagues included 98/99 participants in the analysis of response and adverse events.[33] Jones and colleagues included 179/183 participants in time to event outcomes but only 130/183 in outcomes relating to response and stable disease.[38]

An ITT analysis was not undertaken in three trials of vinorelbine combination therapy.[39,41,92] However, Norris and co-workers reported having used an ITT analysis for toxicity data, but this did not include three participants who withdrew post-randomisation.[41] Namer and colleagues[40] did not include one enrolled participant who did not receive any treatment (having withdrawn their informed consent) in their ITT analysis.

Equivalence trial

The majority of the included trials were comparative trials. However, the trial conducted by Namer and colleagues was reported to have been an equivalence trial.[40] The objective of this trial was to show equivalence in study efficacy (in terms of overall response rate), but a better tolerance profile for vinorelbine when compared to an anthracycline-based regimen (FAC/FEC). However, the equivalence interval was wide at 15% and the power calculation used to calculate the sample size was one-sided, resulting in a small required sample size ($n = 280$). Equivalence trials generally require a much larger sample size than comparative trials.[178] A one-sided design assumes that one intervention is superior to another, but not the other way around. The 90% CI for the overall response rate (–8 to 11%) shows that this was not the case in this study.

It was unclear if the findings of the overall response rate were derived from the ITT or per-protocol analysis. It would have been preferable if both results were reported. By including all participants, an ITT analysis gives the smallest estimate of the difference between the effects of two treatments. In contrast, a per-protocol analysis will maximise the difference. This means that whilst an ITT analysis is the most conservative for comparative trials (investigating treatment difference), a per-protocol analysis is most conservative for trials investigating equivalence.

The results of this analysis undertaken by Namer and colleagues[40] is unclear, in that it is still not known if the interventions are equivalent due to the wide equivalence interval and small sample size used.

Overall quality of included vinorelbine RCTs

Vinorelbine monotherapy

The overall quality of included trials evaluating vinorelbine monotherapy was low in that it cannot be assured that the randomisation procedure was adequate and whether allocation had been concealed in either trial. The level of information regarding important baseline characteristics was limited and measures, such as treatment-free interval, disease bulk, number of previous regimens and histology, were not reported by either trial. Baseline comparability was not achieved for either trial. Neither of the included trials was reported to have used blind outcome assessment, and neither trial used an ITT analysis for all outcome measures.

Vinorelbine combination therapy

The overall quality of the included trials that investigated vinorelbine as combination therapy was low to moderate. Only Namer and colleagues[40] reported the method of randomisation used and the allocation of treatment appeared to be concealed in only two[40,41] of the five trials. The information relating to baseline characteristics was limited, with none of the trials reporting on disease bulk, number of previous regimens and histology. This meant that baseline comparability could not be assured in any of the included trials. Blind outcome assessment was also not reported for any of the included trials. Only Frasci and colleagues reported the reasons for withdrawal or exclusions from the trial adequately[93] and only two trials used an ITT analysis for both safety and effectiveness data.[40,93] One trial was only available as an abstract, giving little methodological detail of the study.[92]

Assessment of effectiveness and toxicity from RCTs

Vinorelbine monotherapy

Tumour response

There were no significant differences between vinorelbine and either melphalan or 5-fluorouracil plus the L-isomer of leucovorin with or without mitoxantrone for partial, complete or overall response.

Complete response, defined as the complete disappearance of all objective disease, was achieved in 5% (4/84) of participants treated with vinorelbine and in 2% (1/46) of those treated with melphalan.[38] Jones and colleagues reported that partial response was achieved in 11% (9/84) of participants treated with vinorelbine and 7% (3/46) of participants treated with melphalan. Partial response was defined as a reduction of ≥ 50% from baseline in size of all clinically measurable tumour areas without the appearance of any new disease, or an increase of ≥ 50% in product of bidimensional measurements of any individual tumour. Complete and partial responses had to be confirmed by a second evaluation at least 4 weeks later.

The second trial, conducted by Venturino and coworkers did not provide a definition for response, but used WHO criteria.[33] Complete response was observed in 6% (2/33) of participants treated with vinorelbine. One participant in each group treated with 5-fluorouracil plus leucovorin with or without mitoxantrone achieved complete response (4 and

3%, respectively). Partial response was observed in 18% (6/33) of the vinorelbine group, 19% (6/32) of the mitoxantrone plus 5-fluorouracil plus leucovorin group and 26% (9/33) of the 5-fluorouracil plus leucovorin group.

Both trials reported on stable disease which, according to Jones and co-workers,[38] was defined as an evaluation that failed to qualify for partial/complete response or progressive disease. The second trial did not clarify what was meant by stable disease.[33] Neither trial found any significant differences between the intervention groups for this outcome measure. The results are presented in *Table 4*.[33,38]

There were no significant differences between vinorelbine and either melphalan or 5-fluorouracil plus leucovorin with or without mitoxantrone for disease progression. Only Jones and colleagues defined progressive disease.[38] This included an increase of ≥ 50% in size of all measurable tumour areas, the appearance of any new lesions, an increase in assessable disease or significant worsening of cancer-related symptoms and/or Karnofsky performance scale score. The same trial reported that progressive disease was observed in 81% (93/115) of participants treated with vinorelbine and 80% (51/64) of participants treated with melphalan. In the second trial, conducted by Venturino and colleagues, disease progression was observed in 24% with vinorelbine, 28% with mitoxantrone plus 5-fluorouracil plus leucovorin, and 24% with 5-fluorouracil plus leucovorin.[33]

Duration of response

Both trials reported on time to treatment failure (*Table 5*).[33,38] Jones and co-workers also reported on time to disease progression[38] and Venturino and co-workers reported on the median duration of overall response (partial or complete).[33] Time to disease progression was defined as the period from the first day of drug treatment to the day when progression or relapse was documented.[38] Time to treatment failure was defined, by both trials, as the period from the first day of treatment to the day when disease progression, treatment-related toxicity resulting in discontinuation of therapy or death (from any cause) occurred, although Venturino and colleagues[33] also included relapse after initial response.

The median time to both disease progression and treatment failure were reported to be significantly longer with vinorelbine compared to with melphalan using Cox's proportional hazards model (12 versus 8 weeks for both outcome measures, $p < 0.001$). However, the HRs, representing the size of the effect, were not presented. The Kaplan–Meier curves for time to disease progression were presented in the publication. Visual inspection of the graph shows both curves to be relatively close together. The graphs run to approximately 800 days. After approximately 300 days, less than 12% (22/179) of participants are included in the figure (due to the need to recruit participants over a 2-year period). No statistical analysis of the duration of disease responses was undertaken by Venturino and colleagues, although they appeared to be similar in the three treatment groups.[33]

Survival

Both trials reported on median survival duration. Jones and colleagues reported that the treatment effect of vinorelbine on survival, compared to melphalan, was significant when analysing the data using Cox's proportional hazards model (median survival was 35 weeks for vinorelbine and 31 weeks for melphalan, $p = 0.034$).[38] However, the HRs were not presented. The Kaplan–Meier survival curves were presented in the publication. Visual inspection of the graph shows that both curves were relatively close together. Venturino and co-workers did not report statistically analysing the data.[33] The median survival for the vinorelbine-treated group was 9.5 months, compared to 9 months in the mitoxantrone plus 5-fluorouracil plus leucovorin-treated group and 9 months in the 5-fluorouracil plus leucovorin-treated group. The authors also reported data on the median survival of participants who achieved overall response with and without those who had stable disease (see *Table 6*).[33,38]

Jones and colleagues reported on 1-year survival rates, which were 35.7% with vinorelbine and 21.7% with melphalan.[38] The actual figures were not presented.

Toxicity

Both trials reported on the incidence of haematological and non-haematological toxicity. However, Jones and colleagues[38] only reported the percentage values, which were converted, for the purpose of the review, to absolute values in order to calculate the RRs for serious adverse events. The RRs must, therefore, be interpreted with caution. The RRs for serious adverse events are reported in *Table 7*.[33,38]

Jones and co-workers reported that grade 3 or 4 granulocytopenia was the primary haematological toxicity associated with vinorelbine, occurring

in 75% of participants.[38] The same trial reported that a similar percentage (69%) of participants treated with melphalan experienced grade 3 or 4 granulocytopenia. Twelve participants treated with vinorelbine and five treated with melphalan were hospitalised for fever, infection, sepsis or pneumonia while granulocytopenic. Unlike melphalan, significant thrombocytopenia with vinorelbine was uncommon (31% with grade 3 and 28% with grade 4 in the melphalan group versus none with grade 3 or 4 in the vinorelbine group).[38] The haematological toxicities reported by Venturino and colleagues included thrombocytopenia, leukopenia and anaemia for which there were no significant differences between the three treatment groups (see *Table 7*).[33] Grade 4 leukopenia occurred in one participant treated with vinorelbine and one participant treated with 5-fluorouracil plus leucovorin.[33]

The most common non-haematological toxicities, reported by Jones and colleagues, with vinorelbine were injection-site phlebitis (15 versus 0%) and pain at the injection site (14 versus 2%) compared to with melphalan.[38] Other adverse effects (including all grades) that occurred more often with vinorelbine compared to with melphalan were asthenia (34 versus 22%), pain (14 versus 2%), alopecia (10 versus 5%), dyspnoea (10 versus 3%), nausea (44 versus 30%), constipation (38 versus 6%), stomatitis (18 versus 5%), diarrhoea (18 versus 8%), anorexia (13 versus 9%), paraesthesia (22 versus 3%) and hypesthesia (9 versus 2%). Vomiting was reported to be more common in participants treated with melphalan (31%) than in those treated with vinorelbine (25%). Grade 3 adverse effects were not very high in either treatment group, and grade 4 only occurred for dyspnoea in 2% of vinorelbine-treated participants and hypesthesia in 1% of participants treated with vinorelbine.[38] The non-haematological adverse events (all grades) reported by Venturino and colleagues included diarrhoea (3% with vinorelbine, 27% with leucovorin plus 5-fluorouracil and 3% with mitoxantrone plus leucovorin plus 5-fluorouracil), mucositis (18% with vinorelbine, 42% with leucovorin plus 5-fluorouracil and 28% with mitoxantrone plus leucovorin plus 5-fluorouracil), nausea/vomiting (27% with vinorelbine, 30% with leucovorin plus 5-fluorouracil and 41% with mitoxantrone plus leucovorin plus 5-fluorouracil), alopecia (15% with vinorelbine, 6% with leucovorin plus 5-fluorouracil and 3% with mitoxantrone plus leucovorin plus 5-fluorouracil), skin problems (0% with vinorelbine, 3% with leucovorin plus 5-fluorouracil and 3% with mitoxantrone plus leucovorin plus 5-fluorouracil) and grade 4 paralytic ileus (3% with vinorelbine, 0% with leucovorin plus 5-fluorouracil and 0% with mitoxantrone plus leucovorin plus 5-fluorouracil).[33] Among participants treated with leucovorin plus 5-fluorouracil, grade 4 diarrhoea and mucositis were observed in three and one participants, respectively.[33]

QoL

Jones and colleagues reported an assessment of QoL from the perspective of the participant and the clinician.[38] QoL from the participant's perspective was assessed every 2 weeks for the first 8 weeks and monthly thereafter. This was done using a questionnaire that was adapted from one used by the Southwest Oncology Group and incorporated measures taken from the medical outcomes study short forms 20 and 36, symptom distress scale, linear analogues self-assessment uniscale and comorbidity questions. Dimensions chosen for assessment included role functioning, physical functioning, symptom distress and global functioning. QoL from the clinician's perspective was based on weekly determination of Karnofsky performance scale score and assessment of symptoms reported in weekly queries to the patient. Analysis of QoL data showed no significant differences between treatment groups for Karnofsky performance scale cancer-related symptoms or QoL assessment from the patient's perspective.

In analyses conducted by Bertsch and Donaldson,[165] group comparison of the median linear time trends indicated that participants treated with vinorelbine compared with melphalan had better physical functioning throughout most of the study (Wilcoxon rank-sum test of equal group distributions of the individual curves showed a significant difference, $p = 0.03$).[165] However, the actual size of the effect was not reported and no actual figures relating to the QoL assessment were presented. Differences between groups in other QoL dimensions were not significant and further data provided within the manufacturers submission showed that vinorelbine was not significantly different than melphalan for symptom distress ($p = 0.37$), role functioning ($p = 0.85$) and global functioning ($p = 0.88$).[11]

Summary of the effectiveness and toxicity of vinorelbine monotherapy

The summary of the findings of vinorelbine monotherapy RCTs are presented in *Table 8*. Two trials investigated the use of vinorelbine monotherapy. Venturino and colleagues[33,166] evaluated its use as second-line or salvage therapy

for MBC, whilst Jones and co-workers[38] used vinorelbine for either first-line (9% of patients), second-line or subsequent treatment for ABC. The number of participants included in the two trials were 99[33] and 183.[38] The overall quality of these trials was low (see quantity and quality of included RCTs section).

There were no statistically significant differences between vinorelbine used as monotherapy and either melphalan[38] or 5-fluorouracil plus leucovorin with or without mitoxantrone[33,166] for partial, complete or overall response. There were no statistically significant differences between the two treatment groups for the outcomes of stable disease and disease progression.[33,38]

When considering survival, median time to treatment failure, median progression-free survival and median overall survival were found to be statistically significantly longer in those treated with vinorelbine compared to those treated with melphalan.[38] However, HRs were not presented. The comparison of median survival between vinorelbine and leucovorin plus 5-fluorouracil with or without mitoxantrone was not assessed statistically and was reported to be 9.5 months for vinorelbine, 9 months for 5-fluorouracil plus leucovorin and 9 months for 5-fluorouracil plus leucovorin plus mitoxantrone.[33] The duration of overall response and time to treatment failure also appeared to be similar in the three intervention groups.

There were no significant differences found between vinorelbine and 5-fluorouracil plus leucovorin with or without mitoxantrone for any of the reported grade 3 or 4 adverse events.[33] There were also no significant differences between vinorelbine and melphalan for grade 3 or 4 adverse events as well as the number of participants hospitalised with fever while granulocytopenic, although the numbers were higher in the vinorelbine group (12/115 versus 5/64).[38]

Participants treated with vinorelbine, when compared with melphalan, were found to have better physical functioning throughout most of the study[38] (Wilcoxon rank-sum test of equal group distributions of the individual curves showed a significant difference, $p = 0.03$[165]). However, the actual size of the effect was not reported and no actual figures relating to the QoL assessment were presented. Differences between groups in other QoL dimensions were not significant.

In conclusion, vinorelbine when used as monotherapy for second-line or subsequent therapy for ABC may be more effective, in terms of progression-free survival and survival, than melphalan. It was not found to be more or less effective than melphalan or 5-fluorouracil plus leucovorin with or without mitoxantrone in terms of tumour response rates. The poor quality and limited data on which these findings are based should be borne in mind. Vinorelbine monotherapy may cause injection-site phlebitis, pain at the injection site, asthenia, pain, nausea, constipation, stomatitis and anorexia.

Vinorelbine combination therapy

Tumour response

Where given, the tumour response rates, along with the RR and 95% CIs, are presented in *Table 9*.[39–41,93] Both trials that evaluated vinorelbine in combination with doxorubicin found no significant differences between the two intervention groups in terms of tumour response as measured by complete, partial and overall response.[39,41] The assessment of tumour response was performed according to the standard WHO criteria in both trials. Complete response was defined as the disappearance of all known lesions on two separate measurements at least 4 weeks apart, and partial response was defined as a reduction of each lesion by ≥ 50%.

Norris and colleagues compared vinorelbine plus doxorubicin with doxorubicin alone and found no significant differences between the two intervention groups for the outcome measures stable disease and disease progression.[41] Stable disease was reported in 47% of participants treated with vinorelbine as combination therapy and in 58% of participants treated with doxorubicin monotherapy. Progressive disease was reported in 15% of participants treated with vinorelbine plus doxorubicin and in 12% of participants treated with doxorubicin alone. Definitions of stable and progressive disease were not provided.

For vinorelbine used in combination with mitoxantrone, the overall tumour response rate was 34.5% compared with 33.3% for FAC/FEC, giving a difference in response rate of 1.2%.[40] When the test of equivalence was applied, the 90% CI of the difference was –8 to 11%, demonstrating vinorelbine plus mitoxantrone to be at least as effective as FAC/FEC ($p = 0.014$, based on an equivalence interval of 15%). Tumour response was assessed according to the WHO criteria. When examining only those participants who had received prior chemotherapy (85% with anthracycline as either

neoadjuvant or adjuvant therapy), vinorelbine plus mitoxantrone was found to be more effective than the anthracycline-containing regimen in terms of overall response rates (15/46 (33%) for vinorelbine plus mitoxantrone versus 6/46 (13%) for FAC/FEC, $p = 0.025$).

For vinorelbine used in combination with escalating doses of docetaxel as second-line therapy, no complete response was registered among the 25 participants who received more than three cycles of chemotherapy (four participants in the docetaxel plus vinorelbine group and five in the gemcitabine plus docetaxel group received less than three cycles due to disease progression).[93] A partial response was seen in two participants treated with docetaxel plus vinorelbine and three participants in the gemcitabine plus docetaxel group. Only one of the 24 participants who had received previous therapy with paclitaxel for advanced disease responded to treatment.

For FUN, Monnier and co-workers reported on the outcome overall tumour response, but only gave percentage values for which it was unclear what the denominators were.[92] It was, therefore, not possible to calculate the RR between treatment groups accurately. Overall response was reported in 26% of participants treated with FUN compared with 33% of participants treated with docetaxel.[92]

Duration of response

Duration of response is the period of time from the first documentation of complete or partial tumour response to the first documentation of tumour progression.[40] There was no significant difference in the median duration of response between vinorelbine as a combination therapy and either doxorubicin monotherapy[41] or the combination therapy of FAC[39] or FAC/FEC.[40] The results are presented in *Table 10*.[39–41,92] All three trials failed to report HRs and gave insufficient information for them to be calculated. Two trials did not report having used any statistical analysis to compare the median duration of response between treatment groups.[39,40] Blajman and colleagues reported a very similar duration of response in participants treated with vinorelbine plus doxorubicin (median = 10.5 months, range 0.5–12) and those treated with FAC (median = 11 months, range 0.5–15).[39] The median duration of response reported by Namer and co-workers was 7 months (range 1–27) in the group treated with vinorelbine plus mitoxantrone and 10 months (range 1–29) in the group treated with FAC or FEC.[40] For the third trial reported by Norris and colleagues, median durations of response in the two treatment groups were reported to have been compared using a stratified log-rank test,[41] and there was no significant difference between the two groups (7.2 months with vinorelbine plus doxorubicin versus 6.8 months with doxorubicin, $p = 0.6$).

Progression-free survival is the same as time to disease progression. Four trials report on this outcome measure, the results of which are presented in *Table 10*.[39–41,92] Progressive disease was defined by Blajman and colleagues as an increase of > 25% or the appearance of new lesions.[39] Time to disease progression is the period of time from date of randomisation[41] or the first day of treatment[38] until the day when progression or relapse is documented.

For the two trials evaluating the combination of vinorelbine plus doxorubicin, no significant differences were found between the treatment groups with regard to progression-free survival.[39,41] Norris and colleagues reported progression-free survival to be very similar in both groups, with those treated with vinorelbine plus doxorubicin having a median value of 6.2 compared to 6.1 months in the doxorubicin treatment group ($p = 0.5$).[41] When compared to FAC, vinorelbine had a slightly shorter, but not significantly different ($p = 0.19$[65]) progression-free survival as reported by Blajman and colleagues (7.5 (range 0.5–479) versus 9 months (range 0.7–59)).[39] Insufficient information was presented by either trial to calculate the HRs. Both trials reported using a stratified log-rank test to compare data. Namer and co-workers reported that the median progression-free survival was 7 months for both participants treated with vinorelbine plus mitoxantrone (range 0–27) and the combination therapy FAC/FEC (range 0–29).[40] Estimates were derived using Kaplan–Meier methodology. Monnier and colleagues reported that the median time to disease progression was 5 months for vinorelbine-treated participants (combined with 5-fluorouracil) and 6 months for participants treated with docetaxel. No measure of variance was presented and no statistical analysis was reported to have been conducted.[92]

Norris and colleagues reported on time to treatment failure, which was defined as the period of time on study from the date of randomisation to time of progressive disease, treatment-related toxicity, withdrawal or death.[41] No significant difference was found between participants treated with vinorelbine plus doxorubicin

and those treated with doxorubicin alone (stratified log-rank test, $p = 0.7$).[41]

Survival

Four trials reported on median overall survival, for which none reported finding any significant difference between the two treatment groups. The results are presented in *Table 11*.[39–41,92] Insufficient information was presented to calculate HRs or any measure of variance.

When comparing vinorelbine plus doxorubicin with FAC, Blajman and colleagues reported similar median overall survival for both groups (17.8 (range 1–50) versus 17.3 months (range 2–40), respectively, log-rank $p = 0.1584$).[39] Norris and colleagues reported that when vinorelbine plus doxorubicin was compared to doxorubicin monotherapy, median overall survival was reported to be 13.8 and 14.4 months, respectively ($p = 0.4$ using a stratified log-rank test).[41] Both trials presented survival curves and reported comparing the data using Cox's proportional hazards model.

Participants treated with vinorelbine plus mitoxantrone were found to have a slightly shorter median overall survival compared to those treated with FAC/FEC,[40] however, this was not found to be significant (17 (range 0–35.5) versus 20 months (range 0–38.5), respectively, $p = 0.27$ using a stratified log-rank test). Kaplan–Meier curves were presented in the published paper.

For FUN, Monnier and colleagues reported that the median survival was 12 months for participants treated with vinorelbine and 13 months for those treated with docetaxel.[92] The trial was presented as an abstract only and no statistical analysis appeared to have been used to compare data.

Toxicity

All five trials reported on the incidence of haematological and non-haematological toxicity. For the study examining FUN, percentage values were reported, but the denominator used was not stated and, therefore, the RRs could not be calculated.[92] The RRs for any adverse events reported by the remaining four trials are reported in *Table 12*.[39–41,93]

There were no significant differences between vinorelbine plus doxorubicin and either doxorubicin monotherapy or FAC for any of the haematological toxicity-related outcomes reported by two of the included trials.[39,41] There was also no significant difference between intervention groups for haematological toxicity in the trial reported by Frasci and co-workers, who investigated vinorelbine plus docetaxel.[93] Namer and colleagues reported that haematological toxicity led to withdrawal of vinorelbine plus mitoxantrone on day 8 in 29% of included participants.[40] Febrile neutropenia required hospitalisation in 2% of participants treated with FAC/FEC and 15% of participants treated with vinorelbine plus mitoxantrone ($p = 0.001$). This toxic event was responsible for the death of one patient in each arm. Monnier and colleagues reported that one of the main grade 3–4 toxicities experienced by included participants was neutropenia (65.5% with FUN and 71% with docetaxel) and febrile neutropenia (2% with FUN and 1.2% with docetaxel).[92]

For non-haematological toxicities, there were no significant differences for most side-effects reported by the two trials that evaluated the use of vinorelbine plus doxorubicin[39,41] and the single trial that investigated vinorelbine plus escalating doses of docetaxel.[93] However, Norris and colleagues found that participants who received doxorubicin monotherapy suffered more gastrointestinal adverse effects than those treated with vinorelbine plus doxorubicin.[41]

Norris and colleagues reported that a participant who suffered from cardiomyopathy in the doxorubicin treatment group died of congestive heart failure.[41] The trial also reported that a total of 11% of participants in the vinorelbine plus doxorubicin treatment group and 4% in the doxorubicin treatment group went off protocol due to toxicity, and more participants refused further protocol treatment in the vinorelbine plus doxorubicin treatment group as compared to the doxorubicin treatment group (8 versus 2%).

Namer and co-workers reported that non-haematological toxicity was in favour of mitoxantrone plus vinorelbine as compared to the combination of FAC/FEC for grades 3 and 4 nausea and vomiting (8 versus 16%, respectively, $p = 0.03$) and grade 3 alopecia (7 versus 30%, respectively, $p = 0.0001$).[40] The same trial also reported that cardiac events were mainly minor and occurred in 19 of the 281 participants (nine treated with mitoxantrone plus vinorelbine and ten treated with FAC/FEC).

The percentage of grade 3 or 4 non-haematological toxicities reported by Monnier and co-workers (published as an abstract) were relatively similar for participants treated with FUN and those treated with docetaxel.[92] These included infection

(1.1 versus 0.6%), nausea/vomiting (1.8 versus 1%), stomatitis (11 versus 1%), diarrhoea (0.5 versus 1.2%), asthenia (2.8 versus 2.4%) and peripheral oedema (0 versus 0.6%). The same trial also reported that seven toxic deaths occurred, which included six (four due to septic shock and two due to hepatic insufficiency) in the FUN group and one (due to cardiac insufficiency) in the docetaxel group.

QoL

Norris and co-workers collected data on global QoL score (measured using the European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire.[41] Nine domains, which included cognitive, emotional, global, physical, role, social, fatigue, nausea/vomiting and pain, were measured. Actual results for each item were not listed separately for intervention and control groups. The authors noted that there were no significant differences between the control and intervention groups in terms of any of the domains at baseline and at follow-up.

Summary of the effectiveness and toxicity of vinorelbine combination therapy

The summary of the findings of vinorelbine combination therapy RCTs are presented in *Table 8*. Five RCTs investigated the use of vinorelbine in combination with other chemotherapy drug(s) as either first-[39–41,92] or second-line therapy[92,93] for ABC or MBC.

Two trials investigated the use of vinorelbine in combination with doxorubicin[39,41] versus either doxorubicin (n = 303) monotherapy[41] or FAC (n = 177).[39] One trial evaluated the use of FUN versus docetaxel as first- (32% of participants) or second-line therapy (n = 178)[92] and one trial examined vinorelbine plus mitoxantrone compared with FAC/FEC (n = 281).[40] Finally, one trial randomised participants to receive either vinorelbine or gemcitabine in combination with escalating doses of docetaxel (n = 34).[93]

The overall quality of the included trials that investigated vinorelbine as combination therapy was low to moderate (see quantity and quality of included RCTs section). One trial was only available as an abstract with very little information presented on the methodology.[92]

No statistically significant differences were found when vinorelbine combined with doxorubicin (used as mainly first-line therapy) was compared to either doxorubicin monotherapy[41] or FAC[39] in terms of tumour response. There was no statistically significant difference between vinorelbine plus docetaxel and gemcitabine plus docetaxel in terms of partial response[93] and there were no significant differences between vinorelbine plus mitoxantrone when compared to FAC or FEC for complete or partial responses and the duration of response.[40]

When considering survival, there were no significant differences between intervention groups when comparing vinorelbine plus doxorubicin with either doxorubicin monotherapy[41] or FAC.[39] The difference between participants treated with FUN compared to those who received docetaxel (for first- or second-line therapy) in terms of median progression-free survival was not statistically analysed but appeared to be very similar in both groups.[92] There were no significant differences between the interventions vinorelbine plus mitoxantrone and FAC/FEC in terms of progression-free and overall survival.[40] None of the trials presented HRs for progression-free or overall survival.

Only one trial that evaluated vinorelbine as combination therapy examined QoL issues, for which the authors reported that there were no significant differences found between the intervention groups (vinorelbine plus doxorubicin versus doxorubicin monotherapy).[41] The actual results for each item were not presented separately for the intervention and control groups.

When comparing vinorelbine plus doxorubicin with doxorubicin monotherapy or FAC, or vinorelbine plus docetaxel versus gemcitabine plus docetaxel, no significant differences were found between the intervention groups in terms of adverse events. For the comparison of vinorelbine plus mitoxantrone with FAC or FEC, febrile neutropenia with hospitalisation was more frequent among participants treated with vinorelbine (p = 0.001), while grades 3 and 4 nausea/vomiting (p = 0.03) and grade 3 alopecia (p = 0.0001) were greater among those treated with FAC/FEC.[40] For the comparison of FUN with docetaxel for either first- or second-line therapy of MBC, adverse events were only reported as percentages and, therefore, RRs could not be calculated accurately.[92] However, there appeared to be no differences between the two intervention groups for any of the adverse events reported apart from toxic death (six with vinorelbine and one with docetaxel).

In conclusion, vinorelbine when used as combination therapy with doxorubicin, docetaxel,

5-fluorouracil or mitoxantrone does not appear to be more effective than alternative combinations of chemotherapy in the treatment of MBC. Toxicities were also approximately equal except that the results from one trial suggested that vinorelbine plus mitoxantrone might cause more febrile neutropenia but less nausea/vomiting and alopecia than FAC/FEC and the results from a single trial (n = 178) that was published as an abstract only suggested that vinorelbine when used in combination with 5-fluorouracil could be associated with toxic death.

Quantity and quality of included uncontrolled Phase II studies

Excluded studies

During the update searches (to identify studies with ≥ 14 participants investigating vinorelbine used as first-line therapy for ABC), 206 studies were ordered as full manuscripts or abstracts and then excluded whilst applying the inclusion criteria. Details of these studies along with reasons for exclusions are presented in appendix 4.

Included studies

This review of uncontrolled studies is concerned only with vinorelbine when used as first-line chemotherapy for the treatment of ABC. Studies of the use of vinorelbine as second-line or subsequent therapy as well as first-line therapy have been included, but only when the results for first-line therapy can be data-extracted separately. In these cases, wherever possible, the demographic details have also been extracted and reported separately, but in some cases the demographic details for a whole study group have had to be reported.

Details of all studies included in this section of the review are presented in appendix 7. The following sections summarise the similarities and differences of this group of studies as part of the assessment of their clinical diversity – an assessment that is required prior to any attempts at pooling data across studies.

It should be noted that a number of the studies included in this review were available as abstracts only and, therefore, only limited details were available. In addition, many studies had multiple publications, some of which included interim analyses. An attempt has been made to categorise them so that each study is only reported once. Details of all the related publications for each study is provided in the data extraction tables in appendix 7.

Vinorelbine monotherapy

A total of 14 uncontrolled studies were identified that investigated vinorelbine monotherapy as first-line therapy for ABC (stages III or IV).[19–32] Details of these studies are presented in appendix 7. These studies differed from each other in a number of ways, including the number of participants recruited, characteristics of the participants included and formulation and dose of vinorelbine utilised.

The number of participants recruited ranged from 16 to 157 participants. Most studies included adult females of all ages (the median ages ranged from 51[19] to 64 years[24]) except for two studies that specifically included elderly women only.[30,32] The main inclusion criterion for these studies was ABC, and none specified MBC. The published reports of the studies did not allow the participants with MBC to be differentiated from those with locally advanced disease and, therefore, the nature of the study groups is unclear. The performance status of participants included in these studies was reported in all but one study,[26] and was uniformly less than 2 (WHO/ECOG criteria) or 70 or more (Karnofsky performance scale).

Although the studies investigated vinorelbine as first-line therapy, five of the 14 studies also included second-line or subsequent therapy.[20,27,28,31,32] For all five studies, the response data pertaining to first-line use could be extracted, but for two studies[28,32] the demographic details could not be separated from those of the whole study group. Where data were reported in the primary studies, the incidence of adjuvant therapy varied widely, ranging from 9 to 78%. The range for the use of adjuvant anthracycline was 4 to 81%.

The 14 studies of vinorelbine monotherapy included 12 using intravenous vinorelbine[19–23,25–31] and two using oral vinorelbine.[24,32] In the majority of the intravenous studies, vinorelbine was administered at a dose of 30 mg/m^2 once per week. In two other studies, the doses were similar at 25 and 30–35 mg/m^2 once per week.[29,31] Despite the similarity of these dose regimens, diversity was introduced by the use of granulocyte colony-stimulating factor (G-CSF) in some[30,31] but not all studies. The final intravenous study was a dose-escalating study, with a starting dose of 8 mg/m^2 on day 1 followed by 4 days continuous infusion at escalating dosage levels up to 30–48 mg/m^2 every 21 or 28 days.[28] The two studies of oral vinorelbine did not use the same dose regimens. One study[24] used vinorelbine at a dose of 130 mg/m^2 once a week and the second study,[32] that investigated

the use of vinorelbine among elderly women, used 80 mg/m^2, or 50 mg/m^2 for participants with decreased marrow reserve. Neither study used G-CSF support.[24,32]

In summary, the main source of clinical diversity within the vinorelbine monotherapy studies is the wide range in proportions of adjuvant chemotherapy. The inclusion of two studies conducted in elderly patients only is also a source of diversity, although a sensitivity analysis that omitted these could be performed. Across all 14 studies, the dose of vinorelbine and G-CSF use varies, however, a subset of intravenous studies that used vinorelbine 25–35 mg/m^2 and did not use G-CSF would be less diverse. A potential source of clinical diversity that cannot be quantified is the inclusion criterion of ABC, which may or may not include locally advanced disease as well as MBC.

Vinorelbine combination therapy

Fifty-one uncontrolled studies investigated vinorelbine in combination with other chemotherapy agents as first-line therapy for ABC.[42–91] Hochster and colleagues reported on two parallel protocols, one with a regimen of vinorelbine plus doxorubicin and one of FUN.[46] For the purpose of this review, both protocols will be discussed as two separate uncontrolled studies. Eleven of these studies included participants who received vinorelbine as either first- or second-line therapy,[44,58,59,63,67,69,71,81,83–85] but, as previously, only the study results from first-line therapy are included in this review.

Details of all studies are presented in appendix 7. As for the monotherapy vinorelbine studies, the studies differed from each other in a number of ways. The main difference between studies was the different combination treatment regimens utilised. To address this source of major clinical diversity, the studies are grouped below by the agent or agents used in combination with vinorelbine. Even so, there are noteworthy sources of diversity within these groupings.

Vinorelbine plus doxorubicin

Eleven studies investigated vinorelbine used in combination with doxorubicin.[42–50,90,91] Only one included participants treated with first- or second-line therapy for ABC and both the results and demographic data pertaining to first-line therapy could be extracted.[44] The number of recruited participants ranged from 34[48] to 165.[44] All studies included adults, and the median age of included participants ranged from 47[43,50] to 62 years.[48] Of the 11 studies, only two specified MBC as the primary inclusion criterion.[45,91] The remainder all specified ABC, and, of these, only two reported the proportion of included participants with locally advanced disease: 3 and 70%, respectively.[49,50] Another study reported that 41% of participants had stage IV disease.[43] The lack of detailed information made it difficult to properly assess the diversity or otherwise of this population relating to their disease at entry to the study. Similarly, performance status data at entry were lacking for five studies.[42,44,48,90,91] Where it was reported, performance status ranged between 0–1 (WHO/ECOG) in three studies,[43,47,50] between 0–2 in two studies[45,49] and up to 70 using the Karnofsky performance scale in one study.[46] The proportion of patients reported to have received adjuvant therapy ranged widely from 2[45] to 52%.[42] Unfortunately, few studies reported any details of adjuvant therapy; one study reported that 26% of participants had received CMF[47] and a second reported that 11% had received doxorubicin (anthracycline).[48]

There was minimal diversity in the dose and treatment regimen of vinorelbine in these studies. Ten of the 11 studies used the same dose of vinorelbine (25 mg/m^2) given intravenously on days 1 and 8 in nine studies[42–47,49,50,91] and days 1 and 5 in one study,[90] every 21 days. In the eleventh study, a slightly lower dose of 20 mg/m^2 vinorelbine was actually administered on days 1 and 4 every 21 days.[48] The dose of doxorubicin varied slightly between studies: a dose of 50 mg/m^2 on day 1 was used in seven studies,[42,44,46,49,50,90,91] 25 mg/m^2 on days 1 and 8 in three studies[43,45,47] and 25 mg/m^2 on days 1 and 4 in one study.[48]

Within this group of studies, clinical diversity appeared to be less than that observed in the monotherapy studies. The dose of doxorubicin used was 25 mg/m^2 (administered twice in one cycle) in some studies and 50 mg/m^2 (administered only once in each cycle) in others. These studies could, therefore, be pooled. However, the proportion of participants that received adjuvant chemotherapy varied, and the inclusion criteria of ABC may or may not have included locally advanced disease as well as MBC, and thus represents a potential source of clinical diversity.

Vinorelbine plus epirubicin

Six studies investigated vinorelbine in combination with epirubicin as first-line therapy for ABC.[51–56] One study did not report any effectiveness data, but did provide some information on adverse effects.[52] Of the studies that reported efficacy data, it could be seen that the studies were not

large, with the number of recruited participants ranging from 19[55] to 54.[56] The median age of included participants ranged from 55[55] to 68 years.[51] Most studies only included participants with MBC.[51,55,56,179] One study included 28 participants with ABC, ten (36%) of whom had locally advanced disease,[53] however, the response data for MBC rather than locally advanced disease was extracted separately. The performance status of participants included in the studies varied. In two studies, it was 0–3 (WHO/ECOG),[54,56] with only one study giving the number of participants with a score of 3 (3/52 (6%)).[54] One study specified a score of 0–2[51] and one study did not report on performance status.[55] Details of the proportion of participants who had received adjuvant chemotherapy were reported for all but one[53] of these six studies. The range was 27[51] to 84%[55] for any adjuvant chemotherapy and 0[56] to 26%[55] for an anthracycline-based regimen.

All five studies that reported response data used a vinorelbine dose of 25 mg/m^2. Three studies administered vinorelbine on days 1 and 8,[51,53,55] one study administered it on days 1 and 5,[56] and in the fifth study it was given once a week in combination with epirubicin 25 mg/m^2 until disease progression.[54] In the other four studies, epirubicin was administered on day 1 but a different dose was used in each: 60–75, 80, 90 and 100 mg/m^2. It is possible, given the dose adjustments that are a normal part of studies in cancer therapies, that the epirubicin dose actually administered in these latter four studies might not have varied as widely as appeared from the specified treatment regimens. All but one of the studies[53] permitted the use of G-CSF.

When excluding the study of Nistico and colleagues,[54] which administered vinorelbine once a week, the clinical diversity of the studies was moderate. Most studies included data pertaining to participants with MBC. The main source of clinical diversity was the proportion of participants who had received adjuvant chemotherapy.

Vinorelbine plus paclitaxel

Five studies examined vinorelbine used in combination with paclitaxel.[57–61] The number of recruited participants who received vinorelbine as first-line therapy for ABC ranged from 15[59] to 49[60] and the median age ranged from 51 to 54 years. Two studies included participants receiving second-line or subsequent therapy.[58,59] Both studies reported demographic data for the group as a whole and not according to line of therapy.

Four studies included only participants with MBC[57–60] whilst one study looked at participants with ABC,[61] for which it was unclear how many had locally advanced rather than metastatic disease. Three of the studies included participants with a performance status ranging from 0–2 (WHO/ECOG)[57,60] or > 70 (Karnofsky performance scale),[59] one specified 0–3 (for which it was not stated how many participants had a score of 3[61]) and the performance status was not reported in one.[58] In the three studies that reported the proportion of participants who had received adjuvant chemotherapy (all of which had utilised vinorelbine as first-line therapy only), the percentage ranged from 52[61] to 68%.[57] The percentage of participants who had received adjuvant anthracycline therapy ranged from 23[61] to 58%.[57]

Three studies used vinorelbine at a dose of 30 mg/m^2 and paclitaxel at 135 mg/m^2.[58–60] Both drugs were administered on day 1 every 3 weeks in two studies,[58,59] and in the third study vinorelbine was administered on days 1 and 8 and paclitaxel on day 1 every 4 weeks.[60] In one study, vinorelbine was used at 25 mg/m^2 on days 1 and 8 and paclitaxel at 150 mg/m^2 on day 1, which was repeated every 3 weeks.[61] In the last study, vinorelbine was started at 36 mg/m^2 and paclitaxel at 175 mg/m^2 every 3 weeks.[57] For these latter two studies, G-CSF support was used.[57,61]

There was some clinical diversity relating to diagnosis, with one study having possibly included participants with locally advance disease. The range of performance status scores was wider than in other drug combinations described thus far, but the range of adjuvant use was less. The main source of diversity appeared to be the treatment regimens and the use of G-CSF (in two studies).

Vinorelbine plus mitoxantrone

Four studies examined vinorelbine in combination with mitoxantrone.[62–65] One study examined the use of vinorelbine as first- or second-line or subsequent therapy,[63] the demographic details for which could not be separated out for those who received first-line therapy.

The number of recruited participants who received vinorelbine as first-line therapy for ABC ranged from 20[63] to 72.[65] The study populations of three of the studies included adults of any age (median age = 54[63,65] to 63 years[62]) whilst the other included only elderly participants aged ≥ 70 years (median age = 73 years).[64] Two studies included only participants with MBC[64,65] and two studies recruited

participants with ABC.[62,63] For these latter two studies, it was not possible to separate the details for patients receiving first-line therapy for MBC from the group of ABC patients as a whole. The performance status in three of the studies (including that of elderly participants) ranged from 0–2[63–65] and was 0–3 in the fourth.[62] In those studies where the percentages of participants who had received adjuvant anthracycline therapy were reported, the data varied considerably between studies, ranging from 34[62] to 100%.[65]

Drug dosages and concomitant use of G-CSF support differed slightly in each of the four studies. For three studies, vinorelbine was used at 25[62,65] and 20 mg/m^2 [64] on days 1 and 8 every 21 days and mitoxantrone (10[64,65] or 12 mg/m^2 [62,65]) was used on day 1 of a 21-day cycle. The final study was a dose-escalation study in which the starting dose intensity level was 15 mg/m^2 per week of vinorelbine and 3 mg/m^2 per week of mitoxantrone.[63] Two of these studies also used G-CSF.[63,65]

The four studies of vinorelbine plus mitoxantrone were clinically diverse. There was significant diversity for all the study and participant characteristics, indicating strongly that pooling of these data was not appropriate.

Vinorelbine plus docetaxel

Four studies investigated vinorelbine used in combination with docetaxel.[66–69] However, one study did not report any effectiveness data, but did provide limited information on adverse effects.[66] The number of recruited participants who received vinorelbine as first-line therapy for ABC in the remaining three studies, ranged from 29[68] to 42.[69] Only two studies reported the median age of included participants, which were 53[67] and 59 years.[69]

Two studies also included patients who had received previous chemotherapy for MBC, but did not report separate demographic data for those who received vinorelbine as first-line therapy for ABC.[67,69] Therefore, for this group of studies, the clinical diversity pertaining to the groups treated with vinorelbine as first-line therapy was difficult to assess.

All four studies included participants with MBC and all included participants whose performance status was 0–2.[66–69] Information on adjuvant chemotherapy was reported in only two studies.[67,69] One study reported adjuvant chemotherapy in 40% of participants[69] and the second reported that 94% had received adjuvant anthracycline.[67]

The drug schedules used differed in all three effectiveness studies. Of the three studies that reported response data, De Paz and colleagues used vinorelbine at 30 mg/m^2 and docetaxel at 70 mg/m^2 on day 1 every 3 weeks.[67] Fumoleau and colleagues used vinorelbine at 20 or 22.5 mg/m^2 on days 1 and 5, followed by docetaxel at 60–100 mg/m^2 on day 1, repeated every 3 weeks.[68] Kornek and co-workers used vinorelbine at 30 mg/m^2 on days 1 and 15 and docetaxel at 30 mg/m^2 on days 1, 8 and 15, repeated every 4 weeks. In addition, depending on the absolute neutrophil counts on the day of scheduled chemotherapeutic drug administration, a 5-day course of G-CSF was also given.[69]

In summary, the demographic data available were unreliable for this group of studies and a source of potential, unquantifiable diversity. Furthermore, the studies used drug regimens that differed greatly from one another. The pooling of these three clinically diverse studies was, therefore, inappropriate.

FUN

Two studies examined FUN.[46,70] The number of recruited participants was 56[46] and 63,[70] and in terms of age the populations appeared similar (median age = 55[70] and 56 years[46]). The studies differed in their inclusion criterion for stage of disease: one study included participants with ABC[46] and the other included only MBC.[70] Forty participants (63[70] and 71%[46]) had received previous adjuvant chemotherapy in both studies (54% with anthracyclines in both studies). Both studies used the same drug schedules (vinorelbine 30 mg/m^2 on days 1 and 5 and 5-fluorouracil 750 mg/m^2 for 5 days consecutively, repeated every 21 days) and neither used G-CSF support. There appeared to be one source of clinical diversity between the two studies: the main inclusion criterion.

Vinorelbine plus 5-fluorouracil plus leucovorin

Two studies investigated the efficacy of the vinorelbine plus 5-fluorouracil combination with the addition of leucovorin.[71,72] One of the studies utilised only first-line therapy,[72] but the other included some participants who were receiving second-line therapy.

The populations were similar in terms of the size of the study groups (37 and 39, respectively) and the age range of the populations (median ages = 55 (range 29–75) and 51 years (range 35–71), respectively).[71,72] The studies differed in the main

inclusion criterion: one specifying MBC only[72] whilst the other specified MBC or locally advanced disease.[71] In the latter study, the findings for MBC could not be differentiated from those for the group as a whole. In both studies, the performance status scores were 0–2 (WHO/ECOG). Both studies reported adjuvant chemotherapy use, but only in one could the proportion relating to those receiving first-line chemotherapy be discerned.[72] In this study, 54% had received adjuvant chemotherapy with 33% having had adjuvant anthracycline.

The drug regimens were rather different from each other. In one study the intervention was vinorelbine 40 mg/m^2 on days 1 and 14 plus 5-fluorouracil 400 mg/m^2 and leucovorin 100 mg/m^2 on days 1–5, every 4 weeks.[71] In this study, G-CSF was also administered on days 6–10 of each cycle. The other study utilised vinorelbine at 25 mg/m^2 on days 1 and 3 plus 5-fluorouracil 350 mg/m^2 and leucovorin (folinic acid) 100 mg/m^2 on days 1–3, repeated every 21 days.[72] There were, therefore, clear differences between these two studies in terms of population and treatment regimen, making pooling inappropriate.

FAN

Two studies investigated the use of FAN in ABC. Both evaluated first-line therapy only. One included 82 participants[73] and the other included 38.[74] The median ages were 55 years in one study[73] and 62 in the other.[74] One study included only MBC sufferers,[74] whereas the other specified ABC as its main inclusion criterion.[73] It was not possible to tell if the latter included any participants with locally advanced disease. The studies reported rather different proportions of participants who had received adjuvant chemotherapy: 51[73] and 24%.[74]

The treatment regimens differed greatly. The larger study used vinorelbine 25 mg/m^2 plus doxorubicin 20 mg/m^2 on days 1 and 8 and 5-fluorouracil 250 mg/m^2 on days 1–15.[73] The smaller study actually used two slightly differing regimens.[74] Twenty-six participants received 5-fluorouracil 500 mg/m^2 and doxorubicin 50 mg/m^2 on day 1 and escalating doses of vinorelbine (15, 20, 25 and 30 mg/m^2) on days 1, 8 and 15 every 3 weeks, whilst 12 received 5-fluorouracil 340 mg/m^2 and folinic acid 200 mg/m^2 on days 1–5, doxorubicin 40 mg/m^2 on day 1 only and escalating doses of vinorelbine (15, 20, 25 and 30 mg/m^2) on days 1 and 5, every 4 weeks (SUPERFAN). The maximum dose of doxorubicin was 400 mg/m^2. Overall, there were clear differences between the two studies, which made pooling inappropriate.

Vinorelbine plus cyclophosphamide plus 5-fluorouracil

Two studies investigated the combination of vinorelbine with cyclophosphamide and 5-fluorouracil.[75,76] One examined just first-line therapy,[76] but the other investigated both first- and second-line therapy.[75] The numbers of patients recruited for first-line therapy were 60[76] and 38.[75] In terms of age, the populations were similar with median ages of 54 and 57 years, respectively. The proportion of patients exposed to adjuvant chemotherapy was fairly similar in the two studies at 42[76] and 53%.[75] In the second study, almost 25% had received adjuvant anthracyclines. Both studies included patients with either locally advanced disease or MBC and their data could not be separated. Both studies included only patients with a WHO/ECOG performance status of 0–2.

The two treatment regimens used in these studies were not the same. In the larger study, vinorelbine 25 mg/m^2 was administered on days 1 and 8, cyclophosphamide 500 mg/m^2 was administered on day 1 and 5-fluorouracil 500 mg/m^2 on days 1 and 8. The cycles were repeated every 21 days for a maximum of eight cycles.[76] In the other study, vinorelbine 25 mg/m^2 was administered on days 1 and 3, with cyclophosphamide 600 mg/m^2 and 5-fluorouracil 750 mg/m^2 being administered on days 1–3. Cycles were repeated every 21 days for six cycles.[75] Although there was no clear diversity relating to the participants entered into these two studies, the amount of drug administered in one study was far greater than in the other, such that pooling was inappropriate.

Vinorelbine plus cyclophosphamide plus epirubicin

This combination as first-line therapy for ABC was investigated in two uncontrolled studies.[77,78] One study[78] was completed with 59 participants recruited with a mean age of 53 years, but the other[77] is ongoing with 20 participants recruited and almost no demographic details reported.

The completed study included participants with both MBC and locally advanced disease, whereas the other study specified MBC only. All participants in the completed study[78] had a Karnofsky performance scale score of no less than 50, and 36% had received adjuvant chemotherapy, none of which had received adjuvant anthracycline. Diversity between these studies on these criteria cannot be checked because too few details have been reported for the ongoing study.

The treatment regimens were different in some respects. Both administered vinorelbine at a dose of 25 mg/m^2 and epirubicin at 30 mg/m^2, and cyclophosphamide 400 mg/m^2 was used in one study[78] compared to 350 mg/m^2 in the other.[77] The main difference was in the timing of drug administration. In one study, all three drugs were administered on days 1 and 8 of a 28-day cycle, whereas in the other study all drugs were administered on days 1 and 3, but in addition epirubicin and cyclophosphamide were given on day 2 and the whole cycle was repeated every 21 days. There were a number of potential but unquantifiable sources of clinical diversity between these studies. These, together with the differences in the treatment regimen, indicated that pooling was inappropriate.

Vinorelbine plus cisplatin

Two studies used this combination, one completed and one with ongoing recruitment.[80] As currently reported, the studies were similar in terms of number of participants recruited (19 and 24, respectively), age of population (median ages = 56 (range 33–73) and 49 years (range 32–67), respectively) and performance status (0–2). There was, however, a difference in the main inclusion criterion, with the completed study having specified MBC and utilised first-line therapy only, whereas the ongoing study is including both MBC and locally advanced disease and has used the study intervention as second-line therapy in a few patients. Adjuvant chemotherapy was used in 32 and 38% of participants, respectively. Furthermore, some of the demographic data from the ongoing study pertain to the whole study group rather than just those receiving first-line therapy.

The treatment regimens were similar but not identical. The completed study administered vinorelbine 25 or 30 mg/m^2 on days 1 and 5 and cisplatin 80–100 mg/m^2 on day 1. The ongoing study gave vinorelbine 30 mg/m^2 on days 1 and 8 with a lower dose of cisplatin (75 mg/m^2) on day 1. There was one source of clinical diversity: the main inclusion criterion differed between the two studies.

Other combinations with vinorelbine

All other combinations with vinorelbine (plus gemcitabine, ifosfamide, mitomycin C, trastuzumab, 5-fluorouracil plus cisplatin, 5-fluorouracil plus epirubicin, mitoxantrone plus carboplatin, mitoxantrone plus cisplatin and doxorubicin plus methotrexate plus leucovorin) have each been studied in a single study, the details of which are given in appendix 7.

Quality of included uncontrolled prospective studies

The quality of included studies was assessed using a checklist for case series, which is presented in appendix 5. A summary of the data is presented in *Table 13*.[19–32,42–91]

Representative sample

As presented in the included studies section, all studies included women with either ABC or MBC. Some studies investigated the use of vinorelbine among elderly participants only,[30,32,64] but the majority of the studies included participants who were 70 years of age or younger. Included studies were generally small with the number of evaluable participants for response data (first-line therapy for ABC) ranging from 14[23] to 145[21] for monotherapy and 14[79] to 70[42,73] for combination therapy. Forty-five studies included < 50 evaluable participants who were unlikely to be a representative sample of the population from which they were drawn.[20,23–25,27–29,32,43,45,47,48,50–53,55–64,66–69,71,72,74,75,77,79–85,88–90]

Explicit inclusion criteria

The majority of the included studies used predefined inclusion and exclusion criteria to select participants. However, three studies of monotherapy[23,26,32] and 20 studies of combination therapy[42–44,47,48,50,52,53,55,56,58,67,73,77,79,80,86,88,90,91] were only presented in abstract form for which there were limited data reported on the type of participants who were recruited.

Individuals entering the study at a similar point

As presented in the included studies section of the report and data extraction tables in appendix 7, many studies had ABC as an inclusion criterion. However, it was unclear in the majority of these studies how many participants had locally advanced disease as opposed to MBC. Fourteen monotherapy[19–32] and 20 combination therapy[42–44,46–50,53,61–63,71,75,76,78,81,83,90] studies included participants with either locally advanced disease or MBC. This included one publication that reported two parallel protocols, which for the purpose of this review, have been treated as two separate studies.[46] Five monotherapy[20,27,28,31,32] and 12 combination therapy[44,58,59,63,67,69,71,80,81,83–85] studies included participants who received vinorelbine as first-line, second-line or subsequent therapy for ABC.

Length of follow-up

Most studies did not report on how long participants were followed up. The primary endpoint for most studies was tumour response. This is usually defined over a short-term period in

Phase II studies, based on the underlying idea that short-term response is a necessary precursor to improved survival and morbidity, which would then be evaluated in Phase III trials.[180] The follow-up was, therefore, deemed to be long enough to assess objective tumour response associated with vinorelbine, but for assessing long-term patient response (such as survival or time to disease progression) the follow-up period may not have been sufficient. For studies that evaluated duration of response, progression-free survival, time to treatment failure or overall survival, duration of follow-up was only reported in one monotherapy study[25] (32 patient-years, mean = 9 months) and 12 combination therapy studies[54,60,64,69,71,72,75,81–83,85,87] (median duration ranged from 10.2 to 28 months and two studies reported mean values of 13[60] and 14[82] months). Some additional studies presented Kaplan–Meier curves from which the duration of follow-up could be estimated.[21,31,45,46,62,63,65,70,78,84] Seven out of ten (70%)[21,22,24,25,29–31] monotherapy and 21 of 32 (66%)[45,46,49,51,54,60–63,65,69,70,72,78,81,82,84,85,87,88] combination therapy studies reported using Kaplan–Meier methodology to assess time to event data. This included one publication that reported two parallel protocols, which, for the purpose of this review, have been treated as two separate studies.[46] Vogel and colleagues reported that survival data were not collected because vinorelbine (monotherapy) was used as first-line therapy and survival would have been influenced by subsequent treatment.[30]

Use of objective criteria or blinding to assess outcomes

Eleven monotherapy[19–22,24,25,27–31] and 25 combination therapy[45,46,49,51,54,59–63,65,66,70–72,74,76,78,81–83,85,87,89] studies used objective measures to assess tumour response. This included one publication that reported two parallel protocols, which have been treated as two separate studies.[46] It was not possible to blind the participants or the clinicians to the use of vinorelbine, and their expectations may have influenced observed outcomes, such as partial response or the reporting of adverse events. Fourteen studies (two monotherapy) reported that response was also measured by independent observers[19,21,22,45,59–61,69,73,82] or confirmed by independent investigators.[71,72,83,85]

Description of the subseries and the distribution of prognostic factors

For vinorelbine monotherapy, three studies[23,26,32] were reported in abstracts only. Twenty included studies were published as abstracts for combination therapy.[42–44,47,48,50,52,53,55,56,58,67,73,77,79,80,86,88,90,91] For the remaining studies, published as full manuscripts, seven (64%) studies of vinorelbine monotherapy[20,21,25,27,28,30,31] and 19 (61%) studies of combination therapy[46,49,51,60,62,63,65,66,70–72,74,75,78,82–84,87] reported on included subseries in full (including the one publication that reported two parallel protocols[46]). Two studies of vinorelbine combination therapy did not include any subseries.[57,61]

Overall quality of included uncontrolled prospective studies

Overall, the included studies were of moderate to poor quality using the quality checklist for case series. Most studies used explicit inclusion and exclusion criteria. However, the majority of studies had ABC as an inclusion criterion and it was unclear how many included participants had locally advanced as opposed to metastatic disease. Relatively small sample sizes were used for which it was difficult to assess whether the sample was representative of the population from which they were drawn. Few studies appeared to have *a priori* sample size calculations making it difficult to assess the statistical significance of the treatment effect. The majority of studies examined short-term outcomes, such as tumour response and adverse effects. Outcome assessment was not reported to be blind in any of the included studies, and who undertook this assessment was not generally reported.

Irrespective of the quality of these studies according to the checklist used, it must be borne in mind that all are uncontrolled studies and, as such, the use of vinorelbine was not compared with an alternative systemic therapy or conventional care. The findings of such studies should be interpreted with caution as they are subject to confounding factors (e.g. the fluctuating natural course of the disease) and bias (e.g. selection bias). In addition, as the included studies were Phase I–II studies (where the primary aim is to assess whether the intervention looks sufficiently promising to warrant its evaluation in subsequent Phase III trials), it is likely that the studies were undertaken by investigators who had high expectations of vinorelbine being effective, which may have influenced the outcomes being measured (Rosenthal effect).

Assessment of effectiveness and toxicity from uncontrolled Phase II studies

Tumour response

The results of tumour response (complete response, overall response, stable disease and

progressive disease) for included uncontrolled studies are presented in *Tables 14–34*. As presented in the included studies section of the review, there was clinical diversity between many of the included studies. Within some subgroups where clinical diversity was limited, the pooled weighted mean for complete and overall response is reported. However, it should be borne in mind that some important differences between studies within these subgroups still remained. Forest plots of all included studies are presented in appendix 10.

Vinorelbine monotherapy

For vinorelbine monotherapy,[19–32] the complete and overall tumour response rates ranged from 0 to 20% and 0 to 60%, respectively. These are presented graphically in appendix 10. For studies that used intravenous administration, complete tumour response ranged from 0 to 20% and overall tumour response ranged from 0 to 60%.[19–23,25–31] Excluding studies that specifically examined the use of vinorelbine among elderly women[30] or used G-CSF support,[30,31] did not alter the ranges over which tumour response rates varied. When pooled, the test for heterogeneity for complete tumour response demonstrated significant heterogeneity and, therefore, the pooled weighted mean for complete tumour response is not reported (*Figure 2*). The pooled weighted mean for overall response was 44.6% (95% CI, 40.7 to 48.5; *Figure 3*). When used orally,[24,32] the ranges for complete and overall tumour response rates for vinorelbine monotherapy were 0 to 9% and 0 to 32%, respectively.

Vinorelbine combination therapy

Vinorelbine plus doxorubicin

Studies of vinorelbine plus doxorubicin reported complete and overall tumour response rates ranging from 6 to 32% and 29 to 74%, respectively.[42–50,90,91] When pooling the data for both complete and overall tumour response, the test for heterogeneity demonstrated significant heterogeneity, and, therefore, the pooled weighted means are not reported (*Figures 4* and *5*).

Vinorelbine and epirubicin

For vinorelbine used in combination with epirubicin, complete tumour response rate ranged from 6 to 19% and overall tumour response ranged from 50 to 77%.[51,53–56] When excluding the findings of Nistico and colleagues,[54] who examined vinorelbine administered only once a week, the pooled weighted means for complete and overall response (for studies reporting response data) were 9.8% (95% CI, 4.9 to 14.7) and 68.4% (95% CI, 60.4 to 76.3), respectively, and are presented in *Figures 6* and *7*.

Vinorelbine and paclitaxel

Studies of vinorelbine plus paclitaxel reported overall tumour response rates of 47–67%. Complete response was reported in only three studies[57,60,61] and ranged from 5 to 8%. These data are presented graphically in appendix 10. Two studies[58,59] used vinorelbine at a dose of 30 mg/m^2 plus paclitaxel 135 mg/m^2, without G-CSF support, administered every 3 weeks. The overall tumour response ranged from 59 to 67% with a pooled weighted mean of 63.0% (95% CI, 46.4 to 79.6; *Figure 8*). Neither study reported complete response.[58,59] The remaining three studies used different dosage schedules.[25,57,61]

Vinorelbine and mitoxantrone

For vinorelbine used with mitoxantrone, complete tumour response ranged from 6 to 13% (as reported in only two studies) and overall tumour response rate ranged from 22 to 67%.[62–65] Data for overall tumour response are presented graphically in appendix 10. Due to clinical diversity, these studies were not pooled.

Vinorelbine and docetaxel

Three studies investigated the combination of vinorelbine plus docetaxel.[67–69] Complete tumour response rate was 19% and overall tumour response rate ranged from 64 to 69%. Data for overall tumour response are presented graphically in appendix 10. Due to clinical diversity between these studies, it was considered inappropriate to pool the data.

FUN

The complete and overall tumour response rates reported in two studies using this combination were 5 and 13% and 45 and 64%, respectively.[46,70] The calculated pooled weighted mean for complete tumour response was 7.9% (95% CI, 3.2 to 12.6) and is presented in *Figure 9*. When pooling the data for overall tumour response, the test for heterogeneity demonstrated significant heterogeneity and, therefore, the pooled weighted mean is not reported (see *Figure 10*).

Vinorelbine plus cisplatin

The complete and overall tumour response rates reported in two studies of vinorelbine plus cisplatin were 1 and 7% and 60 and 71%, respectively.[79,80] The calculated pooled weighted means for complete and overall responses are 1.9% (95% CI, 3.5 to 7.3) and 66.7% (95% CI, 48.3 to 85.1) and are presented in *Figures 11* and *12*. There was some

indication of statistical heterogeneity, probably related to the different inclusion criteria for the two studies. The small sample sizes of both studies added to the difficulties in interpreting the results.

Other combinations
All other combinations (vinorelbine plus 5-fluorouracil plus leucovorin, FAN, vinorelbine plus cyclophosphamide plus 5-fluorouracil, vinorelbine plus cyclophosphamide plus epirubicin, vinorelbine plus gemcitabine, vinorelbine plus ifosfamide, vinorelbine plus mitomycin C, vinorelbine plus trastuzumab, vinorelbine plus 5-fluorouracil plus cisplatin, vinorelbine plus 5-fluorouracil plus epirubicin, vinorelbine plus mitoxantrone plus carboplatin, vinorelbine plus mitoxantrone plus cisplatin or vinorelbine plus doxorubicin plus methotrexate plus leucovorin) were investigated either in two clinically diverse studies or in only one study each. The results of these studies are summarised by combination in *Tables 21–24* and *26–34*. They are included in a Forest plot of all combination therapy studies presented in appendix 10.

Duration of tumour response and survival

The results for duration of tumour response, time to disease progression, time to treatment failure and overall survival for included uncontrolled studies are presented in *Tables 35–54*.

Vinorelbine monotherapy

Nine monotherapy studies[19–23,25,29–31] examined duration of tumour response and eight included survival data (including one study that used oral vinorelbine).[19,21,22,24,25,29–31] The median duration of response for intravenous vinorelbine monotherapy ranged from 1.8 to 9 months. This included one study that specifically looked at the use of vinorelbine among elderly women, and in which the median duration of overall tumour response was 9 months.[30] The median duration of tumour response for oral vinorelbine was not stated.[24] Where reported, the median overall survival for intravenous vinorelbine ranged from 9.9 to 16.8 months. The median time to progression ranged from 3 to 6 months and the median time to treatment failure, which was only reported by three studies, ranged from 4.6 to 6 months.[22,25,31]

Vinorelbine combination therapy

Vinorelbine plus doxorubicin
For vinorelbine used in combination with doxorubicin, only two studies[45,49] reported median duration of response which ranged from 12 to 16 months. Median overall survival, reported in four studies,[45,46,49,91] ranged from 16 to 27.5 months.

Vinorelbine plus epirubicin
For vinorelbine used in combination with epirubicin, according to only two studies,[51,54] the median duration of tumour response was 10 months. Median time to disease progression ranged from 10 to 11 months and overall median survival ranged from 23 to 31 months.[51,54–56]

Vinorelbine plus paclitaxel
For vinorelbine used in combination with paclitaxel, median time to disease progression was 7 months in two studies.[60,61] A third study reported that the median time to disease progression was 7.2 months for participants who received G-CSF support and 3.9 months for those without.[57] The median survival was 17 to 22 months.[60,61]

Vinorelbine plus mitoxantrone
For vinorelbine used with mitoxantrone, one study reported duration of tumour response (7 months).[65] The median time to disease progression, according to three studies, ranged from 9 to 15 months[62–64] and median overall survival ranged from 14 to 19 months.[62,64,65]

FUN
For the FUN combination, median duration of response was only reported by a single study and was 12.3 months.[70] Median time to disease progression was approximately 8 months (7.4 and 8.3 months) according to two studies and median overall survival ranged from 12.2 to 23 months.[46,70]

Vinorelbine plus 5-fluorouracil plus leucovorin
For vinorelbine used in combination with 5-fluorouracil plus leucovorin, duration of tumour response ranged from 9.5 to 10 months, median time to disease progression ranged from 8 to 10.5 months and overall median survival was not yet reached in either study that reported survival data.[71,72]

Vinorelbine plus cisplatin
For the combination of vinorelbine and cisplatin, none of these outcomes were reported, except median time to progression, which was 7.3 months.

Other combinations
For each of the remaining vinorelbine combinations, only a single study reported the findings of either duration of response or survival outcomes. These are presented in *Tables 40* and *43–54*.

Adverse events

Severe adverse events (grade 3 or 4) reported by the uncontrolled studies of vinorelbine

monotherapy and combination therapy are listed in *Tables 55–66* and in the data extraction tables in appendix 7. For combinations of vinorelbine only investigated in single studies (plus gemcitabine, ifosfamide, mitomycin C, trastuzumab, 5-fluorouracil plus cisplatin, 5-fluorouracil plus epirubicin, mitoxantrone plus carboplatin, mitoxantrone plus cisplatin and doxorubicin plus methotrexate plus leucovorin), the summary of serious adverse events is only presented in appendix 7.

Of the 14 studies of vinorelbine monotherapy, 11 studies reported severe leukopenia, ten reported severe nausea/vomiting, eight reported granulocytopenia and eight reported severe constipation. From the 51 studies of vinorelbine combination therapy, the most frequently reported severe adverse events were neutropenia (39 studies), alopecia 30 studies), nausea/vomiting (30 studies), anaemia (21 studies) and leukopenia (19 studies).

Overall, the reporting of adverse events was not consistent. Many of the uncontrolled studies were reported as abstracts with very little space devoted to adverse events. For vinorelbine monotherapy, haematological toxicities, particularly granulocytopenia and leukopenia, were identified. In addition, nausea/vomiting and constipation appeared to be associated with vinorelbine monotherapy. In combination with other agents, neutropenia and other haematological toxicities were apparent. Vinorelbine combination therapy also appeared to be associated with alopecia and nausea/vomiting. There were too few studies with most combinations to describe each specific drug combination adverse event profile. For vinorelbine plus anthracycline, neutropenia, alopecia and nausea/vomiting appeared to be the most common.

Summary of the findings of the prospective uncontrolled studies

Fourteen uncontrolled studies of vinorelbine monotherapy and 51 studies of combination therapy were included in the review. These studies were clinically diverse, investigating various vinorelbine-based regimens in a range of populations. Many of the studies were small with limited follow-up times. Only a few subsets of studies, where the diversity appeared to be minimal, have been investigated by statistical pooling. In some cases, this revealed statistical heterogeneity. It is acknowledged that statistical tests for heterogeneity are not very sensitive and, therefore, even where statistical heterogeneity is not identified, the pooled weighted means must be interpreted with caution.

Overall, for vinorelbine monotherapy used intravenously, the complete tumour response rate ranged form 0 to 20% and the overall tumour response rate ranged from 0 to 60%. The median duration of overall tumour response ranged from 1.8 to 9 months. The median overall survival ranged from 9.9 to 16.8 months. Median time to disease progression ranged from 3 to 6 months and median time to treatment failure ranged from 4.6 to 6 months.

For vinorelbine used as combination therapy, complete tumour response ranged form 5 to 32% and the overall tumour response ranged from 22 to 79%. Studies of vinorelbine plus doxorubicin reported complete and overall tumour response rates ranging from 6 to 32% and 29 to 74%, respectively. For vinorelbine used in combination with epirubicin, complete and overall tumour response rates ranging from 6 to 19% and 50 to 77%, respectively, were reported. Studies of vinorelbine plus paclitaxel reported overall tumour response rates of 47–67%. Other combinations were investigated in small numbers of clinically diverse studies. The median duration of overall tumour response ranged from 6 to 16 months. The median overall survival ranged from 12.3 to 31 months. Median time to disease progression ranged from 3.9 to 15 months and median time to treatment failure ranged from 7 to 12 months.

Vinorelbine monotherapy may be associated with leukopenia and vinorelbine used as combination therapy appeared to be associated with neutropenia.

Effectiveness data derived from uncontrolled Phase II studies compared with that from RCTs

As uncontrolled studies are considered exploratory, it would be expected that any findings would need to be substantiated by well-designed and well-conducted RCTs. However, with an anti-cancer agent, such as vinorelbine, the majority of studies consist of uncontrolled studies. This appears to be due to two reasons: firstly, investigators are keen to try out any new promising therapy, and secondly, there is great uncertainty regarding the best way to use a new agent. Consequently, there is a proliferation of small pilot-type studies lacking a comparator group. Unfortunately, this is accompanied by a lack of RCTs. RCTs are much more difficult to conduct and selecting the most appropriate comparator is problematic when there are so

many treatment options; the real effectiveness of which are unknown.

The number of RCTs conducted with vinorelbine as first-line chemotherapy in ABC is small: none as monotherapy, two in combination with doxorubicin[39,41] and one in combination with mitoxantrone.[40] Overall, these studies found no significant differences between vinorelbine and the control groups in terms of complete or overall tumour responses and overall survival. For vinorelbine plus doxorubicin, complete and overall response rates ranged from 5[41] to 7%[39] and 38[41] to 74%,[39] respectively. For vinorelbine plus mitoxantrone, ten (7%) complete and 49 (35%) overall tumour responses were reported.[40] The median overall survival for vinorelbine plus doxorubicin ranged from 13.8[41] to 17.8[39] months, and for vinorelbine plus mitoxantrone, it was 17 months.[41]

Clearly, the evidence from RCTs is limited. It is possible that additional supporting evidence might be derived from uncontrolled studies. To examine whether or not these studies are homogeneous, and to examine whether or not they reflect the same populations as those in the RCTs, Galbraith plots were used. Galbraith plots can be used to provide a better graphical impression of heterogeneity between included studies than Forest plots.[181] For each study, the *z* statistic (effect size/standard error of the effect size (b/se(b))) was plotted against the reciprocal standard error (1/standard error of the effect size (1/se(b))) using STATA. The slope of the unweighted regression line constrained through the origin, with its 95% CI, represents the overall tumour response. In the absence of heterogeneity, the majority of study results (i.e. about 95%) would be expected to lie within the two outer lines.[15]

When all vinorelbine combination studies (uncontrolled studies and RCTs) are presented within a Galbraith plot, it can be seen that the RCTs, lying on the right hand side of the plot, represent the more precise studies (*Figure 13*). The plot also shows some degree of heterogeneity between the uncontrolled studies, with 15 (29%) lying near or outside the 95% CI. Furthermore, the plot demonstrates significant heterogeneity between the RCTs and the uncontrolled studies as well as between the RCTs themselves, which lie on either side of the 95% CI for the regression line. It should be noted, however, that the regression line is dominated by the results of the uncontrolled studies. In addition, the individual datapoints represent very clinically diverse studies utilising many different agents in combination with vinorelbine, such that there is no real true effect. A Galbraith plot of monotherapy data would be more useful, however, as noted above, there are no RCTs of vinorelbine monotherapy used as first-line therapy. The plot of vinorelbine plus doxorubicin (*Figure 14*), in which the clinical diversity is much less than for combination therapy as a whole, still demonstrates the existence of heterogeneity within the uncontrolled studies and within the RCTs.

Publication bias

To explore publication bias, funnel plots were drawn. These are scatter plots of the treatment effects estimated from individual studies against some measure of precision (1/standard error (1/se)). If there is no publication bias, the plot will resemble an inverted funnel, with estimates from small studies scattered more widely at the bottom of the graph. Small studies that find little treatment effect are often not published: a review of published studies that does not acknowledge these would overestimate the overall treatment effect.

Figures 15 and *16* are funnel plots of the uncontrolled studies and RCTs identified from the literature. Both are difficult to interpret, but *Figure 16* suggests that some studies of vinorelbine combination therapy may be missing from the bottom left hand corner of the plot. These studies would represent those that found a low tumour response rate for the vinorelbine treatment. This finding is reflected in the funnel plot of vinorelbine plus doxorubicin (*Figure 17*). Consequently, even ignoring other problems related to the reliability of the findings from uncontrolled studies, an estimation of the effect of vinorelbine based on the uncontrolled studies included in this review would overestimate the true effect of vinorelbine. This was found to be true of the published Phase II studies presented in the company submission data made to NICE[11] (*Figure 18*), despite including some studies with mixed first- and second-line treatment. A separate Galbraith plot (*Figure 19*) that includes the data from this review and that of the company submission shows that there is no real difference between the studies included in the company submission and those found through the searches for the current review.

Summary of effectiveness data derived from uncontrolled Phase II studies compared with RCTs

The Galbraith plots (*Figures 13* and *14*) appear to demonstrate that there is statistical heterogeneity

between the RCTs and the uncontrolled Phase II studies. The results of the RCTs are shown as outliers, falling either side of the 95% CI for the regression line. In addition, funnel plots (*Figures 15–17*) suggest that there may be some publication bias present. The graphical presentation of the uncontrolled studies appears to show that there may be some studies missing from the bottom left hand corner of the plot. These studies would represent those that found a low tumour response rate to the vinorelbine treatment.

Overall, the uncontrolled Phase II studies appeared to complement the RCT findings. However, as shown by the Galbraith and funnel plots, the findings of the uncontrolled studies do not compensate for the lack of available RCTs. In other words, the data from the uncontrolled studies on their own are inadequate due to the clinical diversity, statistical heterogeneity and lack of precision. This is in addition to the fact that uncontrolled studies give a lower level of evidence due to the biases and lack of rigour that are inherent in such studies.

TABLE 1 *The evidence base for vinorelbine*

	Number of trials in the initial review	**Number of studies in the update review**	**Number of economic evaluations**
Vinorelbine monotherapy			
Vinorelbine as first-line treatment		14 uncontrolled prospective studies[19–32]	
Vinorelbine as second-line treatment	One RCT[33]		Four economic evaluations[34–37]
Vinorelbine as mainly second-line or subsequent treatment	One RCT[38]		
Vinorelbine combination therapy			
Vinorelbine as first-line treatment	Three RCTs[39–41]	51 uncontrolled prospective studies[42–91] (Note, Hochster *et al.* reports two studies[46])	
Vinorelbine as first- or second-line treatment	One RCT[92]		
Vinorelbine as second-line treatment	One RCT[93]		

TABLE 2 *Vinorelbine – summary of included RCTs*

Author	Accrual dates	Line of therapy	Number of participants randomised*	Number of evaluable participants*	Drug dosages for vinorelbine group	Comparator	G-CSF support
Vinorelbine monotherapy							
Jones *et al.*, 1995[38] (data were also extracted from Bertsch and Donaldson, 1995,[165] and company submission data from Pierre Fabre[11])	Aug 1990–Dec 1992	First- (9%) or second-line or subsequent treatment	183	179 (115 vinorelbine, 64 comparator)	30 mg/m^2 i.v. weekly	Melphalan 25 mg/m^2 i.v. every 4 weeks	No
Venturino *et al.*, 2000[33] (interim findings published in abstracts by Venturino *et al.*[166] and Simoni *et al.*, 1995[167])	?–1996	Second line or salvage	99 (33 vinorelbine, 33 comparator 1, 33 comparator 2)	98 (33 vinorelbine, 33 comparator 1, 32 comparator 2)	30 mg/m^2 i.v. weekly	*Comparator 1*: leucovorin (100 mg/m^2 i.v.) followed by 5-fluorouracil (370 mg/m^2 i.v.) on days 1–5 every 28 days *Comparator 2*: Mitoxantrone (12 mg/m^2 i.v. on day 1), leucovorin (100 mg/m^2 i.v.) followed by 5-fluorouracil (370 mg/m^2 i.v.) on days 1–3 every 28 days	No
Combination therapy							
Vinorelbine plus doxorubicin							
Blajman *et al.*, 1999[39] (interim findings were published as abstracts by Blajman *et al.*, 1993[168] and Blajman *et al.*, 1996[169])	April 1991–July 1994	First line	177	170 (85 vinorelbine plus doxorubicin, 85 comparator)	Vinorelbine 25 mg/m^2 i.v. on days 1 and 8 and doxorubicin 50 mg/m^2 i.v. on day 1 repeated every 21 days	5-fluorouracil (500 mg/m^2 i.v. on day 1), adriamycin (doxorubicin; 50 mg/m^2 i.v. on day 1) and cyclophosphamide (500 mg/m^2 on day 1) repeated every 21 days (FAC)	No

continued

TABLE 2 contd *Vinorelbine – summary of included RCTs*

Author	Accrual dates	Line of therapy	Number of participants randomised*	Number of evaluable participants*	Drug dosages for vinorelbine group	Comparator	G-CSF support
***Combination therapy* contd**							
Vinorelbine plus doxorubicin							
Norris *et al.*, 2000[41] (data were also extracted from the company submission data from Pierre Fabre.[11] Interim publications include Norris *et al.*,1996 [170] and Norris *et al.*,1996[171])	Jan 1992–July 1995	First or second line (25%)	303	300 (151 vinorelbine plus doxorubicin, 149 comparator)	Doxorubicin (50 mg/m^2 i.v. on day 1) and vinorelbine (25 mg/m^2 i.v. on days 1 and 8) repeated every 21 days. The dose regimens above were modified to doxorubicin (40 mg/m^2) and vinorelbine (20 mg/m^2) 10 months into the trial when 16 of the first 65 randomised patients suffered from febrile neutropenia using the initial dose regimens	Doxorubicin 70 mg/m^2 i.v. on day 1 every 21 days, which was modified to 60 mg/m^2 10 months into the trial	No
Vinorelbine plus docetaxel							
Frasci *et al.*, 2000[93] (interim findings were published as an abstract by Frasci *et al.*, 1999[172])	Sept 1997–June 1999	Second line	34 (15 vinorelbine plus docetaxel, 19 comparator)	34 (15 vinorelbine plus docetaxel, 19 comparator)	Docetaxel 30 mg/m^2 (n = 3), 35 mg/m^2 (n = 6) or 40 mg/m^2 (n = 6) plus vinorelbine 25 mg/m^2 i.v. on days 1 and 8 every 3 weeks	Docetaxel 30 mg/m^2 (n = 3), 35 mg/m^2 (n = 6), 40 mg/m^2 (n = 6) or 45 mg/m^2 (n = 4) plus gemcitabine 1000 mg/m^2 i.v. on days 1 and 8 every 3 weeks	No
Vinorelbine plus 5-fluorouracil							
Monnier *et al.*, 1998[92] (abstract only; data were also obtained from an interim publication by Bonneterre *et al.*, 1997[173] and the company submission from Pierre Fabre Ltd[11])	?–1998	First (32%) or second line	178	172 (88 vinorelbine plus 5-fluorouracil, 84 comparator)	Vinorelbine 25 mg/m^2 on days 1 and 5 plus 5-fluorouracil 750 mg/m^2 continuously infused from days 1 to 5 (FUN)	Docetaxel 100 mg/m^2 i.v. over 1 hour every 3 weeks	No

continued

TABLE 2 contd *Vinorelbine – summary of included RCTs*

Author	Accrual dates	Line of therapy	Number of participants randomised*	Number of evaluable participants*	Drug dosages for vinorelbine group	Comparator	G-CSF support
***Combination therapy* contd**							
Vinorelbine plus mitoxantrone							
Namer *et al.*, 2001[40] (data were also extracted from interim publications by Namer *et al.*, 1998,[174] Namer *et al.*, 1997,[175] Namer *et al.*, 1997[176] and the company submission from Pierre Fabre Ltd[11])	?	First (75%) and second line (25%)	281 (142 vinorelbine plus mitoxantrone, 139 comparator)	280 (142 vinorelbine plus mitoxantrone, 138 comparator)	Mitoxantrone 12 mg/m^2 i.v. on day 1 plus vinorelbine 25 mg/m^2 i.v. on day 1 and on day 8 if neutrophiles $\geq$ 1000/mm^3 repeated every 21 days	5-fluorouracil 500 mg/m^2 i.v., adriamycin (doxorubicin)/ epirubicin 50 mg/m^2 i.v. and cyclophosphamide 500 mg/m^2 i.v. on day 1 repeated every 21 days (FAC/FEC)	No

i.v. intravenous/intravenously

TABLE 3 *Quality of the included vinorelbine RCTs (according to the checklist presented in appendix 5)*

Study	Sample size (arms)	Randomisation procedure adequate	Allocation concealed	Number randomised stated	Baseline details	Baseline comparability	Eligibility criteria achieved	Co-interventions stated	Blinding of outcome assessors	Blinding of administrators	Participants blinded	Success of blinding checked	Follow-up ≥ 80%	Reasons for withdrawals	ITT
Vinorelbine monotherapy															
Jones *et al.*, 1995[38]	183 (2)	Unclear	Unclear	Yes	Partially	No	Yes	Unclear	No	No	No	NA	Yes	Yes	No
Venturino *et al.*, 2000[33]	99 (3)	Unclear	Unclear	Yes	Partially	No	Yes	No	Unclear	Unclear	Unclear	Unclear	Yes	No	No
Vinorelbine combination therapy															
Vinorelbine plus doxorubicin															
Blajman *et al.*, 1999[139]	177 (2)	Unclear	No	Yes	Partially	Partially	Yes	No	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No
Norris *et al.*, 2000[41]	303 (2)	Unclear	Yes	Yes	Partially	Partially	Yes	No	Unclear	Unclear	Unclear	Unclear	Yes	Partially	No
Vinorelbine plus docetaxel															
Frasci *et al.*, 2000[93]	34 (2)	No	No	Yes	Partially	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Vinorelbine plus 5-fluorouracil															
Monnier *et al.*, 1998[92]	178 (2)	Unclear	Unclear	Yes	Partially	Unclear	No	No	No	No	No	NA	Yes	No	No
Vinorelbine plus mitoxantrone															
Namer *et al.*, 2001[40]	281 (2)	Yes	Yes	Yes	Partially	Partially	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Partially	Unclear

Items were graded in terms of Yes (item properly addressed), No (item not properly addressed), Partially (item partially addressed), Unclear (item unclear or not enough information) or NA (not applicable)

TABLE 4 *Summary of the tumour response for vinorelbine monotherapy*

Outcome	Study	Vinorelbine *n/N* (%)	Control *n/N* (%)	RR
Complete response	Jones *et al.*, 1995[38*]	4/84‡ (5%)	1/46‡ (2%)	2.19 (95% CI, 0.25 to 19.03)
(RR > 1 favours vinorelbine)	Venturino *et al.*, 2000 (a)[33 †]	2/33 (6%)	1/32 (4%)	1.94 (95% CI, 0.18 to 20.35)
	Venturino *et al.*, 2000 (b)[33 †]	2/33 (6%)	1/33 (3%)	2.00 (95% CI, 0.19 to 21.00)
Partial response	Jones *et al.*, 1995[38 *]	9/84‡ (11%)	3/46‡ (7%)	1.64 (95% CI, 0.47 to 5.77)
(RR > 1 favours vinorelbine)	Venturino *et al.*, 2000 (a)[33 †]	6/33 (18%)	6/32 (19%)	0.97 (95% CI, 0.35 to 2.69)
	Venturino *et al.*, 2000 (b)[33 †]	6/33 (18%)	9/33 (27%)	0.67 (95% CI, 0.27 to 1.66)
Overall response	Jones *et al.*, 1995[38 *]	13/84‡ (15%)	4/46‡ (9%)	1.78 (95% CI, 0.62 to 5.14)
(RR > 1 favours vinorelbine)	Venturino *et al.*, 2000 (a)[33 †]	8/33 (24%)	7/32 (22%)	1.11 (95% CI, 0.45 to 2.70)
	Venturino *et al.*, 2000 (b)[33 †]	8/33 (24%)	10/33 (30%)	0.80 (95% CI, 0.36 to 1.77)
Stable disease	Jones *et al.*, 1995[38 *]	26/84‡ (31%)	9/46‡ (20%)	1.58 (95% CI, 0.81 to 3.08)
(RR > 1 favours vinorelbine)	Venturino *et al.*, 2000 (a)[33 †]	17/33 (52%)	16/32 (50%)	1.03 (95% CI, 0.64 to 1.66)
	Venturino *et al.*, 2000 (b)[33 †]	17/33 (52%)	15/33 (45%)	1.33 (95% CI, 0.69 to 1.87)
Progressive disease	Jones *et al.*, 1995[3 8*]	93/115 (81%)	51/64 (80%)	1.01 (95% CI, 0.87 to 1.18)
(RR < 1 favours vinorelbine)	Venturino *et al.*, 2000 (a)[33 †]	8/33 (24%)	9/32 (28%)	0.86 (95% CI, 0.38 to 1.95)
	Venturino *et al.*, 2000 (b)[33 †]	8/33 (24%)	8/33 (24%)	1.00 (95% CI, 0.43 to 2.35)

[*] *The study by Jones* et al., *1995[38] randomised patients to vinorelbine or melphalan*
[†] *The study by Venturino* et al., *2000[33] was a three-way randomisation: (a) vinorelbine versus mitoxantrone plus 5-fluorouracil plus leucovorin, (b) vinorelbine versus 5-fluorouracil plus leucovorin*
[‡] *Analysis of tumour response included only participants with measurable disease who received ≥ one dose of the study drug (*n = *130)*

TABLE 5 *Summary of the duration of response (months) for vinorelbine monotherapy*

Outcome	Study	Vinorelbine		Control	
		N	Median	*N*	Median
Time to disease progression	Jones *et al.*, 1995[38 *]	115	2.77	64	1.85
Duration of overall response	Venturino *et al.*, 2000 (a)[33 †]	33	2 (range 1–9)	32	5.5 (range 2–7)
(complete or partial)	Venturino *et al.*, 2000 (b)[33 †]	33	2 (range 1–9)	33	2.5 (range 1–5)
Time to treatment failure	Jones *et al.*, 1995[38 *]	115	2.77	64	1.85
	Venturino *et al.*, 2000 (a)[33 †]	33	2 (range 1–12)	32	5 (range 1–11)
	Venturino *et al.*, 2000 (b)[33 †]	33	2 (range 1–12)	33	3 (range 1–10)

[*] *The study by Jones* et al., *1995[38] randomised patients to vinorelbine or melphalan*
[†] *The study by Venturino* et al., *2000[33] was a three-way randomisation: (a) vinorelbine versus mitoxantrone plus 5-fluorouracil plus leucovorin, (b) vinorelbine versus 5-fluorouracil plus leucovorin*

TABLE 6 *Summary of the survival data (months) for vinorelbine monotherapy*

Outcome	Study	Vinorelbine		Control	
		N	Median	*N*	Median
Survival	Jones *et al.*, 1995[38 *]	115	8.1	64	7.2
	Venturino *et al.*, 2000 (a)[33 †]	33	9.5 (range 2–24)	32	9.0 (range 2–34)
	Venturino *et al.*, 2000 (b)[33 †]	33	9.5 (range 2–24)	33	9.0 (range 1–52)
Survival of responding	Venturino *et al.*, 2000 (a)[33 †]	8	9.0 (range 4–17)	7	10.0 (range 5–33)
participants	Venturino *et al.*, 2000 (b)[33 †]	8	9.0 (range 4–17)	10	11.0 (range 6–52)
Survival of responding	Venturino *et al.*, 2000 (a)[33 †]	25	10.5 (range 2–24)	23	10.0 (range 5–34)
plus stable participants	Venturino *et al.*, 2000 (b)[33 †]	25	10.5 (range 2–24)	25	10.5 (range 1–52)

[*] *The study by Jones* et al., *1995[38] randomised patients to vinorelbine or melphalan*
[†] *The study by Venturino* et al., *2000[33] was a three-way randomisation: (a) vinorelbine versus mitoxantrone plus 5-fluorouracil plus leucovorin, (b) vinorelbine versus 5-fluorouracil plus leucovorin*

TABLE 7 *Adverse events for vinorelbine monotherapy (RR < 1 favours vinorelbine)*

Adverse event	Study	Vinorelbine *n/N*	Control *n/N*	RR
Haematological toxicity				
Grade 3/4 granulocytopenia	Jones *et al.*, 1995[38] *	87/115	44/64	1.10 (95% CI, 0.92 to 1.36)
Hospitalised with fever while granulocytopenic	Jones *et al.*, 1995[38] *	12/115	5/64	1.34 (95% CI, 0.49 to 3.62)
Grade 3/4 thrombocytopenia (platelets)	Jones *et al.*, 1995[38] *	0/33	1/33	NA
	Venturino *et al.*, 2000 (a)[33] †	0/33	1/32	0.32 (95% CI, 0.01 to 7.66)
	Venturino *et al.*, 2000 (b)[33] †	0/33	0/32	NA
Grade 3/4 leukopenia	Venturino *et al.*, 2000 (a)[33] †	6/33	1/32	5.82 (95% CI, 0.74 to 45.68)
	Venturino *et al.*, 2000 (b)[33] †	6/33	1/33	6.00 (95% CI, 0.76 to 47.14)
Grade 3/4 anaemia (grade 3 only for Venturino *et al.*[33])	Jones *et al.*, 1995[38] *	16/115	22/64	0.40 (95% CI, 0.23 to 0.71)
	Venturino *et al.*, 2000 (a)[33] †	1/33	0/32	NA
	Venturino *et al.*, 2000 (b)[33] †	1/33	0/33	NA
Non-haematological toxicity				
Grade 3/4 mucositis	Venturino *et al.*, 2000 (a)[33] †	1/33	1/32	0.97 (95% CI, 0.06 to 14.85)
	Venturino *et al.*, 2000 (b)[33] †	1/33	5/33	0.20 (95% CI, 0.02 to 1.62)
Grade 3 nausea	Jones *et al.*, 1995[38] *	4/115	3/64	0.74 (95% CI, 0.19 to 2.90)
Grade 3 vomiting	Jones *et al.*, 1995[38] *	3/115	4/64	0.42 (95% CI, 0.11 to 1.63)
Grade 3 nausea/vomiting	Venturino *et al.*, 2000 (a)[33] †	2/33	3/32	0.65 (95% CI, 0.12 to 3.62)
	Venturino *et al.*, 2000 (b)[33] †	2/33	0/33	NA
Grade 3 constipation	Jones *et al.*, 1995[38] *	2/115	1/64	0.11 (95% CI, 0.15 to 8.43)
Grade 3 stomatitis	Jones *et al.*, 1995[38] *	0/115	0/64	NA
Grade 3/4 diarrhoea (grade 3 only for Jones *et al.*[38])	Jones *et al.*, 1995[38] *	0/115	1/64	NA
	Venturino *et al.*, 2000 (a)[33] †	0/33	0/32	NA
	Venturino *et al.*, 2000 (b)[33] †	0/33	4/33	NA
Grade 3 anorexia	Jones *et al.*, 1995[38] *	1/115	1/64	0.56 (95% CI, 0.06 to 5.29)
Grade 3 injection site reaction	Jones *et al.*, 1995[38] *	1/115	0/64	NA
Grade 3 injection site pain	Jones *et al.*, 1995[38] *	3/115	0/64	NA
Grade 3 asthenia	Jones *et al.*, 1995[38] *	4/115	2/64	0.25 (95% CI, 5.12 to 1.30)
Grade 3 pain	Jones *et al.*, 1995[38] *	2/115	0/64	NA
Grade 3 alopecia	Jones *et al.*, 1995[38] *	0/115	1/64	NA
Grade 3/4 dyspnoea	Jones *et al.*, 1995[38] *	1/115	0/64	NA
Grade 3/4 hypesthesia	Jones *et al.*, 1995[38] *	1/115	0/64	NA
Grade 4 paralytic ileus	Venturino *et al.*, 2000 (a)[33] †	1/33	0/32	NA
	Venturino *et al.*, 2000 (b)[33] †	1/33	0/33	NA

* *The study by Jones* et al.*, 1995[38] randomised patients to vinorelbine or melphalan*

† *The study by Venturino* et al.*, 2000[33] was a three-way randomisation: (a) vinorelbine versus mitoxantrone plus 5-fluorouracil plus leucovorin, (b) vinorelbine versus 5-fluorouracil plus leucovorin*

TABLE 8 *Summary of the findings of the vinorelbine RCTs*

Trial source	Type of therapy	Intervention details	Response	Survival	QoL	Adverse events
Vinorelbine monotherapy						
Jones *et al.*, 1995[38] (*n* = 183)	First (9%), second or further line (91%)	Vinorelbine versus melphalan	There were no differences between the groups for partial, complete or overall response, stable disease or disease progression	Time to treatment failure and progression-free survival were significantly longer in vinorelbine group Median overall survival was significantly longer in vinorelbine group (8.08 versus 7.15 months)	Better physical functioning throughout most of the study in the vinorelbine group, but no differences between the groups in other QoL dimensions	Adverse events were not statistically analysed, although there was a higher risk with vinorelbine for injection-site pain and phlebitis, asthenia, pain, alopecia, dyspnoea, nausea, constipation, stomatitis, diarrhoea, anorexia, paraesthesia and hypesthesia. Vomiting was more common in the melphalan group
Venturino *et al.*, 2000[33] (*n* = 99)	Second line/salvage	Vinorelbine versus leucovorin followed by 5-fluorouracil or mitoxantrone plus leucovorin followed by 5-fluorouracil	There were no differences between the groups for partial, complete or overall response, stable disease or disease progression	Time to event outcomes (including duration of overall response, time to treatment failure and survival) were not statistically analysed, however, there appeared to be no differences between the groups (median survival = 9.5 months for vinorelbine, 9 months for 5-fluorouracil plus leucovorin and 9 months for mitoxantrone plus 5-fluorouracil)	Not assessed	No differences between groups for adverse events
Vinorelbine combination therapy						
Vinorelbine plus doxorubicin						
Blajman *et al.*, 1999[39] (*n* = 177)	First line	Vinorelbine plus doxorubicin versus FAC	There were no differences between the groups for complete or partial response, and for duration of response	There were no differences between the groups for progression-free and overall survival	Not assessed	There were no differences between groups for any adverse events
Norris *et al.*, 2000[41] (*n* = 303)	First line	Vinorelbine plus doxorubicin versus doxorubicin (80% of the participants were treated with a dose which was lower than the recommended dose for vinorelbine in combination)	There were no differences between the groups for complete, partial or overall response, stable or progressive disease or duration of response	There were no differences between groups for progression-free and overall survival	There were no differences between the groups for any QoL domains	There were no differences between groups for any adverse events

continued

TABLE 8 contd *Summary of the findings of the vinorelbine RCTs*

Trial source	Type of therapy	Intervention details	Response	Survival	QoL	Adverse events
Vinorelbine combination therapy						
Vinorelbine plus docetaxel						
Frasci *et al.*, 2000[93] (*n* = 34)	Second line	Vinorelbine plus docetaxel (at three different dosage levels) versus gemcitabine plus docetaxel (at four different dosage levels)	No complete responses were registered. There were no differences between the groups for partial response	Not assessed	Not assessed	There were no differences between groups for any adverse events
FUN						
Monnier *et al.*, 1998[92] (abstract only; *n* = 178)	First (32%) or second line	FUN versus docetaxel	Not assessed	Progression-free and overall survival were not statistically analysed, but there did not appear to be a difference between the groups	Not assessed	Not statistically analysed, but there did not appear to be any differences between the groups for any adverse events except toxic death (six with vinorelbine versus one with docetaxel)
Vinorelbine plus mitoxantrone						
Namer *et al.*, 1998[40] (*n* = 281)	First (75%) and second line (25%)	Vinorelbine plus mitoxantrone versus FAC/FEC	There were no differences between the groups for complete or partial response, or duration of response	There were no differences between the groups for progression-free or overall survival	Not assessed	More febrile neutropenia requiring hospitalisation (15 versus 2%) or antibiotics (6 versus 0.6%) in vinorelbine group. More nausea and vomiting (16 versus 8%) and grade 3 alopecia (30 versus 7%) in FAC/FEC group

TABLE 9 *Summary of the tumour response for vinorelbine combination therapy*

Outcome	Study	Vinorelbine *n/N*	Control *n/N*	RR
Complete response (RR > 1 favours vinorelbine)	Blajman *et al.*, 1999[39] *	6/85 (7%)	13/85 (15%)	0.46 (95% CI, 0.18 to 1.16)
	Norris *et al.*, 2000[41] †	7/145 (5%)	5/144 (3%)	1.39 (95% CI, 0.45 to 4.28)
	Namer *et al.*, 2001[40] ‡	10/142 (7%)	10/138 (7%)	0.97 (95% CI, 0.43 to 2.21)
Partial response (RR > 1 favours vinorelbine)	Blajman *et al.*, 1999[39] *	57/85 (67%)	50/85 (59%)	1.14 (95% CI, 0.90 to 1.44)
	Norris *et al.*, 2000[41] †	48/145 (33%)	39/144 (27%)	1.22 (95% CI, 0.86 to 1.74)
	Namer *et al.*, 2001[40] ‡	39/142 (27%)	36/138 (26%)	1.05 (95% CI, 0.71 to 1.55)
Overall response (RR > 1 favours vinorelbine)	Norris *et al.*, 2000[41] †	55/145 (38%)	44/144 (31%)	1.24 (95% CI, 0.90 to 1.71)
	Frasci *et al.*, 2000[93] §	2/15 (13%)	3/19 (16%)	0.84 (95% CI, 0.16 to 4.42)
	Namer *et al.*, 2001[40] ‡	49/142 (35%)	46/138 (33%)	1.04 (95% CI, 0.75 to 1.44)
	Blajman *et al.*, 1999[39] *	63/85 (74%)	63/85 (74%)	1.00 (95% CI, 0.84 to 1.19)
Stable disease (RR > 1 favours vinorelbine)	Norris *et al.*, 2000[41] †	68/145 (47%)	83/144 (58%)	0.81 (95% CI, 0.65 to 1.02)
	Namer *et al.*, 2001[40] ‡	52/142 (37%)	65/138 (47%)	0.78 (95% CI, 0.59 to 1.03)
Progressive disease (RR < 1 favours vinorelbine)	Norris *et al.*, 2000[41] †	22/145 (15%)	17/144 (12%)	1.29 (95% CI, 0.71 to 2.32)
	Frasci *et al.*, 2000[93] §	4/15 (27%)	5/19 (26%)	1.01 (95% CI, 0.33 to 3.13)
	Namer *et al.*, 2001[40] ‡	30/142 (21%)	22/138 (16%)	1.33 (95% CI, 0.81 to 2.18)

* *Blajman* et al., *1999[39] compared vinorelbine plus doxorubicin with FAC*
† *Norris* et al., *2000[41] compared vinorelbine plus doxorubicin with doxorubicin alone*
‡ *Namer* et al., *2001[40] compared vinorelbine plus mitoxantrone with FAC/FEC*
§ *Frasci* et al., *2000[93] compared vinorelbine plus docetaxel with gemcitabine plus docetaxel*

TABLE 10 *Summary of the duration of response (months) for vinorelbine combination therapy*

Outcome	Study	Vinorelbine		Control	
		N	Median	*N*	Median
Response duration	Blajman *et al.*, 1999[39] *	85	10.5	85	11.0
	Namer *et al.*, 1998[40] †	142	7.0	138	10.0
	Norris *et al.*, 2000[41] ‡	145	7.2	144	6.8
Time to disease progression	Blajman *et al.*, 1999[39] *	85	7.5	85	9.0
	Monnier *et al.*, 1998[92] §	88	5.0	84	6.0
	Namer *et al.*, 1998[40] †	142	7.0	138	7.0
	Norris *et al.*, 2000[41] ‡	145	6.2	144	6.1
Time to treatment failure	Norris *et al.*, 2000[41] ‡	145	6.0	144	5.5

* *Blajman* et al., *1999[39] compared vinorelbine plus doxorubicin with FAC*
† *Namer* et al., *2001[40] compared vinorelbine plus mitoxantrone with FAC/FEC*
‡ *Norris* et al., *2000[41] compared vinorelbine plus doxorubicin with doxorubicin alone*
§ *Monnier* et al., *1998[92] compared FUN with docetaxel*

TABLE 11 *Summary of the survival data (months) for vinorelbine combination therapy*

Outcome	Study	Vinorelbine		Control	
		N	Median	*N*	Median
Survival	Blajman *et al.*, 1999[39]*	85	17.8	85	17.3
	Monnier *et al.*, 1998[92]†	89	12.0	86	13.0
	Namer *et al.*, 1998[40]‡	142	17.0	138	20.0
	Norris *et al.*, 2000[41]§	145	13.8	144	14.4

* *Blajman* et al., *1999[39] compared vinorelbine plus doxorubicin with FAC*
† *Monnier* et al., *1998[92] compared FUN with docetaxel*
‡ *Namer* et al., *2001[40] compared vinorelbine plus mitoxantrone with FAC/FEC*
§ *Norris* et al., *2000[41] compared vinorelbine plus doxorubicin with doxorubicin alone*

TABLE 12 *Adverse events for vinorelbine combination therapy (RR < 1 favours vinorelbine)*

Adverse event (grades 3, 4 and 5 only)	Study	Vinorelbine *n/N*	Control *n/N*	RR
Haematological toxicity				
Haemoglobin (anaemia)	Norris *et al.*, 2000[41]*	10/151	12/149	0.82 (95% CI, 0.37 to 1.84)
	Frasci *et al.*, 2000[93]†	8/15	7/19	1.45 (95% CI, 0.68 to 3.08)
Neutropenia	Blajman *et al.*, 1999[39]‡	6/85	6/84	0.99 (95% CI, 0.33 to 2.94)
Febrile neutropenia	Norris *et al.*, 2000[41]*	23/151	15/149	1.51 (95% CI, 0.82 to 2.78)
Febrile neutropenia requiring hospitalisation	Namer *et al.*, 2001[40]§	21/142	3/139	6.85 (95% CI, 2.09 to 22.45)
Granulocytopenia	Norris *et al.*, 2000[41]*	132/151	129/149	1.01 (95% CI, 0.93 to 1.10)
Thrombocytopenia (platelets)	Blajman *et al.*, 1999[39]‡	0/84	2/84	0.20 (95% CI, 0.01 to 4.10)
	Norris *et al.*, 2000[41]*	3/151	4/149	0.74 (95% CI, 0.17 to 3.25)
	Frasci *et al.*, 2000[93]†	4/15	3/19	1.69 (95% CI, 0.44 to 6.42)
Non-haematological toxicity				
Infection	Blajman *et al.*, 1999[39]‡	2/741	1/62	1.68 (95% CI, 0.16 to 18.05)
	Norris *et al.*, 2000[41]*	3/151	3/149	0.99 (95% CI, 0.20 to 4.81)
Cardiac	Blajman *et al.*, 1999[39]‡	0/74	0/62	NA
	Namer *et al.*, 2001[40]§	9/142	10/139	0.88 (95% CI, 0.37 to 2.10)
	Norris *et al.*, 2000[41]*	2/151	2/149	0.99 (95% CI, 0.14 to 6.91)
Constipation	Blajman *et al.*, 1999[39]‡	1/74	0/63	2.56 (95% CI, 0.11 to 61.76)
	Norris *et al.*, 2000[41]*	5/151	2/149	2.47 (95% CI, 0.49 to 12.52)
Neurological (sensory)	Norris *et al.*, 2000[41]*	2/151	0/149	4.93 (95% CI, 0.24 to 101.92)
Neurological (motor)	Norris *et al.*, 2000[41]*	2/151	0/149	4.93 (95% CI, 0.24 to 101.92)
Peripheral neuropathy	Blajman *et al.*, 1999[39]‡	2/63	0/64	5.08 (95% CI, 0.25 to 103.72)
Alopecia	Blajman *et al.*, 1999[39]‡	22/74	23/63	0.81 (95% CI, 0.50 to 1.31)
	Norris *et al.*, 2000[41]*	36/151	36/149	0.99 (95% CI, 0.66 to 1.48)
	Namer *et al.*, 2001[40]§	10/142	41/139	0.24 (95% CI, 0.12 to 0.46)
Local venous reaction	Blajman *et al.*, 1999[39]‡	2/74	0/63	4.27 (95% CI, 0.21 to 87.26)
	Norris *et al.*, 2000[41]*	3/151	0/149	6.91 (95% CI, 0.36 to 132.60)
Diarrhoea	Blajman *et al.*, 1999[39]‡	0/71	0/63	NA
	Norris *et al.*, 2000[41]*	3/151	2/149	1.48 (95% CI, 0.25 to 8.73)
Anorexia	Norris *et al.*, 2000[41]*	3/151	5/149	0.59 (95% CI, 0.14 to 2.43)
Nausea	Norris *et al.*, 2000[41]*	18/151	26/149	0.68 (95% CI, 0.39 to 1.19)
Nausea and vomiting	Namer *et al.*, 2001[40]§	11/142	22/139	0.49 (95% CI, 0.25 to 0.97)
Taste altered	Norris *et al.*, 2000[41]*	0/151	1/149	0.33 (95% CI, 0.01 to 8.01)
Stomatitis	Norris *et al.*, 2000[41]*	8/151	10/149	0.79 (95% CI, 0.32 to 1.95)
Vomiting	Norris *et al.*, 2000[41]*	11/151	19/149	0.57 (95% CI, 0.28 to 1.16)
	Frasci *et al.*, 2000[93]†	0/15	1/19	NA
Nausea/vomiting	Blajman *et al.*, 1999[39]‡	2/74	1/63	1.70 (95% CI, 0.16 to 18.34)
Mucositis	Blajman *et al.*, 1999[39]‡	2/73	2/63	0.86 (95% CI, 0.13 to 5.95)
Skin	Blajman *et al.*, 1999[39]‡	2/73	0/63	2.00 (95% CI, 0.21 to 88.43)
Fatigue	Frasci *et al.*, 2000[93]†	1/15	1/19	1.27 (95% CI, 0.09 to 18.62)

* *Norris* et al., *2000[41] compared vinorelbine plus doxorubicin with doxorubicin alone*
† *Frasci* et al., *2000[93] compared vinorelbine plus docetaxel with gemcitabine plus docetaxel*
‡ *Blajman* et al., *1999[39] compared vinorelbine plus doxorubicin with FAC*
§ *Namer* et al., *2001[40] compared vinorelbine plus mitoxantrone with FAC/FEC*

TABLE 13 *Quality of the included vinorelbine uncontrolled studies (according to the checklist for case series presented in appendix 5)*

Study	Number of participants recruited	Number of participants evaluable for response	Representative sample	Explicit inclusion criteria	Individuals entered the survey at a similar point	Long enough follow-up	Use of objective criteria or blinding to assess outcomes	Sufficient description of the subseries and the distribution of prognostic factors?
Vinorelbine monotherapy								
Bruno *et al.*, 1995[19]	68	63	Unclear	Yes	No	Yes	Yes	Partially
Delgado *et al.*, 1991[20]	36 (26 first line)	25 first line	No	Yes	No	No	Yes	Yes
Fumoleau *et al.*, 1993[21]	157	145	Unclear	Yes	Unclear	Yes	Yes	Yes
Garcia-Conde *et al.*, 1994[22]	54	50	Unclear	Yes	Unclear	Yes	Yes	Partially
Kesselring *et al.*, 1991[23] (abstract)	16	14	No	Unclear	Unclear	Unclear	Unclear	Unclear
Queisser *et al.*, 1991[24]	17	15	No	Yes	Unclear	No	Yes	Partially
Romero *et al.*, 1994[25]	45	44	Unclear	Yes	No	Partially	Yes	Yes
Smith, 1990[26] (abstract)	134	123	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Terenziani *et al.*, 1996[27]	53 (27 first line)	27 first line	No	Partially	Unclear	Yes	Yes	Yes
Toussaint *et al.*, 1995[28]	68 (34 first line)	34 first line	No	Yes	No	Yes	Yes	Yes
Twelves *et al.*, 1994[29]	35	34	No	Yes	Unclear	Yes	Yes	Partially
Vogel *et al.*, 1999[30]	56	56	Unclear	Yes	Unclear	Partially	Yes	Yes
Weber *et al.*, 1995[31]	107 (60 first line)	60 first line	Unclear	Partially	No	Yes	Yes	Yes
Winer *et al.*, 1993[32] (abstract)	92 (22 first line)	22 first line	No	Partially	Unclear	Unclear	Unclear	Unclear
Vinorelbine combination therapy								
Vinorelbine plus doxorubicin								
Alvarez *et al.*, 1994[42] (abstract)	85	70	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Arca *et al.*, 1998[91] (abstract)	76	70	Unclear	Unclear	Unclear	Yes	Unclear	Partially
Baltali *et al.*, 1996[43] (abstract)	37	34	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bonicatto *et al.*, 1998[90] (abstract)	52	47	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Coppola *et al.*, 1994[44] (abstract)	165 (76 first line)	60 first line	Unclear	Unclear	Unclear	Unclear	Unclear	No
Hegg *et al.*, 2001[45]	52	47	Unclear	Yes	Yes	Unclear	Yes	Partially
Hochster *et al.*, 2001[46*]	62	62	Unclear	Yes	Unclear	Yes	Yes	Yes
Siedlecki *et al.*, 1997[47] (abstract)	37	34	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Smalley *et al.*, 1994[48] (abstract)	34	34	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Spielmann *et al.*, 1994[49]	97	89	Unclear	Yes	Partially	Yes	Yes	Yes
Vorobiof *et al.*, 1997[50] (abstract)	40	24	Unclear	Unclear	No	No	Unclear	Unclear

continued

TABLE 13 contd *Quality of the included vinorelbine uncontrolled studies (according to the checklist for case series presented in appendix 5)*

Study	Number of participants recruited	Number of participants evaluable for response	Representative sample	Explicit inclusion criteria	Individuals entered the survey at a similar point	Long enough follow-up	Use of objective criteria or blinding to assess outcomes	Sufficient description of the subseries and the distribution of prognostic factors?
***Vinorelbine combination therapy* contd**								
Vinorelbine plus epirubicin								
Baldini *et al.*, 1998[51]	51	47	Unclear	Yes	Yes	Partially	Yes	Yes
Cottu *et al.*, 1993[52] (abstract)	19	19	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Ezzat *et al.*, 1996[53] (abstract)	28	24	Unclear	Unclear	No	Unclear	Unclear	Unclear
Nistico *et al.*, 1999[54]	52	52	Unclear	Yes	Yes	Yes	Yes	No
Tabiadon *et al.*, 1998[55] (abstract)	19	17	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vici *et al.*, 1999[56] (abstract)	54	46	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Vinorelbine plus paclitaxel								
Ibrahim *et al.*, 2001[57]	38	38	Unclear	Yes	Yes	Unclear	Unclear	NA
Martin, 1999[58] (abstract)	50 (17 first line)	17 first line	Unclear	Unclear	No	Unclear	Unclear	Unclear
Martin *et al.*, 2000[59]	56 (15 first line)	15 first line	Unclear	Yes	No	No	Yes	No
Romero Acuna *et al.*, 1999[60]	49	45	Unclear	Yes	Yes	Yes	Yes	Yes
Vici *et al.*, 2000[61]	43	41	Unclear	Yes	No	Yes	Yes	NA
Vinorelbine plus mitoxantrone								
Ferrero *et al.*, 1995[62]	41	37	Unclear	Yes	Yes	No	Yes	Yes
Frasci *et al.*, 1995[63]	43 (20 first line)	18 first line	Unclear	Yes	No	Unclear	Yes	Yes
Gladieff *et al.*, 1996[64]	25	23	Unclear	Yes	Yes	Unclear	No	Unclear
Llombart-Cussac *et al.*, 1998[65]	72	65	Unclear	Yes	Yes	Yes	Yes	Yes
Vinorelbine plus docetaxel								
Bonneterre *et al.*, 199866	15	15	Unclear	Yes	Yes	No	Unclear	Yes
De Paz *et al.*, 1999[67] (abstract)	34 (16 first line)	16 first line	Unclear	Unclear	No	Unclear	Unclear	No
Fumoleau *et al.*, 1997[68]	29	29	Unclear	Yes	Yes	No	No	No
Kornek *et al.*, 2001[69]	57 (42 first line)	42 first line	Unclear	Yes	No	Unclear	Yes	No
FUN								
Dieras *et al.*, 1996[70]	63	63	Unclear	Yes	Yes	Yes	Yes	Yes
Hochster *et al.*, 2001[46] *	56	56	Unclear	Yes	Unclear	Yes	Yes	Yes

continued

TABLE 13 contd *Quality of the included vinorelbine uncontrolled studies (according to the checklist for case series presented in appendix 5)*

Study	Number of participants recruited	Number of participants evaluable for response	Representative sample	Explicit inclusion criteria	Individuals entered the survey at a similar point	Long enough follow-up	Use of objective criteria or blinding to assess outcomes	Sufficient description of the subseries and the distribution of prognostic factors?
Vinorelbine combination therapy **contd**								
Vinorelbine plus 5-fluorouracil plus leucovorin								
Kornek *et al.*, 1998[71]	53 (37 first line)	37 first line	Unclear	Yes	No	Yes	Yes	Yes
Nole *et al.*, 1997[72]	49	39	Unclear	Yes	Yes	No	Yes	Yes
FAN								
Dieras *et al.*, 1996[73] (abstract)	82	70	Unclear	Yes	Yes	Partially	Unclear	Unclear
Goss *et al.*, 1997[74]	26 + 12 (also received folinic acid)	21 + 9	Unclear	Yes	Yes	Unclear	Yes	Yes
Vinorelbine plus cyclophosphamide plus 5-fluorouracil								
Ardavanis *et al.*, 1998[75]	45	38	Unclear	Yes	No	Yes	Unclear	Yes
Turpin *et al.*, 1999[76]	60	56	Unclear	Yes	No	Unclear	Yes	No
Vinorelbine plus cyclophosphamide plus epirubicin								
Braud *et al.*, 1999[77] (abstract)	20	19	Unclear	Unclear	Yes	No	Unclear	Unclear
Esteban *et al.*, 2000[78]	59	55	Unclear	Yes	Yes	Yes	Yes	Yes
Vinorelbine plus cisplatin								
Audhuy *et al.*, 1998[79] (abstract)	19	14	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hochster *et al.*, 1997[80] (abstract)	24 (20 first line)	19 first line	Unclear	Unclear	No	Unclear	Unclear	Unclear
Vinorelbine plus gemcitabine								
Haider *et al.*, 1999[81]	60 (45 first line)	45 first line	Unclear	Yes	No	Yes	Yes	No
Vinorelbine plus ifosfamide								
Leone *et al.*, 1996[82]	45	43	Unclear	Yes	Yes	Yes	Yes	Yes
Vinorelbine plus mitomycin C								
Kornek *et al.*, 1996[83]	55 (32 first line)	32 first line	Unclear	Yes	No	Yes	Yes	Yes
Vinorelbine plus trastuzumab								
Burstein *et al.*, 2001[84]	40 (19 first line)	19 first line	Unclear	Yes	No	Partially	Unclear	Yes

continued

TABLE 13 contd *Quality of the included vinorelbine uncontrolled studies (according to the checklist for case series presented in appendix 5)*

Study	Number of participants recruited	Number of participants evaluable for response	Represent-ative sample	Explicit inclusion criteria	Individuals entered the survey at a similar point	Long enough follow-up	Use of objective criteria or blinding to assess outcomes	Sufficient description of the subseries and the distribution of prognostic factors?
Vinorelbine combination therapy **contd**								
Vinorelbine plus 5-fluorouracil plus cisplatin								
Nole *et al.*, 2001[85]	100 (48 first line)	45 first line	Unclear	Yes	No	Partially	Yes	No
Vinorelbine plus 5-fluorouracil plus epirubicin								
Guler *et al.*, 2000[86] (abstract)	52	50	Unclear	Unclear	Yes	Yes	Unclear	No
Vinorelbine plus mitoxantrone plus carboplatin								
Kakolyris *et al.*, 1999[87]	50	50	Unclear	Yes	Yes	Yes	Yes	Yes
Vinorelbine plus mitoxantrone plus cisplatin								
Wendling *et al.*, 1995[88] (abstract)	25	20	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Vinorelbine plus doxorubicin plus methotrexate plus leucovorin								
Subramanyan *et al.*, 1999[89]	23	22	Unclear	Partially	Yes	Unclear	Yes	Unclear

Items were graded in terms of Yes (item properly addressed), No (item not properly addressed), Partially (item partially addressed), Unclear (item unclear or not enough information) or NA (not applicable)

* *Hochster* et al.[46] *as a full manuscript reporting two parallel protocols, one with vinorelbine plus doxorubicin, and one of FUN*

TABLE 14 *Summary of tumour response for vinorelbine monotherapy*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Bruno *et al.*, 1995[19]	68	48% (19%)	Vinorelbine 30 mg/m^2 i.v. once a week	No	5/63 (8%)	28/63 (44%, 95% CI, 32 to 56)	8/63 (13%)	27/63 (43%)
Delgado *et al.*, 1991[20]	36 (26 first line)	50% (4%)	Vinorelbine 30 mg/m^2 i.v. once a week	No	5/25 (20%)	15/25 (60%, 95% CI, 41 to 79)	5/25 (20%)	5/25 (20%)
Fumoleau *et al.*, 1993[21]	157	43% (29%)	Vinorelbine 30 mg/m^2 i.v. once a week	No	10/145 (7%)	60/145 (41%, 95% CI, 33 to 49)	44/145 (30%)	41/145 (28%)
Garcia-Conde *et al.*, 1994[22]	54	66% (54%)	Vinorelbine 30 mg/m^2 i.v. once a week	No	1/50 (2%)	25/50 (50%, 95% CI, 36 to 64)	Not stated	Not stated
Kesselring *et al.*, 1991[23] (abstract)	16	43% (not stated)	Vinorelbine 30 mg/m^2 i.v. once a week	No	0/14 (0%)	6/14 (42%)	Not stated	Not stated
Queisser *et al.*, 1991[24]	17	None reported	Vinorelbine 130 mg orally once a week	No	0/15 (0%)	0/15 (0%)	9/15 (60%)	6/15 (40%)
Romero *et al.*, 1994[25]	45	50% (43%)	Vinorelbine 30 mg/m^2 once a week	No	3/44 (7%)	18/44 (41%, 95% CI, 26 to 56)	14/44 (32%)	12/44 (27%)
Smith, 1990[26] (abstract)	134	Not stated	Vinorelbine 30 mg/m^2 once a week	No	Not stated	55/123 (45%)	Not stated	Not stated
Terenziani *et al.*, 1996[27]	53 (27 first line)	78% (44%)	Vinorelbine 30 mg/m^2 once a week (participants 1–20) modified to vinorelbine 30 mg/m^2 on days 1 and 8 every 3 weeks (participants 21–57)	No	3/27 (11%)	16/27 (59%, 95% CI, 35 to 75)	Not stated	Not stated
Toussaint *et al.*, 1995[28]	68 (34 first line)	72% (55%) of all participants (first and second line)	Vinorelbine 8 mg/m^2 on day 1 followed by 4 days of continuous infusion at escalating dosage levels (resulting in 30–48 mg/m^2) every 21 or 28 days	No	2/34 (6%)	11/34 (32%)	Not stated	Not stated
Twelves *et al.*, 1994[29]	35	9% (not stated)	Vinorelbine 25 mg/m^2 once a week	No	2/34 (6%)	17/34 (50%, 95% CI, 34 to 66)	12/34 (35%)	5/34 (15%)
Vogel *et al.*, 1999[30]	56	27% (13%)	Vinorelbine 30 mg/m^2 once a week for 13 weeks and every 2 weeks thereafter	Yes	2/56 (4%)	21/56 (38%, 95% CI, 24 to 51)	21/56 (38%)	14/56 (25%)
Weber *et al.*, 1995[31]	107 (60 first line)	53% (not stated)	Vinorelbine 30–35 mg/m^2 once a week	Yes	9/60 (15%)	21/60 (35%, 95% CI, 21 to 48)	18/60 (30%)	21/60 (35%)
Winer *et al.*, 1993[32] (abstract)	92 (22 first line)	Not stated	Vinorelbine 50 mg/m^2 (for participants with decreased marrow reserve) or 80 mg/m^2 orally once a week	No	2/22 (9%)	7/22 (32%)	Not stated	Not stated

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 15 *Summary of tumour response for vinorelbine plus doxorubicin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Alvarez *et al.*, 1994[42]	85	52% (not stated)	Vinorelbine 25 mg/m^2 on days 1–8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days	No	4/70 (6%)	49/70 (70%)	Not stated	Not stated
Arca *et al.*, 1998[91]	76	Not stated	Vinorelbine 25 mg/m^2 on days 1–8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days	No	7/70 (10%)	48/70 (68%)	Not stated	Not stated
Baltali *et al.*, 1996[43]	37	Not stated	Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 8, repeated every 21 days	No	11/34 (32%)	21/34 (62%, 95% CI, 46 to 78)	Not stated	Not stated
Bonicatto *et al.*, 1998[90]	52	42% (not stated)	Vinorelbine 25 mg/m^2 on days 1 and 5 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days	No	5/47 (11%)	33/47 (70%)	Not stated	Not stated
Coppola *et al.*, 1994[44]	165 (76 first line)	Not stated	Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days	No	5/60 (8%)	42/60 (70%, 95% CI, 58 to 82)	Not stated	Not stated
Hegg *et al.*, 2001[45]	52	2% (not stated)	Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 8, repeated every 21 days	No	9/47 (19%)	38/47 (73%, 95% CI, 61 to 85)	Not stated	Not stated
Hochster *et al.*, 2001[46†]	62	40% (0%)	Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 3 weeks	No	7/62 (11%)	34/62 (55%, 95% CI, 42 to 68)	18/62 (29%)	5/62 (8%)
Siedlecki *et al.*, 1997[47]	37	26% (0%)	Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 8, repeated every 21 days	No	8/34 (23%)	25/34 (74%)	6/34 (17%)	3/34 (9%)
Smalley *et al.*, 1994[48]	34	47% (12%)	Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 4 (19 patients were treated with vinorelbine at a reduced dose of 20 mg/m^2)	Yes	2/34 (6%)	10/34 (29%, 95% CI, 14 to 44)	Not stated	Not stated

continued

TABLE 15 contd *Summary of tumour response for vinorelbine plus doxorubicin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Spielmann *et al.*, 1994[49]	97	30% (22%)	Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 3 weeks	No	19/89 (21%)	66/89 (74%, 95% CI, 65 to 85)	20/89 (22%)	3/89 (3%)
Vorobiof *et al.*, 1997[50]	40	Not stated	Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 3 weeks	No	2/24 (8%)	13/24 (54%, 95% CI, 34 to 74)	Not stated	Not stated

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses; except for Alvarez* et al.[42] *where the denominator is the number of participants recruited*
† *Hochster et al.*[46] *as a full manuscript reporting two parallel protocols, one with vinorelbine plus doxorubicin, and one of FUN*

TABLE 16 *Summary of tumour response for vinorelbine plus epirubicin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Baldini *et al.*, 1998[51]	51	27% (not stated)	Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 90 mg/m^2 on day 1, repeated every 21 days	For grade 4 neutropenia only	4/47 (9%)	33/47 (70%, 95% CI, 55 to 83)	11/47 (23%)	3/47 (6%)
Ezzat *et al.*, 1996[53]	28	Not stated	Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 60–75 mg/m^2 on day 1, repeated every 21 days	No	*Overall*: 2/24 (8%) *Stage IV*: 1/16 (6%) *Stage III*: 1/8 (12.5%)	*Overall*: 12/24 (50%) (95% CI, 30 to 70) *Stage IV*: 6/16 (37.5%) *Stage III*: 6/8 (75%)	Not stated	Not stated
Nistico *et al.*, 1999[54]	52	67% (10%)	Vinorelbine 25 mg/m^2 plus epirubicin 25 mg/m^2 once a week	Yes (only for for neutropenia in first 35 patients)	10/52 (19%)	40/52 (77%, 95% CI, 66 to 88)	12/52 (23%)	0/52 (0%)
Tabiadon *et al.*, 1998[55]	19	84% (26%)	Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 80 mg/m^2 on day 1, repeated every 21–28 days	For grade 2 neutropenia	1/17 (6%)	13/17 (76%)	Not stated	Not stated
Vici *et al.*, 1999[56]	54	37% (0%)	Vinorelbine 25 mg/m^2 on days 1 and 5 plus epirubicin 100 mg/m^2 on day 1, repeated every 3 weeks	Yes	7/46 (15%)	33/46 (72%)	Not stated	Not stated

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses; except for Baldini* et al.,*[51] Tabiadon* et al.*[55] and Vici* et al.*[56] where the denominator is the number of participants recruited*

TABLE 17 *Summary of tumour response for vinorelbine plus paclitaxel*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Ibrahim *et al.*, 2001[57]	38	68% (58%)	The starting doses were paclitaxel 175 mg/m^2 and vinorelbine 36 mg/m^2 (on day 1?), repeated every 3 weeks. In the group that did not receive G-CSF, the doses were reduced to vinorelbine 25 mg/m^2 and paclitaxel 150 mg/m^2. In the group that did receive G-CSF, vinorelbine ranged from 25 to 46 mg/m^2 and paclitaxel could be reduced to 150 mg/m^2	Used in 13 patients (25 without)	*Overall*: 3/38 (8%) *Group that received G-CSF*: 2/13 (15%) *Group that did not receive G-CSF*: 1/25 (4%)	*Overall*: 18/38 (47%) *Group that received G-CSF*: 8/13 (61%) *Group that did not receive G-CSF*: 10/25 (40%)	*Overall*: 15/38 (39%) *Group that received G-CSF*: 3/13 (23%) *Group that did not receive G-CSF*: 12/25 (48%)	*Overall*: 5/38 (13%) *Group that received G-CSF*: 2/13 (15%) *Group that did not receive G-CSF*: 3/25 (12%)
Martin, 1999[58]	50 (17 first line)	Not stated for first line (42% for all patients)	Vinorelbine 30 mg/m^2 plus paclitaxel 135 mg/m^2 on day 1, repeated every 3 weeks	No	Not stated	10/17 (59%)	Not stated	Not stated
Martin *et al.*, 2000[59]	56 (15 first line)	Not stated for first line (39% for all patients)	Vinorelbine 30 mg/m^2 plus paclitaxel 135 mg/m^2 on day 1, repeated every 3 weeks	No	Not stated	10/15 (67%)	Not stated	Not stated
Romero Acuna *et al.*, 1999[60]	49	59% (45%)	Vinorelbine 30 mg/m^2 on days 1 and 8 plus paclitaxel 135 mg/m^2 on day 1, repeated every 4 weeks	No	3/45 (7%)	27/45 (60%, 95% CI, 46 to 74)	12/45 (27%)	6/45 (13%)
Vici *et al.*, 2000[61]	43	52% (23%)	Vinorelbine 25 mg/m^2 plus paclitaxel 150 mg/m^2 on day 1, repeated every 3 weeks	Yes	2/41 (5%)	20/41 (49%, 95% CI, 34 to 64)	12/41 (29%)	9/41 (22%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses; except for Romero Acuna* et al.[60] *where the denominator is the number of participants recruited*

TABLE 18 *Summary of tumour response for vinorelbine plus mitoxantrone*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Ferrero *et al.*, 1995[62]	41	34% (29%)	Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitoxantrone 12 mg/m^2 on day 1, repeated every 21 days until disease progression or toxicity	No	5/37 (13%)	19/37 (51%, 95% CI, 45 to 74)	11/37 (30%)	7/37 (19%)
Frasci *et al.*, 1995[63]	43 (20 first line)	Not stated	The starting dose intensity was mitoxantrone 3 mg/m^2/week plus vinorelbine 15 mg/m^2/week, without G-CSF support. There were three different schedules for mitoxantrone: total dose on day 1, dose divided between days 1 and 8 and dose divided between days 1, 8 and 15. Vinorelbine was administered once a week. The dose was escalated by 1 mg/m^2/week for mitoxantrone and by 5 mg/m^2/week for vinorelbine. Dose escalation continued until dose-limiting toxicity occurred	G-CSF was administered from the second dose level	Not stated	12/18 (67%)	Not stated	Not stated
Gladieff *et al.*, 1996[64]	25	8% (8%)	Vinorelbine 20 mg/m^2 on days 1 and 8 plus mitoxantrone 10 mg/m^2 on day 1, repeated every 21 days	No	Not stated	5/23 (22%)	2/23 (4%)	16/23 (70%)
Llombart-Cussac *et al.*, 1998[65]	72	100% (100%)	Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitoxantrone 10 mg/m^2 (except for the first six patients who received 12 mg/m^2) on day 1, repeated every 3 weeks	G-CSF only allowed as curative treatment of febrile neutropenia	4/65 (6%)	32/65 (49%, 95% CI, 37 to 63). When analysed on an ITT basis = 32/69 (46%, 95% CI, 34 to 59)	17/65 (26%)	16/65 (25%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses; except for Ferrero* et al.[62] *and Gladieff* et al.[64] *where the denominator is the number of participants recruited*

TABLE 19 *Summary of tumour response for vinorelbine plus docetaxel*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
De Paz *et al.*, 1999[67]	34 (16 first line)	Not stated (94% of all patients)	Vinorelbine 30 mg/m^2 plus docetaxel 70 mg/m^2 on day 1, repeated every 3 weeks	No	3/16 (19%)	11/16 (69%)	Not stated	Not stated
Fumoleau *et al.*, 1997[68]	29	Not stated	Vinorelbine 20 or 22.5 mg/m^2 on days 1 and 5, followed by docetaxel 60–100 mg/m^2 on day 1, repeated every 3 weeks	No	Not stated	*Overall:* 19/29 (66%) *For doxorubicin 85 mg/m^2 plus vinorelbine 20 mg/m^2:* 8/10 (80%) *For doxorubicin 75 mg/m^2 plus vinorelbine 20 mg/m^2:* 4/6 (67%)	Not stated	Not stated
Kornek *et al.*, 2001[69]	57 (42 first line)	47% (not stated)	Vinorelbine 30 mg/m^2 on days 1 and 15 plus docetaxel 30 mg/m^2 on days 1, 8 and 15, repeated every 4 weeks	G-CSF dependant on granulocyte count on day of therapy	8/42 (19%)	27/42 (64%, 95% CI, 48 to 78)	11/42 (26%)	4/42 (9.5%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses; except for De Paz* et al.[67] *where the denominator is the number of participants recruited*

TABLE 20 *Summary of tumour response for FUN*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Dieras *et al.*, 1996[70]	63	64% (54%)	Vinorelbine 30 mg/m^2 on days 1 and 5 plus 5-fluorouracil 750 mg/m^2 for 5 days consecutively, repeated every 21 days	No	8/63 (13%)	40/63 (64%)	13/63 (20%)	10/63 (16%)
Hochster *et al.*, 2001[46†]	56	71% (54%)	Vinorelbine 30 mg/m^2 on days 1 and 5 plus 5-fluorouracil 750 mg/m^2 on days 1–5, repeated every 3 weeks	No	3/56 (5%)	25/56 (45%, 95% CI, 31 to 59)	18/56 (32%)	11/56 (20%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

† *Hochster* et al.[46] *as a full manuscript reporting two parallel protocols, one with vinorelbine plus doxorubicin, and one of FUN*

TABLE 21 *Summary of tumour response for vinorelbine plus 5-fluorouracil plus leucovorin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Kornek *et al.*, 1998[71]	53 (37 first line)	35% (not stated)	Vinorelbine 40 mg/m^2 on days 1 and 14 plus 5-fluorouracil 400 mg/m^2 plus leucovorin 100 mg/m^2 on days 1–5, repeated every 4 weeks	G-CSF on days 6–10 (note: earlier abstracts say days 6–12)	5/37 (13%)	22/37 (59%)	10/37 (27%)	5/37 (14%)
Nole *et al.*, 1997[72]	49	54% (33%)	Vinorelbine 25 mg/m^2 on days 1 and 3 plus 5-fluorouracil 350 mg/m^2 and folinic acid 100 mg/m^2 on days 1–3, repeated every 21 days	No	7/39 (18%)	24/39 (62%, 95% CI, 47 to 77)	9/39 (23%)	6/39 (15%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 22 *Summary of tumour response for FAN*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Dieras *et al.*, 1996[73]	82	60% (40%)	Vinorelbine 25 mg/m^2 plus doxorubicin 20 mg/m^2 on days 1 and 8 plus 5-fluorouracil 250 mg/m^2 on days 1–15	No	4/70 (6%)	44/70 (63%, 95% CI, 51 to 74)	16/70 (23%)	10/70 (14%)
Goss *et al.*, 1997[74]	26 + 12 (plus folinic acid)	*FAN*: 24% (0%) *SUPERFAN*: 44% (0%)	*FAN*: 5-fluorouracil 500 mg/m^2 plus doxorubicin 50 mg/m^2 on day 1, and escalating doses of vinorelbine (15, 20, 25 and 30 mg/m^2) on days 1, 8 and 15, repeated every 3 weeks (maximum dose of doxorubicin was 400 mg/m^2) *SUPERFAN*: 5-fluorouracil 340 mg/m^2 plus folinic acid 200 mg/m^2 on days 1–5, doxorbicin 40 mg/m^2 on day 1 only plus escalating doses of vinorelbine (15, 20, 25 and 30 mg/m^2) on days 1 and 5, repeated every 4 weeks (maximum dose of doxorubicin was 400 mg/m^2)	No	*FAN*: 3/21 (12%) *SUPERFAN*: 0/9 (0%)	*FAN*: 10/21 (48%) *SUPERFAN*: 2/9 (22%)	*FAN*: 9/21 (43%) *SUPERFAN*: 6/9 (67%)	*FAN*: 2/21 (9%) *SUPERFAN*: 1/9 (11%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoaduvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 23 *Summary of tumour response for vinorelbine plus cyclophosphamide plus 5-fluorouracil*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Ardavanis *et al.*, 1998[75]	45 (38 first line)	53% (25%) of all patients	Vinorelbine 25 mg/m^2 on days 1 and 3, plus cyclophosphamide 600 mg/m^2 plus 5-fluorouracil 750 mg/m^2 on days 1–3, repeated every 21 days for six cycles	No	4/38 (11%)	19/38 (50%)	13/38 (34%)	6/38 (16%)
Turpin *et al.*, 1999[76]	60	42% (not stated)	Vinorelbine 25 mg/m^2 plus 5-fluorouracil 500 mg/m^2 on days 1 and 8 plus cyclophosphamide 500 mg/m^2 on day 1, repeated every 21 days	No	*Locally ABC and MBC together*: 4/60 (7%, 95% CI, 0 to 13)	*Locally ABC and MBC together*: 27/60 (45%, 95% CI, 32 to 58)	*Locally ABC and MBC together*: 15/60 (25%)	*Locally ABC and MBC together*: 14/60 (23%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 24 *Summary of tumour response for vinorelbine plus cyclophosphamide plus epirubicin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Braud *et al.*, 1999[77]	20	Not stated	Vinorelbine 25 mg/m^2 on days 1 and 3 plus epirubicin 30 mg/m^2 plus cyclophosphamide 350 mg/m^2 on days 1–3, repeated every 21 days. After six cycles doses were reduced by 30%	G-CSF if required	4/19 (21%)	15/19 (79%)	Not stated	Not stated
Esteban *et al.*, 2000[78]	59	37.5% (0%)	Vinorelbine 25 mg/m^2 + epirubicin 30 mg/m^2 + cyclophosphamide 400 mg/m^2, all given on days 1 and 8, repeated every 28 days	G-CSF for grade 4 neutropenia with fever or infection	5/55 (9%)	28/55 (51%, 95% CI, 37 to 63)	25/55 (45%)	2/55 (4%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 25 *Summary of tumour response for vinorelbine plus cisplatin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Audhuy *et al.*, 1998[79]	19	32% (not stated)	Vinorelbine 30 mg/m^2 on days 1 and 5 and cisplatin 100 mg/m^2 on day 1, repeated every 3 weeks	No	1/14 (7%)	10/14 (71%, range 48–95)	Not stated	Not stated
Hochster *et al.*, 1997[80]	24 (20 first line)	38% (not stated) for all patients	Vinorelbine 30 mg/m^2 on days 1 and 8 plus cisplatin 75 g/m^2 on day 1, repeated every 3 weeks	No	*MBC*: 1/10 (1%) *Locally ABC*: 2/9 (22%)	*MBC*: 6/10 (60%) *Locally ABC*: 8/9 (89%)	Not stated	Not stated

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses; except Hochster* et al.[80] *where the denominator was recruited participants*

TABLE 26 *Summary of tumour response for vinorelbine plus gemcitabine*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Haider *et al.*, 1999[81]	60 (45 first line)	32% (not stated)	Vinorelbine 40 mg/m^2 on days 1, and 21 plus gemcitabine 1000 mg/m^2 on days 15 and 21, repeated every 5 weeks	Yes	5/45 (11%)	25/45 (55.5%, 95% CI, 40 to 70)	12/45 (27%)	8/45 (18%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 27 *Summary of tumour response for vinorelbine plus ifosfamide*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Leone *et al.*, 1996[82]	45	39.5% (23%)	Vinorelbine 35 mg/m^2 on days 1 and 15 (vinorelbine 17.5 mg/m^2 on days 8 and 22 during first cycle only) plus ifosfamide 2 g/m^2/day for 3 days, repeated every 28 days	No	6/43 (14%)	25/43 (58%, 95% CI, 43 to 73)	10/43 (23%)	8/43 (19%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 28 *Summary of tumour response for vinorelbine plus mitomycin C*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Kornek *et al.*, 1996[83]	55 (32 first line therapy)	40% (not stated)	Vinorelbine 50 mg/m^2 in the first 36 patients, but then, due to toxicity, reduced to 40 mg/m^2 every 3 weeks plus mitomycin C 15 mg/m^2 every 6 weeks	Yes	9/32 (28%)	24/32 (75%)	7/32 (22%)	1/32 (3%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 29 *Summary of tumour response for vinorelbine plus trastuzumab*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Burstein *et al.*, 2001[4]	40 (19 first line)	58% (20%)	Vinorelbine 25 mg/m^2 weekly plus trastuzumab 2 mg/m^2 (except for first dose of 4 mg/m^2) weekly on same day. The vinorelbine dose, but not the trastuzumab dose, could be adjusted if there were signs of toxicity	G-CSF if treatment delays due to neutropenia or for febrile neutropenia	Not stated	16/19 (84%)	Not stated	Not stated

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 30 *Summary of tumour response for vinorelbine plus 5-fluorouracil plus cisplatin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Nole *et al.*, 2001[85]	100 (48 first line)	67% (47%)	Vinorelbine 20 mg/m^2 on days 1 and 3 plus cisplatin 60 mg/m^2 on day 1 plus 5-fluorouracil 200 mg/m^2/day (number of days not stated), repeated every 3 weeks	No	2/45 (5%)	30/45 (66%)	11/45 (25%)	4/45 (9%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 31 *Summary of tumour response for vinorelbine plus 5-fluorouracil plus epirubicin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Guler *et al.*, 2000[86]	52	Not stated (40%)	Vinorelbine 25 mg/m^2 plus epirubicin 35–40 mg/m^2 plus 5-fluorouracil 350 mg/m^2 on days 1 and 8, repeated every 3 weeks	No	7/50 (14%)	35/50 (70%)	12/50 (12%)	3/50 (6%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 32 *Summary of tumour response for vinorelbine plus mitoxantrone plus carboplatin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Kakolyris *et al.*, 1999[87]	50	34% (not stated)	Vinorelbine 30 mg/m^2 plus mitoxantrone 12 mg/m^2 on day 1 plus caroplatin 250 mg/m^2 on day 2, repeated every 3 weeks. Initially, vinorelbine was also to be given on day 8, but this was dropped after first four patients due to toxicity	G-CSF if grade 3–4 neutropenia in cycle 1	4/50 (8%)	28/50 (56%, 95% CI, 42 to 70)	12/50 (24%)	10/50 (20%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 33 *Summary of tumour response for vinorelbine plus mitoxantrone plus cisplatin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Wendling *et al.*, 1995[88]	25	75% (60%)	Vinorelbine 25 mg/m^2 plus mitoxantrone 12 mg/m^2 on day 1 plus cisplatin 25 mg/m^2 on days 1–3	G-CSF used for 35% of courses	5/20 (25%)	16/20 (75%)	Not stated	Not stated

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

TABLE 34 *Summary of tumour response for vinorelbine plus doxorubicin plus methotrexate plus leucovorin*

Study	Number of participants recruited	Received previous adjuvant chemotherapy (previous anthracycline)*	Drug dosages	G-CSF support	Complete response	Overall response (complete and partial response)	Stable disease	Progressive disease
Subramanyan *et al.*, 1999[89]	23	32% (not stated)	Starting dose levels: vinorelbine 20 mg/m^2 plus doxorubicin 40 mg/m^2 plus methotrexate 100 mg/m^2 on day 1 plus leucovorin 10 mg/m^2 for 6 days starting on day 2 Dose of vinorelbine was increased by 5 mg/m^2 if ≥ three patients completed the 21-day course with no dose-limiting toxicity. Maximum dose of vinorelbine = 30 mg/m^2. Doxorubicin 50 and 60 mg/m^2 were also used with vinorelbine 25 mg/m^2 in some patients	No	3/22 (14%)	8/22 (36%)	5/22 (23%)	8/22 (36%)

* *Percentage of evaluable participants who had received previous chemotherapy in the neoadjuvant or adjuvant setting, and the percentages of evaluable participants who had received previous anthracycline therapy are in parentheses*

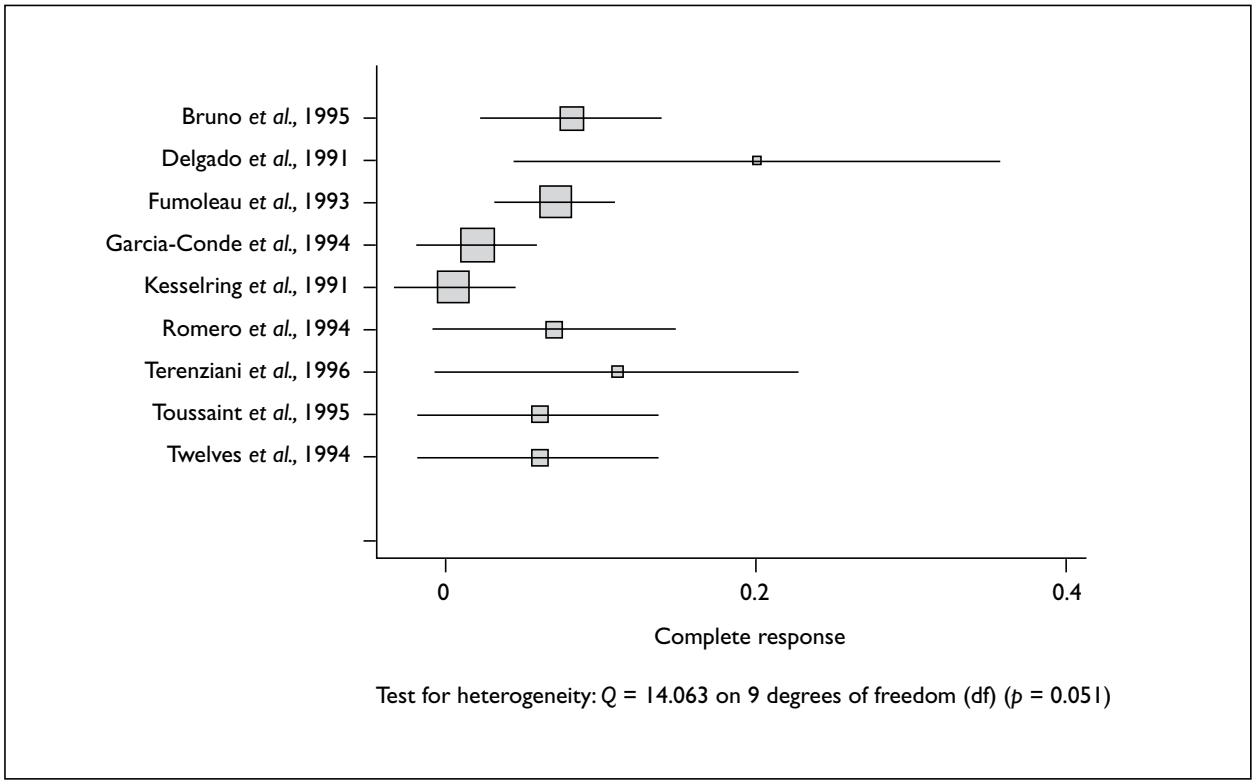


FIGURE 2 *Vinorelbine as monotherapy: complete tumour response data (excluding studies of oral vinorelbine, elderly women or G-CSF support)*

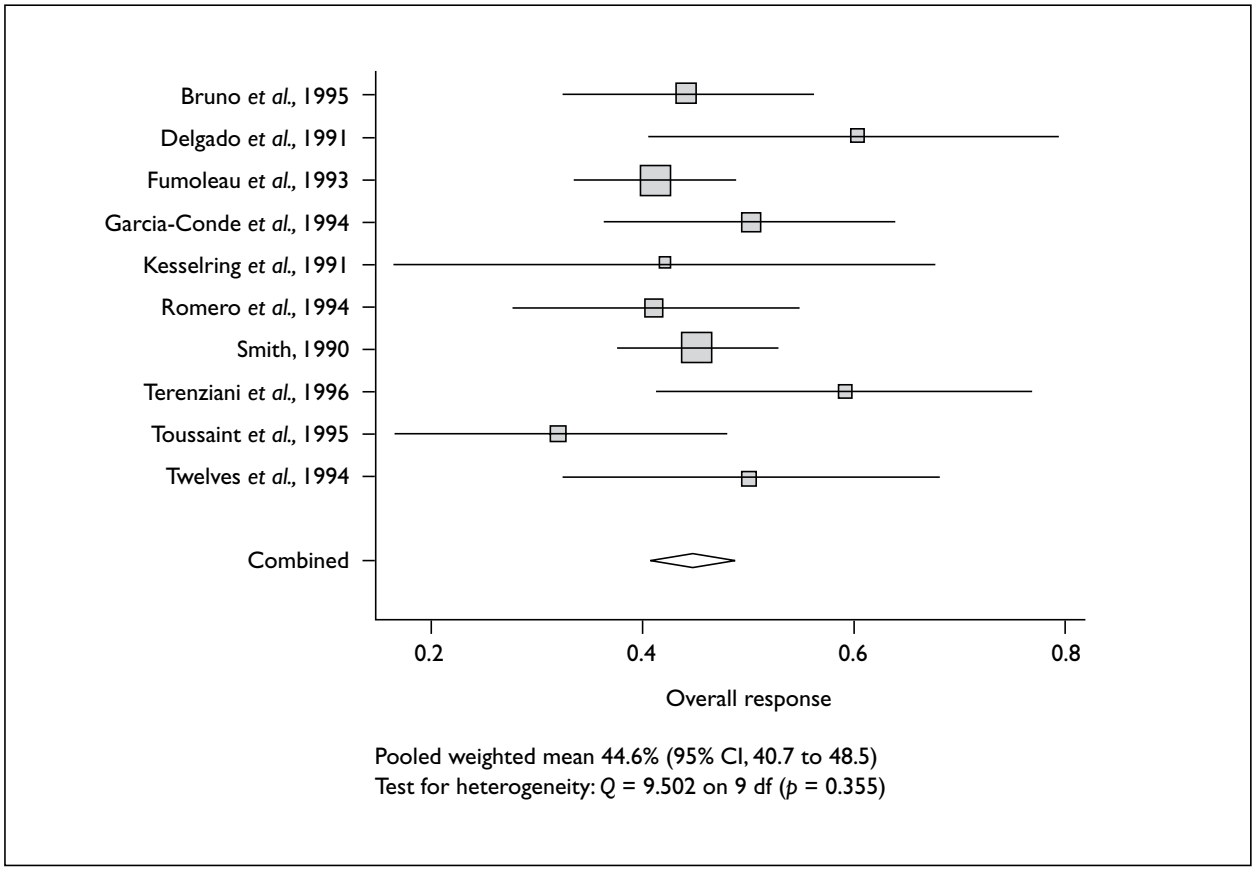


FIGURE 3 *Vinorelbine as monotherapy: overall tumour response data (excluding studies of oral vinorelbine, elderly women or G-CSF support)*

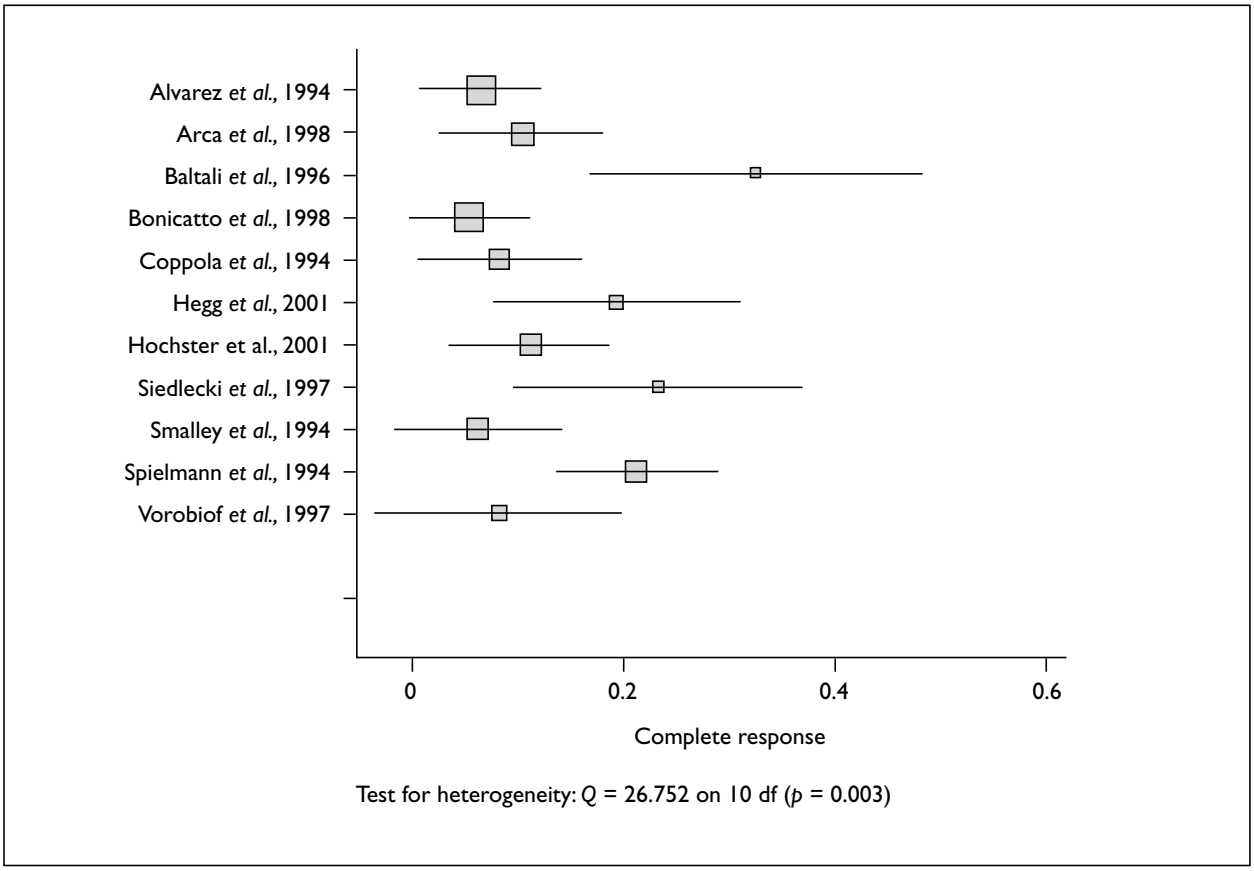


FIGURE 4 *Vinorelbine plus doxorubicin: complete tumour response data*

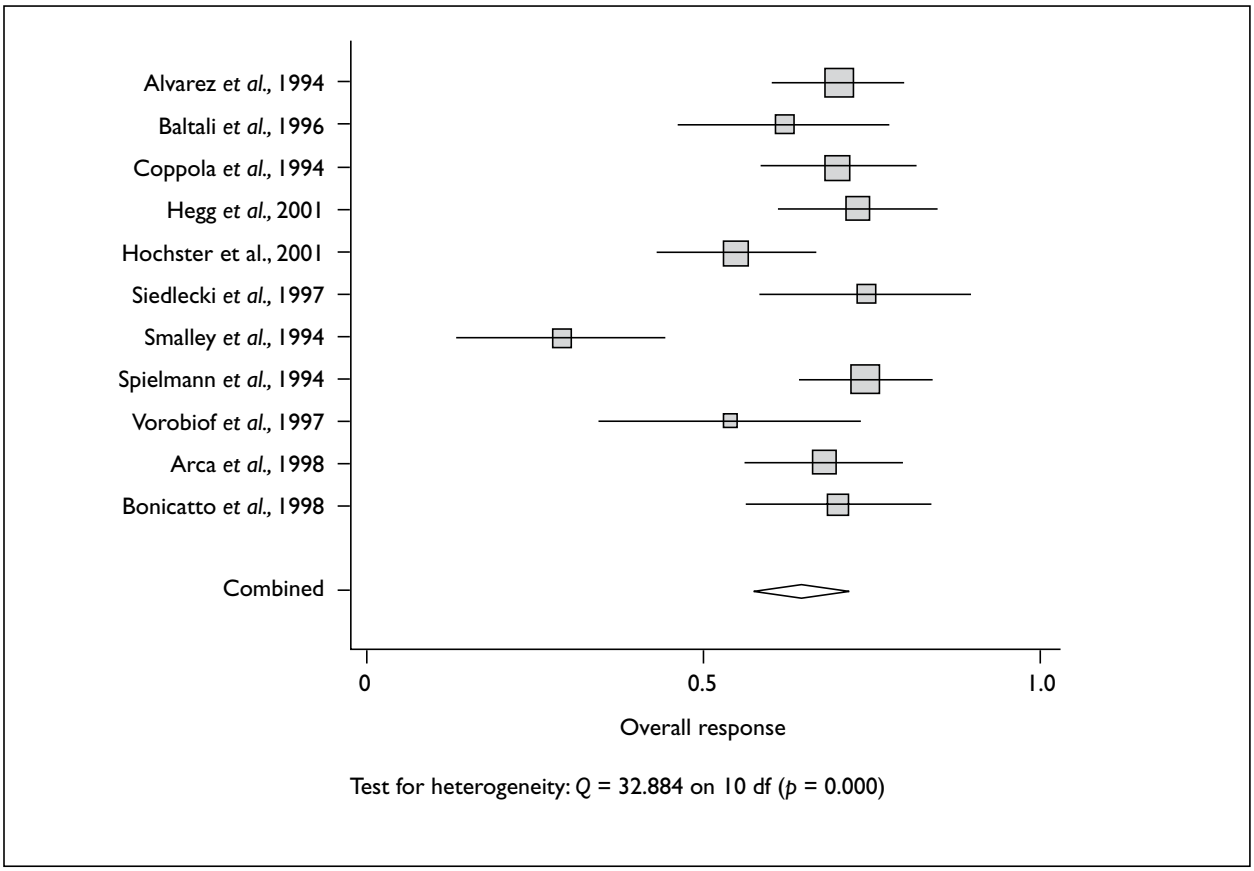


FIGURE 5 *Vinorelbine plus doxorubicin: overall tumour response data*

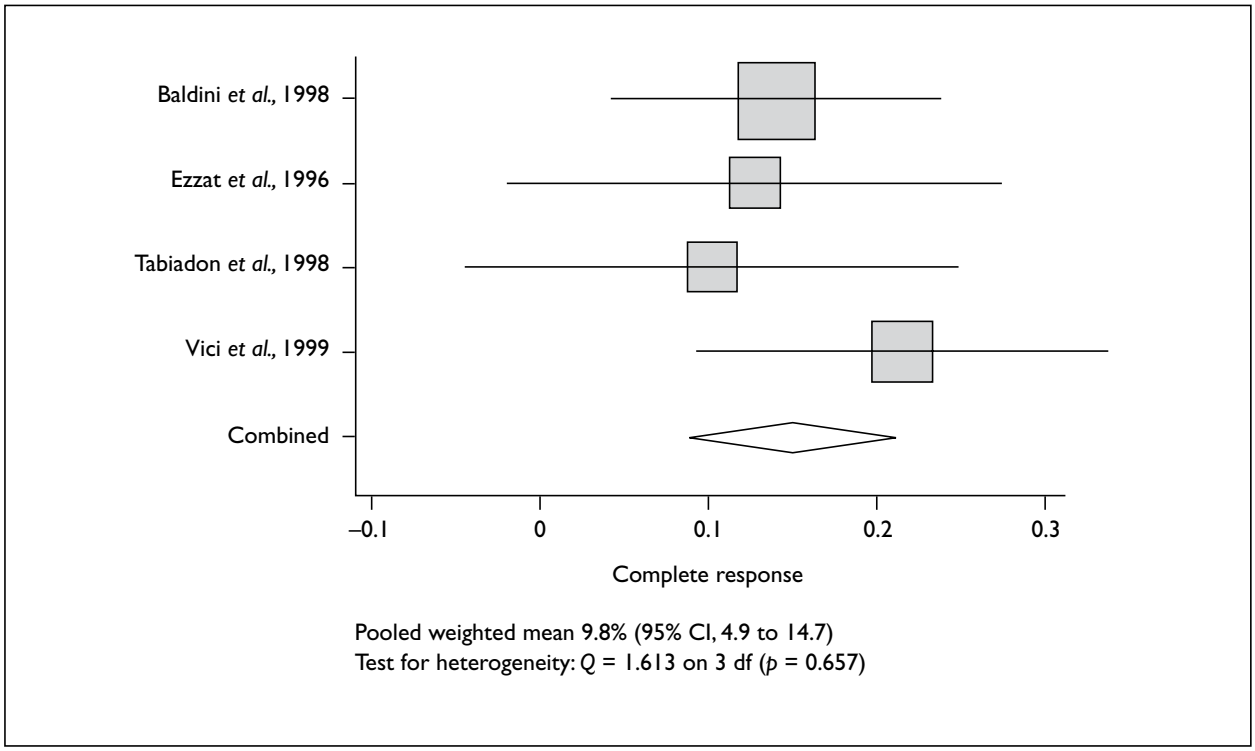


FIGURE 6 *Vinorelbine plus epirubicin: complete tumour response data (all)*

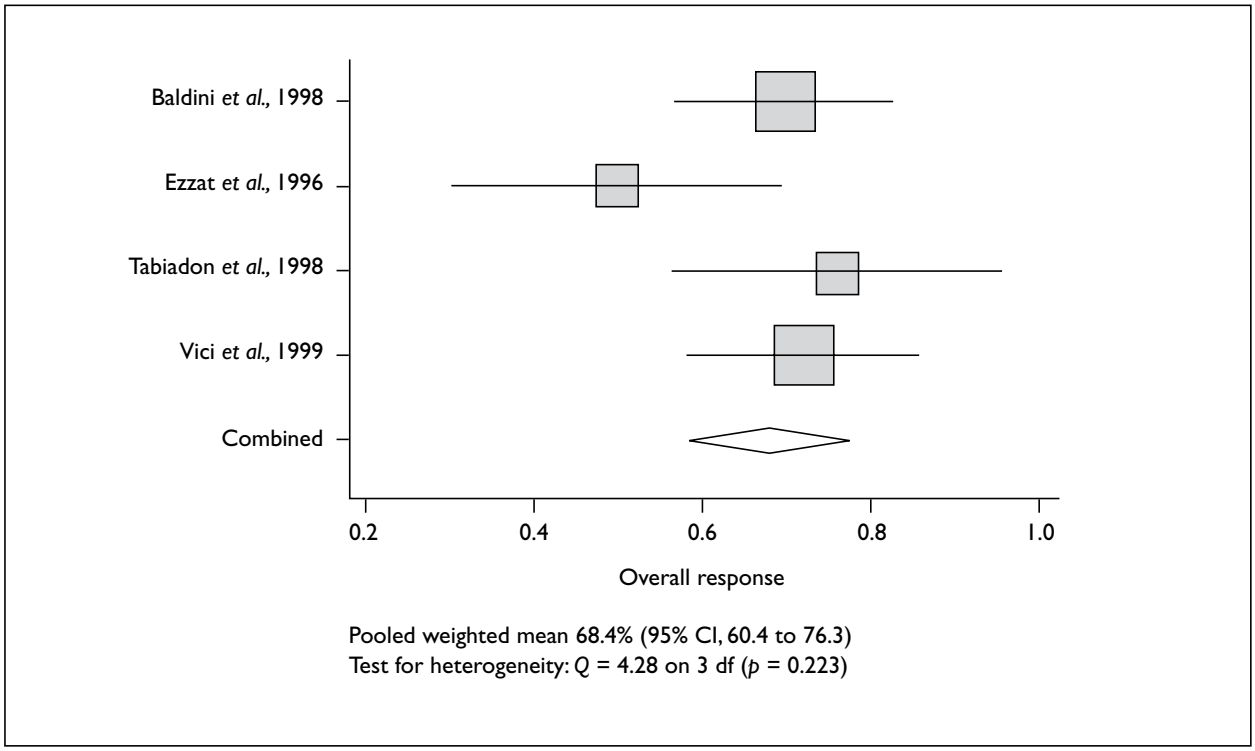


FIGURE 7 *Vinorelbine plus epirubicin: overall tumour response data (all)*

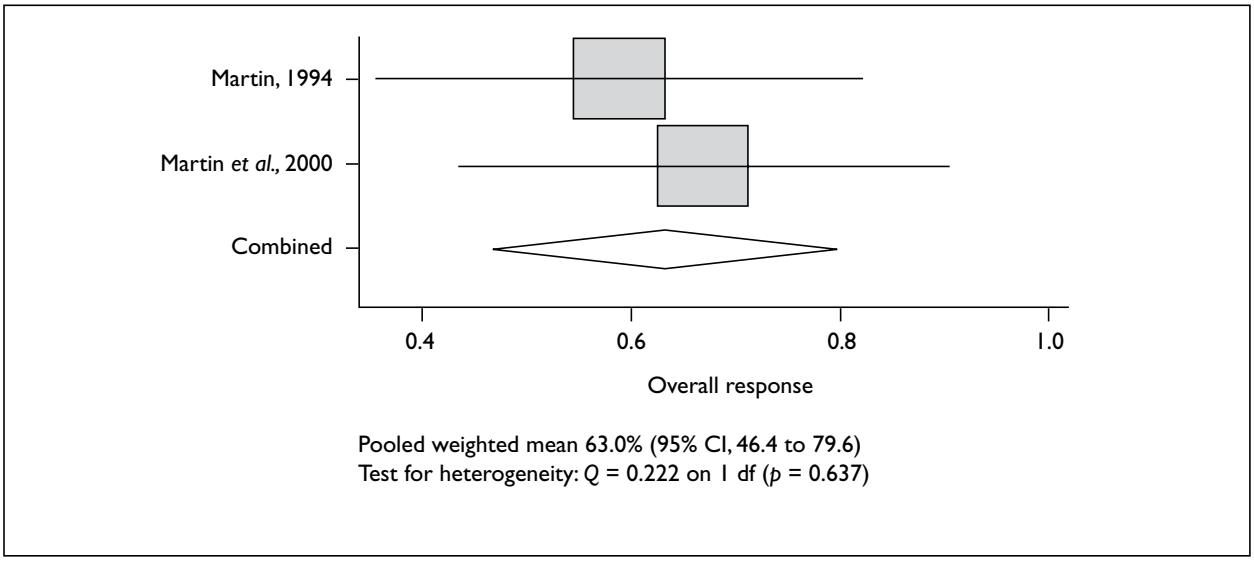


FIGURE 8 *Vinorelbine (30 mg/m^2) plus paclitaxel (135 mg/m^2): overall tumour response data*

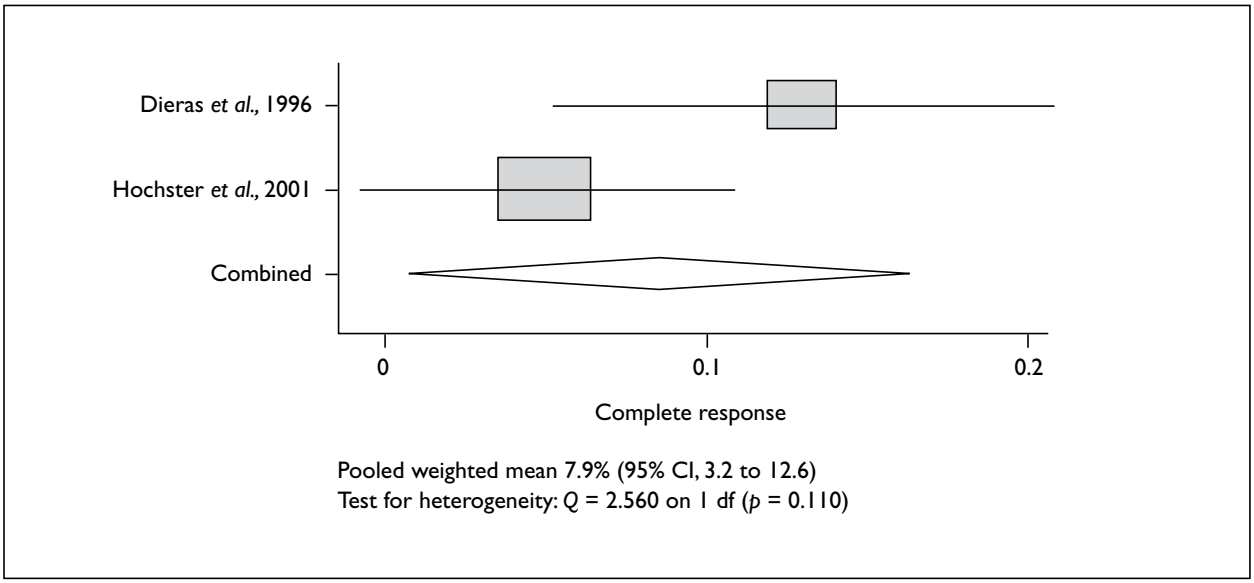


FIGURE 9 *FUN: complete tumour response data*

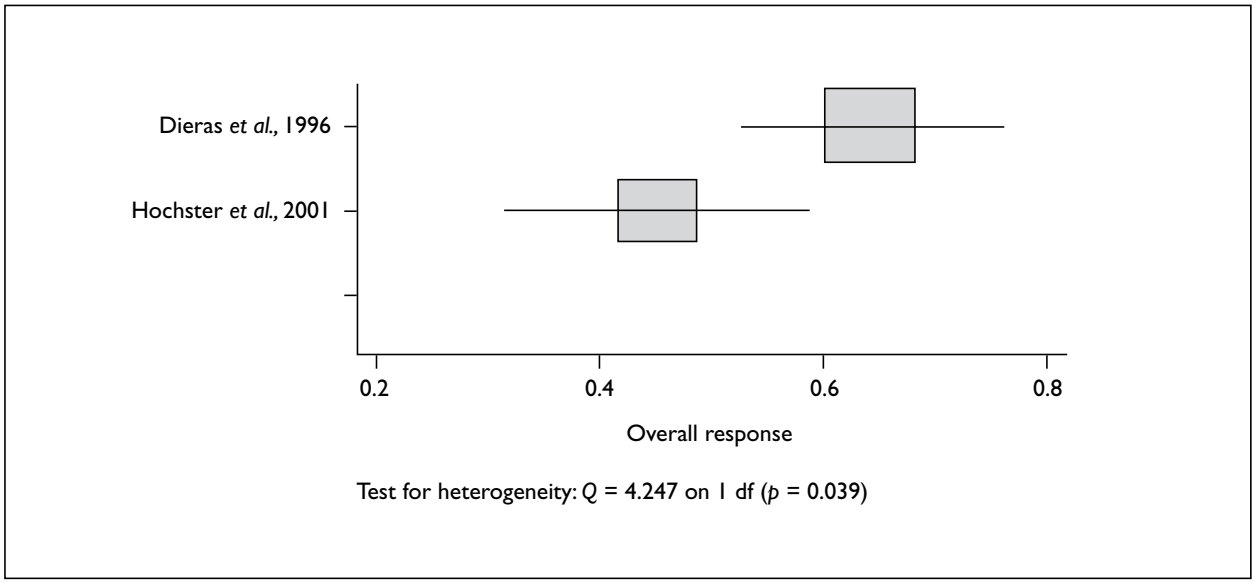


FIGURE 10 *FUN: overall tumour response data*

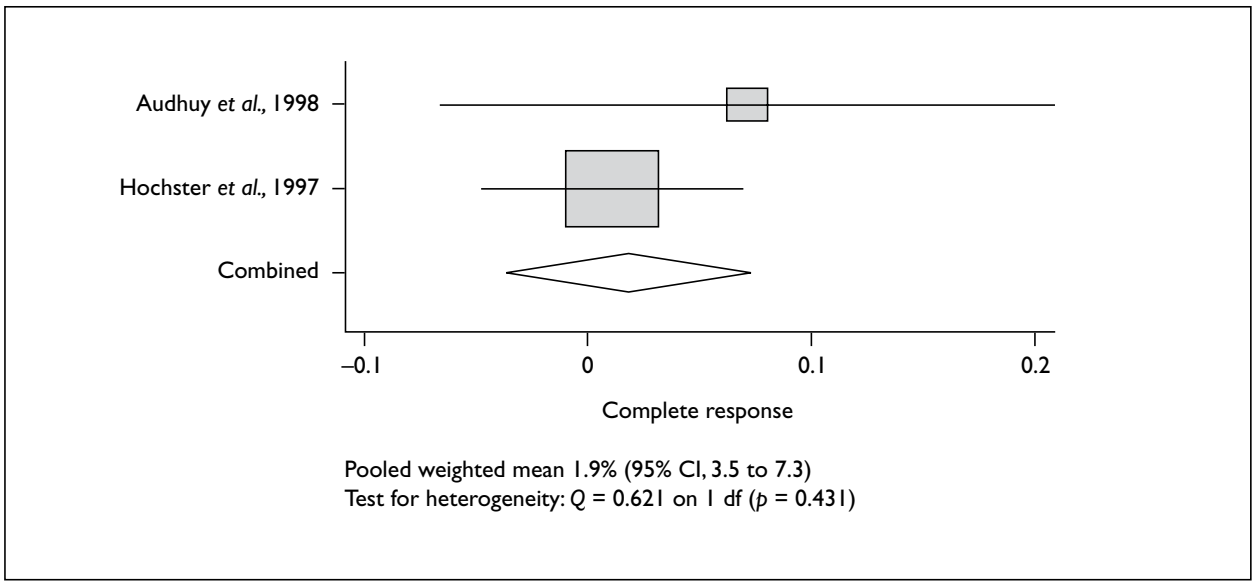


FIGURE 11 *Vinorelbine plus cisplatin: complete tumour response data*

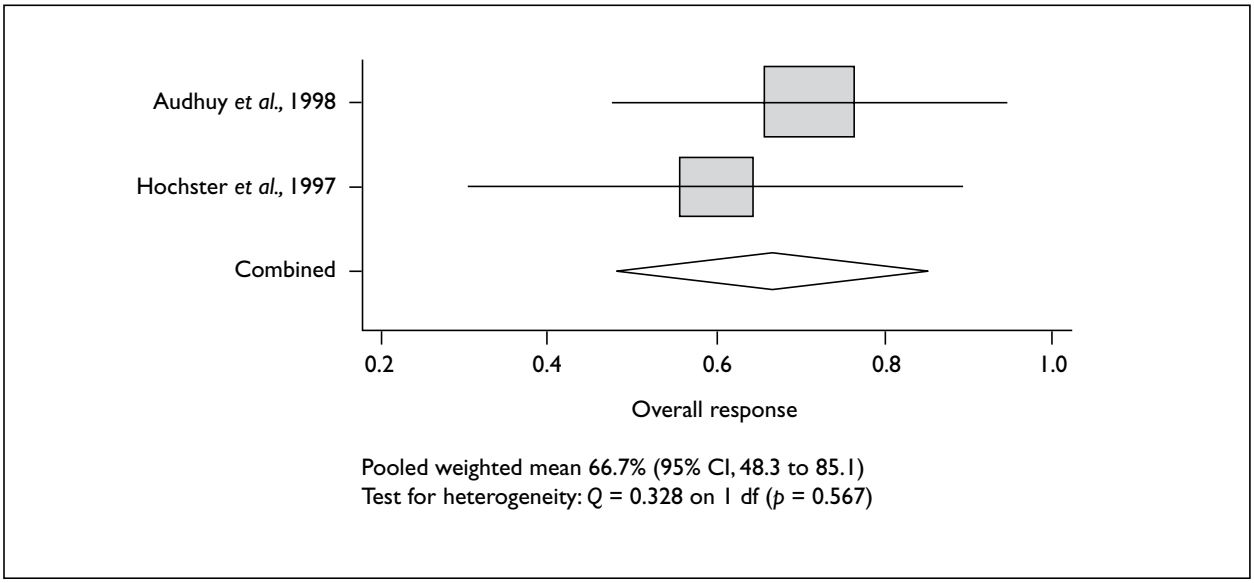


FIGURE 12 *Vinorelbine plus cisplatin: overall tumour response data*

TABLE 35 *Summary of duration of tumour response and survival data for vinorelbine monotherapy*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Bruno *et al.*, 1995[19]	68	63	Vinorelbine 30 mg/m^2 once a week	No	17.9 weeks (range 7–52)	12.9 weeks (range 2–52)	Not stated	50.3 weeks (range 2–188)
Delgado *et al.*, 1991[20]	36 (26 first line)	25	Vinorelbine 30 mg/m^2 once a week	No	23 weeks (range 9–58)	Not stated	Not stated	Not stated
Fumoleau *et al.*, 1993[21]	157	145	Vinorelbine 30 mg/m^2 once a week	No	34 weeks (range 9–141)	25 weeks	Not stated	73 weeks
Garcia-Conde *et al.*, 1994[22]	54	50	Vinorelbine 30 mg/m^2 once a week	No	36 weeks (range 14–70)	19 weeks (range 0–70)	5 months	65 weeks (range 2–105)
Kesselring *et al.*, 1991[23]	16	14	Vinorelbine 30 mg/m^2 once a week	No	8 weeks (range 4–12)	Not stated	Not stated	Not stated
Queisser *et al.*, 1991[24]	17	15	Vinorelbine 130 mg orally once a week	No	Not stated	3 months (for stable disease, *n* = 9, no complete or partial responses observed)	Not stated	Not stated
Romero *et al.*, 1994[25]	45	44	Vinorelbine 30 mg/m^2 once a week	No	9 months (range 1–15)	Not stated	6 months (range 1–15)	Not yet reached
Twelves *et al.*, 1994[29]	35	34	Vinorelbine 25 mg/m^2 once a week	No	5.8 months (range 2.3–9.8)	4.4 months (range 0.9–> 14.4)	Not stated	9.9 months (range 1.8–> 21.1)
Vogel *et al.*, 1999[30]	56	56	Vinorelbine 30 mg/m^2 once a week for 13 weeks and every 2 weeks thereafter	Yes	9 months	6 months	Not stated	Not stated
Weber *et al.*, 1995[31]	107 (60 first line)	60	Vinorelbine 30–35 mg/m^2 once a week	Yes	34 weeks	17 weeks	20 weeks	67 weeks

TABLE 36 *Summary of duration of tumour response and survival data for vinorelbine plus doxorubicin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Arca *et al.*, 1998[91] (abstract)	76	70	Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days	No	Not stated	Not stated	Not stated	16 months
Hegg *et al.*, 2001[45]	52	47	Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 8, repeated every 21 days	No	16 months (range 2–48)	Not stated	Not stated	22.7 months (range 1–48)
Hochster *et al.*, 2001[46*]	62	62	Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 3 weeks	No	Not stated	34 weeks	32 weeks	92 weeks (95% CI, 72 to 128). The 1-year survival rate was 75.5%
Spielmann *et al.*, 1994[49]	97	89	Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 g/m^2 on day 1, repeated every 3 weeks	No	12 months (range 2.4–40.5)	Not stated	Not stated	27.5 months (range 4–46)

[*] *Hochster* et al.[46] *as a full manuscript reporting two parallel protocols, one with vinorelbine plus doxorubicin, and one of FUN*

TABLE 37 *Summary of duration of tumour response and survival data for vinorelbine plus epirubicin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Baldini *et al.*, 1998[51]	51	47	Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 90 mg/m^2 on day 1, repeated every 21 days	For grade 4 neutropenia only	10 months (range 1–21)	11 months (range 1–21+)	Not stated	23 months (range 2–32)
Nistico *et al.*, 1999[54]	52	52	Vinorelbine 25 mg/m^2 plus epirubicin 25 mg/m^2 once a week	Yes (only for neutropenia in first 35 patients)	10 months (range 4–16)	10 months (range 4–24)	Not stated	31 months, and 24-month survival rate = 61%
Tabiadon *et al.*, 1998[55]	19	17	Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 80 mg/m^2 on day 1, repeated every 21–28 days	For grade 2 neutropenia	Not stated	7+ months (median not reported)	Not stated	7+ months (median not reported)
Vici *et al.*, 1999[56]	54	46	Vinorelbine 25 mg/m^2 on days 1 and 5 plus epirubicin 100 mg/m^2 on day 1, repeated every 3 weeks	Yes	Not stated	Not yet reached	Not stated	Not yet reached

TABLE 38 *Summary of duration of tumour response and survival data for vinorelbine plus paclitaxel*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Ibrahim *et al.*, 2001[57]	38	38	The starting doses were paclitaxel 175 mg/m^2 and vinorelbine 36 mg/m^2 (on day 1?), repeated every 3 weeks. In the group that did not receive G-CSF, the doses were reduced to vinorelbine 25 mg/m^2 and paclitaxel 150 mg/m^2. In the group that received G-CSF, vinorelbine ranged from 25 to 46 mg/m^2 and paclitaxel could be reduced to 150 mg/m^2	Used in 13 participants (25 without)	*Group that did not receive G-CSF*: not stated *Group that received G-CSF*: not stated	*Group that did not receive G-CSF*: 17 weeks (range 6–56) *Group that received G-CSF*: 31 weeks (range 9–41)	*Group that did not receive G-CSF*: not stated *Group that received G-CSF*: not stated	*Group that did not receive G-CSF*: not stated *Group that received G-CSF*: not stated
Romero Acuna *et al.*, 1999[60]	49	45	Vinorelbine 30 mg/m^2 on days 1 and 8 plus paclitaxel 135 mg/m^2 on day 1, repeated every 4 weeks	No	Not stated	7 months	Not stated	17 months
Vici *et al.*, 2000[61]	43	41	Vinorelbine 25 mg/m^2 and paclitaxel 150 mg/m^2 on day 1, repeated every 3 weeks	Yes	Not stated	7 months (range 3–35)	Not stated	22 months (range 3–35)

TABLE 39 *Summary of duration of tumour response and survival data for vinorelbine plus mitoxantrone*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Ferrero *et al.*, 1995[62]	41	37	Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitoxantrone 12 mg/m^2 on day 1, repeated every 21 days until disease progression or toxicity	No	Not stated	9 months (range 2–24)	Not stated	14 months (range 1–26)
Frasci *et al.*, 1995[63]	43 (20 first line)	18 first line	The starting dose intensity was mitoxantrone 3 mg/m^2/week plus vinorelbine 15 mg/m^2/week, without G-CSF support. There were three different schedules for mitoxantrone: total dose on day 1, divided between days 1 and 8 and divided between days 1, 8 and 15. Vinorelbine was administered once a week. The dose was escalated by 1 mg/m^2/week for mitoxantrone and by 5 mg/m^2/week for vinorelbine. Dose escalation continued until dose-limiting toxicity occurred	G-CSF was administered from second dose level	Not stated	15 months	Not stated	Not stated
Gladieff *et al.*, 1996[64]	25	23	Vinorelbine 20 mg/m^2 days 1 and 8 plus mitoxantrone 10 mg/m^2 on day 1, repeated every 21 days	No	Not stated	13 months (range 5–36)		17 months (range 3–38) and 1-year survival = 43.8% (95% CI, 23.4 to 66.4)
Llombart-Cussac *et al.*, 1998[65]	72	65	Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitoxantrone 10 mg/m^2 (except for the first six patients who received 12 mg/m^2) on day 1, repeated every 3 weeks	G-CSF only allowed as curative treatment of febrile neutropenia	7 months (range 2.6–27)	Not stated	Not stated	19 months (range 2–48) and after a median time (of the study) of 3 years, 6 patients were alive

TABLE 40 *Summary of duration of tumour response and survival data for vinorelbine plus docetaxel*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Kornek *et al.*, 2001[69]	57 (42 first line)	42 first line	Vinorelbine 30 mg/m^2 on days 1 and 15 plus docetaxel 30 mg/m^2 on days 1, 8 and 15, repeated every 4 weeks	G-CSF depending upon absolute granulocyte count on day of scheduled therapy	8.0 months	12 months (range 2.5–19+)	Not stated	> 19.5 months

TABLE 41 *Summary of duration of tumour response and survival data for FUN*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Dieras *et al.*, 1996[70]	63	63	Vinorelbine 30 mg/m^2 on days 1 and 5 plus 5-fluorouracil 750 mg/m^2 for 5 days consecutively, repeated every 21 days	No	12.3 months	8.3 months	Not stated	23 months (all patients) and 28.1 months (patients with a complete response)
Hochster *et al.*, 2001[46*]	56	56	Vinorelbine 30 mg/m^2 on days 1 and 5 plus 5-fluorouracil 750 mg/m^2 on days 1–5, repeated every 3 weeks	No	Not stated	32 weeks	30 weeks	53 weeks (95% CI, 47 to 64) and 1-year survival rate = 50.2%

[*] *Hochster* et al.[46] *as a full manuscript reporting two parallel protocols, one with vinorelbine plus doxorubicin, and one of FUN*

TABLE 42 *Summary of duration of tumour response and survival data for vinorelbine plus 5-fluorouracil plus leucovorin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Kornek *et al.*, 1998[71]	53 (37 first line)	37 first line	Vinorelbine 40 mg/m^2 on days 1 and 14 plus 5-fluorouracil 400 mg/m^2 plus leucovorin 100 mg/m^2 on days 1–5, repeated every 4 weeks	G-CSF 5 µg/kg/day on days 6–10 (note: earlier abstracts say days 6–12)	9.5 months (range 4–21)	10.5 months (range 2-23)	Not stated	Not yet reached, > 13 months (range 1.5–26+)
Nole *et al.*, 1997[72]	49	39	Vinorelbine 25 mg/m^2 on days 1 and 3 plus 5-fluorouracil 350 mg/m^2 and folinic acid 100 mg/m^2 on days 1–3, repeated every 21 days	No	10 months (range 6–24+)	8 months (range 2–24+)	Not stated	Not yet reached, and 12-month survival rate = 78%

TABLE 43 *Summary of duration of tumour response and survival data for FAN*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Dieras *et al.*, 1996[73]	82	70	Vinorelbine 25 mg/m^2 plus doxorubicin 20 mg/m^2 on days 1 and 8 plus 5-fluorouracil 250 mg/m^2 on days 1–15	No	Not stated	Not yet reached	Not stated	Not yet reached

TABLE 44 *Summary of duration of tumour response and survival data for vinorelbine plus cyclophosphamide plus 5-fluorouracil*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Ardavanis *et al.*, 1998	45	38	Vinorelbine 25 mg/m^2 on days 1 and 3 plus cyclophosphamide 600 mg/m^2 plus 5-fluorouracil 750 mg/m^2 on days 1–3, repeated every 21 days for six cycles	No	Not stated	10.5 months	Not stated	Not calculated
Turpin *et al.*, 1999[76]	60	56	Vinorelbine 25 mg/m^2 plus 5-fluorouracil 500 mg/m^2 on days 1 and 8 plus cyclophosphamide 500 mg/m^2 on day 1, repeated every 21 days	No	Duration of complete response = 45.4 weeks (range 20.3–45.4+), duration of partial response = 37.4 weeks (range 13–36+)	Not stated	Not stated	66.4 weeks (range 3+–80+)

TABLE 45 *Summary of duration of tumour response and survival data for vinorelbine plus cyclophosphamide plus epirubicin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Esteban *et al.*, 2000[78]	59	55	Vinorelbine 25 mg/m^2 plus epirubicin 30 mg/m^2 plus cyclophosphamide 400 mg/m^2 on days 1 and 8, repeated every 28 days	The use of G-CSF permitted in the presence of grade 4 neutropenia with fever or documented infection	54 weeks	47 weeks (range 35–59)	Not stated	90 weeks (range 62–119)

TABLE 46 *Summary of duration of tumour response and survival data for vinorelbine plus cisplatin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Audhuy *et al.*, 1998[79]	19	16	Vinorelbine 30 mg/m^2 on days 1 and 5 plus cisplatin 100 mg/m^2 on day 1, repeated every 3 weeks	No	Not stated	7.3 months (range 1.6–15.2+)	Not stated	Not stated

TABLE 47 *Summary of duration of tumour response and survival data for vinorelbine plus gemcitabine*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Haider *et al.*, 1999[81]	60 (45 first line)	45 first line	Vinorelbine 40 mg/m^2 on days 1 and 21 plus gemcitabine 1000 mg/m^2 on days 15 and 21, repeated every 5 weeks	G-CSF was administered at 5 µg/kg/day on days 2–6 and 22–26 during each cycle	Not stated	9.5 months (range 1.5–28)	Not stated	> 14.0 months (not yet reached)

TABLE 48 *Summary of duration of tumour response and survival data for vinorelbine plus ifosfamide*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Leone *et al.*, 1996[82]	45	43	Vinorelbine 35 mg/m^2 on days 1 and 15 (vinorelbine 17.5 mg/m^2 on days 8 and 22 during first cycle only) plus ifosfamide 2 g/m^2/d for 3 days, repeated every 28 days	No	Not stated	Not stated	12 months (range not stated)	Median survival 19 months (range not stated)

TABLE 49 *Summary of duration of tumour response and survival data for vinorelbine plus mitomycin C*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Kornek *et al.*, 1996[83]	55 (32 first line)	32 first line	Vinorelbine 50 mg/m^2 in the first 36 patients, but then reduced to 40 mg/m^2 every 3 weeks due to toxicity, plus mitomycin C 15 mg/m^2 every 6 weeks	G-CSF on days 2–7 following each drug	10.8 months (range 3.5–22+)	12.0 months (range 2–24+)	Not stated	> 15.5 months

TABLE 50 *Summary of duration of tumour response and survival data for vinorelbine plus trastuzumab*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Burstein *et al.*, 2001[84]	40 (19 first line)	19 first line	Vinorelbine 25 mg/m^2 plus trastuzumab 2 mg/m^2 (except for first dose of 4 mg/m^2) weekly administered on the same day. The vinorelbine dose, but not the trastuzumab dose, could be adjusted if there were signs of toxicity	G-CSF was to be permitted if treatment delays of more than 2 weeks were occurring due to neutropenia or febrile neutropenia	Not stated	34 weeks	Not stated	Not reached

TABLE 51 *Summary of duration of tumour response and survival data for vinorelbine plus 5-fluorouracil plus cisplatin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Nole *et al.*, 2001[85]	100 (48 first line)	45 first line	Vinorelbine 20 mg/m^2 on days 1 and 3 plus cisplatin 60 mg/m^2 on day 1 and 5-fluorouracil 200 mg/m^2/day (number of days not stated), repeated every 3 weeks	No	Not stated	8 months (range 0.7–21.4)	Not stated	Not reached

TABLE 52 *Summary of duration of tumour response and survival data for vinorelbine plus 5-fluorouracil plus epirubicin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Guler *et al.*, 2000[86]	52	50	Vinorelbine 25 mg/m^2 plus epirubicin 35–40 mg/m^2 plus 5-fluorouracil 350 mg/m^2 on days 1 and 8, repeated every 3 weeks	No	Not stated	*Survival analyses in 31 patients*: 7 months (range 2–22)	Not stated	*Survival analyses in 31 patients*: 14 months (range 5–32+)

TABLE 53 *Summary of duration of tumour response and survival data for vinorelbine plus mitoxantrone plus carboplatin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Kakolyris *et al.*, 1999[87]	50	50	Vinorelbine 30 mg/m^2 plus mitoxantrone 12 mg/m^2 on day 1 plus carboplatin 250 mg/m^2 on day 2, repeated every 3 weeks. Initially, vinorelbine was also to be given on day 8, but this was dropped after the first four patients due to toxicity	G-CSF in subsequent cycles if grade 3–4 neutropenia in cycle 1	6 months (range 1.5–33)	7 months (range 3–38)	Not stated	26 months (range 2–38), and 1- and 2-year survival = 76 and 57%, respectively

TABLE 54 *Summary of duration of tumour response and survival data for vinorelbine plus doxorubicin plus methotrexate plus leucovorin*

Study	Number of participants	Number of evaluable participants	Drug dosages	G-CSF support	Median duration of response	Median time to progression	Median time to treatment failure	Median survival
Subramanyan *et al.*, 1999[89]	23	22	*Starting dose levels*: vinorelbine 20 mg/m^2 plus doxorubicin 40 mg/m^2 plus methotrexate 100 mg/m^2 on day 1 plus leucovorin 10 mg/m^2 for 6 days starting on day 2 Dose of vinorelbine increased by 5 mg/m^2 if ≥ three patients completed the 21-day course with no dose limiting toxicity. Maximum dose of vinorelbine used was 30 mg/m^2. Doses of 50 and 60 mg/m^2 doxorubicin were also used with vinorelbine 25 mg/m^2 in some patients	No	Not stated	Not stated	Not stated	25 months

TABLE 55 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine monotherapy derived from uncontrolled studies*

Adverse event	Number of studies	Reference
Granulocytopenia	8	Bruno *et al.*, 1995[19] Delgado *et al.*, 1991[20] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Romero *et al.*, 1994[25] Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31] Winer *et al.*, 1993[32]
Hospitalised with fever while granulocytopenic	2	Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Neutropenia	3	Toussaint *et al.*, 1995[28] Twelves *et al.*, 1994[29] Vogel *et al.*, 1999[30] (neutropenic fever)
Thrombocytopenia	6	Bruno *et al.*, 1995[19] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Romero *et al.*, 1994[25] Toussaint *et al.*, 1995[28] Vogel *et al.*, 1999[30]
Leukopenia	11	Bruno *et al.*, 1995[19] Delgado *et al.*, 1991[20] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Kesselring *et al.*, 1991[23] Queisser *et al.*, 1991[24] Romero *et al.*, 1994[25] Toussaint *et al.*, 1995[28] Twelves *et al.*, 1994[29] Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Anaemia	7	Bruno *et al.*, 1995[19] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Romero *et al.*, 1994[25] Toussaint *et al.*, 1995[28] Twelves *et al.*, 1994[29] Weber *et al.*, 1995[31]
Mucositis	1	Toussaint *et al.*, 1995[28]
Infection	6	Bruno *et al.*, 1995[19] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Romero *et al.*, 1994[25] Toussaint *et al.*, 1995[28] Twelves *et al.*, 1994[29]
Nausea and vomiting	10	Bruno *et al.*, 1995[19] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Kesselring *et al.*, 1991[23] Queisser *et al.*, 1991[24] Romero *et al.*, 1994[25] Toussaint *et al.*, 1995[28] Twelves *et al.*, 1994[29] Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Constipation	8	Bruno *et al.*, 1995[19] Delgado *et al.*, 1991[20] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Romero *et al.*, 1994[25] Twelves *et al.*, 1994[29] Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Stomatitis	4	Bruno *et al.*, 1995[19] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Romero *et al.*, 1994[25]
Diarrhoea	4	Bruno *et al.*, 1995[19] Queisser *et al.*, 1991[24] Twelves *et al.*, 1994[29] Vogel *et al.*, 1999[30]
Anorexia	1	Toussaint *et al.*, 1995[28]
Asthenia	4	Toussaint *et al.*, 1995[28] Twelves *et al.*, 1994[29] Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Neuropathy	3	Bruno *et al.*, 1995[19] Fumoleau *et al.*, 1993[21] Romero *et al.*, 1994[25]
Pain	1	Weber *et al.*, 1995[31]
Alopecia	6	Bruno *et al.*, 1995[19] Delgado *et al.*, 1991[20] Fumoleau *et al.*, 1993[21] Queisser *et al.*, 1991[24] Romero *et al.*, 1994[25] Twelves *et al.*, 1994[29]
Dyspnoea	1	Weber *et al.*, 1995[31]
Phlebitis	5	Bruno *et al.*, 1995[19] Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Kesselring *et al.*, 1991[23] Twelves *et al.*, 1994[29]
Paraesthesia	1	Delgado *et al.*, 1991[20]
Fever	5	Fumoleau *et al.*, 1993[21] Garcia-Conde *et al.*, 1994[22] Toussaint *et al.*, 1995[28] Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Sepsis	1	Weber *et al.*, 1995[31]
Hospitalisation for sepsis	2	Romero *et al.*, 1994[25] Twelves *et al.*, 1994[29]
Death due to neutropenic sepsis	3	Twelves *et al.*, 1994[29] Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Abdominal pain	2	Vogel *et al.*, 1999[30] Weber *et al.*, 1995[31]
Generalised pain	1	Vogel *et al.*, 1999[30]
Chest pain	1	Vogel *et al.*, 1999[30]

TABLE 56 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus doxorubicin derived from uncontrolled studies*

Adverse event	Number of studies	Reference
Granulocytopenia	2	Hochster *et al.*, 2001[46] Siedlecki *et al.*, 1997[47]
Neutropenia	6	Baltali *et al.*, 1996[43] Bonicatto *et al.*, 1998[90] Hegg *et al.*, 2001[45] Smalley *et al.*, 1994[48] Spielmann *et al.*, 1994[49] Vorobiof *et al.*, 1997[50]
Hospitalised for febrile neutropenia	1	Smalley *et al.*, 1994[48]
Thrombocytopenia	1	Bonicatto *et al.*, 1998[90]
Leukopenia	3	Hegg *et al.*, 2001[45] Hochster *et al.*, 2001[46] Spielmann *et al.*, 1994[49]
Anaemia	3	Hegg *et al.*, 2001[45] Hochster *et al.*, 2001[46] Spielmann *et al.*, 1994[49]
Mucositis	2	Bonicatto *et al.*, 1998[90] Spielmann *et al.*, 1994[49]
Haematological	3	Arca *et al.*, 1998[91] Alvarez *et al.*, 1994[42] Coppola *et al.*, 1994[44]
Infection	4	Arca *et al.*, 199891 Alvarez *et al.*, 1994[42] Baltali *et al.*, 1996[43] Hegg *et al.*, 2001[45]
Nausea and vomiting	8	Arca *et al.*, 1998[91] Alvarez *et al.*, 1994[42] Baltali *et al.*, 1996[43] Hegg *et al.*, 2001[45] Hochster *et al.*, 2001[46] Smalley *et al.*, 1994[48] Spielmann *et al.*, 1994[49] Vorobiof *et al.*, 1997[50]
Constipation	4	Baltali *et al.*, 1996[43] Hegg *et al.*, 2001[45] Hochster *et al.*, 2001[46] Spielmann *et al.*, 1994[49]
Stomatitis	4	Hegg *et al.*, 2001[45] Hochster *et al.*, 2001[46] Smalley *et al.*, 1994[48] Vorobiof *et al.*, 1997[50]
Diarrhoea	2	Hegg *et al.*, 2001[45] Hochster *et al.*, 2001[46]
Anorexia	1	Hochster *et al.*, 2001[46]
Asthenia	1	Hochster *et al.*, 2001[46]
Neuropathy	2	Hegg *et al.*, 2001[45] Spielmann *et al.*, 1994[49]
Pain	1	Hochster *et al.*, 2001[46]
Alopecia	9	Arca *et al.*, 1998[91] Baltali *et al.*, 1996[43] Bonicatto *et al.*, 1998[90] Coppola *et al.*, 1994[44] Hegg *et al.*, 2001[45] Hochster *et al.*, 2001[46] Siedlecki *et al.*, 1997[47] Spielmann *et al.*, 1994[49] Vorobiof *et al.*, 1997[50]
Cardiac	1	Spielmann *et al.*, 1994[49]
Phlebitis	5	Arca *et al.*, 1998[91] Alvarez *et al.*, 1994[42] Bonicatto *et al.*, 1998[90] Hegg *et al.*, 2001[45] Vorobiof *et al.*, 1997[50]
Paraesthesia	1	Hochster *et al.*, 2001[46]
Hypesthenia	1	Hochster *et al.*, 2001[46]
Fever	2	Hochster *et al.*, 2001[46] Spielmann *et al.*, 1994[49]
Sepsis	1	Hochster *et al.*, 2001[46]
Death due to neutropenic sepsis	3	Hochster *et al.*, 2001[46] Spielmann *et al.*, 1994[49] Vorobiof *et al.*, 1997[50]
Abdominal pain	1	Hochster *et al.*, 2001[46]
Paralytic ileus	1	Spielmann *et al.*, 1994[49]

TABLE 57 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus epirubicin derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Neutropenia	6	Baldini *et al.*, 1998[51] Cottu *et al.*, 1993[52] (neutropenic fever) Ezzat *et al.*, 1996[53] Nistico *et al.*, 1999[54] Tabiadon *et al.*, 1998[55] Vici *et al.*, 1999[56] (and neutropenic fever)	Infection	1	Ezzat *et al.*, 1996[53]
			Nausea and vomiting	3	Baldini *et al.*, 1998[51] Cottu *et al.*, 1993[52] Ezzat *et al.*, 1996[53]
Hospitalised for febrile neutropenia	1	Baldini *et al.*, 1998[51]	Constipation	1	Ezzat *et al.*, 1996[53]
			Diarrhoea	1	Baldini *et al.*, 1998[51]
Thrombocytopenia	1	Baldini *et al.*, 1998[51]	Asthenia	1	Nistico *et al.*, 1999[54]
			Pain	1	Nistico *et al.*, 1999[54]
Leukopenia	1	Cottu *et al.*, 1993[52]	Alopecia	4	Ezzat *et al.*, 1996[53] Nistico *et al.*, 1999[54] Tabiadon *et al.*, 1998[55] Vici *et al.*, 1999[56]
Anaemia	3	Baldini *et al.*, 1998[51] Nistico *et al.*, 1999[54] Vici *et al.*, 1999[56]	Cardiac	1	Nistico *et al.*, 1999[54]
			Phlebitis	1	Nistico *et al.*, 1999[54]
Mucositis	3	Baldini *et al.*, 1998[51] Tabiadon *et al.*, 1998[55] Vici *et al.*, 1999[56]	Paralytic ileus	1	Baldini *et al.*, 1998[51]

TABLE 58 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus paclitaxel derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Granulocytopenia	2	Ibrahim *et al.*, 2001[57] Romero Acuna *et al.*, 1999[60]	Constipation	1	Romero Acuna *et al.*, 1999[60]
			Stomatitis	1	Ibrahim *et al.*, 2001[57]
Neutropenia	4	Ibrahim *et al.*, 2001[57] (neutropenic fever) Martin, 1999[58] (neutropenic fever) Martin *et al.*, 2000[59] Vici *et al.*, 2000[61]	Diarrhoea	1	Ibrahim *et al.*, 2001[57]
			Asthenia	2	Ibrahim *et al.*, 2001[57] Martin *et al.*, 2000[59]
Hospitalised for febrile neutropenia	1	Romero Acuna *et al.*, 1999[60]	Neuropathy	2	Martin, 1999[58] Martin *et al.*, 2000[59]
Thrombocytopenia	2	Martin *et al.*, 2000[59] Romero Acuna *et al.*, 1999[60]	Pain	1	Ibrahim *et al.*, 2001[57]
Leukopenia	2	Romero Acuna *et al.*, 1999[60] Vici *et al.*, 2000[61]	Alopecia	2	Romero Acuna *et al.*, 1999[60] Vici *et al.*, 2000[61]
Anaemia	3	Martin *et al.*, 2000[59] Romero Acuna *et al.*, 1999[60] Vici *et al.*, 2000[61]	Dyspnoea	1	Romero Acuna *et al.*, 1999[60]
Hepatoxicity	1	Vici *et al.*, 2000[61]	Phlebitis	1	Martin *et al.*, 2000[59]
Infection	1	Romero Acuna *et al.*, 1999[60]	Myalgia	3	Ibrahim *et al.*, 2001[57] Martin, 1999[58] Martin *et al.*, 2000[59]
Nausea and vomiting	2	Martin *et al.*, 2000[59] Romero Acuna *et al.*, 1999[60]			

TABLE 59 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus mitoxantrone derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Granulocytopenia	1	Llombart-Cussac *et al.*, 1998[65]	Infection	1	Llombart-Cussac *et al.*, 1998[65]
Neutropenia	2	Ferrero *et al.*, 1995[62] Gladieff *et al.*, 1996[64]	Nausea and vomiting	2	Ferrero *et al.*, 1995[62] Llombart-Cussac *et al.*, 1998[65]
Hospitalised for febrile neutropenia	1	Llombart-Cussac *et al.*, 1998[65]	Constipation	2	Ferrero *et al.*, 1995[62] Llombart-Cussac *et al.*, 1998[65]
Thrombocytopenia	3	Frasci *et al.*, 1995[63] Gladieff *et al.*, 1996[64] Llombart-Cussac *et al.*, 1998[65]	Stomatitis	1	Llombart-Cussac *et al.*, 1998[65]
Leukopenia	2	Ferrero *et al.*, 1995[62] Frasci *et al.*, 1995[63]	Alopecia	2	Ferrero *et al.*, 1995[62] Llombart-Cussac *et al.*, 1998[65]
Anaemia	3	Ferrero *et al.*, 1995[62] Frasci *et al.*, 1995[63] Llombart-Cussac *et al.*, 1998[65]	Cardiac	1	Llombart-Cussac *et al.*, 1998[65]
Mucositis	1	Ferrero *et al.*, 1995[62]	Hospitalisation for sepsis	1	Ferrero *et al.*, 1995[62]

TABLE 60 *Serious adverse events (grade 3 and/or 4) associated with vinorelbine plus docetaxel derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Neutropenia	4	Bonneterre *et al.*, 1998[66] De Paz *et al.*, 1999[67] (neutropenic fever) Fumoleau *et al.*, 1997[68] Kornek *et al.*, 2001[69]	Infection	1	Kornek *et al.*, 2001[69]
			Nausea and vomiting	1	Kornek *et al.*, 2001[69]
			Stomatitis	1	Kornek *et al.*, 2001[69]
Hospitalised for febrile neutropenia	1	Bonneterre *et al.*, 1998[66]	Neuropathy	1	Kornek *et al.*, 2001[69]
			Alopecia	2	De Paz *et al.*, 1999[67] Kornek *et al.*, 2001[69]
Thrombocytopenia	1	Kornek *et al.*, 2001[69]			
Leukopenia	1	Kornek *et al.*, 2001[69]	Skin/nail alterations	1	Kornek *et al.*, 2001[69]
Anaemia	1	Kornek *et al.*, 2001[69]	Hospitalisation for infection	1	Kornek *et al.*, 2001[69]
Mucositis	1	Fumoleau *et al.*, 1997[68]			

TABLE 61 *Severe adverse events (grade 3 and/or 4) associated with FUN derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Neutropenia	1	Dieras *et al.*, 1996[70]	Neuropathy	1	Dieras *et al.*, 1996[70]
Hospitalised for neutropenic fever	1	Dieras *et al.*, 1996[70]	Diarrhoea	2	Dieras *et al.*, 1996[70] Hochster *et al.*, 2001[46]
Thrombocytopenia	1	Dieras *et al.*, 1996[70]	Asthenia	1	Hochster *et al.*, 2001[46]
Leukopenia	2	Dieras *et al.*, 1996[70] Hochster *et al.*, 2001[46]	Alopecia	2	Dieras *et al.*, 1996[70] Hochster *et al.*, 2001[46]
Anaemia	2	Dieras *et al.*, 1996[70] Hochster *et al.*, 2001[46]	Cardiac event	1	Hochster *et al.*, 2001[46]
Infection	1	Dieras *et al.*, 1996[70]	Paraesthesia	1	Hochster *et al.*, 2001[46]
Nausea and vomiting	2	Dieras *et al.*, 1996[70] Hochster *et al.*, 2001[46]	Hypesthenia	1	Hochster *et al.*, 2001[46]
Constipation	2	Dieras *et al.*, 1996[70] Hochster *et al.*, 2001[46]	Fever	1	Hochster *et al.*, 2001[46]
Stomatitis	2	Dieras *et al.*, 1996[70] Hochster *et al.*, 2001[46]	Sepsis	1	Hochster *et al.*, 2001[46]
			Death due to neutropenic sepsis	1	Hochster *et al.*, 2001[46]

TABLE 62 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus 5-fluorouracil plus leucovorin derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Granulocytopenia	1	Nole *et al.*, 1997[72]	Nausea and vomiting	1	Kornek *et al.*, 1998[71]
Hospitalised for granulocytopenic complications	1	Nole *et al.*, 1997[72]	Constipation	1	Nole *et al.*, 1997[72]
Neutropenia	1	Kornek *et al.*, 1998[71]	Stomatitis	2	Kornek *et al.*, 1998[71] Nole *et al.*, 1997[72]
Thrombocytopenia	1	Kornek *et al.*, 1998[71]	Injection site reaction	1	Nole *et al.*, 1997[72]
Leukopenia	1	Kornek *et al.*, 1998[71]	Neuropathy	1	Nole *et al.*, 1997[72]
Anaemia	1	Kornek *et al.*, 1998[71]	Alopecia	1	Kornek *et al.*, 1998[71]
Infection	1	Kornek *et al.*, 1998[71]	Hospitalisation for sepsis	1	Kornek *et al.*, 1998[71]

TABLE 63 *Severe adverse events (grade 3 and/or 4) associated with FAN derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Granulocytopenia	1	Goss *et al.*, 1997[74]	Stomatitis	1	Goss *et al.*, 1997[74]
Neutropenia	2	Dieras *et al.*, 1996[73] Goss *et al.*, 1997[74]	Diarrhoea	1	Goss *et al.*, 1997[74]
Leukopenia	1	Goss *et al.*, 1997[74]	Anorexia	1	Goss *et al.*, 1997[74]
Mucositis	1	Dieras *et al.*, 1996[73]	Hypotension	1	Goss *et al.*, 1997[74]
Infection	1	Goss *et al.*, 1997[74]	Alopecia	1	Goss *et al.*, 1997[74]
Nausea and vomiting	1	Goss *et al.*, 1997[74]	Dyspnoea	1	Goss *et al.*, 1997[74]
Constipation	1	Goss *et al.*, 1997[74]			

TABLE 64 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus cyclophosphamide plus 5-fluorouracil derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Neutropenia	2	Ardavanis *et al.*, 1998[75] Turpin *et al.*, 1999[76]	Constipation	2	Ardavanis *et al.*, 1998[75] Turpin *et al.*, 1999[76]
Mucositis	1	Ardavanis *et al.*, 1998[75]	Alopecia	2	Ardavanis *et al.*, 1998[75] Turpin *et al.*, 1999[76]
Nausea and vomiting	1	Turpin *et al.*, 1999[76]			

TABLE 65 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus cyclophosphamide plus epirubicin derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Neutropenia	2	Braud *et al.*, 1999[77] Esteban *et al.*, 2000[78]	Anaemia	1	Esteban *et al.*, 2000[78]
			Mucositis	1	Esteban *et al.*, 2000[78]
Thrombocytopenia	1	Esteban *et al.*, 2000[78]	Nausea and vomiting	1	Esteban *et al.*, 2000[78]
Leukopenia	1	Esteban *et al.*, 2000[78]	Alopecia	1	Esteban *et al.*, 2000[78]

TABLE 66 *Severe adverse events (grade 3 and/or 4) associated with vinorelbine plus cisplatin derived from uncontrolled studies*

Adverse event	Number of studies	Reference	Adverse event	Number of studies	Reference
Neutropenia	2	Audhury *et al.*, 1998[79] Hochster *et al.*, 1997[80]	Leukopenia	1	Hochster *et al.*, 1997[80]
			Infection	1	Audhury *et al.*, 1998[79]
Hospitalised for febrile neutropenia	1	Audhury *et al.*, 1998[79]	Nausea and vomiting	1	Hochster *et al.*, 1997[80]

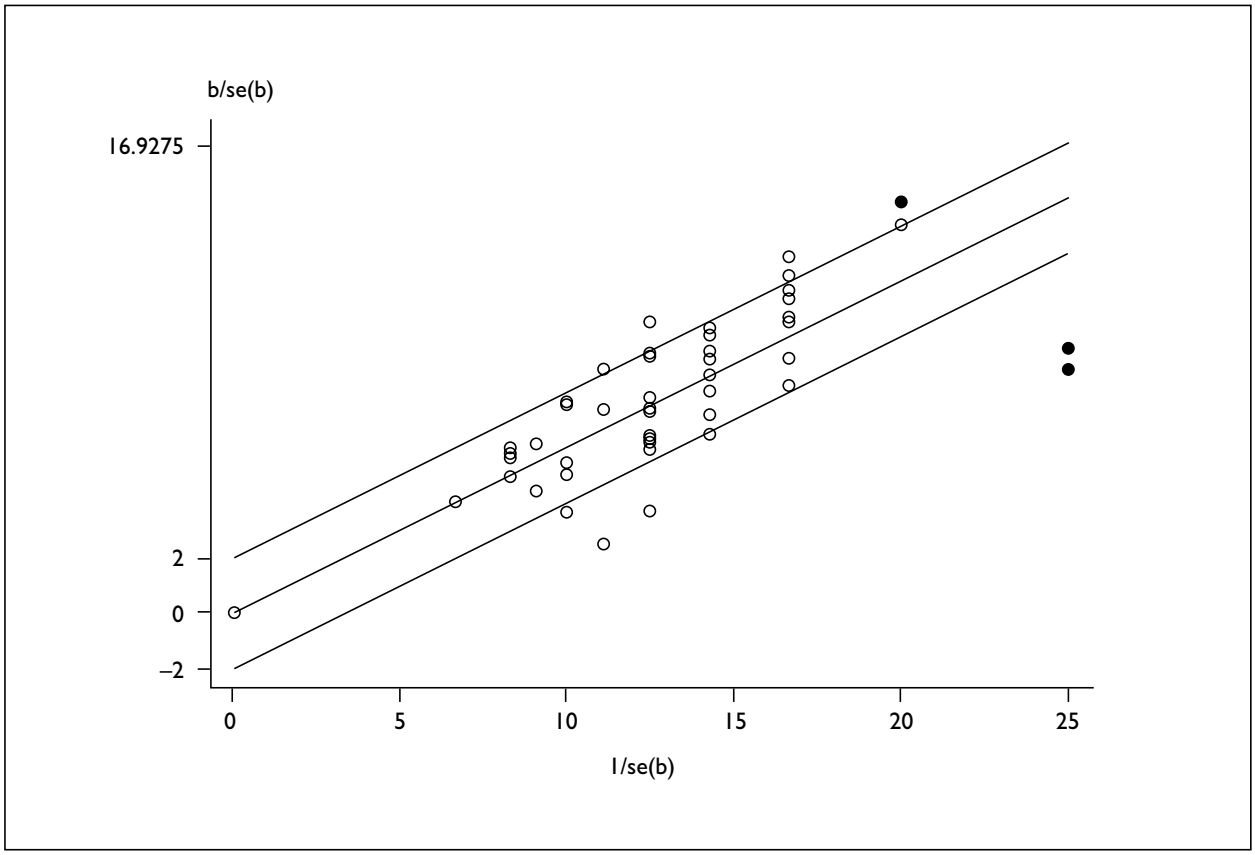


FIGURE 13 *Galbraith plot of combination therapy: overall response data (○, ●, b/se(b); ——, fitted values; ○, uncontrolled studies; ●, RCTs)*

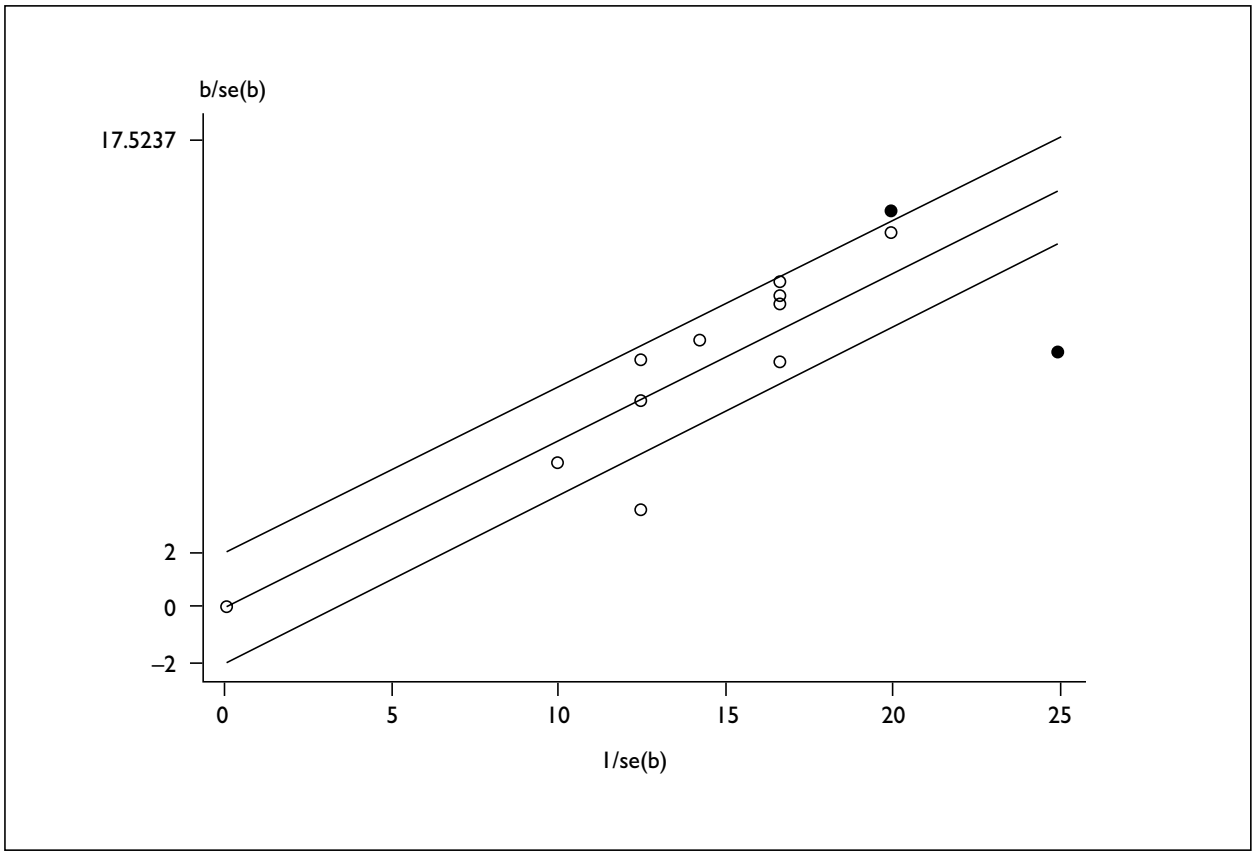


FIGURE 14 *Galbraith plot of doxorubicin: overall response data (○, ●, b/se(b); ——, fitted values; ○, uncontrolled studies; ●, RCTs)*

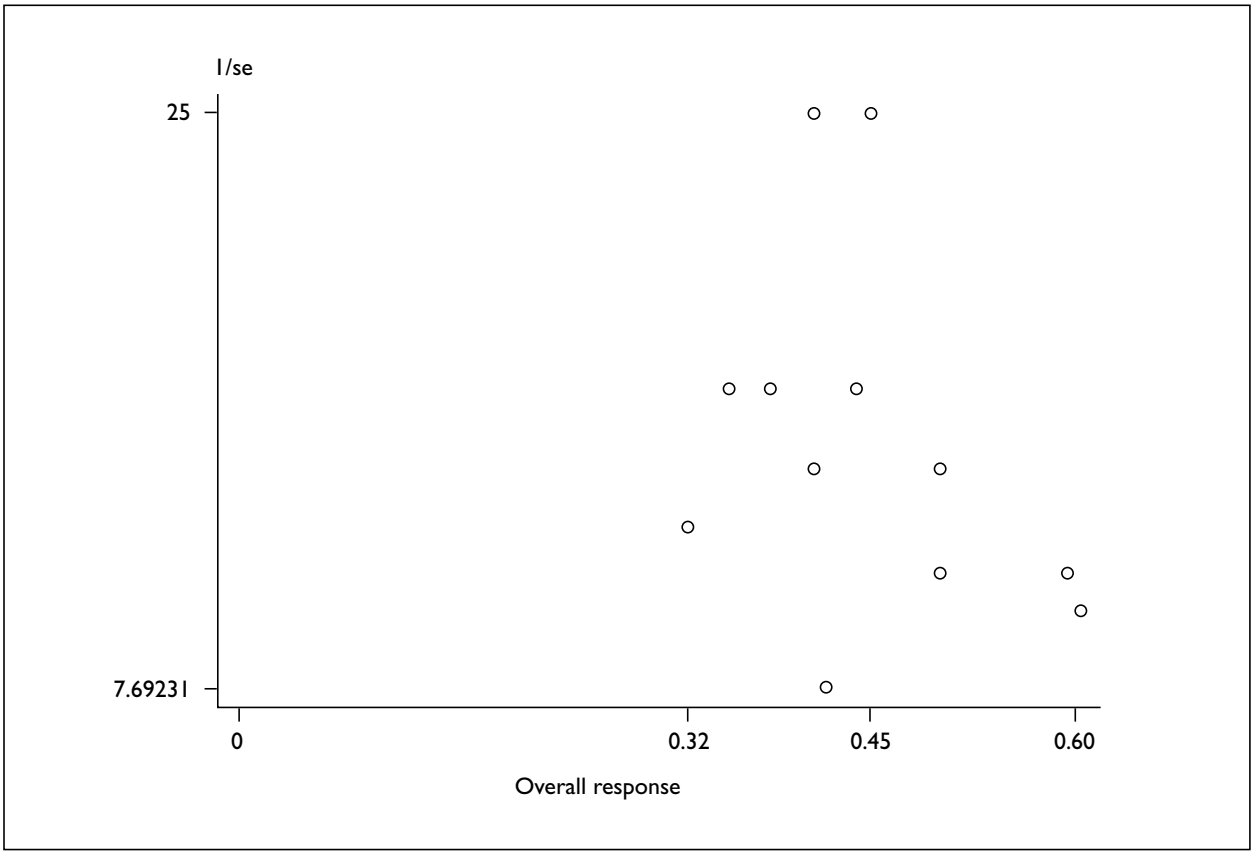


FIGURE 15 *Funnel plot of the vinorelbine monotherapy uncontrolled (Phase II) studies*

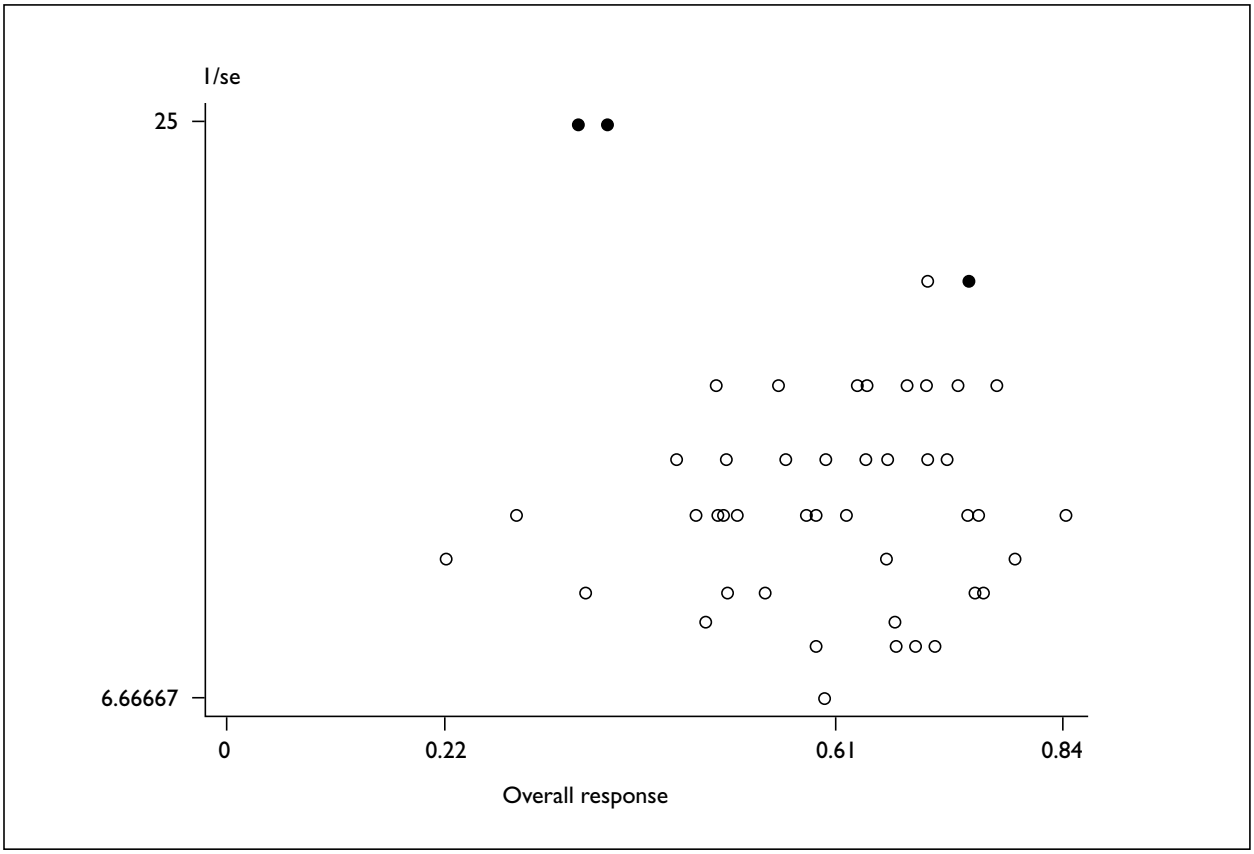


FIGURE 16 *Funnel plot of the vinorelbine combination therapy RCTs and uncontrolled (Phase II) studies (○, uncontrolled studies; ●, RCTs)*

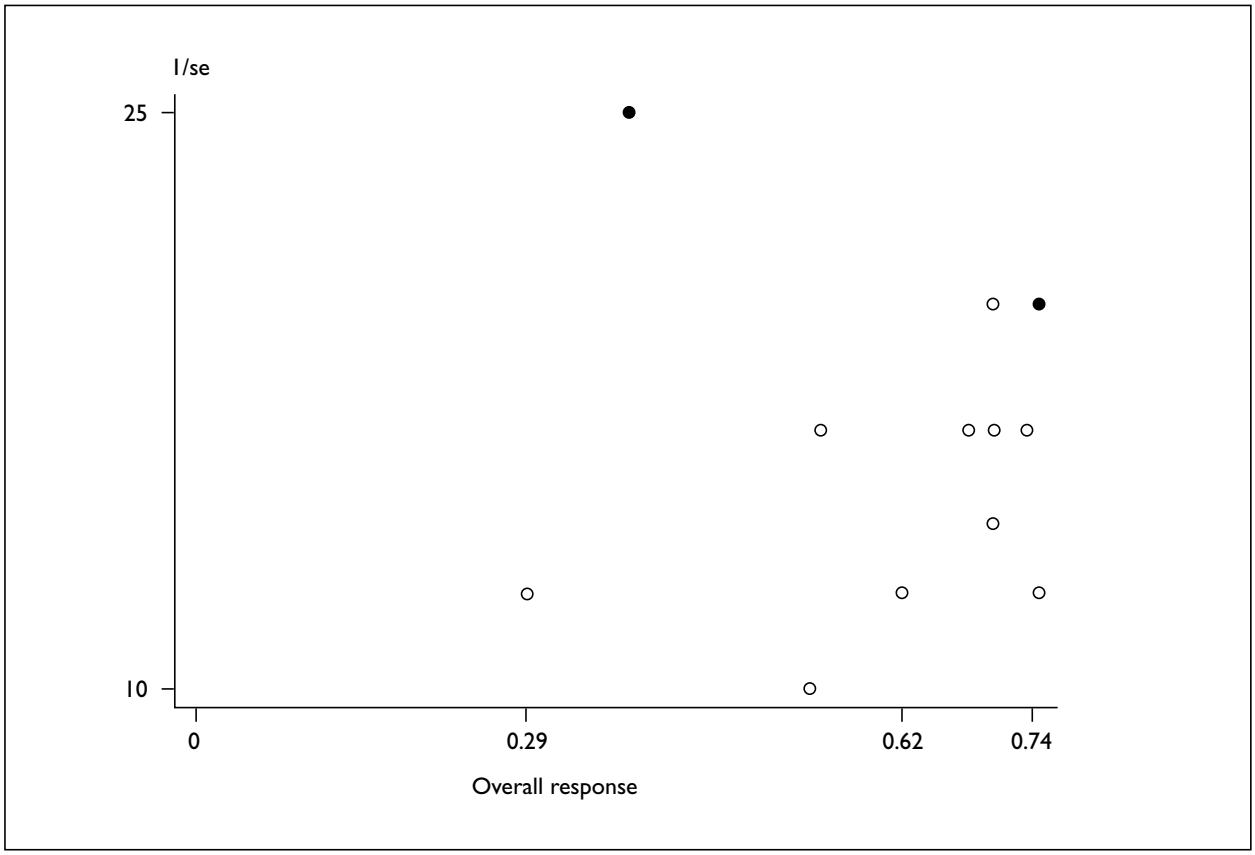


FIGURE 17 *Funnel plot of the vinorelbine plus doxorubicin RCTs and uncontrolled (Phase II) studies (○, uncontrolled studies; ●, RCTs)*

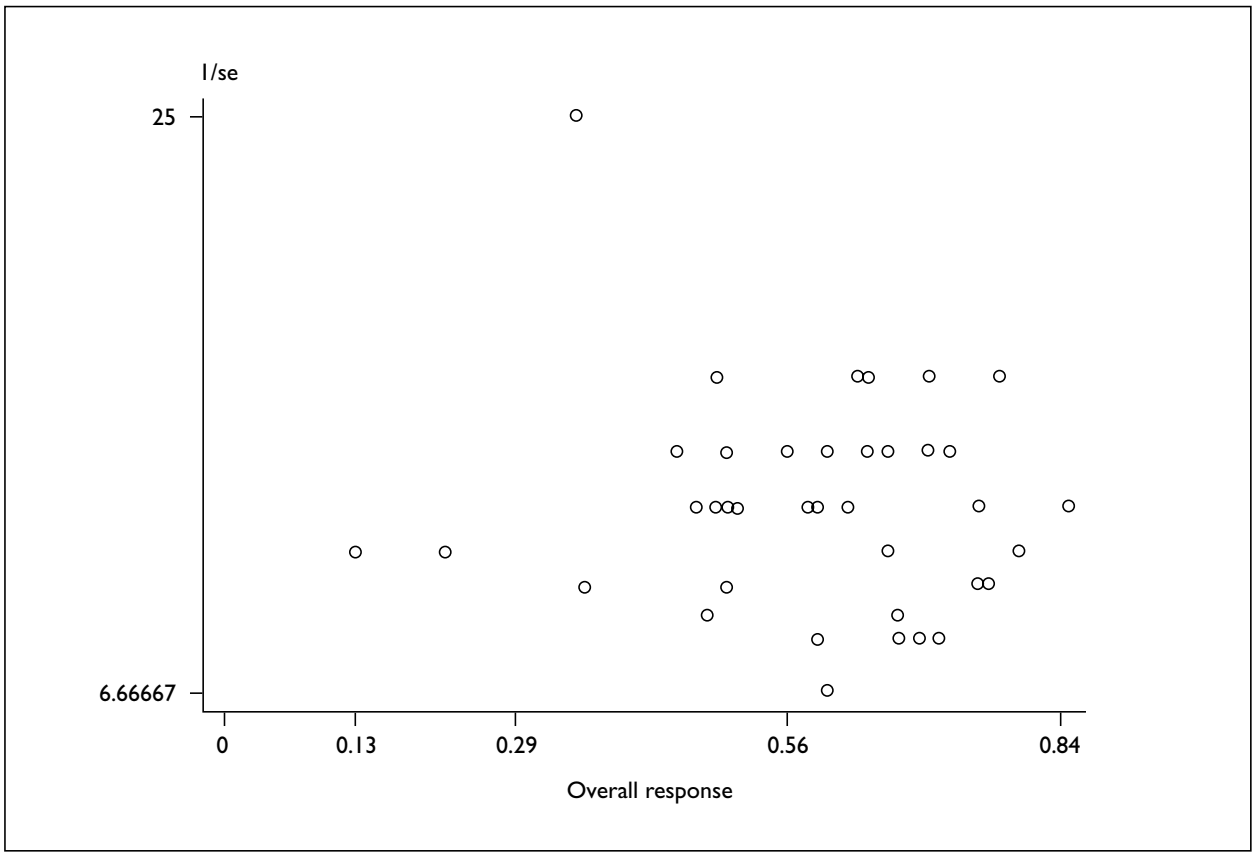


FIGURE 18 *Funnel plot of the vinorelbine uncontrolled (Phase II) studies included in the industry submission submitted to NICE*

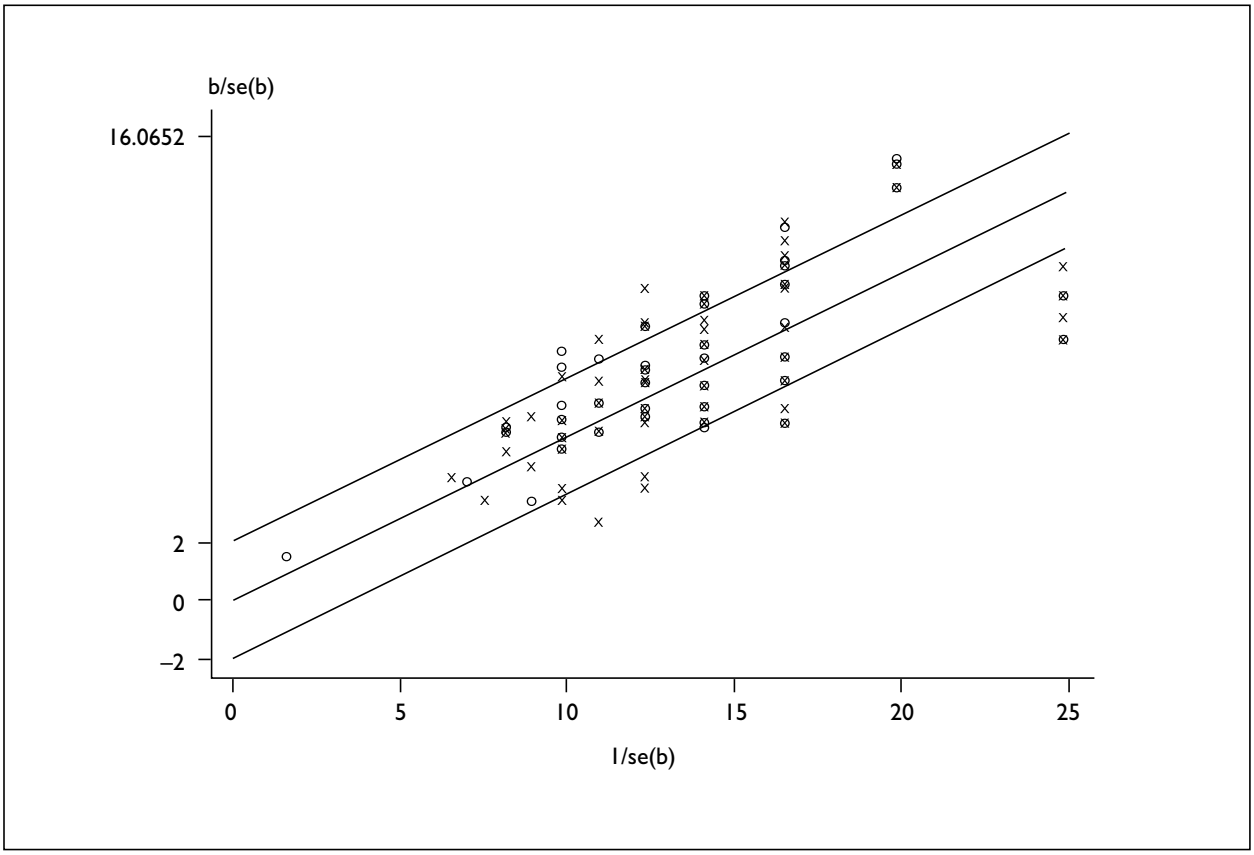


FIGURE 19 *Galbraith plot of the vinorelbine uncontrolled studies included in the industry submission submitted to NICE and studies included in the current vinorelbine review (X, studies included in this report by the Centre for Reviews and Dissemination; O, studies included by the Pierre Fabre Ltd submission; ——, fitted values)*

Chapter 4

Results – cost-effectiveness

Quantity and quality of included economic evaluations

Included studies

Four economic evaluations of vinorelbine used as monotherapy were found to meet the inclusion criteria.[34–37] Details of these studies are presented in appendix 8. No economic evaluation that investigated vinorelbine as combination therapy was found. One economic evaluation was only available in a conference abstract[35] and three studies were available as published papers.[34,36,37] All the studies included a CUA,[34–37] and one study also included a CEA.[36]

Two economic evaluations investigated the use of vinorelbine in the treatment of anthracycline-resistant MBC,[35,37] one of which also included patients with MBC resistant to paclitaxel. Other chemotherapy agents also evaluated by these two studies included docetaxel,[37] paclitaxel,[37] 5-fluorouracil[35] and gemcitabine used as monotherapy.[35] A third study also examined the cost-effectiveness of docetaxel, paclitaxel and vinorelbine as second-line treatment in participants with MBC, but no details were given about previous therapy.[36] One study evaluated the use of docetaxel in comparison with vinorelbine and paclitaxel as salvage therapy in patients with anthracycline-resistant ABC.[34]

Only one economic evaluation was based in the UK reporting on costs in £ sterling.[34] The remaining three studies were undertaken in France (using FF),[36] Canada (using Can$)[37] and the USA (using US$).[35] The cost years used were 1993,[36] 1998[35] and 1999,[37] and one study did not state the cost year used.[34]

One study reported performing the economic analysis from the Canadian societal perspective, but considered the cost to the Canadian healthcare system only.[37] One economic evaluation[36] was reported to have used the perspective of the healthcare system and patient, while the study by Brown and colleagues[34] used the perspective of the UK NHS. The other economic evaluation (only available as an abstract) did not state what perspective was used.[35]

Source of effectiveness data

For three economic evaluations that investigated the cost-effectiveness of vinorelbine, docetaxel and paclitaxel, the source of effectiveness data was multiple RCTs[34,37] and non-comparative Phase II studies.[34,36,37] More specifically, Launois and colleagues[36] reported obtaining the effectiveness data for docetaxel from the results of the drug registration master file, that is, the pooling of three published Phase II studies that included patients with anthracycline-resistant ABC/MBC (docetaxel was used as second-line therapy for ABC in one study). For paclitaxel, interim results from the BMTSG trial were used (see the sources of data for Launois and colleagues in appendix 8), and for vinorelbine, data were taken from a single published non-controlled study that evaluated the efficacy and tolerability of vinorelbine in refractory ABC and/or MBC (all patients had previously received at least one chemotherapy regimen including an anthracycline for advanced disease[182]). The reference details of all the studies used in the economic evaluation were provided.[36] Leung and colleagues reported that measures of effectiveness required for the decision model were obtained from three published Phase III RCTs (only one arm used from each trial) for which the reference details were provided.[37] Only one of these trials evaluated the effectiveness of vinorelbine (comparing the use of vinorelbine with melphalan for second-line therapy of ABC) and is included in the effectiveness section of this review.[38] The effectiveness data for the final economic evaluation, reported by Brown and co-workers, were derived from the results of published RCTs and proportions analysis of all the clinical trial data available for vinorelbine, docetaxel and paclitaxel within their UK licensed setting.[34] Response rates and side-effects were obtained from Phase III clinical trials involving docetaxel, one Phase III trial and several Phase II studies involving paclitaxel and one Phase III trial involving vinorelbine.[38] For the remaining economic evaluation, very little detail was given with regard to the source of effectiveness (the study was published as an abstract). It was reported that response rates and toxicity incidence for capecitabine were obtained from the registration trial, and the data were obtained from the literature and discussed by a panel of North American oncologists

(modified Delphi approach) for vinorelbine, 5-fluorouracil and gemcitabine.[35]

Health outcomes

Clinical effectiveness of vinorelbine, docetaxel and paclitaxel were estimated using objective response, duration of response, time to progression and main toxicities for one study.[37] The second study reported using toxic death rates, treatment-limiting toxicity rates and tumour response rates as measures of effectiveness for the model.[36] The third economic evaluation that evaluated the cost-effectiveness of docetaxel, vinorelbine and paclitaxel reported using response rates, time to progression, median survival, rate of grade 4 febrile neutropenia and toxicity rates as measures of effectiveness.[34] The final economic evaluation of vinorelbine, 5-fluorouracil and gemcitabine did not report the results of the effectiveness data used, which included response rates, time to disease progression, median survival, rate of grade 4 febrile neutropenia and toxicity rates related to the chemotherapeutic agent.[35]

Measures of benefit

For the economic evaluations of vinorelbine, docetaxel and paclitaxel, benefit was measured in terms of health-related QoL (HRQoL).[34,36,37] For one study, HRQoL values were based on preferences for certain health outcomes compared with perfect health. These utilities were determined using the time trade-off technique. The utility data were obtained from 25 healthy oncology care providers. Twenty-five breast cancer patients were also interviewed to obtain utility scores for comparison.[37] For the second evaluation, HRQoL measures were obtained using the standard gamble method.[36] The utility data were obtained from 20 oncology nurses who were used as proxies for the patients. The third study also reported using utilities of oncology nurses (n = 30) obtained using the standard gamble method.[34,183]

For the economic evaluation of vinorelbine, 5-fluorouracil and gemcitabine, quality-adjusted life-months (QALMs) were calculated by adjusting progression-free survival months for treatment-associated toxicities and modes of delivery. Penalty scores for toxicities and modes of delivery (resulting in diminution in QoL months) were assigned on the basis of oncology nurses' response to a modified standard gamble questionnaire.[35]

Resource use

The resource data for one study that investigated vinorelbine, docetaxel and paclitaxel were derived from a retrospective study in five hospitals.[36] For the second economic evaluation that examined the use of the same drugs, information regarding resource use was derived from a retrospective chart review of 88 patients who had received paclitaxel (n = 34), docetaxel (n = 29) or vinorelbine (n = 25).[37] Patients who had received vinorelbine were reported to have had a higher median number of metastatic sites and had received a slightly greater cumulative dose of anthracycline previously. Patients were identified through the database of the Department of Pharmaceutical Services. Only individuals who had relapsed within 12 months after anthracycline-based adjuvant therapy or had disease progression after treatment with anthracyclines (alone or in combination) for metastatic disease were considered.

Resource use data for the UK-based trial comparing vinorelbine, docetaxel and paclitaxel were estimated using an expert panel of five oncologists.[34] One oncologist defined the resource use estimate while the other four reviewed these estimates. These estimates were designed to reflect current treatment practices in the UK. The source of data relating to resource use for the final economic evaluation (published as an abstract) was not stated.[35]

Costs

The type of costs considered by the study that evaluated vinorelbine, docetaxel and paclitaxel by Launois and colleagues included those relating to second-line treatment, follow-up assessment of responders, management of toxicity, management of metastatic complications, third-line treatment and palliative end-of-life treatment.[36] Standard costs were based on national accounting costs by diagnosis-related groups and direct medical costs were calculated using a standard cost method (defined as the product of a standard quantity and standard price).

The type of costs considered by the study that evaluated the vinorelbine, docetaxel and paclitaxel by Leung and co-workers included acquisition, preparation and administration costs of the chemotherapy, premedications, laboratory tests, hospitalisation, clinic visits, the management of complications of adverse effects and all related physician fees.[37] The cost of drugs and supplies were estimated from pharmacy order catalogues (1998). Costs of laboratory tests and diagnostic imaging were reported to have been obtained from the relevant departments. The cost of daily hospitalisation was taken from the Ontario Hospital Association (1996) for a teaching

hospital, and the cost of oncologist fees were obtained from the Schedule of Benefits. Future costs and benefits were not discounted because of the short-term period involved. The total cost for all patients was divided by the total number of cycles to obtain a mean cost per cycle for each agent.

The unit costs for the third study that investigated docetaxel, vinorelbine and paclitaxel were taken from UK national databases, hospital data and published sources, such as the *Monthly Index for Medical Specialties* for drug costs. The study considered the costs of consultations with healthcare professionals, inpatient stays, drug administration together with the cost of management and treatment of adverse events. Costs were discounted at 6% where appropriate.[34] The economic analysis was based on an updated version of the Hutton and colleagues model (1996).[159]

One economic evaluation that studied vinorelbine, 5-fluorouracil and gemcitabine only reported measuring direct costs and marginal cost-effectiveness using the Health Care Financing Administration's 1998 reimbursements for professional and facility fees and average wholesale price for drugs.[35]

Modelling

The economic analysis of vinorelbine, docetaxel and paclitaxel was based on a Markov model in two studies[34,36] and a decision analysis tree in the third study.[37] The time-frame for the economic evaluation by Leung and colleagues was from the first cycle of chemotherapy (paclitaxel, docetaxel or vinorelbine) until up to 3 weeks after the last cycle, identified for each patient.[37] The time interval used in the economic evaluation by Launois and co-workers was from the start of second-line treatment until death.[36] This was subdivided into equal time intervals of 3 weeks, which were referred to as cycles. The economic evaluation based on the UK NHS considered the period of 3 years starting from initiation of salvage therapy.[34] A Markov model was reported to have been used to evaluate HRQoL and health-related direct costs of therapy using capecitabine, vinorelbine, 5-fluorouracil and gemcitabine.[35] No further details were provided.

Synthesis

For one economic evaluation that examined vinorelbine, docetaxel and paclitaxel, the estimated costs and benefits were synthesised using quality-adjusted progression-free survival.[37] A second economic evaluation investigating the same treatment regimens used quality-adjusted life-years (QALYs).[34] For the remaining economic evaluation that included the same drugs, the costs and benefits were not synthesised, but the data available showed docetaxel to be the dominant treatment.[36] For the economic evaluation examining the use of vinorelbine, capecitabine, 5-fluorouracil and gemcitabine, cost and benefit were synthesised using a CER, with QALMs as a measure of effect.[35]

Quality of included economic evaluations

The quality of the included economic evaluations of vinorelbine were evaluated using a checklist (appendix 5). A summary is presented in *Table 67*.[184]

Study question

The viewpoint of the analysis was considered to be clearly stated and justified for three of the economic evaluations that examined the use of vinorelbine, docetaxel and paclitaxel.[34,36,37] For the remaining study, it was not stated what perspective was taken into account.[35]

Selection of alternatives

The comparators used for the three economic evaluations of vinorelbine, docetaxel and paclitaxel were clearly justified and information relating to them were available in the referenced papers.[34,36,37] For the remaining economic evaluation, the authors stated that they evaluated four chemotherapeutic options (vinorelbine, capecitabine, 5-fluorouracil and gemcitabine) currently used to treat anthracycline- and paclitaxel-resistant MBC, but gave no further details.[35] The rationale for choosing the alternative therapies was not stated.

Form of evaluation

The form of economic analysis used was justified for three studies that examined the use of vinorelbine, docetaxel and paclitaxel.[34,36,37] For the final study that included a CUA using QALMs until disease progression, the justification of why a short time-frame was used was not given.[35]

Effectiveness data

The source of the effectiveness data was clearly stated for the three studies that investigated the use of vinorelbine, docetaxel and paclitaxel.[34,36,37] Leung and colleagues reported using three separate Phase III RCTs for each drug.[37] For the economic evaluation reported by Launois and colleagues, the data for docetaxel were based on the results of the drug registration file which included pooled results from three non-comparative Phase II studies.[36] For paclitaxel,

TABLE 67 *Quality checklist for the economic evaluations of vinorelbine*

Quality check list	Study			
	Brown *et al.*, 2000[34]	**Launois *et al.*, 1996[36]**	**Leung *et al.*, 1999[37]**	**Silberman *et al.*, 1999[35]**
Study question				
The viewpoint(s) of the analysis are clearly stated and justified (e.g. provider, institution, societal)	Yes	Yes	Yes	No
Selection of alternatives				
Relevant alternatives are compared	Yes	Yes	Yes	Yes
The alternatives been compared are clearly described	Yes	Yes	Yes	Partially
The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	No
Form of evaluation				
The choice of form of economic evaluation is justified in relation to the question addressed	Yes	Yes	Yes	No
Effectiveness data				
The source(s) of effectiveness estimates used are stated (e.g. single study, review, delphi panel)	Yes	Yes	Yes	Partially
Grade of evidence using those developed by members of the NHS R&D Centre for Evidence-Based Medicine[184] (see appendix 9)	B	B	B	Not stated/ not enough information/ unclear
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Yes	Not appropriate	Not appropriate	Yes
Benefit measurement and valuation				
The primary outcome measure(s) for the economic evaluation are clearly stated (i.e. cases detected, life years, QALYs, willingness to pay, etc)	Yes	Yes	Yes	Yes
Methods to value states and other benefits are stated (e.g. time trade-off, standard gamble)	Yes	Yes	Yes	Yes
Details of individuals from whom valuations were obtained are given	Yes	Yes	Yes	Yes
Costing				
Quantities of resources are reported separately from their unit costs (e.g. days in hospital)	No	No	Yes	No
Methods for estimation of quantities are described	Yes	Yes	Yes	No
Methods for estimation of costs are described	Yes	Yes	Yes	Yes
The relevance of productivity changes to the study question is discussed	Yes	No	No	No
Productivity changes (if included) are reported separately	Not appropriate	Not appropriate	Not appropriate	Not appropriate
Currency and price date are reported	Yes	Yes	Yes	Yes
Details of currency of price adjustments for inflation or currency conversion are given	Not appropriate	Not appropriate	Yes	Not appropriate
Modelling				
Details of any model used are given (i.e. decisions-tree model, epidemiology model, regression model, etc)	Yes	Yes	Yes	Yes
The choice of model used and the key parameters on which it is based are justified	Yes	Yes	Yes	No

continued

***TABLE 67* contd** *Quality checklist for the economic evaluations of vinorelbine*

Quality check list	Study			
	Brown *et al.*, 2000[34]	**Launois *et al.*, 1996[36]**	**Leung *et al.*, 1999[37]**	**Silberman *et al.*, 1999[35]**
Adjustments for timing of costs and benefits				
Time horizon of costs and benefits is stated	Yes	Yes	Yes	Yes
The discount rate(s) is stated	Yes	No	Not appropriate	Not appropriate
The choice of rate is justified	Partially	Not appropriate	Not appropriate	Not appropriate
A convincing explanation is given if cost or benefits are not discounted	Partially	No	Not appropriate	No
Allowance for uncertainty				
Details of statistical tests and confidence intervals are given for stochastic data	Not appropriate	Not appropriate	Yes	No
The approach to sensitivity analysis is given (i.e. multivariate, univariate, threshold analysis, etc)	No	No	No	No
The choice of variables for sensitivity analysis is justified	Yes	Yes	Yes	No
The ranges over which the variables are varied are stated	Partially	Yes	Yes	No
Presentation of results				
Incremental analysis is reported	Yes	Yes	No	Yes
Major outcomes are presented in disaggregated and aggregated form	No	Yes	Yes	No
Applicable to the NHS setting	Yes	Limited	Limited	No

interim results from one trial were used and vinorelbine data taken from a single published non-controlled study. The best source of evidence for establishing effectiveness in economic evaluations is from RCTs that include a comparison of the interventions that are included in the economic evaluation. However, there are no head-to-head trials of vinorelbine, paclitaxel and docetaxel. Therefore, both economic evaluations have taken effectiveness data for individual drugs from separate studies and brought them together in a comparison. This is not ideal because the study populations may not be comparable and may, therefore, differ in terms of prognosis and responsiveness to treatment. The results should, therefore, be treated with caution. Despite the effectiveness data for both economic evaluations having been taken from cohorts of patients from separate trials/studies, the effectiveness data used by Leung and co-workers (derived from RCTs) will represent better and more conservative estimates than those taken from non-comparative studies by Launois and co-workers.

Similarly, the economic evaluation based on the UK NHS conducted by Brown and colleagues of vinorelbine, paclitaxel, and docetaxel also reported using published Phase III and Phase II trials as the source of effectiveness data and used data for individual drugs from separate studies and brought them together in a comparison.[34] Again, the effectiveness data were not based on a head-to-head comparison, rather these data were derived from weighted average efficacy and adverse event rates for each drug.

For the final economic evaluation,[35] information relating to capecitabine was reported to have been taken from the registration trial and information relating to vinorelbine, 5-fluorouracil and gemcitabine were derived from the literature and discussed by a panel of North American oncologists (a modified Delphi approach). No information was reported on the type of literature used to derive this information and reference details were not provided.[35]

Benefit measurement and valuation

The primary outcome measures used for all economic evaluations of vinorelbine were clearly stated,[34–37] and the methods used to value states were reported.

Costing

Only one economic evaluation that examined vinorelbine, docetaxel and paclitaxel reported the quantities of resources separately from their unit

costs.[37] All three economic evaluations of vinorelbine, docetaxel and paclitaxel included a description of the methods used to estimate quantities and costs.[34,36,37] The remaining evaluation did not specify how quantities were estimated[35] but this study reported the methods used to estimate the costs.[35] The currency and price date used was reported by all four studies.[34–37]

Modelling

The details of the model used were reported by all of the economic evaluations.[34–37] The choice of the parameters used were also justified by the three evaluations that examined vinorelbine, docetaxel and paclitaxel.[34,36,37]

Adjustment for timing of costs and benefits

The time-frame used was stated for all four economic evaluations.[34–37] The discount rate of costs was reported and justified in one economic evaluation that compared docetaxel, vinorelbine and paclitaxel.[34] However, this study did not discount benefits (in the base case analysis) and, as the costs and effects were measured over a 3-year period, this is an oversight. In one economic evaluation that investigated vinorelbine, docetaxel and paclitaxel, the model considered a time interval from the start of second-line treatment until death.[36] However, it was not obvious whether this exceeded 1 year, for which discounting would have been appropriate because costs would have included palliative care until death. The discounting was not applicable for the two remaining economic evaluations due to the short time-frame of the analysis.[35,37]

Allowances for uncertainty

The details of statistical tests and CIs were given for stochastic data in only one[37] of the three economic evaluations that investigated vinorelbine, docetaxel and paclitaxel.[34,35,37]

The approach used in the sensitivity analysis (e.g. multivariate) was not stated by any of the included economic evaluations.[34–37] The choice of variables and the ranges over which they were varied were reported by all three studies of vinorelbine, docetaxel and paclitaxel.[34,36,37]

Presentation of results

An incremental analysis was reported by three of the included economic evaluations,[34,36,37] and major outcomes were presented in disaggregated and aggregated forms for two of the evaluations.[36,37]

Applicability to the NHS

Only one of the economic studies was based in the UK and, therefore, its findings are considered to be applicable to the NHS.[34] This study evaluated the use of docetaxel, vinorelbine and paclitaxel. The other two economic evaluations that investigated vinorelbine, docetaxel and paclitaxel were based in France[36] and Canada[37] and are, thus, of limited applicability to the NHS.

The final economic evaluation was based in the USA with little data being presented about the economic analysis.[35] It was felt that this study had limited applicability to the UK.

Overall evaluation of quality

Overall, the three full publications of economic evaluations of vinorelbine, docetaxel and paclitaxel were fairly well conducted given the data available.[34,36,37] The viewpoint was clearly stated and justified, as was the choice of comparators. The choice of economic evaluation was appropriate. The effectiveness data were derived from published trials/studies for which reference details were presented. However, these economic evaluations have taken effectiveness data for individual drugs from separate studies and brought them together in a comparison. This means that the intervention groups are unlikely to be comparable and may differ with regards to some important prognostic factors. Leung and colleagues[37] and Brown and co-workers[34] used effectiveness data derived from three RCTs (only one arm used from each trial), which is more likely to represent more conservative estimates than those used by Launois and colleagues[36] who used effectiveness data taken from non-comparative studies. It was, therefore, felt that the evidence used by Leung and colleagues and Brown and co-workers was stronger than that of Launois and colleagues.

The methods used for estimating costs and quantities were described for all economic evaluations. However, only Leung and colleagues provided information on the quantities of the resources separately from the unit costs.[37] As Launois and co-workers and Brown and colleagues did not illustrate these separately, it is difficult to verify their cost data.[34,36] The currency and price data were provided by all economic evaluations. Benefit was measured and valued correctly and information relating to the source of utility data was provided. The choice of modelling used was considered to be appropriate. Launois and colleagues reported a time-frame that should have entailed a discount rate being applied, but no rate seemed to have been used.[36] The discounting was not applicable for the second economic evaluation due to the short time-frame

of the analysis.[37] Brown and co-workers discounted costs appropriately but not effects in the base-case analysis, although discounting of the effects was included in the sensitivity analysis. A sensitivity analysis undertaken by the three economic evaluations of vinorelbine, docetaxel and paclitaxel appeared to be appropriate, although Launois and colleagues only included effectiveness data and costs were, therefore, open to uncertainties. However, it was unclear what type of sensitivity analysis was performed (i.e. univariate or multivariate) for these economic evaluations, although Brown and colleagues appeared to perform one-way sensitivity analysis. One economic evaluation was noted to have been supported in part by an unrestricted educational grant from GlaxoSmithKline Canada Inc.[37] However, GlaxoSmithKline do not market vinorelbine as treatment for ABC, and this sponsorship is, therefore, unlikely to have biased the study in favour of vinorelbine. One economic evaluation was noted to have been sponsored by Aventis, the manufacturer of docetaxel.[34]

For the remaining economic evaluation of capecitabine, vinorelbine, 5-fluorouracil and gemcitabine, there was insufficient information to properly judge the overall quality of the analysis as the study was only available as an abstract.[35] Nevertheless, it was felt that the cost data in this analysis were limited.[35] This economic evaluation used a short time-frame, reporting QALMs until disease progression. It would have been useful to add a lifetime analysis, such as survival, life-years gained or QALYs, or justify why a lifetime analysis was not performed.

Assessment of cost-effectiveness

Economic evaluations of vinorelbine, docetaxel and paclitaxel as monotherapy

Clinical outcomes/benefits

Launois and colleagues, 1996[36]

Reported clinical data showed vinorelbine to be less effective than docetaxel and paclitaxel in terms of overall response (57.1% with docetaxel, 28.9% with paclitaxel and 16% with vinorelbine), duration of response (28 weeks with docetaxel and paclitaxel and 21 weeks with vinorelbine) and time to progression (21 weeks with docetaxel, 18 weeks with paclitaxel and 12.9 weeks with vinorelbine). The main toxicities were as follows: febrile neutropenia occurred in 17.9, 2.0 and 3.0% of patients treated with docetaxel, paclitaxel and vinorelbine, respectively; arthralgia was found in 16.0% and severe neurotoxicities in 6.0% of patients treated with paclitaxel only; and severe fluid retention was found only in docetaxel patients, leading to interrupted treatment in 1.9% and no interruption of treatment in 2.9% of patients. Sensitivity analyses were conducted in order to account for the uncertainties surrounding the effectiveness data, which included using a response rate of 29% for docetaxel. Docetaxel was still found to be the dominant treatment.

Progression-free survival was reported to be longer for docetaxel (173 days (0.473 years)) compared to paclitaxel (145 days (0.398 years)) and vinorelbine (99 days (0.271 years)). Quality-adjusted progression-free survival was also longest for docetaxel (125 days) compared with paclitaxel (103 days) and vinorelbine (68 days).

Leung and colleagues, 1999[37]

Measures of effectiveness used in the decision model showed vinorelbine to be inferior to both paclitaxel and docetaxel in terms of response rates (21% with paclitaxel, 30% with docetaxel and 16% with vinorelbine) and time to progression (16.8 weeks with paclitaxel, 19 weeks with docetaxel and 12 weeks with vinorelbine). In terms of discontinuation due to toxicity (4% with paclitaxel, 4.4% with docetaxel and 0% with vinorelbine) and toxic deaths (0.40% with paclitaxel, 2% with docetaxel and 0% with vinorelbine), vinorelbine was found to be superior. When QoL was taken into consideration, all three drugs resulted in similar benefit. Duration of quality-adjusted progression-free survival using healthy volunteers was 38.0 days with vinorelbine, 37.2 days with paclitaxel and 33.6 days with docetaxel. The quality-adjusted progression-free survival using breast cancer patients was also similar for the three drugs (39.8 days with paclitaxel, 35.0 days with vinorelbine and 33.2 days with docetaxel).

Brown and colleagues, 2000[34]

Measures of effectiveness used in this decision model again showed vinorelbine to be inferior to both paclitaxel and docetaxel in terms of response rates (28% with paclitaxel, 41.7% with docetaxel and 16% with vinorelbine) and time to progression (21 weeks with paclitaxel, 24 weeks with docetaxel and 12 weeks with vinorelbine). When QoL was taken into consideration, vinorelbine (QALY value = 0.48[22]) was inferior to both docetaxel (0.73[47]) and paclitaxel (0.65[85]). This resulted in docetaxel having the equivalence of an additional 29 days of perfect health when compared with paclitaxel and 91 days of perfect health compared with vinorelbine.

Costs

Launois and colleagues, 1996[36]

Total costs for the three drugs considered in the study were FF 250,400 with docetaxel, FF 251,100 with paclitaxel and FF 257,200 with vinorelbine. The primary reason for the lower costs of docetaxel was due to the lower cost of 'treatment-related complications' and 'disease-related complications', which were reported to be as a result of less complications due to metastases or disease progression.

Leung and colleagues, 1999[37]

The estimated mean cost per cycle for each study drug was Can $503 (95% CI, 453 to 641) for 180 cycles with vinorelbine, Can$1680 (95% CI, 1574 to 1976) for 139 cycles with paclitaxel and Can$2653 (95% CI, 2363 to 3053) for 138 cycles with docetaxel. The favourable economic profile of vinorelbine was primarily due to the lower acquisition cost of the drug, the shorter administration time, the minimal premedications and the better toxicity profile. The mean overall treatment cost for each strategy for vinorelbine was Can$3259 per patient compared with Can$6039 and Can$10,090 for paclitaxel and docetaxel, respectively.

Brown and colleagues, 2000[34]

The average patient costs were found to be £4268 for vinorelbine, £7645 for paclitaxel and £7817 for docetaxel. Vinorelbine was, therefore, considerably less expensive than both docetaxel and paclitaxel, but also less effective. The relative cost difference between vinorelbine and paclitaxel was similar to that of Leung and co-workers. The additional cost of docetaxel in this study is lower than that concluded by Leung and colleagues but higher than that of the Launois study where docetaxel was estimated to be less expensive than vinorelbine. Despite extensive sensitivity analysis, vinorelbine was less expensive than docetaxel under a variety of scenarios.

Results of the economic evaluation

Launois and colleagues, 1996[36]

Docetaxel used for second-line therapy of MBC was found to be more effective and less costly than vinorelbine and paclitaxel. Docetaxel was the dominant treatment. Vinorelbine as compared with docetaxel was found to have higher costs and poorer outcomes (matrix score C, see *Figure 1*).

Leung and colleagues, 1999[37]

In terms of the observed clinical outcome measures of response rates and time to progression, vinorelbine was found to be less effective than paclitaxel and docetaxel but more effective in terms of discontinuation rates due to toxicity and toxic deaths. After taking QoL into account in the CUA, vinorelbine was shown to be more beneficial overall. Vinorelbine used as treatment for anthracycline-resistant MBC was found to be more effective and less costly than paclitaxel and docetaxel (matrix score G). Vinorelbine was the dominant treatment. The utility in days was transformed to years for the CUA. The average cost per quality-adjusted progression-free year was Can$31,220 for vinorelbine, Can$59,096 for paclitaxel and Can$110,072 for docetaxel.

Brown and colleagues, 2000[34]

For the treatment of ABC, vinorelbine was found to be less effective than both docetaxel and paclitaxel and less expensive (matrix score I). Docetaxel was found to be more effective and more expensive than vinorelbine and paclitaxel. The incremental cost per QALY for docetaxel was £14,500 compared with vinorelbine and £1990 compared with paclitaxel.

Economic evaluation of capecitabine, vinorelbine, 5-fluorouracil and gemcitabine

Benefits

Response rates and toxicity incidence were not stated. Expected QALMs ranged from 2.92 to 3.49, however, the intervention was not stated and there were no further details.[35]

Costs

Expected total cost per patient of treatment and toxicity management ranged from US$4668 to US$9586, however, the intervention was not stated and there were no further details).[35]

Results of the economic evaluation

For the treatment of anthracycline-resistant MBC, capecitabine was reported to be the most cost-effective therapy with a CER of US$1436 and a marginal CER of US$687 per QALM with 5-fluorouracil as the reference therapy.[35]

Overall findings of the economic evaluation of vinorelbine

When comparing vinorelbine, docetaxel and paclitaxel as monotherapy, one economic evaluation (based in Canada) of second-line therapy for MBC found vinorelbine to be the most dominant regimen (more effective and less costly than paclitaxel and docetaxel).[37] The average cost per quality-adjusted progression-free year was Can$31,220 for vinorelbine, Can$59,096 for paclitaxel and Can$110,072 for docetaxel.

One economic evaluation (based in the UK), found vinorelbine to be less effective and less expensive than both docetaxel and paclitaxel for the treatment of ABC.[34] Docetaxel was found to be more effective and more expensive than vinorelbine and paclitaxel. The incremental cost per QALY for docetaxel was £14,500 compared with vinorelbine and £1990 compared with paclitaxel. While these results appear to provide a case in favour of docetaxel, it was noted that the economic evaluation was sponsored by Aventis, the manufacturer of docetaxel. The third economic evaluation (based in France) that examined the treatment of anthracycline-resistant MBC found docetaxel to be the most dominant treatment.[36] Vinorelbine was found to have higher costs and poorer outcomes when compared to docetaxel or paclitaxel. When generalising these data to the UK, vinorelbine is usually considered as an alternative to taxane therapy for patients who cannot tolerate intensive treatment, rather than a replacement for it.

The two economic evaluations that refer to settings outside the UK reported conflicting results.[36,37] The main reasons for this difference in costs included the use of different sources of effectiveness, different levels of resource use, different sources of unit costs in different settings and time, a variation in modelling techniques and different methods of eliciting utilities. The findings of both economic evaluations refer to their corresponding settings and should be transferred with caution. Sensitivity analyses were used to explore the effect of uncertainty on the study results. However, Launois and colleagues[36] only reported analyses on effectiveness inputs and not on costs, which restricts the generalisability of the results.

The two economic evaluations reported different response rates for docetaxel, which were based on the findings of existing literature at the time the economic evaluations were undertaken. Leung and co-workers[37] used response rates derived from Phase III trials, which included more conservative estimates than those used by Launois and co-workers[36] (the authors of the earlier published evaluation), which were derived from Phase II studies. However, Launois and colleagues[36] reported the results from a sensitivity analysis where a lower response rate for docetaxel was used (similar to the one used in the economic evaluation undertaken by Leung and co-workers[37]). This did not alter their findings. The different prices of vinorelbine used in the models were justified, as these were relevant in the different settings used. In interpreting the findings for the UK setting, it would be necessary to compare the costs with the current drug acquisition costs of vinorelbine in the NHS.

For the comparison of vinorelbine, capecitabine, 5-fluorouracil and gemcitabine, capecitabine was found to be the most cost-effective. However, capecitabine is not currently licensed in the UK for MBC,[11] which greatly limits the generalisability of the findings to the NHS.

Cost implications of vinorelbine to the NHS

According to the industry submission, the annual cost to the NHS of supplying vinorelbine as first-line therapy would be £5.3–10.6 million (based on the estimation that 4000–8000 patients per year are eligible to receive vinorelbine).[11] Annual cost to the NHS of supplying vinorelbine as second-line and later therapy would be £6.6 million (based on the estimation that 5000 patients per year are eligible to receive vinorelbine). The total cost for treating the maximum number of first- and second-line participants is estimated at £17.2 million.

Chapter 5

Discussion and conclusions

Main results

Effectiveness data from RCTs

Vinorelbine as monotherapy

Two included trials investigated the use of vinorelbine monotherapy. Both studies were primarily of second-line therapy, although one included a small number (9%) of first-line patients. The chemotherapy regimens used as comparators were melphalan and 5-fluorouracil plus leucovorin with or without mitoxantrone. The overall quality of these trials was poor. The main quality issue was the lack of assurance that the randomisation procedure and allocation concealment were adequate in either trial. Previous research has demonstrated that RCTs and non-randomised controlled trials can produce different results,[185] and that RCTs that have not used an adequate randomisation procedure or have not clearly demonstrated allocation concealment may overestimate the treatment effect size.[185] Neither of the included trials reported outcomes being assessed by investigators that were blind to the treatment group assignment. In addition, the most important baseline characteristics, as determined by the expert panel for this review, were not all reported by any of the vinorelbine RCTs, and it cannot, therefore, be assured that the participants in each treatment group did not differ in terms of prognosis and responsiveness to treatment. It is important in any trial that baseline characteristics are comparable between intervention groups. Both RCTs investigating vinorelbine monotherapy reported how many participants had received previous anthracycline treatment. Neither trial reported using an ITT analysis for all outcome measures. Ignoring the findings of all withdrawals/dropouts and non-responders means that only those who fully complied with treatment are included in the analysis. This could lead to an overestimation of the average treatment effect or, worse, a biased comparison, if compliance level is influenced by effectiveness (although this may not be likely for intravenous therapy).

There were no significant differences between vinorelbine and any comparator for any parameter of tumour response. Time to treatment failure, progression-free survival and median overall survival were found to be statistically significantly longer in those treated with vinorelbine compared to those treated with melphalan. However, melphalan is not considered to be an appropriate comparator because it is not representative of conventional treatment for MBC, which limits the generalisability of the findings to the clinical setting. When compared to 5-fluorouracil plus leucovorin with or without mitoxantrone the median survival, duration of overall response and time to treatment failure appeared to be similar in all three groups. There were no significant differences found between the intervention groups in either trial for any of the reported grade 3 or 4 adverse events. One of the trials assessed QoL and differences between groups were not significant for all but one QoL dimension, which was physical function.

Vinorelbine as combination therapy

Five included trials investigated the use of vinorelbine in combination with other chemotherapy agents for MBC. The overall quality of the included trials that investigated vinorelbine as combination therapy was moderate to poor. Only one trial reported the method of randomisation used and the allocation of treatment appeared to be concealed in only two of the five trials. None of the trials used blind outcome assessment. The information relating to baseline characteristics was limited, with none of the trials reporting on disease bulk, number of previous regimens and histology. The importance of these factors has been discussed previously. Only two out of the five RCTs examining vinorelbine as combination therapy reported this information, and it was not reported by treatment group so baseline comparability could not be assessed. Only two trials used an ITT analysis for both safety and effectiveness data and only one reported on the reasons for withdrawal or exclusions from the trial adequately.

When vinorelbine in combination with doxorubicin was compared with doxorubicin alone as mainly first-line therapy, no statistically significant differences for any of the parameters of tumour response or survival were found. No differences in adverse events or QoL measures were identified. These data would suggest that the addition of vinorelbine conferred no treatment benefit above

that of doxorubicin alone. However, it is unclear whether the non-significant results are due to a small sample size or the fact that the interventions are similar. In addition, 80% of the participants were treated with a dose (20 mg/m^2) that is lower than the recommended dose for vinorelbine when used in combination schedules, due to the occurrence of febrile neutropenia.

No statistically significant differences in terms of effectiveness or adverse events were identified when vinorelbine plus doxorubicin was compared with FAC for first-line therapy. Similarly, there were no statistically significant differences between vinorelbine plus mitoxantrone and FAC/FEC in terms of tumour response or progression-free or overall survival. However, serious febrile neutropenia was more frequent in the vinorelbine/mitoxantrone group, whilst severe nausea and vomiting and alopecia occurred more frequently in the FAC/FEC group.

The comparison of vinorelbine plus docetaxel with docetaxel plus gemcitabine used as second-line therapy found no statistically significant differences between the treatments for tumour response. No survival data were reported.

Minimal data were available for the final trial, which compared FUN with docetaxel as first- or second-line therapy (available as an abstract only). Median progression-free survival appeared similar, but there were no statistical comparisons. No tumour response data were reported. The report suggested that toxic deaths in the vinorelbine group were more frequent, however, the reliability of the reporting is debatable.

The findings of the individual combination therapy RCTs may not be reliable and none of the findings detailed above can be considered definitive. Unfortunately, the use of different combinations and different comparators means that the results of individual trials could not be directly combined in an attempt to derive a more precise estimate of the effectiveness of vinorelbine used as combination therapy. It is also not possible to discern the true effect of vinorelbine itself from that of any interaction that occurs between vinorelbine and other agents when used in the different combinations included in this review.

Further issues to be taken into consideration in the interpretation of the results from the included RCTs

Due to the nature of the disease and of the drugs being given, intravenous cancer chemotherapy trials are usually not double-blind (where the administrators and patients are blind to treatment allocation). However, the lack of blinding, even though it may not be possible to achieve, can still result in bias. Previous research has shown that non-blinded studies can overestimate the treatment effect.[186] Non-blindness of administrators can also result in biased administration of co-interventions. This should, therefore, be taken into consideration when interpreting the results.

When reporting an RCT with survival-type data, the recommended appropriate summary statistics that should be used are the log HR and its variance.[187] Survival data for included trials were often presented inadequately with no HR or measure of its variance reported. Trial authors often stated that there was a significant difference in survival and gave *p*-values from a log-rank test, but did not present median survival and its variance. Follow-up times were rarely stated and often had to be estimated from Kaplan–Meier survival curves. The numbers included in the group comparisons at the end of survival curves were often not given.

Response to treatment is a surrogate outcome measure for assessing the effects of treatment on survival or QoL. As the study population of women with MBC has such poor prognosis, tumour shrinkage may alleviate symptoms (especially pain) and improve QoL, which means that information relating to complete or partial response would be important but not independent from QoL. However, these outcomes were not addressed by most of the trials, which is surprising because these outcomes are probably the most important for this patient group. As partial response is a surrogate measure for complete response, conclusions about effectiveness should be drawn from the complete response findings. Conclusions should not be drawn on the findings of partial response when used as a surrogate measure, unless outcomes relating to symptom relief are also reported or the results of both partial and complete responses are in the same direction.

Definitions of outcome measures were often not clearly stated (for example whether partial response referred to a 25 or 50% reduction in size of a tumour) and details of how outcomes were measured were generally not reported. This limits the comparability of studies.

Many of the included RCTs reported that there were no significant differences between the intervention groups. However, this does not mean that equivalence has been proven or that it can be concluded that the intervention was the same

or 'as good as' the comparator/conventional treatment. Most of the trials in this review were set up to explore whether the intervention was superior to the comparator (that is, to reject the null hypotheses that there is no difference between the intervention groups). Power calculations used to estimate the number of participants that would need to be recruited were based on this assumption. If the findings of the trial were not statistically significant, then the null hypotheses cannot be rejected. It is not possible to ascertain whether this is due to the interventions being similar or because the trial was not large enough. Trials that are set up to show equivalence generally need to be much larger than comparative trials.[178] Equivalence trial design also requires that the investigators choose the magnitude of the effect within which the estimated difference between the two treatment groups must lie in order to prove equivalence (or exceed if trying to demonstrate that the new treatment is not inferior to the conventional treatment) a priori (that is, during the planning stage). Only one included trial reported by Namer and colleagues, was set up to show equivalence in terms of response rate.[40] However, the chosen equivalence interval was wide at 15% and the power calculation used to calculate the sample size was one-sided (which assumes that one intervention is superior to another, but not the other way around), resulting in a small required sample size (n = 280).

Effectiveness data from uncontrolled Phase II studies

Fourteen uncontrolled studies of vinorelbine monotherapy and 51 studies of combination therapy were included in the review. These studies were clinically diverse and investigated various vinorelbine-based regimens in a range of populations. Many of the studies were small with limited follow-up. Only a few subsets of studies, where the diversity appeared to be minimal, were investigated by statistical pooling and even these results must be interpreted with caution.

Overall, for vinorelbine monotherapy used intravenously, the complete tumour response rate ranged from 0 to 20% and the overall tumour response rate ranged from 0 to 60%. The median duration of overall tumour response ranged from 1.8 to 9 months. The median overall survival ranged from 9.9 to 16.8 months. Median time to disease progression ranged from 3 to 6 months and median time to treatment failure ranged from 4.6 to 6 months.

For vinorelbine used as combination therapy, complete tumour response ranged form 5 to 32% and overall tumour response ranged from 22 to 79%. Studies of vinorelbine plus doxorubicin reported complete and overall tumour response rates of 6–32% and 29–74%, respectively. For vinorelbine used in combination with epirubicin, reported complete and overall tumour response rates were 6–19% and 50–77%, respectively. Studies of vinorelbine plus paclitaxel reported overall tumour response rates of 47 to 67%. Other combinations were investigated in small numbers of clinically diverse studies. The median duration of overall tumour response ranged from 6 to 16 months, the median overall survival ranged from 12.3 to 31 months, the median time to disease progression ranged from 3.9 to 15 months and the median time to treatment failure ranged from 7 to 12 months.

Vinorelbine monotherapy may be particularly associated with leukopenia, granulocytopenia, nausea/vomiting and constipation. Vinorelbine used as combination therapy appeared to be associated with neutropenia, alopecia and nausea/vomiting. However, different combinations will have differing profiles, the exact nature of which were difficult to discern from the limited data available.

As the Phase II studies included in the review did not compare the use of vinorelbine with an alternative systemic therapy or conventional care, their results should be interpreted with caution. When investigating the use of an intervention, it is important to consider that the observed effect may not necessarily be due to the therapeutic intervention itself. It is possible that the observed effect could be due to confounding factors, which include the natural course of the disease (that is, variability in the disease status or the influence of different prognostic factors), extraneous factors (such as lifestyle, the use of other medication and placebo effect) and information errors (such as incorrect assessment or reporting of the outcome measure). Using a well-conducted double-blind RCT means that these confounding factors are controlled for providing an unbiased estimate of the effect. In other words, the observed effect will either be due to the intervention or chance (random variation), which can be minimised by using a large enough sample size. Observational studies, on the other hand, may yield estimates of association that may deviate from true underlying relationships beyond the play of chance.[15]

As was seen with the included RCTs, the uncontrolled Phase II studies did not report blind outcome assessments and rarely reported follow-up times.

Comparison of effectiveness data from RCTs and uncontrolled Phase II studies

The evidence from uncontrolled Phase II studies appears to complement the RCT findings. However, as shown by the Galbraith plots and the funnel plots presented in the results section the findings of the uncontrolled studies do not compensate for the lack of available RCTs. In other words, the data from the uncontrolled studies on their own are inadequate due to the clinical diversity, statistical heterogeneity and lack of precision. This is in addition to the fact that uncontrolled studies are of a lower level of evidence due to the biases and lack of rigour that are inherent in such studies.

The gold standard for investigating the effectiveness of any intervention is the RCT. However, there are certain circumstances where it may not be feasible to undertake an RCT and, therefore, uncontrolled studies that evaluate the efficacy of a new drug may be considered as an alternative. A group of statisticians involved in the AIDS trials have proposed a list of criteria that should be met before uncontrolled studies are considered as an alternative to RCTs.[188] These criteria include the following.

(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 benefit to the patients will be sufficiently large to make interpretation of the results of a non-randomised trial unambiguous.
(5) The scientific rational for the treatments must be sufficiently strong that a positive result would be widely accepted.

When considering vinorelbine for the treatment of ABC, although criteria (2) and (5), and possibly (1), for later lines of therapy, may apply, criteria (3) and (4) are not met. The results of the review show that vinorelbine may be associated with grade 3–4 neutropenia and possibly other less severe side-effects and appeared to result in only moderate benefit to the patients.

Economic data

Four economic evaluations were included in the review. Three evaluated vinorelbine, docetaxel and paclitaxel and one compared capecitabine, vinorelbine, 5-fluorouracil and gemcitabine. No economic evaluation that included the same drug regimens presented in the effectiveness section were found via the literature search and no further economic evaluations were included in the industry submission. The economic evaluations of vinorelbine, docetaxel and paclitaxel were fairly well conducted. For the remaining economic evaluation, there was insufficient information to properly judge the overall quality of the analysis as it was only available as an abstract.

One economic evaluation (based in Canada) comparing vinorelbine, docetaxel and paclitaxel found vinorelbine to be the dominant treatment (more effective and less costly than paclitaxel and docetaxel) when used for the treatment of anthracycline-resistant MBC. The average cost per quality-adjusted progression-free year was Can$31,220 for vinorelbine, Can$59,096 for paclitaxel and Can$110,072 for docetaxel. One economic evaluation (based in the UK) found vinorelbine to be less effective and less expensive than both docetaxel and paclitaxel for the treatment of ABC. Docetaxel was found to be more effective and more expensive than vinorelbine and paclitaxel.

The incremental cost per QALY for docetaxel was £14,500 compared with vinorelbine and £1990 compared with paclitaxel. However, it was noted that the economic evaluation was sponsored by Aventis – the manufacturer of docetaxel. The third economic evaluation (based in France) that investigated the treatment of anthracycline-resistant MBC found docetaxel to be the most dominant treatment. Vinorelbine, when compared to docetaxel or paclitaxel, was found to have higher costs and poorer outcomes. When generalising these data to the UK, vinorelbine is usually considered as an alternative to taxane therapy for patients who cannot tolerate intensive treatment, rather than a replacement for it.

In the comparison of capecitabine, vinorelbine, 5-fluorouracil and gemcitabine (published as an abstract), capecitabine was reported to be the most cost-effective therapy for the treatment of anthracycline-resistant MBC with a CER of $1436 and a marginal CER of $687 per QALM with 5-fluorouracil as the reference therapy. However, capecitabine is not currently licensed in the UK for MBC,[11] which limits the generalisability of the findings to the NHS.

Issues to be taken into consideration in the interpretation of the results from the cost-effectiveness data

It is important that, where possible, the data on the effectiveness for different interventions used in economic evaluations are derived from the same controlled trial, otherwise the effectiveness of the intervention cannot be assured. This is because the study population used in the different studies may not be comparable and could, therefore, differ in terms of prognosis and responsiveness to treatment (selection bias). Economic evaluations of vinorelbine did not include a head-to-head comparison for the effectiveness data.

For most included CEAs, the measure of benefit was dependent on survival, which was extrapolated from short-term analyses, and no allowance was made for uncertainty. It is very important that these assumptions and uncertainties are explored in sensitivity analyses, which were limited in all included economic evaluations.

Budget impact of vinorelbine to the NHS

According to data provided in the industry submission, if all eligible patients with MBC were treated with vinorelbine, the annual drug acquisition costs would be £5.3–10.6 million for first-line use and £6.6 million for second-line use.[11]

Assumptions, limitations and uncertainties

This systematic review depended heavily on the reports of studies found in the published literature. Often the reporting of important details, particularly those relating to the quality of the study was poor. This problem is particularly acute when the only publication available for a given study is an abstract.

Six studies[96,160,161,164,189,190] were excluded from the initial review (of RCTs) because they were not reported in one of the languages considered for inclusion, however, none of them were thought to meet the remaining inclusion criteria for the review. Authors whose first language is not English may be more likely to publish positive findings in English language journals because they are considered to have a greater international impact.[191] This means that the exclusion of non-English studies could lead to overoptimistic conclusions. The language restrictions used in this review were due to the time constraints and it is acknowledged that some publication bias may, therefore, be present (although unlikely as described above).

Need for further research

Further research into effectiveness

Further large well-conducted RCTs are required to investigate the use of vinorelbine in the settings for which it is currently indicated (as first- or second-line or later treatment in ABC following failure of an anthracycline-containing regimen). Such trials should pay particular attention to the research question (whether they are trying to demonstrate a difference or equivalence) and include sufficient numbers of participants to answer the research question. Randomisation procedures (including allocation concealment) should be adequate and clearly reported, as should the duration of the treatment. Outcome assessments should be blind where possible. Baseline characteristics of participants should be reported (including data on distribution), and any discrepancies should be controlled for in the analysis. All outcomes should be clearly presented (not just as percentages) and measures of variance given where appropriate. All withdrawals from the trial should be clearly reported and handling of missing data should be explicit. In trials trying to demonstrate a difference, an ITT analysis should always be undertaken ideally. Outcomes assessed should include alleviation of symptoms and pain. The number of people in the control group who received the treatment under investigation due to disease progression should also be clearly reported. When reporting survival data, HRs should be presented.

The most relevant comparators for RCTs of vinorelbine used as second- or third-line therapy would be CMF (if not given before), oxaliplatin, mitomycin C, antimetabolites or gemcitabine. Possible comparators for vinorelbine used as first-line therapy for MBC would include capecitabine or taxotere.

Further research into cost-effectiveness

CEAs of vinorelbine used in the same combinations as the included effectiveness trials is required. Further CEAs should be undertaken at the same time as future RCTs of vinorelbine used in the setting indicated for use in the UK where data on costs and effectiveness are collected simultaneously.

Conclusions

According to the evidence derived from RCTs, vinorelbine monotherapy for first- or second-line or subsequent therapy for ABC may be more

effective in terms of progression-free survival and survival than melphalan. However, melphalan is not representative of conventional treatment for MBC, which limits the generalisability of the findings to the clinical setting. Vinorelbine monotherapy was not found to be more effective than other chemotherapy regimens in terms of response rates. In addition, the poor quality of the data on which these findings are based should be borne in mind.

Vinorelbine when used as combination therapy with doxorubicin, 5-fluorouracil or mitoxantrone did not appear to be more effective than alternative combinations of chemotherapy in the treatment of MBC. Vinorelbine plus mitoxantrone may be associated with less nausea/vomiting and alopecia than FAC/FEC but may result in more febrile neutropenia.

The evidence from RCTs showed that there were no data to support the use of vinorelbine, either as a single agent or in combination therapy, over standard first-line chemotherapy with anthracyclines or other non-taxane-containing regimens. The efficacy and toxicity profiles were similar, with no suggestion of superiority over existing treatments. Vinorelbine may be one possible option when an alternative agent is required.

The evidence from uncontrolled Phase II studies appeared to indicate that vinorelbine has antitumour activity and an acceptable toxicity profile, but may be associated with leukopenia, granulocytopenia, nausea/vomiting and constipation when used as monotherapy and neutropenia, alopecia and nausea/vomiting when used as combination therapy. The data from the uncontrolled studies on their own were inadequate due to the clinical diversity, statistical heterogeneity and lack of precision. This is in addition to the fact that uncontrolled studies are of a lower level of evidence due to the biases and lack of rigour that are inherent in such studies.

The economic studies included in the review tended to compare vinorelbine monotherapy with taxane therapy. When comparing the cost-effectiveness of vinorelbine, paclitaxel and docetaxel, one economic evaluation reported that vinorelbine was more effective and less costly than taxane therapy, one found vinorelbine to be less effective and less expensive than either of the taxanes and a third evaluation found vinorelbine to be less effective and more expensive than taxane therapy. These findings suggest that vinorelbine monotherapy may be appropriate for patients unable to tolerate taxane therapy.

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Contributions of authors

Ruth Lewis, Research Fellow, was the lead reviewer responsible for producing the protocol and final review. She was involved in the selection of studies, data extraction, checking of data entry and synthesis of data, and she wrote the report. Anne-Marie Bagnall, Research Fellow, was involved in the selection of studies, extraction and synthesis of data and some report writing during the initial review process. Sarah King, Research Fellow, assisted with data extraction and synthesis of data during the update review process and read a draft copy of the report. Nerys Woolacott, Research Fellow, assisted with data extraction, checking of data entry, synthesis of data and some report writing during the update review process, and read a draft copy of the report. Carol Forbes, Research Fellow, assisted with data extraction and the development of the protocol and read a draft copy of the initial report. Liz Shirran, Research Fellow, was involved in writing the scope, and assisted with study selection and protocol development during the initial review process. Steven Duffy, Information Officer, devised the search strategy, conducted literature searches and wrote the search methodology sections of the protocol and final report. Jos Kleijnen, Director, commented on various versions of the report. Rob Riemsma, Senior Research Fellow, was the review manager responsible for overall management of the project, and commented on various versions of the report, assisted with data extraction and checked data entry. Gerben ter Riet, Senior Research Fellow, assisted in the development of the adapted economic and quality checklists and provided advice and comments on the scope, protocol and the initial final report.

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Appendix 1

Staging of breast cancer

Simplified Union Internationale Contre le Cancer staging of breast cancer[192]

T (tumour size)	T1	Tumour < 2 cm
	T2	Tumour 2–5 cm
	T3	Tumour > 5 cm
	T4	Tumour of any size fixed to skin or chest wall
N (presence of axillary nodes)	N0	No palpable axillary lymph nodes
	N1	Mobile ipsilateral nodes
	N2	Fixed ipsilateral nodes
	N3	Supraclavicular or infraclavicular nodes
M (presence of metastases)	M0	No distant metastases
	M1	Distant metastases

Combinations of these are used to define clinical staging. Early breast cancer is comprised of stages I and II and advanced of stages III and IV.

Stage	**Features**
I	Small tumour (< 2 cm)
II	Tumour > 2 cm but < 5 cm and lymph nodes negative **or** Tumour < 5 cm and lymph nodes positive with no detectable distant metastases
III	Large tumour (> 5 cm) **or** Tumour of any size with invasion of skin or chest wall **or** Associated with positive lymph nodes in the supraclavicular region but with no detectable distant metastases
IV	Tumour of any size and lymph nodes either positive or negative with distant metastases

Appendix 2

Search strategies

Scoping search

A rapid appraisal to identify ongoing and completed systematic reviews was undertaken on the 3 June 2000. The rapid appraisal search process involved searching a checklist of resources for the drug names (vinorelbine/Navelbine) and breast cancer.

Main literature search

The following databases and Internet sites were searched.

MEDLINE: SilverPlatter (CD-ROM)

The search strategy was designed to find RCTs and cost-effectiveness studies and, therefore, used relevant methodological filters. Breast cancer terms and the drug names (vinorelbine/Navelbine) were then added to the quality filters. The MEDLINE searches covered the date range 1986 to August 2000. The searches were carried out on 5 September 2000 and identified 172 records for vinorelbine/Navelbine.

#1 randomized controlled trial in pt
#2 explode "randomized controlled trials"/all subheadings
#3 "random allocation"/all subheadings
#4 "double blind method"/all subheadings
#5 "single blind method"/all subheadings
#6 clinical trial in pt
#7 explode "clinical trials"/all subheadings
#8 "controlled clinical trials"/all subheadings
#9 (clin* near3 trial*) in ti,ab
#10 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*)) in ti,ab
#11 placebo* in ti,ab
#12 "placebos"/all subheadings
#13 random* in ti,ab
#14 explode "research design"/all subheadings
#15 explode "Evaluation-Studies"/all subheadings
#16 "Follow-Up-Studies"/all subheadings
#17 "Prospective-Studies"/all subheadings
#18 (control* or prospectiv* or volunteer*) in ti,ab
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 tg=animal
#21 tg=human
#22 #20 not (#20 and #21)
#23 #19 not #22
#24 explode "economics"/all subheadings
#25 (cost or costs or costed or costly or costing) in ti,ab
#26 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti,ab
#27 #25 near #26
#28 (economic* or pharmacoeconomic* or price* or pricing) in ti,ab
#29 #24 or #27 or #28
#30 #23 or #29
#31 explode "breast neoplasms"/all subheadings
#32 (breast* near4 (cancer* or tumo?r* or malignant*)) in ti,ab
#33 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
#34 #31 or #32 or #33
#35 vinorelbine in ti,ab,nm
#36 navelbine in ti,ab
#37 #35 or #36
#38 #34 and #37
#39 #30 and #38

EMBASE: SilverPlatter (CD-ROM)

The MEDLINE search strategy above was translated and adapted to run in the EMBASE database. The EMBASE searches covered the date range 1989 to July 2000. The searches were carried out on 5 September 2000 and identified 325 records for vinorelbine/Navelbine.

#1 "randomized-controlled-trial"/all subheadings
#2 "randomisation"/all subheadings
#3 "double-blind-procedure"/all subheadings
#4 "single-blind-procedure"/all subheadings
#5 (random* near control* trial*) in ti,ab
#6 (clin* near3 trial*) in ti,ab
#7 explode "clinical trial"/all subheadings
#8 explode "controlled study"/all subheadings
#9 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*)) in ti,ab
#10 placebo* in ti,ab
#11 "placebo"/all subheadings
#12 "evaluation"/all subheadings
#13 "follow up"/all subheadings
#14 "prospective study"/all subheadings
#15 (control* or prospective* or volunteer*) in ti,ab
#16 random* in ti,ab

#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 (explode "animal"/all subheadings) or (explode "animal experiment"/all subheadings)
#19 (explode "human"/all subheadings) or (explode "human experiment"/all subheadings)
#20 #18 not (#18 and #19)
#21 #17 not #20
#22 explode "economics"/all subheadings
#23 explode "health economics"/all subheadings
#24 (cost or costs or costed or costly or costing) in ti,ab
#25 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti,ab
#26 #24 near #25
#27 #22 or #23 or #26
#28 #21 or #27
#29 explode "breast-cancer"/all subheadings
#30 (breast* near4 (cancer* or tumo?r* or malignant*)) in ti,ab
#31 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
#32 #29 or #30 or #31
#33 vinorelbine in ti,ab,tn
#34 "vinorelbine"/all subheadings
#35 navelbine in ti,ab
#36 #33 or #34 or #35
#37 #32 and #36
#38 #28 and #37

CANCERLIT: SilverPlatter (CD-ROM)

The MEDLINE search strategy above was translated and adapted to run in the CANCERLIT database. The Cancerlit searches covered the date range 1995 to June 2000. The searches were carried out on 7 September 2000 and identified 231 records for vinorelbine/Navelbine.

#1 randomized controlled trial in pt
#2 explode "randomized controlled trials"/all subheadings
#3 "random allocation"/all subheadings
#4 "double blind method"/all subheadings
#5 "single blind method"/all subheadings
#6 clinical trial in pt
#7 explode "clinical trials"/all subheadings
#8 "controlled clinical trials"/all subheadings
#9 (clin* near3 trial*) in ti,ab
#10 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*)) in ti,ab
#11 placebo* in ti,ab
#12 "placebos"/all subheadings
#13 random* in ti,ab
#14 explode "research design"/all subheadings
#15 explode "Evaluation-Studies"/all subheadings
#16 "Follow-Up-Studies"/all subheadings
#17 "Prospective-Studies"/all subheadings
#18 (control* or prospectiv* or volunteer*) in ti,ab
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 explode "economics"/all subheadings
#21 (cost or costs or costed or costly or costing) in ti,ab
#22 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti,ab
#23 #21 near #22
#24 (economic* or pharmacoeconomic* or price* or pricing) in ti,ab
#25 #20 or #23 or #24
#26 #19 or #25
#27 explode "breast neoplasms"/all subheadings
#28 (breast* near4 (cancer* or tumo?r* or malignant*)) in ti,ab
#29 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
#30 #27 or #28 or #29
#31 vinorelbine in ti,ab,nm
#32 navelbine in ti,ab
#33 #31 or #32
#34 #30 and #33
#35 #26 and #34

BIOSIS-Web: Edina (Internet <http://edina.ed.ac.uk/biosis/>)

BIOSIS-Web was searched via Edina on the Internet. As this interface only accepts simple search strategies, the RCTs and cost-effectiveness studies filters were not used. A simple search strategy using the drug names (vinorelbine/Navelbine) and breast cancer terms was used. The resulting references were then checked for duplication against those records already found. The BIOSIS-Web searches covered the date range 1993 to 2000. The searches were carried out on 7 September 2000 and identified 252 records for vinorelbine/Navelbine.

(vinorelbine or navelbine) and breast*

ISTP: Web of Science (Internet <http://wos.mimas.ac.uk/>)

The Web of Science interface used to search ISTP only accepts simple search strategies, therefore, the RCTs and cost-effectiveness filters were not used. A simple search combining the drug names and breast cancer terms was implemented. The ISTP searches covered the date range 1990 to 2000. The searches were carried out on 11 September 2000 and identified 46 records for vinorelbine/Navelbine.

(vinorelbine or navelbine) and breast*

CCTR: Cochrane Library (CD-ROM 2000, issue 3)

The CCTR was searched to find completed trials. A relatively simple search was used, combining the drug names with terms for breast cancer. The search strategy did not require methodological filters for RCTs because the database only consists of such references. The searches were carried out on 6 September 2000 and identified 27 records for vinorelbine/Navelbine.

#1 BREAST-NEOPLASMS*:ME
#2 (BREAST* AND ((((CANCER*) or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
#3 (BREAST* AND ((ONCOLOG*) or CARCINOMA*))
#4 ((#1 or #2) or #3)
#5 VINORELBINE
#6 NAVELBINE
#7 (#5 or #6)
#8 (#4 and #7)

DARE: Cochrane Library (CD-ROM 2000, issue 3)

The DARE was searched at the same time as the CCTR database, using the same strategy (see above). The searches were carried out on 6 September 2000 and identified no records.

NHS EED: Cochrane Library (CD-ROM 2000, issue 3)

The NHS EED was searched at the same time as the CCTR database, using the same strategy (see above). The searches were carried out on 6 September 2000 and identified no records.

National Research Register (CD-ROM 2000, issue 3)

The National Research Register was searched to find further ongoing and completed trials. A relatively simple search strategy was used, combining the drug names and terms for breast cancer. The searches were carried out on 12 September 2000 and identified 15 ongoing and ten complete trials for vinorelbine/Navelbine.

#1 BREAST-NEOPLASMS*:ME
#2 (BREAST* AND ((((CANCER*) or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
#3 (BREAST* AND ((ONCOLOG*) or CARCINOMA*))
#4 ((#1 or #2) or #3)
#5 VINORELBINE
#6 NAVELBINE
#7 (#5 or #6)
#8 (#4 and #7)

Internet resources

A number of Internet sites were chosen to search for information about further ongoing trials. The sites included the main trials registers: United Kingdom Coordinating Committee on Cancer Research Register, National Institute of Health, Current Controlled Trials and CenterWatch Clinical Trials Listing Service. The trials register of the National Cancer Institute was also searched (CANCERNET). In addition, the American Society of Clinical Oncology (ASCO) website was searched for abstracts from their annual conference proceedings. The search strategy for all of the Internet sites consisted of the drug terms only. The results were then browsed to find references dealing with breast cancer only.

VINORELBINE NAVELBINE

United Kingdom Coordinating Committee on Cancer Research Register <http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html>
This site was searched on 14 September 2000 and identified no trials for vinorelbine/Navelbine.

National Institute of Health <http://clinicaltrials.gov/ct/gui/c/r>
This site was searched on 14 September 2000 and identified four trials for vinorelbine/Navelbine.

Current Controlled Trials <http://www.controlled-trials.com/login.cfm?returnto=home_page.cfm>
This site was searched on 14 September 2000 and identified four trials for vinorelbine/Navelbine.

CenterWatch Clinical Trials Listing Service <http://www.centerwatch.com/main.htm>
This site was searched on 14 September 2000 and identified one trial for vinorelbine/Navelbine.

National Cancer Institute <http://cancernet.nci.nih.gov/trialsrch.shtml>
This site was searched on 14 September 2000 and identified three trials for vinorelbine/Navelbine.

ASCO <http://www.asco.org/>
This site was searched on 14 September 2000 and identified five ASCO abstracts on vinorelbine/Navelbine. Abstracts that had already been found in the previous database searches were discounted.

The search results from MEDLINE, EMBASE, CANCERLIT, BIOSIS-Web, ISTP and the CCTR were downloaded and imported into Endnote (ISI ReSearchSoft, USA) reference management software and duplicate records were deleted. The search results from the National Research Register were downloaded in full into a text file. The search results from the Internet were saved as HTML files.

Update search

An update search was undertaken in order to find more information about Phase II trials. It was decided to rerun the original searches without the RCT and economic evaluation methodological search filters. Methodological filters were not used in the original searches for the BIOSIS, ISTP, CCTR and the National Research Register databases, so remained exactly the same.

Main literature search

The following databases were searched.

MEDLINE: SilverPlatter (CD-ROM)

The search strategy was designed to find all studies and was, therefore, kept very simple for sensitive results. Breast cancer terms and the drug names (vinorelbine/Navelbine) were combined in the search strategy. The MEDLINE search covered the date range 1986 to May 2001. The search was carried out on 13 August 2001 and identified 274 records.

#1 vinorelbine in ti,ab,nm
#2 navelbine in ti,ab,nm
#3 #1 or #2
#4 explode "Breast-Neoplasms"/all subheadings
#5 (breast near4 (cancer* or tumo?r* ot malignant*)) in ti,ab
#6 (breast near4 (oncolog* or carcinoma*)) in ti,ab
#7 #4 or #5 or #6
#8 #3 and #7
#9 tg=animal
#10 tg=human
#11 #9 not (#9 and #10)
#12 #8 not #11

EMBASE: SilverPlatter (CD-ROM)

The MEDLINE search strategy above was translated and adapted to run in the EMBASE database. The EMBASE search covered the date range 1989 to July 2001. The search was carried out on 13 August 2001 and identified 568 records

#1 vinorelbine in ti,ab,tn
#2 navelbine in ti,ab,tn
#3 #1 or #2
#4 explode "breast-cancer"/all subheadings
#5 (breast* near4 (cancer* or tumo?r* or malignant*)) in ti,ab
#6 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
#7 #4 or #5 or #6
#8 #3 and #7
#9 (explode "animal"/all subheadings) or (explode "animal-experiment"/all subheadings)
#10 (explode "human"/all subheadings) or (explode "human experiment"/all subheadings)
#11 #9 not (#9 and #10)
#12 #8 not #11

CANCERLIT: SilverPlatter (CD-ROM)

The MEDLINE search strategy above was translated and adapted to run in the CANCERLIT database. The CANCERLIT search covered the date range 1995 to March 2001. The search was carried out on 13 August 2001 and identified 420 records.

#1 explode "breast neoplasms"/all subheadings
#2 (breast* near4 (cancer* or tumo?r* or malignant*)) in ti,ab
#3 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
#4 #1 or #2 or #3
#5 vinorelbine in ti,ab,nm
#6 navelbine in ti,ab,nm
#7 #5 or #6
#8 #4 and #7

BIOSIS-Web: Edina (Internet <http://edina.ed.ac.uk/biosis/>)

BIOSIS-Web was searched via Edina on the Internet. A simple search strategy using the drug names (vinorelbine/Navelbine) and breast cancer terms was used. The resulting references were then checked for duplication against those records already found. The BIOSIS-Web search covered the date range 1993 to 2001. The search was carried out on 13 August 2001 and identified 345 records.

(vinorelbine or navelbine) and breast*

ISTP: Web of Science (Internet <http://wos.mimas.ac.uk/>)

The Web of Science interface was used to search ISTP. A simple search combining the drug names and breast cancer terms was implemented. The ISTP search covered the date range 1990 to 2001. The search was carried out on 13 August 2001 and identified 49 records.

(vinorelbine or navelbine) and breast*

CCTR: Cochrane Library (CD-ROM 2001, issue 3)

The CCTR was searched to find completed trials. A relatively simple search was used, combining the drug names with terms for breast cancer. The search was carried out on 13 August 2001 and identified 51 records.

#1 BREAST-NEOPLASMS*:ME
#2 (BREAST* AND ((((CANCER*) or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
#3 (BREAST* AND ((ONCOLOG*) or CARCINOMA*))
#4 ((#1 or #2) or #3)
#5 VINORELBINE
#6 NAVELBINE
#7 (#5 or #6)
#8 (#4 and #7)

DARE: Cochrane Library (CD-ROM 2001, issue 3)

The DARE was searched at the same time as the CCTR, using the same strategy (see above). The searches were carried out on 13 August 2001 and identified no records.

NHS EED: Cochrane Library (CD-ROM 2001, issue 3)

The NHS EED was searched at the same time as the CCTR, using the same strategy (see above). The searches were carried out on 13 August 2001 and identified no records.

National Research Register (CD-ROM 2001, issue 2)

The National Research Register was searched to find further ongoing and completed trials. A relatively simple search strategy was used, combining the drug names and terms for breast cancer. The search was carried out on 13 August 2001 and identified 14 ongoing and 21 complete trials.

#1 BREAST-NEOPLASMS*:ME
#2 (BREAST* AND ((((CANCER*) or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
#3 (BREAST* AND ((ONCOLOG*) or CARCINOMA*))
#4 ((#1 or #2) or #3)
#5 VINORELBINE
#6 NAVELBINE
#7 (#5 or #6)
#8 (#4 and #7)

The search results from MEDLINE, EMBASE, CANCERLIT, BIOSIS-Web, ISTP and the CCTR were downloaded and imported into Endnote (ISI ReSearchSoft, USA) reference management software and duplicate records were deleted. The search results from the National Research Register were downloaded in full into a text file.

Appendix 3

Industry submission data from Pierre Fabre Ltd presented to NICE

Effectiveness data

The submission data were based on a literature review. Phase III and supportive Phase II trials were searched for (search strategy provided). Four Phase III studies were identified (Jones and colleagues, 1995,[38] Bonneterre and colleagues, 1998,[173] (referenced in the current review as the publication by Monnier and colleagues, 1998[92]), Blajman and colleagues, 1999[39] and Namer and colleagues, 2000 (referenced in the current review as the publication by Namer and colleagues, 1998[40]). All four RCTs had already been identified for inclusion in the current NICE review, however, some additional details were provided in the industry submission for all four trials. The extra details were minor except in the case of Namer and colleagues,[40] which had only been published as an abstract. The industry submission had extracted data from a full manuscript, which was reported to be 'in press'.

Industry-submitted safety data were compiled from more than one study, details of which were not given and, therefore, this information was not included in the initial review because it was unclear whether the studies used a randomised design.

Ninety-four Phase II studies were identified by the industry submission review. It was unclear whether any of these studies included a control group and, therefore, were not included in the initial review, unless they had already been identified from the literature searches as randomised Phase II trials. However, for the update review, all Phase II studies that included more that 14 participants and evaluated the use of vinorelbine as first-line therapy for ABC were included.

Economic data

The review submitted by industry included a search for economic evaluations (search strategy provided) and three studies were found (Launois and colleagues, 1996,[36] Leung and colleagues, 1999[37] and Martin and colleagues, 2000[136]). All three had previously been identified for inclusion in the current NICE review. One economic paper[136] was not considered to be a full economic evaluation and was published in French and, therefore, it did not meet the inclusion criteria for the review. Data from the remaining two economic evaluations[36,37] had been extracted for the current review using methods similar to those used in the industry submission. No additional information on these publications was, therefore, gained from the industry submission.

Appendix 4

Excluded studies

List of excluded studies from the initial searches

To be included in the initial review, studies had to fulfil all of the following criteria.

- The study design had to be an RCT or a full economic evaluation (CEA/CMA, CUA or CBA).
- The study must have evaluated vinorelbine (Navelbine) alone or in combination with other agents versus systemic therapy without vinorelbine.
- The study had to include individuals with breast cancer.
- The study had to include one of the following outcome measures: tumour response (including complete and partial response), progression-free survival, overall survival, symptom relief, QoL, adverse effects or costs.

Study	Study design	Intervention	Population	Comments
Aapro, 1997[94]	No	Yes	Yes	Non-systematic review
Abeloff, 1995[12]	No	Yes	Yes	Non-systematic review
Adenis *et al.*, 1996[101]	No	Yes	Yes	No comparison group, neoadjuvant therapy
Agostara *et al.*, 1994[102]	No	Yes	Yes	No comparison group, second-line therapy for MBC
Anderson and Cox, 2000[162]	No	Yes	Yes	Abstract of a systematic review, not enough details to be able to include study
Ardavanis *et al.*, 1998[75]	No	Yes	Yes	No comparison group, 38/45 received first-line chemotherapy for ABC, the results of whom were presented separately. The study is, therefore, included in the update review
Azim, 1996[103]	No	Yes	Yes	No comparison group, second-line therapy
Aziz *et al.*, 1999[104]	No	Yes	Yes	No comparison group, second-line therapy
Baldini *et al.*, 1996[105]	No	Yes	Yes	No comparison group, not stated if first- or second-line therapy for ABC
Baldini *et al.*, 1998[51]	No	Yes	Yes	No comparison group, first-line therapy for MBC and, therefore, included in the update review
Baltali *et al.*, 1996[43]	No	Yes	Yes	No comparison group, first-line therapy for MBC and, therefore, included in the update review
Barni *et al.*, 1994[106]	No	Yes	Yes	No comparison group, second-line therapy
Barth, 1999[161]	No	Yes	Yes	German language, description of drug and not a trial
Bercez *et al.*, 1997[193]	No	Yes	Yes	Abstract only, and did not appear to be a full economic analysis
Berdeaux *et al.*, 1997[163]	No	Yes	Yes	Critique of an included economic evaluation (Launois *et al.*, 1996)
Bergeron *et al.*, 1995[153]	No	Yes	No	Case reports, lung carcinoma
Blomqvist *et al.*, 1995[107]	No	Yes	Yes	Dose-escalating study with no comparison group. Not stated if first- or second-line therapy for MBC
Bonneterre *et al.*, 1998[66]	No	Yes	Yes	No comparison group, first-line therapy for MBC and, therefore, included in update review
Borguez *et al.*, 1999[108]	No	Yes	Yes	No comparison group, second-line therapy

continued

Study	Study design	Intervention	Population	Comments
Braud *et al.*, 1999[109]	No	Yes	Yes	No comparison group, neoadjuvant therapy
Brocksein *et al.*, 1996[110]	No	Yes	Yes	No comparison group, mainly second-line therapy (6/21 had first-line therapy for ABC)
Budman, 1997[194]	No	Yes	Yes	Non-systematic review
Budmann *et al.*, 1997[111]	No	Yes	Yes	Phase I trial with no comparison group and neurotoxic side-effects. Very little data presented on study design
Buonadonna *et al.*, 1997[112]	No	Yes	Yes	No comparison group, only 12/31 (39%) participants were treated with first-line therapy for MBC, the results of whom were presented separately
Burstein *et al.*, 1999[113]	No	Yes	Yes	No comparison group and ongoing, second-line therapy for MBC
Campisi *et al.*, 1999[114]	No	Yes	Yes	No comparison group. Anthracycline-resistant patients (prior treatment could be adjuvant or in metastatic setting, but numbers not reported). Results of first-line therapy not presented separately
Canobbio *et al.*, 1989[115]	No	Yes	Yes	No comparison group, 19/24 received first-line therapy for ABC, the results of whom were presented separately. This study is, therefore, included in the update review
Cardamakis and Ginopoulos, 1998[116]	No	Yes	Yes	Not a study, no effectiveness data
Carmichael *et al.*, 1997[95]	No	Yes	Yes	Overview of three Phase II uncontrolled studies
Chang *et al.*, 1996[117]	No	Yes	Yes	No comparison group, second-line therapy for MBC
Chang *et al.*, 1999[118]	No	Yes	Yes	No comparison group, only nine participants with breast cancer (eight had non-small cell lung cancer)
Chollett *et al.*, 1997[119]	No	Yes	Yes	No comparison group, neoadjuvant therapy
Cocconi *et al.*, 2000[120]	No	Yes	Yes	No comparison group, second-line therapy for MBC
Cole *et al.*, 1994[121]	No	Yes	Yes	No comparison group, only 9/15 received chemotherapy as first-line treatment for MBC
Colleoni *et al.,* 1997[155]	No	Yes	Yes	Dose-finding study – vinorelbine given in both arms, second-line therapy for ABC
Conti and Vici, 1998[96]	No	Yes	Yes	Non-systematic review, non-English language
Coudert, 1999[156]	No	Yes	Yes	All patients received vinorelbine and 5-fluorouracil, but were randomised to receive the vinorelbine at different times. Second-line therapy for MBC
Cure *et al.*, 1997[164]	No	Yes	Yes	French language, non-randomised, neoadjuvant therapy
de Matteis *et al.*, 2000[154]	No	Yes	Yes	Case reports of intestinal side-effects
Dieras *et al.*, 1991[122]	No	Yes	Yes	No comparison group, first-line chemotherapy for ABC and, therefore, included in the update review
Dieras *et al.*, 1996[73]	No	Yes	Yes	No comparison group, first-line chemotherapy for ABC and, therefore, included in the update review
Extra *et al.*, 1991[123]	No	Yes	Yes	No comparison group, first- and second-line chemotherapy for ABC, but not stated how many received first-line therapy and results not presented separately
Ezzat *et al.*, 1996[53]	No	Yes	Yes	No comparison group, first-line therapy for ABC and, therefore, included in the update review

continued

Study	Study design	Intervention	Population	Comments
Fabi *et al.*, 1995[124]	No	Yes	Yes	No comparison group, 29/33 received second-line chemotherapy for MBC
Ferrari *et al.*, 1999[125]	No	Yes	Yes	No comparison group, study population described as heavily pretreated
Froudarakis *et al.*, 1998[126]	No	Yes	Yes	No comparison group, second-line therapy for MBC
Fumoleau *et al.*, 1992[97]	No	Yes	Yes	Non-systematic review of two Phase II uncontrolled studies (first-line therapy for ABC)
Gaafar *et al.*, 1999[127]	No	Yes	Yes	No comparison group, neoadjuvant therapy
Galvez *et al.*, 1997[128]	No	Yes	Yes	No comparison group, unclear if first- or second-line chemotherapy for MBC
Garcia-Conde *et al.*, 1992[129]	No	Yes	Yes	No comparison group, first-line chemotherapy for ABC and, therefore, included in the update review
Gomez-Bernal *et al.*, 1999[130]	No	Yes	Yes	No comparison group. All participants had received previous therapy, but it was not stated if this was in adjuvant or palliative setting
Goss *et al.*, 1997[74]	No	Yes	Yes	Phase I study, no comparison group. First-line therapy for MBC and, therefore, included in the update review
Gralow *et al.*, 1999[131]	No	Yes	Yes	No comparison group. The median number of prior treatment regimens for MBC was one (n = 32)
Hegg *et al.*, 1996[132]	No	Yes	Yes	No comparison group, first-line treatment for MBC and, therefore, included in the update review
Hillner *et al.*, 1996[158]	No	No	Yes	Not a vinorelbine trial
Hochster *et al.*, 1994[133]	No	Yes	Yes	No comparison group, first-line treatment for MBC and, therefore, included in the update review
Hochster, 1995[98]	No	Yes	Yes	Non-systematic review
Hutton *et al.*, 1996[159]	No	No	Yes	Not a vinorelbine trial
Kornek *et al.*, 1996[134]	No	Yes	Yes	No comparison group, 18/29 participants received first-line chemotherapy for ABC, the results of whom were presented separately. This study was, therefore, included in the update review
Kornek *et al.*, 1996[152]	No	Yes	Yes	No comparison group, 24/36 evaluable participants received first-line chemotherapy for MBC, the results of whom were presented separately. This study was, therefore, included in the update review
Kornek *et al.*, 1999[135]	No	Yes	Yes	No comparison group, 19/27 evaluable participants received first-line chemotherapy for ABC, the results of whom were presented separately. This study was, therefore, included in the update review
Launois *et al*, 1997[189]	No	Yes	Yes	French language version of Launois *et al.*, 1996[36] (already included)
Lozano *et al.*, 1997[157]	No	Yes	Yes	Both groups received vinorelbine as an intervention (combination therapy). Included participants with ABC or non-small cell lung cancer. Not stated how many had breast cancer
Marchal *et al.*, 1995[190]	No	Yes	Yes	Not a full economic analysis. Retrospective cost analysis of consecutive cancer patients. Did not specifically set out to study vinorelbine or breast cancer but both were a feature. Spanish language

continued

Study	Study design	Intervention	Population	Comments
Martin *et al.*, 2000[136]	No	Yes	Yes	Descriptive, not a full economic evaluation
Martin, 1999[137]	No	Yes	Yes	No comparison group, second-line therapy for MBC
Masters *et al.*, 1997[138]	No	Yes	Yes	No comparison group, ongoing study with only seven participants recruited
Mlineritsch *et al.*, 1996[139]	No	Yes	Yes	No comparison group, 24/49 received two or three prior chemotherapy regimens. The results of first-line therapy for MBC were not presented separately
Mobus, 2000[100]	No	Yes	Yes	German language, non-systematic review
Morere *et al.*, 1999[151]	No	Yes	Yes	No comparison group, second-line therapy for MBC
Mustacchi *et al.,* 1994[140]	No	Yes	Yes	No comparison group, 12/28 participants received first-line chemotherapy for MBC, but the results were not presented separately
Nistico *et al.*, 1995[141]	No	Yes	Yes	No comparison group, results were based on 13/15 evaluable participants with ABC
Pawlicki *et al.*, 1996[142]	No	Yes	Yes	No comparison group. First-line therapy for ABC and, therefore, included in the update review
Pienkowski *et al.*, 1999[143]	No	Yes	Yes	No comparison group. All participants had been previously treated with chemotherapy, but it was not stated whether this was palliative or adjuvant therapy. Participants were described as being heavily pretreated
Pronzato *et al.*, 1996[145]	No	Yes	Yes	No comparison group, not known if participants received first- or second-line therapy for MBC
Pronzato *et al.,* 1999[144]	No	Yes	Yes	No comparison group, only 13/32 received first-line chemotherapy for ABC
Rodriguez *et al.*, 1999[146]	No	Yes	Yes	No comparison group, second-line therapy for MBC
Ruger *et al.*, 1995[147]	No	Yes	Yes	No comparison group, second-line chemotherapy in 13/22 participants. Data were not presented separately for first- and second-line therapy
Scheithauer *et al.*, 1994[148]	No	Yes	Yes	No comparison group, first-line therapy for ABC and, therefore, included in the update review
Schubert, 1995[195]	No	Yes	Yes	CEA that was presented as a conference abstract with very little details of the economic evaluation and no results
Spielmann *et al.*, 1992[99]	No	Yes	Yes	Non-systematic review of two Phase II uncontrolled studies. First-line therapy for ABC and, therefore, included in the update review
Spielmann *et al.,* 1994[49]	No	Yes	Yes	No comparison group, first-line therapy for ABC and, therefore, included in the update review
Spielmann, 1996[160]	No	Yes	Yes	French language, not a trial.
Taylor and Alberts, 1996[149]	No	Yes	Yes	No comparison group, second-line therapy for ABC
Zambetti *et al.*, 1997[150]	No	Yes	Yes	No comparison group, second-line therapy for MBC

For the purpose of this table, second-line therapy also denotes subsequent therapy (i.e. third-, fourth-, fifth-line therapy, etc.) for ABC/MBC

List of excluded studies from the update searches

To be included in the update review, studies had to fulfil all of the following criteria.

- The study design had to be a cohort study, case–control study or a case series. Studies must have recruited a minimum of 14 participants.
- The study must have evaluated vinorelbine (Navelbine) alone or in combination with other agents versus systemic therapy without vinorelbine.
- The study had to include individuals with ABC for which vinorelbine was used as first-line therapy.
- The study had to include one of the following outcome measures: tumour response (including complete and partial response), progression-free survival, overall survival, symptom relief, QoL, adverse effects or costs.

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Aapro, 1997[94]	No	Yes	Yes	Yes	Non-systematic review
Abeloff, 1995[12]	No	Yes	Yes	Yes	Non-systematic review
Abrahamova *et al.*, 1998[196]	Yes	Yes	No	Yes	Neoadjuvant therapy
Adams, 1994[197]	No	Yes	Yes	No	Laboratory-based study
Adams and Knick, 1992[198]	No	Yes	Yes	No	Laboratory-based study
Adenis *et al.*, 1995[199]	Yes	Yes	No	Yes	Not all participants had ABC (75 had stage II and 29 had stage III breast cancer)
Adenis *et al.*, 1996[101]	Yes	Yes	No	Yes	Neoadjuvant therapy
Anonymous, 1991[200]	No	Yes	Yes	Yes	Non-systematic review
Anonymous, 1995[201]	No	Yes	Yes	Yes	A discussion paper about a study conducted by other researchers (see Ibrahim *et al.*, 2001[57] in included studies section of this review) that was presented at a conference (Ibrahim *et al.*, 1995[202])
Anonymous, 1996[203]	No	Yes	Yes	Yes	Non-systematic review
Anonymous, 1997[204]	Yes	Yes	No	Yes	19/27 received first-line chemo-therapy for ABC, but the results were not presented separately. These were interim results that only included 13 evaluable participants
Ardavanis *et al.*, 1998[205]	Yes	Yes	No	Yes	Neoadjuvant therapy (locally ABC)
Baldini *et al.*, 1996[105]	Yes	Yes	No	Yes	Not stated if first- or second-line chemotherapy for ABC
Barni *et al.*, 1999[206]	Yes	Yes	No	Yes	Neoadjuvant therapy (locally ABC)
Bash-Babula *et al.*, 2001[207]	No	Yes	Yes	No	Laboratory-based study
Besenval *et al.*, 1989[208]	No	Yes	No	Yes	Overview with no separate data for first-line therapy for breast cancer
Blomqvist *et al.*, 1995[107]	Yes	Yes	No	Yes	Dose-escalating study. Not stated if first- or second-line therapy for MBC
Borguez *et al.*, 1999[108]	Yes	No	Yes	Yes	Second-line therapy for MBC
Botto *et al.*, 1998[209]	Yes	Yes	No	Yes	Second-line chemotherapy for MBC. Study compares the use of docetaxel with vinorelbine plus paclitaxel, but not reported to be randomised

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Bowen *et al.*, 1992[210]	Yes	Yes	No	Yes	Phase I study that included participants with non-small cell lung cancer and breast cancer
Braud *et al.*, 1999[109]	Yes	Yes	No	Yes	Neoadjuvant
Brocksein *et al.*, 1996[110]	Yes	Yes	No	Yes	Mainly second-line therapy (6/21 had first-line therapy for ABC)
Budman *et al.*, 1999[211]	Yes	Yes	No	Yes	Second-line therapy for inoperable or recurrent breast cancer
Buonadonna *et al.*, 1997[112]	Yes	Yes	No	Yes	Only 12/31 participants were treated with first-line therapy for MBC, the results of whom were presented separately
Burris *et al.*, 2000[212]	No	Yes	Yes	Yes	Non-systematic review
Burstein *et al.*, 1999[213]	Yes	Yes	No	Yes	First- and second-line therapy used, but insufficient data reported to distinguish between the two
Burstein *et al.*, 1999[113]	Yes	Yes	No	Yes	Only seven patients received first-line therapy for MBC, but results were presented separately for first- and second-line therapy
Cannizzaro *et al.*, 1995[214]	Yes	Yes	Yes	No	Pharmacokinetics data
Cany *et al.*, 1996[215]	Yes	Yes	No	Yes	Mainly second-line therapy (60%) and data on first-and second-line therapy were not presented separately
Cardamakis and Ginopoulos, 1998[116]	Yes	Yes	No	Yes	Discussion paper, no effectiveness data
Carmichael *et al.*, 1997[95]	No	Yes	Yes	Yes	Overview of three Phase II trials presented in an abstract
Cattan and Oberg, 1999[216]	Yes	Yes	No	Yes	A case study of vinorelbine-induced pulmonary oedema
Chadjaa *et al.*, 1992[217]	Yes	Yes	No	Yes	Only 11/20 participants received first-line therapy. Data on first- and second-line therapy were not presented separately
Chang *et al.*, 1995[218]	Yes	Yes	No	Yes	Only one patient with breast cancer (that received second-line chemotherapy)
Chang *et al.*, 1996[117]	Yes	Yes	No	Yes	Second-line therapy for MBC. Ongoing study with only nine participants recruited so far
Chang *et al.*, 1999[118]	Yes	Yes	No	Yes	Only nine participants with breast cancer (eight had non-small cell lung cancer)
Charrier *et al.*, 1997[219]	Yes	Yes	No	No	No effectiveness data
Charrier *et al.*, 1997[220]	Yes	Yes	No	Yes	Neoadjuvant and adjuvant therapy
Charrier *et al.*, 1998[221]	Yes	Yes	No	No	Mainly neoadjuvant therapy (3/15 (20%) received first-line therapy for MBC) and no effectiveness data
Charrier *et al.*, 1998[222]	Yes	Yes	No	No	Mainly neoadjuvant therapy (15/43 (35%) received first-line therapy for MBC) and no effectiveness data

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Charrier *et al.*, 2000[223]	Yes	Yes	No	No	Mainly neoadjuvant therapy (5/43 (19%) received first-line therapy for MBC) and no effectiveness data
Chevallier *et al.*, 1996[224]	No	Yes	No	Yes	Interim findings that only included 13 evaluable participants for response data. Only 15/24 (63%) participants were reported to have received first-line therapy for ABC
Chollet *et al.*, 1997[225]	Yes	Yes	No	Yes	Neoadjuvant therapy
Chollet *et al.*, 1997[226]	Yes	Yes	No	Yes	Neoadjuvant therapy
Cohen *et al.*, 2000[227]	Yes	Yes	No	Yes	Not clear how many participants received chemotherapy as first line for ABC. 15/18 had received one or more prior chemotherapy regimens
Cole *et al.*, 1994[121]	Yes	Yes	No	Yes	Only 9/15 received chemotherapy as first line for MBC
Colleoni *et al.*, 1995[228]	Yes	Yes	No	Yes	Only presented the results of ten participants with side-effects. Only 45/135 included participants had breast cancer
Colleoni *et al.*, 1996[229]	Yes	Yes	No	Yes	Only eight participants with breast cancer, the remaining 18 had lung cancer
Colleoni *et al.*, 1997[230]	No	Yes	No	Yes	Only six participants (evaluable for response) with MBC (20 with lung cancer), and it was not possible to ascertain if chemotherapy was used as first or second line
Colleoni *et al.*, 1997[155]	Yes	Yes	No	Yes	Second-line therapy for ABC
Colleoni, 1997[231]	Yes	Yes	No	Yes	Second-line therapy for MBC
Colleoni *et al.*, 1998[232]	Yes	Yes	No	Yes	Neoadjuvant therapy. Included two groups, one that received vinorelbine and one that did not. No separate data presented for the vinorelbine group
Colleoni *et al.*, 1998[233]	Yes	Yes	No	Yes	Neoadjuvant therapy. Included various combinations of chemo-therapy drugs. Outcomes were not presented according to different chemotherapy regimens
Colleoni *et al.*, 1999[234]	Yes	Yes	No	Yes	Neoadjuvant therapy
Colleoni *et al.*, 2000[235]	Yes	Yes	No	Yes	Neoadjuvant therapy
Coudert, 1999[156]	Yes	Yes	No	Yes	Second-line therapy for MBC
Craig *et al.*, 1993[236]	Yes	Yes	No	Yes	Study included 14 participants with either non-small cell lung cancer or breast cancer
Crivellari *et al.*, 1999[237]	Yes	Yes	No	Yes	Not stated if there were any participants who received first-line therapy for MBC (anthracycline-resistant). Median number of chemotherapy lines in metastatic phase was three

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Culine *et al.*, 1998[238]	No	Yes	Yes	No	*In vitro* study
Culine *et al.*, 1999[239]	No	Yes	Yes	No	*In vitro* study
Cure *et al.,* 1997[164]	Yes	Yes	No	Yes	French language, neoadjuvant therapy
Daldoul *et al.*, 1999[240]	Yes	Yes	No	Yes	First-line chemotherapy in only 13/33 patients with MBC
de Boer, 2000[241]	Yes	Yes	No	Yes	Second-line therapy for ABC
de Braud *et al.*, 1995[242]	No	Yes	No	No	Nine patients with ABC and only report on extrapyramidal-like reaction
de Matteis *et al.*, 2000[154]	No	Yes	No	Yes	Case reports of intestinal side-effects. Not clear if chemotherapy was first line for MBC
Delecroix *et al.*, 1997[243]	Yes	No	No	Yes	A study of anthracycline therapy (second line) in patients with MBC who had been previously treated with taxotere (alone or in combination with vinorelbine)
Deplanque *et al.*, 1998[244]	Yes	Yes	No	Yes	Not stated if first- or second-line therapy for MBC
Dittrich *et al.*, 1994[245]	No	Yes	No	Yes	Only eight patients and second-line therapy for MBC
Ellis and Smith, 1996[246]	No	Yes	No	Yes	A non-systematic review of neoadjuvant therapy
Ellis *et al.*, 1998[247]	Yes	Yes	No	Yes	Not stated if chemotherapy was first line for MBC. Median number of previous regimens was one (range 1–3) and all participants had received prior treatment with anthracycline
Ellis *et al.*, 1999[248]	Yes	Yes	No	Yes	Second-line chemotherapy for MBC in 22/32 (69%) of participants. Data for first-line therapy were not presented separately
Escudero *et al.*, 1998[249]	Yes	Yes	No	Yes	Not stated if any of the participants received chemotherapy as first line for MBC (which was anthracycline-resistant)
Extra *et al.*, 1991[123]	Yes	Yes	No	Yes	First- and second-line chemo-therapy for ABC. Not stated how many received first-line therapy and results were not presented separately
Ferrero *et al.*, 1997[250]	Yes	Yes	No	Yes	Neoadjuvant therapy
Ferrero *et al.*, 1997[251]	Yes	Yes	No	Yes	Neoadjuvant therapy
Fety *et al.*, 1996[252]	Yes	Yes	Yes	No	Pharmacokinetics data
Frassoldati, 1999[253]	No	Yes	No	Yes	Only 11 patients (with untreated ABC)
Fumoleau, 1990[254]	No	Yes	Yes	Yes	Non-systematic review of four Phase II studies presented as an abstract

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Fumoleau *et al.*, 1992[97]	No	Yes	Yes	Yes	Non-systematic review of two Phase II studies investigating first-line therapy for ABC where the data from the two studies were combined
Fumoleau *et al.*, 1996[255]	No	Yes	No	Yes	Preliminary results (first-line therapy for MBC). Although 22 participants entered the study, only seven were evaluable for response
Fumoleau *et al.*, 1996[256]	Yes	Yes	No	Yes	Preliminary results (presented as an abstract) with only seven participants evaluable for response. First-line chemotherapy for MBC
Fumoleau *et al.*, 1999[257]	Yes	Yes	No	Yes	Second-line chemotherapy for ABC
Gaafar *et al.,* 1999[127]	Yes	Yes	No	Yes	Neoadjuvant therapy
Galvez *et al.*, 1997[128]	Yes	Yes	No	Yes	Not stated if chemotherapy was first or second line for MBC. All participants had received previous anthracycline therapy
Gandia *et al.*, 1997[258]	Yes	Yes	No	No	First-line therapy for MBC. Only information on three participants was presented and no response data were given
Garcia Carbonero *et al.*, 1998[259]	Yes	Yes	No	No	Only 8/33 received first-line chemotherapy for MBC
Gardillou *et al.*, 1999[260]	No	Yes	Yes	No	Single case and no effectiveness data
Gardin *et al.*, 1997[261]	Yes	Yes	No	Yes	Second-line therapy for MBC
Gardin *et al.*, 1998[262]	Yes	Yes	No	Yes	All participants had received prior anthracycline-containing chemotherapy, but it was not stated in what setting, i.e. as adjuvant therapy or for ABC
Gasco *et al.*, 1997[263]	Yes	Yes	No	Yes	Second-line therapy for MBC
Gasmi *et al.*, 1999[264]	Yes	Yes	No	Yes	Neoadjuvant therapy
Gasparini *et al.,* 1994[265]	Yes	Yes	No	Yes	Second-line chemotherapy for ABC/MBC
Gebbia *et al.*, 1999[266]	No	Yes	Yes	Yes	Only 11 patients, and not stated if participants had received previous therapy for their MBC
Gomez-Bernal *et al.*, 1999[130]	Yes	Yes	No	Yes	Not stated if chemotherapy was given as first or second line for MBC. All participants had received previous anthracycline therapy
Gorzegano *et al.*, 2000[267]	Yes	Yes	No	Yes	Second-line chemotherapy for ABC
Gralow *et al.*, 1999[131]	Yes	Yes	No	Yes	Not stated if any participants received chemotherapy as first line for MBC. The median number of prior treatment regimens for MBC was one (n = 32)
Graif *et al.*, 1996[268]	Yes	Yes	No	Yes	Second-line chemotherapy for MBC
Gunel *et al.*, 1999[269]	Yes	Yes	No	Yes	All had received previous anthracycline-containing therapy, but it was not stated if this was in adjuvant or palliative setting

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Gunel *et al.*, 2000[270]	Yes	Yes	No	Yes	Second-line chemotherapy for ABC
Harris Spiridonidis, 1992[271]	No	Yes	Yes	Yes	Non-systematic review
Havlin, 1995[272]	Yes	Yes	No	No	Not clear if first- or second-line chemotherapy for MBC (inclusion criterion was no more than two previous regimens for MBC). No results were presented
Hoff *et al.*, 1998[273]	Yes	Yes	Yes	No	No effectiveness data, only a description of 4/60 participants who had hand–foot syndrome. Not stated if used as first-line therapy for MBC
Hortobagyi, 1996[274]	No	Yes	Yes	Yes	Non-systematic review
Ibrahim *et al.*, 1996[275]	No	Yes	Yes	Yes	Only 13 patients (first-line therapy for MBC)
Ibrahim *et al.*, 1996[276]	Yes	Yes	No	Yes	Second-line therapy for MBC
Ibrahim *et al.*, 1998[277]	Yes	Yes	No	Yes	Second-line therapy for MBC
Ibrahim *et al.*, 1999[278]	Yes	Yes	No	Yes	Second-line therapy for MBC
Ibrahim *et al.*, 2000[279]	No	Yes	Yes	Yes	Three case reports of ischaemic colitis associated with docetaxel plus vinorelbine therapy
Ionta *et al.*, 2001[280]	Yes	Yes	No	Yes	Neoadjuvant treatment, no effectiveness data were reported
Jaremtchuk *et al.*, 1997[281]	Yes	Yes	No	Yes	7/15 participants received second-line therapy, results of first- and second-line therapy were not reported separately
Jiang *et al.*, 1996[282]	Yes	Yes	No	Yes	Chinese language. Study included 14 participants with refractory MBC, but not known if first- or second-line chemotherapy
Joel, 1995[283]	No	Yes	Yes	Yes	Non-systematic review
Kardinal *et al.*, 1995[284]	Yes	Yes	No	Yes	First-line chemotherapy for ABC in only 11 participants
Kariya *et al.*, 2000[285]	Yes	Yes	No	Yes	Japanese language and only 7 participants included
Kayitalire *et al.*, 1993[286]	Yes	Yes	No	Yes	Only 12 participants received first-line chemotherapy for MBC. This is an interim report of the study reported by Llombart Cussac, 1998,[65] which was included in the review
Kennedy, 1996[287]	Yes	Yes	No	Yes	Not stated how many received first- or second-line chemotherapy. Inclusion criterion was a maximum of one prior chemotherapy regimen for MBC
Koriech and Mughal, 1995[288]	Yes	Yes	No	Yes	Ongoing study with only 12 participants recruited to date. Not stated if first- or second-line chemotherapy for ABC

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Kourousis *et al.*, 1998[289]	Yes	Yes	No	Yes	Second-line chemotherapy for ABC
Laufman *et al.*, 1998[290]	Yes	Yes	No	Yes	Included patients with advanced malignancies, but the number with breast cancer was not stated
Leonard and Anderson, 2000[291]	No	Yes	Yes	Yes	Systematic review of docetaxel plus paclitaxel plus vinorelbine presented as an abstract
Lepine *et al.*, 1999[292]	Yes	Yes	No	Yes	Not stated how many received first-line therapy for MBC (n = 16). French language
Linke *et al.,* 2000[293]	Yes	Yes	No	Yes	Not stated in abstract if chemotherapy used as first or second line for ABC and MBC. Czech language
Livingston *et al.*, 1995[294]	Yes	Yes	No	Yes	Only 12 participants with refractory MBC
Livingston *et al.*, 1997[295]	Yes	Yes	No	Yes	Mainly second-line therapy for refractory MBC (data for first-line therapy were not presented separately)
Lokich *et al.*, 1999[296]	Yes	Yes	No	Yes	Only 3/27 participants had breast cancer
Lombardi *et al.*, 2000[297]	Yes	Yes	No	Yes	Not stated if first- or second-line chemotherapy. Participants described as being heavily pretreated
Louboutin *et al.*, 1996[298]	Yes	Yes	No	Yes	Not clear if first- or second-line chemotherapy. No effectiveness data were presented, only data on adverse events
Lozano, 1997[157]	Yes	Yes	No	Yes	RCT where both groups received vinorelbine. 8/16 participants were treated with first-line chemo-therapy for MBC, but the results were not presented separately
Maisano *et al.*, 1997[299]	Yes	Yes	No	Yes	Only 19/41 participants had breast cancer (results were not presented separately) and all of whom received different combinations of vinorelbine
Martin *et al.*, 1998[300]	Yes	Yes	No	Yes	Second-line therapy for MBC
Martin *et al.*, 1998[301]	Yes	Yes	No	Yes	Only 9/33 received first-line chemotherapy for MBC
Martin, 1999[137]	Yes	Yes	No	Yes	Second-line therapy for MBC
Marty *et al.*, 1989[302]	Yes	Yes	No	Yes	Second-line therapy for ABC
Masters *et al.*, 1997[138]	Yes	Yes	No	Yes	Ongoing study with only seven participants recruited to date
McGuirt *et al.*, 1996[303]	Yes	Yes	No	Yes	Not stated if participants received first-line chemotherapy for MBC. Anthracycline- and taxane-refractory MBC
Michelotti *et al.*, 1996[304]	Yes	Yes	No	Yes	Only 8/34 received first-line therapy for ABC

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Michelotti, 1996[305]	Yes	Yes	No	Yes	Only 2/37 participants received first-line chemotherapy for MBC
Michl *et al.*, 1992[306]	Yes	Yes	No	Yes	Second-line therapy for MBC
Minchella *et al.*, 1999[307]	Yes	Yes	No	Yes	Neoadjuvant therapy
Minchella *et al.*, 1999[308]	Yes	Yes	No	Yes	Only 8/35 participants had ABC
Mlineritsch *et al.*, 1996[139]	Yes	Yes	No	Yes	25/49 participants were reported to have been chemotherapy-naive for whom the results were not reported separately (24 patients had received two or three prior chemotherapy regimens)
Moiseyenko *et al.*, 1999[309]	Yes	Yes	No	Yes	Not stated if chemotherapy was first or second line for MBC. Participants were described as having heavily pretreated anthracycline-resistant MBC
Morere *et al.*, 1999[151]	Yes	Yes	No	Yes	Second-line therapy for MBC
Mouret-Reynier *et al.*, 1999[310]	Yes	Yes	No	Yes	Neoadjuvant therapy
Mustacchi *et al.*, 1994[140]	Yes	Yes	No	Yes	12/28 participants received first-line chemotherapy for MBC, but the results were not presented separately
Mustacchi *et al.*, 1999[311]	Yes	Yes	No	Yes	12/23 participants received first-line chemotherapy for MBC
Mustafa *et al.*, 1999[312]	Yes	Yes	No	Yes	Only 12/32 received vinorelbine as first-line chemotherapy for MBC
Niitani *et al.*, 1994[313]	Yes	Yes	No	Yes	Japanese language. Various types of tumours included
Nistico *et al.*, 1998[314]	Yes	Yes	No	Yes	Neoadjuvant therapy
Nistico, 1995[141,179]	Yes	Yes	No	Yes	Results were based on 13/15 evaluable participants with ABC
Nistico *et al.*, 1995[315]	Yes	Yes	No	Yes	Not stated if chemotherapy was first or second line. All participants had received previous therapy
Nistico *et al.*, 2000[316]	Yes	Yes	No	Yes	Only 6/40 received first-line chemotherapy for MBC
Nole *et al.*, 1996[317]	Yes	Yes	No	Yes	Not stated if first- or second-line chemotherapy for MBC
Nole *et al.*, 1997[318]	Yes	Yes	No	Yes	5/46 of the participants received second-line therapy for MBC, the results of whom were not presented separately
Nole *et al.*, 1998[319]	Yes	Yes	No	Yes	Second-line therapy for MBC
Nole *et al.*, 1999[320]	Yes	Yes	No	Yes	Neoadjuvant therapy, only 2/39 participants had ABC
Nole *et al.*, 2000[321]	Yes	Yes	No	Yes	26/33 participants received second-line therapy for MBC
O'Shaughnessy *et al.*, 1999[322]	No	Yes	Yes	Yes	Non-systematic review

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Ozguroglu *et al.*, 1999[323]	Yes	Yes	No	Yes	Not stated how many received first- or second-line chemotherapy for refractory MBC
Pan *et al.*, 2000[324]	Yes	Yes	No	Yes	Japanese language. Unclear whether first- or second-line chemotherapy for ABC
Peacock *et al.*, 1998[325]	Yes	Yes	No	Yes	Only 7/17 patients had breast cancer
Pienkowski *et al.*, 1999[143]	Yes	Yes	No	Yes	All participants had been previously treated with chemotherapy, but it was not stated whether this was palliative or adjuvant. Patients were described as being heavily pre-treated and, therefore, chemo-therapy was likely to be second line
Pienkowski *et al.*, 2000[326]	Yes	Yes	No	Yes	Second-line therapy for MBC
Pronzato *et al.*, 1996[145]	Yes	Yes	No	Yes	Not known if participants received first- or second-line therapy for MBC
Pronzato *et al.*, 1997[327]	Yes	Yes	No	Yes	Only 10/25 participants received first-line chemotherapy for MBC
Pronzato *et al.*, 1998[328]	Yes	Yes	No	Yes	Only ten participants received first-line therapy for MBC
Pronzato *et al.*, 1999[144]	Yes	Yes	No	Yes	Only 13/32 received first-line chemotherapy for ABC
Provencio *et al.,* 1999[329]	Yes	Yes	No	Yes	20/24 participants had received previous chemotherapy, but it was not stated if this was palliative. Patients were described as being heavily pretreated
Queiber and Doss, 1990[330]	No	Yes	Yes	Yes	Two Phase II studies (of untreated participants with non-small cell lung cancer and breast cancer) were discussed as an abstract, but no results were presented
Raderer *et al.*, 1996[331]	Yes	Yes	No	Yes	A case report
Ranuzzi *et al.*, 1996[332]	Yes	Yes	No	Yes	Second-line therapy for ABC
Ray Coquard *et al.*, 1998[333]	Yes	Yes	No	Yes	Second-line therapy for MBC
Ray Coquard *et al.*, 1995[334]	Yes	Yes	No	Yes	Not stated if first- or second-line chemotherapy. 56/59 participants had received previous anthracycline or taxane
Robieux *et al.*, 1995[335]	Yes	Yes	No	No	Not stated if first- or second-line chemotherapy for ABC. No effectiveness data presented (pharmacokinetics data)
Robieux *et al.*, 1995[336]	Yes	Yes	No	No	No effectiveness data presented (pharmacokinetics data)
Saeki *et al.*, 2000[337]	?	Yes	?	?	Japanese language. May be a review
Shamseddine *et al.*, 1999[338]	Yes	Yes	No	Yes	Only 5/23 received first-line chemotherapy for MBC
Shparyk, 1997[339]	Yes	Yes	No	No	Neoadjuvant therapy and no primary data

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Sorio *et al.*, 1997[340]	Yes	Yes	No	Yes	13/25 had been pretreated with one or two chemotherapy regimens
Tagliabue *et al.*, 1999[341]	Yes	Yes	No	Yes	Not stated if participants received first- or second-line chemotherapy for MBC. All participants were reported to have received previous anthracycline with or without taxanes, but it was not stated in what setting
Tamelini *et al.*, 1998[342]	Yes	Yes	No	Yes	Second-line or subsequent therapy for ABC
Tassinara *et al.*, 1997[343]	Yes	Yes	No	Yes	A discussion of acute dyspnoea as a side-effect of vinorelbine
Taylor and Alberts, 1996[149]	Yes	Yes	No	Yes	Second-line therapy for ABC
Terzoli *et al.*, 1995[344]	Yes	Yes	No	Yes	Preliminary results. Only 9/15 previously untreated participants with ABC were evaluable
Terzoli *et al.*, 1996[345]	Yes	Yes	No	Yes	Second-line chemotherapy for ABC
Terzoli *et al.,* 1999[346]	Yes	Yes	No	Yes	Not stated if chemotherapy was given as first or second line for ABC. Participants were described as being heavily pretreated
Tominaga and Nomura, 1994[347,348]	Yes	Yes	No	Yes	Japanese language. Phase II study of vinorelbine in ABC or recurrent breast cancer
Tominaga *et al.*, 1998[349]	Yes	Yes	No	Yes	Not stated if first- or second-line chemotherapy for ABC
Tortoriello *et al.*, 1998[350]	Yes	Yes	No	Yes	Second-line therapy for MBC
Toussaint *et al.*, 1994[28]	Yes	Yes	No	Yes	Only 20/46 received chemotherapy as first line for MBC. The results were not presented separately for these participants
Tres *et al.*, 1998[351]	Yes	Yes	No	Yes	Participants had anthracycline-resistant MBC. It was not stated if they received first- or second-line chemotherapy
Tresca *et al.*, 1990[352]	Yes	Yes	No	Yes	Probably second-line therapy. It was not stated how many participants received second-line therapy, however, one of the inclusion criterion was "no more than one previous chemotherapy regimen for MBC"
Tueni *et al.*, 1990[353]	Yes	Yes	No	Yes	Included patients with various solid tumours (n = 16). It was not stated how many had breast cancer
van Cantfort *et al.*, 1989[354]	Yes	Yes	No	No	Only two patients and no effectiveness data presented
van Praagh *et al.*, 1995[355]	Yes	Yes	No	Yes	Neoadjuvant therapy
Variol, 1996[356]	Yes	Yes	Yes	No	Pharmacokinetics data
Vici *et al.,* 1996[357]	Yes	Yes	No	Yes	Second-line therapy for ABC

continued

Study	Study design	Intervention	First-line therapy for ABC*	Outcome measures	Comments
Vogel *et al.*, 1994[358]	Yes	Yes	No	Yes	Second analyses of data from two multicentre studies. Not stated if chemotherapy was first line for ABC
Wang *et al.*, 2000[359]	Yes	Yes	Yes	Yes	Japanese language. Not all participants received first-line therapy, but results appeared to have been presented separately
Wei *et al.*, 2000[360]	Yes	Yes	No	Yes	Included patients with various tumours, of which only five had breast cancer. Japanese language
Weiselberg *et al.*, 1996[361]	Yes	Yes	No	Yes	Only ten evaluable participants and not stated if they received first-line therapy for MBC
Weiss and Wellens, 1999[362]	Yes	Yes	No	Yes	Not stated if first- or second-line chemotherapy for ABC
Willey *et al.*, 1998[363]	Yes	Yes	No	Yes	Only 12 participants were enrolled, and not stated if they received first-line therapy for MBC
Zambetti *et al.*, 1999[364]	Yes	Yes	No	Yes	Neoadjuvant therapy
Zelek *et al.*, 1999[365]	Yes	Yes	No	Yes	Second-line therapy for ABC

For the purpose of this table, second-line therapy also denotes subsequent therapy (i.e. third-, fourth-, fifth-line therapy, etc.) for ABC/MBC

* *Studies that failed one of the first two inclusion criteria (e.g. reviews that have "No" inserted for study design or intervention) had "Yes" inserted for this criterion if they included ABC, which may not necessarily have used first-line treatment. However, studies that passed the first two criteria (study design and intervention) must also have included the use of vinorelbine as first-line therapy for ABC for inclusion in the review*

Appendix 5

Quality checklists

Studies of clinical effectiveness

RCTs were assessed using the following criteria, based on Centre for Reviews and Dissemination Report 4:[69]

(1) Was the method used to assign participants to the treatment groups really random? (Computer generated random numbers and random number tables were accepted as adequate, whilst inadequate approaches included the use of alternation, case record numbers, birth dates or days of the week.)
(2) Was the allocation of treatment concealed? (Concealment was deemed adequate where randomisation was centralised or pharmacy-controlled, or where the following were used: serially numbered containers, on-site computer-based systems where assignment was unreadable until after allocation, other techniques with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches included 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 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 ITT analysis included?

Case series were assessed according to the following criteria, based on Centre for Reviews and Dissemination Report No. 4:[69]

(1) Was the study based on a representative sample selected from a relevant population?
(2) Were the criteria for inclusion explicit?
(3) Did all individuals enter the survey at a similar point in their disease progression?
(4) Was the follow-up long enough for important events to occur?
(5) Were outcomes assessed using objective criteria or was blinding used?
(6) If comparisons of subseries were being made, was there sufficient description of the series and the distribution of prognostic factors?

Items were graded in terms of Yes (item properly addressed), No (item not properly addressed), Partially (item partially addressed), Unclear (item unclear or not enough information) or NA (not applicable).

Studies of cost-effectiveness

Studies of cost-effectiveness were assessed using the following criteria, based on the checklist developed by Drummond and Jefferson, 1996:[366]

Study question

(1) The viewpoint(s) of the analysis were clearly stated and justified (provider institution, individual clinician, professional organisation, patient or patient group, purchaser or healthcare or society).

Selection of alternatives

(2) Relevant alternatives were compared.
(3) The alternatives being compared were clearly described (who did what, to whom, where and how often).

(4) The rationale for choosing the alternative programmes or interventions compared was stated.

Form of evaluation

(5) The choice of form of economic evaluation was justified in relation to the questions addressed (CBA – whether benefits were greater than costs for one intervention; CMA – if effects were equal, what was less costly; CEA – if costs and effects varied; CUA – best way to spend a given budget).

Effectiveness data

(6) The source(s) of effectiveness estimates used were stated (single study, selection of studies, systematic review, Delphi panel).
(7) The source(s) of effectiveness estimates were graded as A, B, C or D according to the grading system developed by members of the NHS R&D Centre for Evidence-Based Medicine[184] (see appendix 11).
(8) Details of the method of synthesis or meta-analysis of estimates were given (if based on an overview of a number of effectiveness studies).

Benefit measurement and valuation

(9) The primary outcome measure(s) for the economic evaluation were clearly stated (e.g. cases detected, life-years, QALYs, willingness to pay).
(10) Methods to value health states and other benefits were stated (e.g. time trade off, standard gamble, willingness to pay, contingent valuation).
(11) Details of the individuals from whom valuations were obtained were given (e.g. patients, members of the public, healthcare professionals).

Costing

(12) Quantities of resources were reported separately from their unit costs (e.g. days in hospital).
(13) Methods for estimation of quantities were described.
(14) The relevance of productivity changes to the study question was discussed.
(15) Productivity changes (if included) were reported separately.
(16) Currency and price data were reported.
(17) Details of adjustments for inflation or currency conversion were given.

Modelling

(18) Details of any model used were given (e.g. decisions tree model, epidemiology model, regression model).
(19) The choice of model used and the key parameters on which it was based were justified.

Adjustments for timing of costs and benefits

(20) The time-frame of costs and benefits was stated.
(21) The discount rate(s) were stated.
(22) The choice of rate was justified.
(23) A convincing explanation was given if cost or benefits were not discounted.

Allowance for uncertainty

(24) Details of statistical tests and CIs were given for stochastic data.
(25) The approach to sensitivity analysis was given (e.g. multivariate, univariate, threshold analysis)
(26) The choice of variables for sensitivity analysis was justified.
(27) The ranges over which the variables were varied were stated.

Presentation of results

(28) Incremental analysis was reported.
(29) Major outcomes were presented in a dissaggregated as well as aggregated form.
(30) Applicable to the NHS setting.

Items were graded in terms of Yes (item properly addressed), No (item not properly addressed), Partially (item partially addressed), Unclear (item unclear or not enough information) or NA (not applicable).

Appendix 6

Included vinorelbine RCTs

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
Blajman *et al.*, 1999[39] (interim findings were pubished as abstracts by Blajman *et al.*, 1993[168] and Blajman *et al.*, 1996[169]) ***Study design*** Multicentre Phase III RCT ***Method of randomisation*** Not stated ***Length of follow-up*** 60 months ***Follow-up time*** Outcome 1: 60 months Outcome 2: 60 months Outcome 3: 60 months	***Number of participants*** 177 (170 evaluable participants; recruited from April 1991 to July 1994) ***Type of breast cancer*** Recurrent breast cancer or MBC (stage M1) ***Age*** Overall: median = 53–54 years (range 28–71) Vinorelbine plus doxorubicin: median = 53 years (range 28–71) FAC: median = 54 years (range 30–71) ***Inclusion criteria*** Histological evidence of breast carcinoma with recurrent or metastatic disease. Aged ≤ 70 years. Performance status (WHO scale) of ≤ 2. Progressive disease with measurable or assessable lesions. Patients who had received adjuvant treatment with or without anthracyclines were eligible if they were disease-free for ≥ 6 months after completing that treatment. Patients who had received hormones as adjuvant therapy or for metastatic disease were included only with clear evidence of progression. Blood counts had to be within normal limits (white blood cells ≥ 3000/mm^2, granulocyte count ≥ 1500/mm^2, bilirubin < 1.5 mg/dl, prothrombin time > 70% and creatinine < 2 mg/dl) ***Exclusion criteria*** Patients were excluded if they had a history of preexisting heart disease, including clinical or echocardiogram signs of cardiac failure or coronary artery disease, left ventricular hypertrophy, left bundle branch block, right bundle branch block with left anterior or posterior hemiblock and left ventricular ejection fraction < 70% measured by echocardiography. Patients with a history of other malignancy (except for skin carcinoma or carcinoma *in situ* of the cervix), active infection or signs of leptomeningeal and brain involvement were excluded ***Previous treatment*** There was an imbalance between the vinorelbine plus doxorubicin and FAC groups in the number of patients who had received previous adjuvant chemotherapy (44 (52%) in the vinorelbine plus doxorubicin group versus 21	***Type of therapy*** First line ***Intervention*** FAC (*n* = 85) **Dosage** Doxorubicin 50 mg/m^2 i.v. plus 5-fluorouracil 500 mg/m^2 i.v. plus cyclophosphamide 500 mg/m^2 on day 1, repeated every 21 days **Number of cycles** Median = 5 (range 1–10) ***Comparator*** Vinorelbine plus doxorubicin (*n* = 85) **Dosage** Vinorelbine 25 mg/m^2 i.v. on days 1 and 8 plus doxorubicin 50 mg/m^2 i.v. on day 1, repeated every 21 days **Number of cycles** Median = 4 (range 1–10)	***Withdrawals*** Seven participants could not be assessed (four were considered lost to follow-up immediately after inclusion, one had received previous treatment for metastatic disease, one received vinorelbine plus epirubicin instead of vinorelbine plus doxorubicin and one received intensive chemotherapy for bone marrow transplant) ***Adverse effects*** Toxicity was assessed using WHO criteria every 21 days. The trial monitor visited each centre to check every patient file with the investigator Of those that received vinorelbine plus doxorubicin, 46% had (WHO) grade 1–2 neutropenia and 7% experienced grade 3–4 neutropenia. In the FAC group, the respective percentages were 51 and 7%. No patient in the vinorelbine plus doxorubicin group had grade 3–4 thrombocytopenia compared with 2% in the FAC group. Anaemia was not reported. Cardiac toxicity was more common in the FAC group (p = 0.029), with 11% of patients reporting grades 1 and 2 compared with 2% in the vinorelbine plus doxorubicin group. Constipation was more common with vinorelbine plus doxorubicin (27 versus 3% reporting grade 1 or above, p = 0.0002) than in the FAC group. Peripheral neuropathy was more common with vinorelbine plus doxorubicin	***Author's conclusions*** The efficacy of the two drug regimens studied was very similar. There was no excess of grade 3–4 toxicity with vinorelbine plus doxorubicin. Vinorelbine plus doxorubicin may be more active in a subset of patients with visceral metastatic disease, particularly liver involvement ***Other comments*** The reason for patients not to be included in the evaluation was not broken down by randomisation group, nor was the original number randomised to intervention or control group given. Analysis did not include the seven participants that were not assessed For the outcome measures of survival, duration of response and time to progression, the imbalance between treatment groups (with regards to previous chemotherapy treatment) was adjusted for in the analysis (vinorelbine plus doxorubicin and FAC were found to be equally effective). It was not stated how this was done (e.g. using multivariate analysis) For time-to-event outcome measures, the actual size of the effect (the difference between the treatment groups) with CIs were not presented, although Cox HRs were reported to have been used. The authors only report the extent to which the difference is significant (p values) Allocation was not reported to have been concealed and it was not stated if blinding had been undertaken. Participants were randomised in two groups in cohorts of four patients (e.g. A-B-A-B), which means that after the randomisation of two or three participants it would have been possible to guess what intervention the next randomised participant would be allocated. This could lead to selection bias Vinorelbine plus doxorubicin appeared to be slightly more toxic than FAC, except for cardiac toxicity, which was slightly reduced in the FAC group compared with the vinorelbine plus doxorubicin group

continued

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
contd **Blajman *et al.*, 1999**[39] (interim findings were pubished as abstracts by Blajman *et al.*, 1993[168] and Blajman *et al.*, 1996[169])	(25%) in the FAC group; $p = 0.00047$). The numbers that had received prior hormonal therapy were 36 (42%) with vinorelbine plus doxorubicin and 46 (54%) with FAC, and prior radiotherapy were 55 (65%) with vinorelbine plus doxorubicin and 46 (54%) with FAC ***Other factors*** **Pre/postmenopausal** Premenopausal: 26(31%) with vinorelbine plus doxorubicin versus 20 (24%) with FAC Postmenopausal: 59 (69%) with vinorelbine plus doxorubicin versus 65 (76%) with FAC **Hormone receptor status** Positive: 19 (22%) with vinorelbine plus doxorubicin versus 20 (23%) with FAC Negative: 18 (21%) with vinorelbine plus doxorubicin versus 9 (11%) with FAC Unknown: 48 (57%) with vinorelbine plus doxorubicin versus 48 (66%) with FAC **Tumour involvement** Skin, bone, lymph nodes: 37 with vinorelbine plus doxorubicin versus 43 with FAC Liver only: 21 with vinorelbine plus doxorubicin versus 16 with FAC Lung only: 22 with vinorelbine plus doxorubicin versus 22 with FAC Lung and liver: 5 with vinorelbine plus doxorubicin versus 4 with FAC **Number of sites** One: 13 with vinorelbine plus doxorubicin versus 16 with FAC Two: 33 with vinorelbine plus doxorubicin versus 35 with FAC Three or more: 39 with vinorelbine plus doxorubicin versus 34 with FAC		(16 versus 2% reporting grade 1 or above, $p = 0.001$). Phlebitis was also more common in the vinorelbine plus doxorubicin group (54 versus 16% reporting grade 1 or above, $p = 0.001$). Adverse reactions involving the skin were also more common with vinorelbine plus doxorubicin ($p = 0.004$), with 8% reporting grade 1 and 1% reporting grade 4 reactions compared with none greater than grade 0 in the FAC group. For all other adverse events reported (alopecia, diarrhoea, hepatic reactions, haemorrhage, infection, mucositis and nausea and vomiting), the incidences in the two treatment groups were not statistically significantly different	

continued

Results				
Outcome 1: Partial or complete response rate	**Outcome 2: Overall response rate**	**Outcome 3: Progression-free survival adjusted to adjuvant treatment (median time to progression)**	**Outcome 4: Median overall survival adjusted to adjuvant treatment; Cox's proprotional hazard model**	**Outcome 5: Median duration of response**
Assessment of responses was performed according to the WHO criteria after two cycles of therapy with clinical and routine imaging procedures. Complete response was defined as the disappearance of all known lesions on two separate measurements at least 4 weeks apart. Partial response was defined as a reduction of each lesion by at least 50% ***Duration of follow-up*** 60 months ***Complete response*** **Previous adjuvant treatment** 31 with vinorelbine plus doxorubicin versus 14 with FAC **No previous treatment** 26 with vinorelbine plus doxorubicin versus 36 with FAC ***Partial response*** **Previous adjuvant treatment** 2 with vinorelbine plus doxorubicin versus 1 with FAC **No previous treatment** 4 with vinorelbine plus doxorubicin versus 12 with FAC	***Duration of follow-up*** 60 months ***Overall response rate*** 75% (95% CI, 66 to 84) with vinorelbine plus doxorubicin versus 74% (95% CI, 65 to 83) with FAC **Previous adjuvant treatment** 75 with vinorelbine plus doxorubicin versus 71 with FAC **No previous treatment** 75 with vinorelbine plus doxorubicin versus 75 with FAC	Stable disease was defined as a decrease of < 50% or an increase of < 25% with no new lesions. Progressive disease was defined as an increase of > 25% or the appearance of new lesions ***Duration of follow-up*** 60 months. Complete patient review was undertaken by an external review panel in November 1997 ***Median time to progression*** 7.5 months (range 0.5–47) with vinorelbine plus doxorubicin (n = 85) versus 9 months (range 0.7–59) with FAC (n = 85), log-rank p = 0.1965	***Duration of follow-up*** Complete patient review was undertaken by an external review panel in November 1997 ***Median overall survival*** 17.8 months (range 1–50) with vinorelbine plus doxorubicin (n = 85) versus 17.3 months (range 2–40) with FAC (n = 85), log-rank p = 0.1584 ***Median survival in patients with liver metastases*** 13.2 months with vinorelbine plus doxorubicin (n = 26) versus 8.5 months with FAC (n = 20), log-rank p = 0.04	Duration of complete and partial responses were calculated from the day on which treatment was first initiated to the day on which progression was first noted ***Duration of follow-up*** Complete patient review was undertaken by an external review panel in November 1997 ***Median duration of response*** 10.5 months (range 0.5–12) with vinorelbine plus doxorubicin versus 11 months (range 0.5–15) with FAC

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
Frasci *et al.*, 2000[93] (interim findings were published as an abstract by Frasci *et al.*, 1999[172]) ***Study design*** Phase I RCT ***Method of randomisation*** Patients were 'alternatively enrolled' to one of the two treatment groups ***Length of follow-up*** Not stated ***Follow-up time*** Not stated	***Number of participants*** 34 (recruited between September 1997 and June 1999) ***Type of breast cancer*** ABC (locally ABC (n = 8) or MBC (n = 26)) ***Age*** Median = 49 (range 33–70) ***Inclusion criteria*** Women with histologically/cytologically-proven ABC who had not responded or relapsed after anthracycline-based chemotherapy for ABC. Previous exposure to paclitaxel was also allowed. Other requirements included measurable or assessable disease, age ≤ 70 years, ECOG performance status ≤ 2, and adequate haematological, renal and hepatic function ***Previous treatment*** Reported for group as a whole (n = 34) and not according to intervention groups **Prior chemotherapy** Cisplatin plus epirubicin plus paclitaxel = 24 High-dose epirubicin = 4 FEC = 6 12 participants had also received adjuvant chemotherapy (type not stated) ***Other factors*** **Oestrogen receptor status** Positive: 18 Negative: 11 Unknown: 5 **Main site of tumour involvement** Breast (locally advanced): 8 Lung: 4 Liver: 6 Bone: 12 Soft tissue: 4	***Type of therapy*** Second line ***Intervention*** Docetaxel (at four different dose levels) plus gemcitabine (n = 19) **Dosage** Docetaxel 30 mg/m^2 (n = 3), 35 mg/m^2 (n = 6), 40 mg/m^2 (n = 6) or 45 mg/m^2 (n = 4) plus 1000 mg/m^2 gemcitabine i.v. on days 1 and 8, repeated every 3 weeks **Number of cycles** Total 53 ***Comparator*** Docetaxel (at three different dose levels) plus vinorelbine (n = 15) **Dosage** Docetaxel 30 mg/m^2 (n = 3), 35 mg/m^2 (n = 6) or 40 mg/m^2 (n = 6) plus 25 mg/m^2 vinorelbine i.v. on days 1 and 8, repeated every 3 weeks **Number of cycles** Total 41 In the presence of grade 1 neutropenia or thrombocytopenia, chemotherapy was omitted on day 1, while on day 8 it was given at 75% of the planned dose ***Concurrent treatment*** Oral dexamethasone (for hypersensitivity reactions and fluid retention) 12 and 4 hours before docetaxel administration and for 3 days after treatment	***Withdrawals*** One participant of the vinorelbine group refused to continue treatment after the fourth cycle because of the occurrence of grade 2 peripheral neuropathy. A total of nine participants (five with docetaxel plus gemcitabine and four with docetaxel plus vinorelbine) received fewer than three chemotherapy cycles because of the occurrence of early disease progression ***Adverse effects*** **Haematological toxicity** Grades 3 or 4 neutropenia occurred in seven (37%) participants receiving docetaxel plus gemcitabine (grade 4 in two cases) and eight (53%) participants who received docetaxel plus vinorelbine (three grade 4 cases). Two episodes of neutropenic sepsis were observed (both in the vinorelbine group). Thrombocytopenia (grade 3 or 4) occurred in three (16%) participants treated with gemcitabine and four (26%) treated with vinorelbine **Non-haematological toxicity** Negligible in the majority of cases. Mild fluid retention occurred in three participants (two with docetaxel plus gemcitabine and one with docetaxel plus vinorelbine). Severe emesis occurred in one participant of the last docetaxel plus gemcitabine cohort. Fatigue occurred in seven (37%) of the participants treated with docetaxel plus gemcitabine and six of those receiving docetaxel plus vinorelbine, and was severe in two cases (one in each group). Peripheral neutropathy was observed in a total of 16 (47%) participants (six with docetaxel plus gemcitabine and ten with docetaxel plus vinorelbine). One participant of the vinorelbine group refused to continue treatment after the fourth cycle because of the occurrence of grade 2 peripheral neuropathy. 14/16 participants showing neurotoxicity had previously received weekly cisplatin plus epirubicin plus paclitaxel. Protracted constipation was observed in two participants receiving docetaxel plus gemcitabine and four participants treated with docetaxel plus vinorelbine	***Author's conclusions*** The weekly docetaxel administration in combination with either gemcitabine or vinorelbine is a well-tolerated treatment for heavily pretreated ABC patients. This approach, although sometimes capable of achieving a major response, does not seem advisable in ABC patients refractory to both anthracyclines and paclitaxel ***Other comments*** This may not have been a true randomised study as participants were described as being 'alternatively enrolled in one of two groups'. No further details were given in the paper, however, it was stated in the abstract that participants were randominsed to one of the two intervention groups Baseline characteristics were only presented for the study sample as a whole and, therefore, it is not possible to ascertain if the two treatment groups were comparable at baseline It was not stated how many participants received chemotherapy as third-line or subsequent treatment for ABC No definitions of outcome measures were reported and it is not stated how they were measured and by whom. It was also not stated if outcome assessment was blinded. Furthermore, the length of follow-up was not reported

continued

Results	
Outcome 1: **Complete response**	**Outcome 2:** **Partial response**
No complete responses were registered among the 25 participants assessed for response after three cycles	***Docetaxel plus gemcitabine*** 3/19 (responses were observed at the docetaxel dose of 35 mg/m^2 (*n* = 1) and 40 mg/m^2 (*n* = 2)) ***Docetaxel plus vinorelbine*** 2/15 (responses were observed at the docetaxel dose of 35 mg/m^2 (*n* = 2)) ***Overall response rate*** 15% (95% CI, 5 to 31; *n* = 34) Response occurred in liver in three cases, and in lung and soft tissue in the others. One partial response was observed among the 24 participants who had received weekly dose-dense paclitaxel. Four objective responses were recorded for the remaining ten participants who had previously received an anthracycline-based treatment not including paclitaxel

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
Jones *et al.*, 1995[38] (data also extracted from Bertsch and Donaldson, 1995[165] (attrition and QoL) and company submission data by Pierre Fabre Ltd[11]) ***Study design*** Multicentre Phase III RCT ***Method of randomisation*** Not stated ***Follow-up time*** Not stated. QoL was assessed every 2 weeks for first 8 weeks and then monthly. Last assessment was at 25 weeks ***Further details*** Evaluation of tumour response was based on scanning, radiography or physical assessments in patients with measurable disease. Clinical assessment and radiographs were repeated every 4 weeks	***Number of participants*** 183 (recruitment occurred between August 1990 and December 1992) ***Type of breast cancer*** ABC ***Age*** Vinorelbine: median = 53 years (range 29–83) Melphalan: median = 56 years (range 37–80) ***Inclusion criteria*** Karnofsky performance score of ≥ 70%, life expectancy > 16 weeks, microscopically confirmed carcinoma of the breast. Not required to have measurable disease. Prior radiotherapy was acceptable if disease area was outside the radiation portal. At least 2 weeks beyond prior surgery, 3 weeks beyond radiotherapy and 3 weeks beyond prior chemotherapy. ***Exclusion criteria*** Excluded if pregnant, had metastatic central nervous system (CNS) disease, clinically significant peripheral neuropathy (except for abnormalities caused by cancer), history of other malignancy (except basal cell carcinoma of the skin or *in situ* carcinoma of the cervix), or laboratory values indicating poor liver, kidney or bone marrow function ***Previous treatment*** Eligible patients were those who experienced treatment failure while receiving, or within 6 months of completing, an anthracycline-containing adjuvant regimen and patients who had experienced treatment failure after one or two cytotoxic regimens for advanced disease, at least one of which contained an anthracycline 12 had prior vinorelbine exposure (seven given vinorelbine and five given melphalan) in adjuvant setting. The majority of participants (91% on vinorelbine and 92% on melphalan) had received anthracyclines in advanced or advanced plus adjuvant treatment settings. Failure of adjuvant anthracycline treatment within 6 months of therapy completion was experienced by 9%	**Type of therapy** First-line (9%), second-line or subsequent treatment (91%) ***Intervention*** Vinorelbine (*n* = 115) **Dosage** Started at 30 mg/m^2 i.v. weekly, diluted with 75–125 ml normal saline or 5% dextrose in water injection and infused for 20 minutes followed by a flush every week **Number of cycles** Median = 9 ***Comparator*** Melphalan (*n* = 64) **Dosage** 25 mg/m^2 i.v. every 4 weeks **Number of cycles** Median = 2 **Duration** 4 weeks ***Further details*** All participants received full supportive care but none received palliative radiotherapy or antineoplastic agents concurrently. Dose modification was based on observed toxicity. Treatment repeated as scheduled until disease progression, toxicity warranting discontinuation or patient request.	***Withdrawals*** Four participants (not stated which group they were randomised to) received no treatment and were not included in the analysis: one refused treatment, one was found to have a brain metastasis (an exclusion criterion) and two deteriorated after screening evaluation and were unable to participate No withdrawals due to adverse events were reported Reported attrition: 24.4% from vinorelbine group after course 1 and 82.6% after course 4 versus 51.6% from melphalan group after course 1 (p = 0.002) and 90.6% after course 4 Efficacy and safety analysis included participants who received ≥ one dose of either drug ***Adverse effects*** **Non-haematological toxicities** Vinorelbine (*n* = 115): injection site reaction 15%, injection site pain 14%, asthenia 34%, pain 14%, alopecia 10%, dyspnoea 10%, nausea 44%, vomiting 25%, constipation 38%, stomatitis 18%, diarrhoea 18%, anorexia 13%, paraesthesia 22%, hypesthesia 9% Melphalan (*n* = 64): injection site reaction 0%, injection site pain 2%, asthenia 22%, pain 2%, alopecia 5%, dyspnoea 3%, nausea 30%, vomiting 31%, constipation 6%, stomatitis 5%, diarrhoea 8%, anorexia 9%, paraesthesia 3%, hypesthesia 2%	***Author's conclusions*** This RCT demonstrates a survival benefit in anthracycline-refractory ABC. Vinorelbine was well tolerated and demonstrated activity superior to melphalan in anthracycline-refractory ABC without compromising QoL. Based on activity of single-agent vinorelbine in this difficult to treat patient population, investigations of vinorelbine in combination with other anticancer drugs are warranted ***Other comments*** The percentage of participants aged ≥ 65 years was slightly higher in the melphalan group, and a slightly greater proportion of patients in the vinorelbine group had lymph node metastases Allocation was not reported to have been concealed. Authors noted that the trial could not be blinded because drug administration schedules in the two treatment arms were different. This may have led to bias in assessing outcome measures Reasons for withdrawals were not given by group. Efficacy and safety results included all patients who received ≥ one dose of either drug (179/183). Analysis of tumour response included only patients with measurable disease who received ≥ one dose of the study drug (*n* = 130) For outcome measures that included time to event, the actual size of the effect (the difference between the treatment groups) with CIs were not presented, although Cox HRs were reported to have been used. The authors only reported the extent to which the difference between groups was significant (p-values) The Kaplan–Meier curves for time to disease progression were presented. Visual inspection of the graphs shows both curves to be relatively close together. After approximately 300 days, < 22/179 participants are included in the figure (due to the need to recruit participants over a 2-year period). The significant difference found between the groups

continued

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
contd **Jones et *al.*, 1995**[38] (data also extracted from Bertsch and Donaldson, 1995[165] (attrition and QoL) and company submission data by Pierre Fabre Ltd[11])	in the vinorelbine group and 8% in the melphalan group. The majority had experienced failure of FAC regimen, and 27 (16 on vinorelbine and 11 on melphalan) had experienced failure with mitoxantrone. Overall, 69% had had prior radiotherapy and 69% prior hormonal therapy ***Other factors*** **Baseline Karnofsky performance scale scores > 70%** 14% in vinorelbine group versus 23% in melphalan group **Pre/postmenopausal** Premenopausal: 39/115 in vinorelbine group versus 37/64 in melphalan group Postmenopausal: 61/115 in vinorelbine group versus 63/64 in melphalan group **Oestrogen receptor status** Positive: 37/115 in vinorelbine group versus 34/64 in melphalan group Negative: 51/115 in vinorelbine group versus 55/64 in melphalan group ≥ **2 metastatic sites** 75/115 in vinorelbine group versus 66/64 in melphalan group	Participants on either drug who required a dosing delay of > 3 weeks due to toxicity were removed from the study	**Haematological toxicities** 75% vinorelbine patients and 69% melphalan patients had grade 3 or 4 granulocytopenia. 12/115 vinorelbine patients were hospitalised while granulocytopenic versus 5/64 melphalan patients 0% vinorelbine patients versus 59% melphalan patients had grade 3 or 4 thrombocytopenia. 14% vinorelbine patients versus 34% melphalan patients had grade 3 or 4 anaemia There were 0% septic deaths in both groups	was, therefore, based on < 12% of the included population at the duration/follow-up of 300 days or above

continued

Results						
Outcome 1: Required dose reduction	**Outcome 2: Median time to disease progression**		**Outcome 3: Median time to treatment failure**	**Outcome 4: Median survival duration**	**Outcome 5: Survival rate at 1 year**	**Outcome 6: Partial response**
In the vinorelbine group, 76/115 required dose reduction and 86/115 required delay in dosing These were not reported for the melphalan group	Time to disease progression was defined as the period from the first day of drug treatment to the day when progression or relapse was documented. Time to disease progression was reported to be based on Kaplan–Meier product limit estimates ***Length of follow-up*** Survival curves ran up to 800 days (no further information given) ***Time to disease progression*** 12 weeks (3 months) with vinorelbine (n = 115) versus 8 weeks with melphalan (n = 64; Cox's proportional hazards model $p < 0.001$)		Time to treatment failure was defined as the period from the first day of treatment to the day when disease progression, treatment-related toxicity resulting in discontinuation of therapy or death (from any cause) occurred based on Kaplan–Meier product limit estimates ***Time to treatment failure*** 12 weeks with vinorelbine (n = 115) versus 8 weeks with melphalan (n = 64; Cox's proportional hazards model $p < 0.001$)	Kaplan–Meier curves given in paper ***Median survival duration*** 35 weeks with vinorelbine (n = 115) versus 31 weeks with melphalan (n = 64; Cox's proportional hazards model $p = 0.034$)	35.7% with vinorelbine versus 21.7% with melphalan	Partial response was defined as a reduction of ≥ 50% from baseline in size of all clinically measurable tumour areas without the appearance of any new disease or the increase of > 50% in the product of bidimensional measurements of any individual tumour. Confirmed by second evaluation at least 4 weeks later ***Partial response*** 9/84 (11%) with vinorelbine versus 3/46 (7%) with melphalan
Outcome 7: Complete response	**Outcome 8: Overall response (complete + partial)**	**Outcome 9: Stable disease**	**Outcome 10: Complete response + partial response + stable disease**	**Outcome 11: Progressive disease**	**Outcome 12: QoL**	
Complete response was defined as the complete disappearance of all objective disease. Confirmed by second evaluation at least 4 weeks later ***Complete response*** 4/84 (5%) with vinorelbine versus 1/46 (2%) with melphalan	13/84 (16%) with vinorelbine versus 4/46 (9%) with melphalan (Fisher's exact test $p = 0.415$)	26/84 (31%) with vinorelbine versus 9/46 (20%) with melphalan	39/84 (46%) with vinorelbine versus 13/46 (28%) with melphalan (Fisher's exact test $p = 0.06$)	93/115 (81%) with vinorelbine versus 51/64 (80%) with melphalan	QoL was measured using medical outcomes study short forms 20 and 36, symptom distress scale, linear analogues self-assessment uniscale and comorbidity questions ***Length of follow-up*** Assessed at 25 weeks Median linear time trends indicate that participants treated with vinorelbine compared with melphalan had better physical functioning throughout most of the study (a Wilcoxon rank-sum test of equal group distributed the individual QoL slopes showed that the groups differed: $p = 0.03$). Differences between groups in other QoL dimensions were not significant[165] Further QoL data provided within the company submission data[11] had a data cut-off of 29 August 1997. The statistical test used was analysis of variance. Vinorelbine was not significantly different than melphalan for symptom distress ($p = 0.37$), role functioning ($p = 0.85$) or global functioning ($p = 0.88$)	

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
Monnier *et al.*, 1998[92] (also included data from interim publication Bonneterre *et al.*, 1997[173] and company submission data by Pierre Fabre Ltd[11]) ***Study design*** Open-label, multicentre Phase III RCT (ongoing) ***Method of randomisation*** Not stated ***Length of follow-up*** Not stated	***Number of participants*** As of April 1998, 178 out of 180 planned participants were randomised (results of 172 participants with measurable or evaluable disease presented) ***Type of breast cancer*** MBC ***Age*** Median = 55.3 years (range 27–79) ***Inclusion criteria*** Patients with MBC who have been previously treated with an anthracycline-based chemotherapy regimen ***Previous treatment*** **Prior chemotherapy** 32% adjuvant or neoadjuvant only, 46% advanced disease only and 22% both adjuvant and advanced disease It was reported that there were no significant baseline differences in those patient characteristics measured (no further details presented) ***Other factors*** **Median performance status** 1 (range 0–2) **Sites of disease** Liver: 64% Bone: 43% Lung: 34% Skin and soft tissue: 32% **Number of involved sites** One: 26% Two: 32% Three: 20% > three: 17%	***Type of therapy*** First (32%) and second line (68%) ***Intervention*** Docetaxel (*n* = 86, 84 evaluable participants) **Dosage** 100 mg/m^2 1 hour i.v. infusion every 3 weeks **Number of cycles** Median = 6 (range 1–12) ***Comparator*** FUN (*n* = 89, 88 evaluable participants) **Dosage** 25 mg/m^2 vinorelbine on days 1 and 5 plus 750 mg/m^2 continuous infusion of 5-fluorouracil on days 1–5 **Number of cycles** Median = 6 (range 1–9)	***Withdrawals*** Six participants were not included in the follow-up analysis ***Adverse effects*** The main grade 3/4 toxicities Neutropenia: 65.5% with FUN versus 71% with docetaxel Infection: 1.1% with FUN versus 0.6% with docetaxel Febrile neutropenia: 2% with FUN versus 1.2% with docetaxel Nausea/vomiting: 1.8% with FUN versus 1% with docetaxel Stomatitis: 11% with FUN versus 1% with docetaxel Diarrhoea: 0.5% with FUN versus 1.2% with docetaxel Asthenia: 2.8% with FUN versus 2.4% with docetaxel Peripheral oedema: 0% with FUN versus 0.6% with docetaxel Toxic deaths: 6 (4 septic shocks, 2 hepatic insufficiencies) with FUN versus 1 (cardiac insufficiency) with docetaxel	***Author's conclusions*** Compared to standard combination, docetaxel monotherapy confirms to be as active and less toxic ***Other comments*** This study was only available as an abstract and, therefore, very little information is presented on the methodology. The publication is an interim report, having recruited 178 of the planned 180 participants The allocated treatment group of all participants who withdrew was not stated. It was not reported how many participants were included in the analysis This was an open-label trial and, therefore, blinding was not undertaken. Random allocation was not reported to have been concealed The study was sponsored by Rhône–Poulenc Rorer

continued

Results		
Outcome 1: **Overall response rate (*n* = 138)**	**Outcome 2:** **Median time to disease progression**	**Outcome 3:** **Median overall survival (*n* = 175)**[11]
Overall response rate for all patients 26% with FUN versus 33% with docetaxel ***Overall response rate in those that had had prior chemotherapy < 12 months before*** 37% with FUN versus 43% with docetaxel ***Overall response rate in those that had been previously resistant and refractory (n = 45)*** 37% with FUN versus 43% with docetaxel	5 months with FUN versus 6 months with docetaxel	12 months with FUN (*n* = 89) versus 13 months with docetaxel (*n* = 86)
continued		

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
Namer *et al.*, 2001[40] (also included data from interim publications by Namer, 1998,[174] Namer *et al.*, 1997,[175] Namer *et al.*, 1997[176] and company submission data by Pierre Fabre Ltd[11]) ***Study design*** Multicentre Phase III RCT ***Method of randomisation*** Participants centrally randomised via computer network to one of the two treatment regimens.[11] Participants were stratified according to prior adjuvant chemotherapy and institution. All patients in each centre received the same regimen, either FAC or FEC – as decided by the centre at the start of the study ***Length of follow-up*** Median = 24 months (range 8.7–40.8) Tumour responses (WHO criteria) were assessed every two cycles. The first evaluation was performed at least 15 days after the second cycle	***Number of participants*** 281 (280 evaluable participants: 142 in the mitoxantrone plus vinorelbine group and 138 in the FAC/FEC group); recruited between April 1993 and December 1995) ***Type of breast cancer*** Locally ABC (stage III) or MBC (stage IV) ***Age*** Median = 60 years (range 33–75) with mitoxantrone plus vinorelbine Median = 60 years (range 33–75) with FAC/FEC ***Inclusion criteria*** Histologically documented locally ABC or MBC, ≥ one measurable lesion; age 18–75 years; ECOG performance status ≤ 2; life expectancy ≥ 3 months; adequate haematological, renal, hepatic and cardiac (left ventricular ejection fraction) function ***Exclusion criteria*** Prior chemotherapy for unresectable locally ABC or MBC; pleural effusion; ascites; lymphangitis and bone metastasis as sole lesion; relapse < 12 months after adjuvant chemotherapy; prior treatment with > 300 mg/m^2 doxorubicin or > 400 mg/m^2 epirubicin or 72 mg/m^2 mitoxantrone; clinical or electrocardiogram signs of heart disease or congestive heart failure; brain involvement; prior cancer (except basal cell carcinoma of the skin or carcinoma *in situ* of the cervix) ***Previous treatment*** 89 patients had received prior adjuvant chemotherapy (48 (34%) with mitoxantrone plus vinorelbine and 41 (30%) with FAC/FEC). In the ITT analysis, there were 46 in both arms. 76 had received anthracycline (40 in the mitoxantrone plus vinorelbine group and 36 in the FAC/FEC group). Previous hormonal therapy for MBC had been received by 55 (39%) in the mitoxantrone plus vinorelbine group and 43 (31%) in the FAC/FEC group ***Other factors*** **Performance status (ECOG)** 0: 53% with mitoxantrone plus vinorelbine versus 59% with FAC/FEC	***Type of therapy*** First line (75%) and second line (25%) ***Intervention*** Mitoxantrone plus vinorelbine (*n* = 142) **Dosage** Mitoxantrone 12 mg/m^2 i.v. on day 1 plus vinorelbine 25 mg/m^2 i.v. on days 1, and on day 8 if neutrophils ≥ 1000/mm^3, repeated every 21 days. The mean relative dose intensity was 92% and 77% **Number of cycles** Median = 5 (range 1–12) ***Comparator*** FAC/FEC (*n* = 139) **Dosage** 5-fluorouracil 500 mg/m^2 i.v. plus adriamycin (doxorubicin) or epirubicin 50 mg/m^2 i.v. plus cyclophosphamide 500 mg/m^2 i.v. on day 1, repeated every 21 days. The mean relative dose intensity was 95%, 96% and 96% **Number of cycles** Median = 6 (range 1–18) ***Further details*** Haematological toxicity delayed treatment cycles in 17% of those on FAC/FEC therapy and 27% of those on mitoxantrone plus	***Withdrawals*** One patient was enrolled, but never treated after withdrawal of informed consent. Thirteen patients (5%) did not meet all the eligibility criteria (five in the FAC/FEC arm and eight in the mitoxantrone plus vinorelbine arm), but were included in the analysis performed on an ITT basis. Nine patients (3%) were randomised in the wrong stratum (five in the FAC/FEC arm and four in the mitoxantrone plus vinorelbine arm) ***Adverse effects (according to WHO criteria)*** Haematological toxicity led to withdrawal of vinorelbine on day 8 in 29%. During the first six cycles, grade 3 or 4 neutropenia was observed in 8% of cycles of FAC/FEC at day 21 versus 15% of cycles of mitoxantrone plus vinorelbine. Febrile neutropenia required hospitalisation in 2% (*n* = 3) of the FAC/FEC group and 15% (*n* = 21) of the mitoxantrone plus vinorelbine group ($p = 0.001$) and antibiotics were required by 0.6% and 6% of patients, respectively Non-haematological toxicity was in favour of mitoxantrone plus vinorelbine for grades 3 and 4 nausea and vomiting (22 (16%) with FAC/FEC versus 11 (8%) with mitoxantrone plus vinorelbine, $p = 0.03$) and grade 3 alopecia (41 (30%) with FAC/FEC versus 10 (7%) with mitoxantrone plus vinorelbine, $p = 0.0001$).	***Author's conclusions*** Mitoxantrone plus vinorelbine represents a chemotherapy combination with equivalent efficacy to standard FAC/FEC and improved results for patients who have previously received adjuvant chemotherapy. Toxicity must be balanced to allow for increased haematological supression and risk of febrile neutropenia with mitoxantrone plus vinorelbine compared with a higher risk of subjectively unpleasant side-effects, such as nausea/vomiting and alopecia, with FAC/FEC ***Other comments*** The objective of this trial was to show equivalence in terms of efficacy (overall response rate). However, the equivalence interval was wide at 15% and the power calculation used to calculate the sample size was one-sided, resulting in a small required sample size. Equivalence trials generally require a much larger sample size than comparative trials.[178] A one-sided design assumes that one intervention is superior to another, but not the other way around. The 90% CI for the overall response rate (–8 to 11%) shows that this was not the case in this study It was unclear if the findings of the overall response rate were derived from the ITT or per-protocol analysis. It would have been preferable if both results were reported. When looking at comparative studies, an ITT analysis is the most conservative analysis, whereas for eqivalence trials the per-protocol analysis is the most conservative and, therefore, the results of the per-protocol analysis should also have been presented It was not stated if the trial had included blinding and it was not stated if any concomitant medications were allowed/used. It was not stated how many included participants had stage III disease It was not stated if the results of median time to progression and overall survival were derived from the ITT or per-protocol analysis

continued

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
contd **Namer *et al.*, 2001**[40] (also included data from interim publications by Namer, 1998,[174] Namer *et al.*, 1997,[175] Namer *et al.*, 1997[176] and company submission data by Pierre Fabre Ltd[11])	1: 39% with mitoxantrone plus vinorelbine versus 31% with FAC/FEC 2: 8% with mitoxantrone plus vinorelbine versus 9% with FAC/FEC **Pre/postmenopausal** Premenopausal: 16% with mitoxantrone plus vinorelbine versus 16% with FAC/FEC Postmenopausal: 84% with mitoxantrone plus vinorelbine versus 84% with FAC/FEC **MBC at diagnosis** 19% with mitoxantrone plus vinorelbine versus 17% with FAC/FEC **Dominant site of disease** *Visceral* 118 (83%) with mitoxantrone plus vinorelbine versus 112 (81%) with FAC/FEC Liver: 67 with mitoxantrone plus vinorelbine versus 70 with FAC/FEC Lung: 43 with mitoxantrone plus vinorelbine versus 36 with FAC/FEC Other: 8 with mitoxantrone plus vinorelbine versus 6 with FAC/FEC *Non-visceral* 24 (17%) with mitoxantrone plus vinorelbine versus 26 (19%) with FAC/FEC **Number of visceral sites per patient** One: 95 with mitoxantrone plus vinorelbine versus 83 with FAC/FEC Two: 20 with mitoxantrone plus vinorelbine versus 20 with FAC/FEC ≥ three: 3 with mitoxantrone plus vinorelbine versus 9 with FAC/FEC	vinorelbine therapy. Haematological toxicity led to withdrawal of vinorelbine on day 8 in 29% of patients	Mostly minor cardiac events occurred in 19 patients (ten FAC/FEC and nine mitoxantrone plus vinorelbine) Febrile neutropenia resulted in one death in each treatment arm. Other deaths, reported as not related to the study, consisted of one pulmonary embolism, one sudden cardiac arrest, one patient who committed suicide and another who developed septic shock after withdrawal from the study	

continued

Results					
Outcome 1: Overall tumour response rate (complete and partial response)	**Outcome 2: Complete response and partial response**	**Outcome 3: Stable disease and progressive disease**	**Outcome 4: Median duration of response**	**Outcome 5: Median progression-free survival**	**Outcome 6: Median overall survival**
According to WHO criteria 90% CI of the difference of the overall response was calculated and the significance limit was determined by using the Dunnett and Gent χ^2 test as a means of establishing equivalence between the two arms ***Overall response rate*** 49/142 (34.5%) with mitoxantrone plus vinorelbine versus 46/138 (33.3%) with FAC/FEC; 90% CI: –8 to 11, p equivalency = 0.014 ***Overall response rate in those that had had prior adjuvant chemotherapy*** 15/46 (33%) with mitoxantrone plus vinorelbine versus 6/46 (13%) with FAC/FEC; p = 0.025 ***Overall response rate in those that had not had prior adjuvant chemotherapy*** 34/96 (35%) with mitoxantrone plus vinorelbine versus 40/92 (43%) with FAC/FEC; p = 0.26	According to WHO criteria ***Complete response*** 10/142 (7%) with mitoxantrone plus vinorelbine versus 10/138 (7%) with FAC/FEC ***Complete response in those that had had prior adjuvant chemotherapy*** 4/46 (9%) with mitoxantrone plus vinorelbine versus 0/46 with FAC/FEC ***Complete response in those that had not had prior adjuvant chemotherapy*** 6/96 (6%) with mitoxantrone plus vinorelbine versus 10/92 (11%) with FAC/FEC ***Partial response*** 39/142 (27%) with mitoxantrone plus vinorelbine versus 36/138 (26%) with FAC/FEC ***Partial response in those that had had prior adjuvant chemotherapy*** 11/46 (24%) with mitoxantrone plus vinorelbine versus 6/46 (13%) with FAC/FEC ***Partial response in those that had not had prior adjuvant chemotherapy*** 28/96 (29%) with mitoxantrone plus vinorelbine versus 30/92 (33%) with FAC/FEC	According to WHO criteria ***Stable disease*** 52/142 (37%) with mitoxantrone plus vinorelbine versus 65/138 (47%) with FAC/FEC ***Stable disease in those that had had prior adjuvant chemotherapy*** 19/46 (41%) with mitoxantrone plus vinorelbine versus 28/46 (61%) with FAC/FEC ***Stable disease in those that had not had prior adjuvant chemotherapy*** 33/96 (34%) with mitoxantrone plus vinorelbine versus 37/92 (40%) with FAC/FEC ***Progressive disease*** 30/142 (21%) with mitoxantrone plus vinorelbine versus 22/138 (16%) with FAC/FEC ***Progressive disease in those that had had prior adjuvant chemotherapy*** 6/46 (13%) with mitoxantrone plus vinorelbine versus 10/46 (22%) with FAC/FEC ***Progressive disease in those that had not had prior adjuvant chemotherapy*** 24/96 (25%) with mitoxantrone plus vinorelbine versus 12/92 (13%) with FAC/FEC ***Those in which it was not possible to determine disease status*** 11/142 (8%) with mitoxantrone plus vinorelbine versus 5/138 (4%) with FAC/FEC	Durations of partial and complete responses were assessed from start of treatment and from first documentation of a complete response to the first documentation of tumour progression, respectively ***Duration of response*** 7 months (range 1–27) with mitoxantrone plus vinorelbine (n = 142) versus 10 months (range 1–29) with FAC/FEC (n = 138) 12 patients in each arm had not progressed at the time of the analysis	Estimated by Kaplan–Meier method and compared in each strata and arm (log-rank test). Progression-free and overall survival in each arm were also compared, adjusted to the stratification for prior chemotherapy (Cox's proportional hazards model) ***Progression-free survival*** 7 months (range 0–27) with mitoxantrone plus vinorelbine (n = 142) versus 7 months (range 0–29) with FAC/FEC (n = 138) ***Progression-free survival in those that had had prior chemotherapy*** 8 months (range 1–27) with mitoxantrone plus vinorelbine versus 5 months (range 1–18) with FAC/FEC, p = 0.0007 ***Progression-free survival in those that had not had prior chemotherapy*** 6 months (range 0–26) with mitoxantrone plus vinorelbine versus 9 months (range 0–29) with FAC/FEC, p = 0.014	Estimated by Kaplan–Meier method and compared in each strata and arm (log-rank test) ***Overall survival*** 17 months (range 0–35.5) with mitoxantrone plus vinorelbine (n = 142) versus 20 months (range 0–38.5) with FAC/FEC (n = 138), p = 0.27 ***Overall survival in those that had had prior chemotherapy*** 20 months (range 0–35.5) with mitoxantrone plus vinorelbine versus 16 months (range 0–33) with FAC/FEC, p = 0.25 Showed same divergence when prior adjuvant therapy was taken into account ***Overall survival in those that had not had prior chemotherapy*** 16 months (range 0–31) with mitoxantrone plus vinorelbine versus 22 months (range 0–38.5) with FAC/FEC, p = 0.027

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
Norris et *al.*, 2000[41] (data also extracted from the company submission data by Pierre Fabre Ltd.[11] Interim publications include Norris *et al.*, 1996[170] and Norris *et al.*, 1996[171]) ***Study design*** Multicentre Phase III RCT (National Cancer Institute of Canada Clinical Trials Group study MA-8) ***Method of randomisation*** Randomisation was performed centrally at the National Cancer Institute of Canada Clinical Trials Group central office, and patients were stratified for measurable versus assessable disease and for one regimen versus no prior chemotherapy ***Length of follow-up*** Median = 29 months Preliminary analysis was performed in November 1995 and a final analysis was conducted in March 1996 ***Follow-up time*** Response every 6 weeks up to 37 weeks; blood counts, biochemical tests and QoL every 3 months	***Number of participants*** 303 (study accrued patients between 15 January 1992 and 17 July 1995) ***Type of breast cancer*** MBC ***Age*** Intervention group: median = 55 years (range 28–75) Control group: median = 55 years (range 34–75) ***Inclusion criteria*** Women were included if they were aged 18–75 years and had a performance status of 0–2; an estimated life expectancy > 16 weeks; granulocyte counts of ≥ 1.5 x 10^9/l; platelet count of ≥ 100 x 10^9/l; bilirubin level within normal limits; provided informed consent; were capable of the QoL questionnaire; and available for both treatment and follow-up ***Exclusion criteria*** Women were excluded if they had: previously received a vinca alkaloid, an anthracycline or mitoxantrone; had previous radiation therapy that encompassed their sole site of measurable or assessable disease, or that had involved an estimated 40% or more of the active bone marrow; significant heart disease; clinically significant neuropathy, infection or brain metastases; second primary cancer (except *in situ* cervical cancer or non-melanomatous skin cancer or non-metastatic treated colon, invasive cervix or uterine cancer without recurrence more than 5 years before the diagnosis of breast cancer). In addition, ≥ 3 weeks should have elapsed after the last dose of previous chemotherapy or radiotherapy before study entry ***Previous treatment*** **Radiotherapy** 104/151 (69%) with doxorubicin plus vinorelbine versus 98/149 (66%) with doxorubicin alone **Adjuvant hormone therapy** 47/151 (31%) with doxorubicin plus vinorelbine versus 37/149 (25%) with doxorubicin alone **Adjuvant chemotherapy** 54/151 (36%) with doxorubicin plus vinorelbine versus 52/149 (35%) with doxorubicin alone **Hormone therapy for metastatic disease** 76/151 (50%) with doxorubicin plus vinorelbine versus 81/149 (54%) with doxorubicin alone	***Type of therapy*** First line ***Intervention*** Doxorubicin plus vinorelbine (*n* = 151) **Dosage** Doxorubicin 50 mg/m^2 i.v. on day 1 plus vinorelbine 25 mg/m^2 i.v. on days 1 and 8, repeated every 21 days. The dose regimens listed above were modified 10 months into the trial to doxorubicin 40 mg/m^2 plus vinorelbine 20 mg/m^2 when 16 of the first 65 randomised patients suffered from febrile neutropenia using the initial dose regimens **Number of cycles** Approximately 11 ***Comparator*** Doxorubicin (*n* = 149) **Dosage** 70 mg/m^2 i.v. on day 1, repeated every 21 days. The dose regimen above was modified 10 months into the trial to 60 mg/m^2 when 16 of the first 65 randomised patients suffered from febrile neutropenia using the initial dose regimens **Number of cycles** Approximately 7	***Withdrawals*** Three women were excluded post-randomisation (not described in terms of the study groups) because they had significant preexisting arrhythmia (*n* = 1), absence of assessable disease (*n* = 1) and a previous malignancy (*n* = 1) 289/303 patients were assessable for response and 300/303 were assessable for toxicity. All patients who completed ≥ two QoL questionnaires and ≥ either three (*n* = 230) or six cycles (*n* = 191) of protocol chemotherapy were used to model the mean QoL scores Toxicity data were available for all participants in the doxorubicin plus vinorelbine group, but response data were only available for 145/151 (96%) of the women (no further details of reasons for withdrawal). Ten women in the intervention group received non-protocol treatments including one woman who received only doxorubicin (no further details). There were 134 relapses and 106 deaths in the intervention group Toxicity data were available for all participants in the doxorubicin alone group, but response data were only available for 144/149 (97%) of the women (no further details of reasons for withdrawal). Seventeen women in the control group received non-protocol treatments (no further details). There were 136 relapses and 105 deaths in the control group ***Adverse effects*** The major dose-limiting toxicity was granulocytopenia (88% with doxorubicin plus vinorelbine versus 86% with doxorubicin experiencing grade 3/4 toxicity). Other adverse events included grade 3/4 thrombocytopenia (2% with doxorubicin plus vinorelbine versus 3% with doxorubicin),	***Author's conclusions*** The survival with doxorubicin and vinorelbine is not superior to doxorubicin alone in MBC ***Other comments*** ITT analysis was reported to have been performed for toxicity data but not for response data. However, the analysis did not include the three participants who withdrew before receiving any therapy For outcome measures relating to median time to event (such as overall survival and time to treatment failure) only the *p*-value was given (i.e. showing whether there was a significant difference between the two arms or not), the actual size or measure of the effect (such as Cox HR, which was reported to have been used) was not presented. For QoL global scores, the mean and standard deviation values were presented for the sample as a whole, i.e. not listed separately for the intervention and the control group. Once again, only *p*-values for each item (showing the significant difference between the two arms) were presented Blinding was not reported to have been undertaken

continued

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
contd **Norris *et al.*, 2000**[41] (data also extracted from the company submission data by Pierre Fabre Ltd.[11] Interim publications include Norris *et al.*, 1996[170] and Norris *et al.*, 1996[171])	**Chemotherapy for metastatic disease** 38/151 (25%) with doxorubicin plus vinorelbine versus 37/149 (25%) with doxorubicin alone ***Other factors*** **WHO performance status** 0: 36/151 (24%) with doxorubicin plus vinorelbine versus 36/149 (24%) with doxorubicin alone 1–2: 115/151 (76%) with doxorubicin plus vinorelbine versus 113/149 (76%) with doxorubicin alone **Oestrogen receptor status** Unknown: 9/151 (6%) with doxorubicin plus vinorelbine versus 24/149 (16%) with doxorubicin alone Negative: 57/151 (38%) with doxorubicin plus vinorelbine versus 51/149 (34%) with doxorubicin alone Positive: 85/151 (56%) with doxorubicin plus vinorelbine versus 74/149 (50%) with doxorubicin alone **Disease-free interval median** 25 months (range 0–105) with doxorubicin plus vinorelbine versus 26 months (range 0–190) with doxorubicin alone **Post-relapse period median** 3.4 months (range 0–80) with doxorubicin plus vinorelbine versus 7.0 months (range 0–94) with doxorubicin alone **Time since diagnosis median** 38 months (range 0.3–172) with doxorubicin plus vinorelbine versus 43 months (range 0.2–261) with doxorubicin alone **Number of disease sites** One: 30/151 (20%) with doxorubicin plus vinorelbine versus 28/149 (19%) with doxorubicin alone Two: 45/151 (30%) with doxorubicin plus vinorelbine versus 37/149 (25%) with doxorubicin alone ≥ three: 76/151 (50%) with doxorubicin plus vinorelbine versus 84/149 (56%) with doxorubicin alone Other reported characteristics included: menstrual status, disease type (assessable versus measurable) and disease sites (bone, breast, liver, lung, pleural effusion, lymph nodes) Both study groups were comparable at baseline in terms of all of the characteristics investigated, except the number of patients with bone metastases (66% in the intervention group versus 55% in the control group) and pleural effusions (18% in the intervention group and 30% in the control group)	***Further details*** Treatment was continued until doxorubicin reached 450 mg/m^2 or the occurrence of disease progression, severe toxicity not managed by dose reduction, an increase in bilirubin of > 50 µmol/l, persistent grade 2 (or higher) neurotoxicity lasting > 3 weeks, clinical congestive heart failure or a confirmed fall in left ventricular ejection fraction of ≥ 25% compared with baseline or a confirmed absolute left ventricular ejection fraction value of < 40%	grade 3/4 anaemia (7% with doxorubicin plus vinorelbine versus 8% with doxorubicin), grade 3/4 neurotoxicity (9/151 (6%) with doxorubicin plus vinorelbine versus 2/149 (1%) with doxorubicin), constipation (71/151 (47%) with doxorubicin plus vinorelbine versus 29/149 (20%) with doxorubicin) and mild grade 1/2 sensory neuropathy (53/151 (35%) with doxorubicin plus vinorelbine versus 10/149 (7%) with doxorubicin). Persistent neurotoxicity after protocol treatment was observed in the intervention group (one case of severe constipation, three cases of motor weakness resulting in functional impairment and two cases of sensory neuropathy with functional impairment). More grade 2/3 venous reactions were seen in the intervention group (33/151 (22%)) compared with the control group (3/149 (2%), $p < 0.0001$). Acute gastrointestinal and cardiovascular toxicities were similar between the two study groups and delayed cardiac toxicity was seen in both groups after protocol treatment (two with doxorubicin plus vinorelbine versus one with doxorubicin). The patient who suffered from cardiomyopathy in the control group died of congestive heart failure. A total of 11% of patients in the doxorubicin plus vinorelbine group and 4% in the doxorubicin group went off protocol due to toxicity, and more patients refused further protocol treatment in the intervention than in the control group (8 versus 2%)	

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Results				
Outcome 1: Complete response	**Outcome 2: Partial response**	**Outcome 3: Overall response**	**Outcome 4: Stable disease**	**Outcome 5: Progressive disease**
Standard WHO criteria of response were used ***Complete response*** 5% (7/145) with doxorubicin plus vinorelbine versus 3% (5/144) with doxorubicin alone, Fisher's exact test $p = 0.2$	Standard WHO criteria of response were used ***Partial response*** 33% (48/145) with doxorubicin plus vinorelbine versus 27% (39/144) with doxorubicin alone	Standard WHO criteria of response were used ***Overall response*** 55/145 (38%, 95% CI, 30 to 46) with doxorubicin plus vinorelbine versus 44/144 (30%, 95% CI, 23 to 38) with doxorubicin alone	Standard WHO criteria of response were used ***Stable disease*** 47% (68/145) with doxorubicin plus vinorelbine versus 58% (83/144) with doxorubicin alone	Standard WHO criteria of response were used ***Progressive disease*** 15% (22/145) with doxorubicin plus vinorelbine versus 12% (27/144) with doxorubicin alone
Outcome 6: Median duration of response	**Outcome 7: Median time to disease progression or relapse**	**Outcome 8: Median time to treatment failure**	**Outcome 9: Median overall survival time**	**Outcome 10: Global QoL score**
Standard WHO criteria of response were used ***Median duration of response*** 7.2 months with doxorubicin plus vinorelbine versus 6.8 months with doxorubicin alone, log-rank $p = 0.6$	Time to disease progression was the time on study from the date of randomisation to the time when disease progressed or relapsed ***Median time to disease progression*** 6.2 months with doxorubicin plus vinorelbine ($n = 145$) versus 6.1 months with doxorubicin alone ($n = 144$), log-rank $p = 0.5$	Time to treatment failure was the time on study from the date of randomisation to time of progressive disease, treatment-related toxicity withdrawal or death ***Median time to treatment failure*** 6.0 months with doxorubicin plus vinorelbine ($n = 145$) versus 5.5 months with doxorubicin alone ($n = 144$), log-rank $p = 0.7$	Overall survival was the time on study from the date of randomisation to date of death ***Median overall survival*** 13.8 months with doxorubicin plus vinorelbine ($n = 145$) versus 14.4 months with doxorubicin alone (n = 144), log-rank $p = 0.4$ A comparison of the Kaplan–Meier curves showed no significant difference	Measured using the EORTC core QoL questionnaire. Nine domains included: cognitive, emotional, global, physical, role, social, fatigue, nausea/vomiting, pain Actual results were not listed separately for intervention and control groups. There were no significant differences between the control and intervention groups in terms of any of the domains at baseline There were no significant differences between the two groups in any of the eight domains at follow-up

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
Venturino *et al.*, 2000[33] (interim findings published as abstracts by Venturino *et al.*[166] and Simoni *et al.*, 1995[167]) ***Study design*** Multicentre Phase II RCT ***Method of randomisation*** Not stated ***Length of follow-up*** Not stated ***Follow-up time*** Responses were evaluated after two courses of chemotherapy	***Number of participants*** 99 (98 evaluable participants) ***Type of breast cancer*** Refractory MBC ***Stage of disease*** ABC ***Age*** Vinorelbine: median = 62.5 years (range 34–74) 5-fluorouracil plus leucovorin: median = 60 years (range 49–70) Mitoxantrone plus 5-fluorouracil plus leucovorin: median = 60.5 years (range 41–71) ***Inclusion criteria*** Aged ≤ 75 years, histopathologically confirmed diagnosis of breast cancer, progressive metastatic disease with assessable lesions, one previous chemotherapy for MBC, and ECOG performance status ≤ 2. Prior radiotherapy and/or hormonotherapy were allowed, no chemotherapy or radiotherapy in the previous 4 weeks, adequate bone marrow, cardiac, liver and renal functions, absence of active infections and life expectancy > 3 months. Previous combination chemotherapy included CMF or CEF regimens ***Previous treatment*** **Adjuvant chemotherapy** Total: 19 with vinorelbine versus 18 with 5-fluorouracil plus leucovorin versus 19 with mitoxantrone plus 5-fluorouracil plus leucovorin With anthracycline: 10 with vinorelbine versus 9 with 5-fluorouracil plus leucovorin versus 10 with mitoxantrone plus 5-fluorouracil plus leucovorin **Adjuvant hormone therapy** 11 with vinorelbine versus 9 with 5-fluorouracil plus leucovorin versus 13 with mitoxantrone plus 5-fluorouracil plus leucovorin **Palliative chemotherapy** Total: 33 with vinorelbine versus 33 with 5-fluorouracil	***Type of therapy*** Second line or salvage ***Intervention*** Vinorelbine (*n* = 33) **Dosage** 30 mg/m^2 i.v. weekly **Number of cycles** Median = 7 (range 2–15) ***Comparator 1*** 5-fluorouracil plus leucovorin (*n* = 33) **Dosage** Leucovorin 100 mg/m^2 i.v. plus 5-fluorouracil 370 mg/m^2 i.v. on days 1–5, repeated every 28 days **Number of cycles** Median = 6 (range 2–8) ***Comparator 2*** Mitoxantrone plus 5-fluorouracil plus leucovorin (*n* = 32) **Dosage** Mitoxantrone 12 mg/m^2 i.v. only on day 1 plus leucovorin 100 mg/m^2 i.v. plus 5-fluorouracil 370 mg/m^2 i.v. on days 1–3, repeated every 28 days **Number of cycles** Median = 5 (range 2–8)	***Withdrawals*** One participant (in the mitoxantrone plus 5-fluorouracil plus leucovorin group) was lost at the time of randomisation. All other participants were assessable for response and toxicity ***Adverse effects*** Toxicity was analysed according to the WHO criteria **Vinorelbine** Mucositis (grade 3 *n* = 1), anaemia (grade 3 *n* = 1), leukopenia (grade 3 *n* = 5, grade 4 *n* = 1), paralytic ileus (grade 4 *n* = 1), nausea/vomiting (grade 3 *n* = 2) **5-fluorouracil plus leucovorin** Diarrhoea (grade 3 *n* = 1, grade 4 *n* = 3), mucositis (grade 3 *n* = 4, grade 4 *n* = 1), leukopenia (grade 4 *n* = 1) **Mitoxantrone plus 5-fluorouracil plus leucovorin** Mucositis (grade 3 *n* = 1), leukopenia (grade 3 *n* = 1), thrombocytopenia (grade 3 *n* = 1), nausea/vomiting (grade 3 *n* = 3)	***Author's conclusions*** We observed low response rates, and no survival benefit even in responding patients treated with vinorelbine or leucovorin plus 5-fluorouracil or mitoxantrone plus leucovorin plus 5-fluorouracil. We conclude that these therapies provide, if any, little benefit in previously treated patients with MBC. The use of different endpoints, for example, the clinical benefit response, is suggested for more adequate evaluation of salvage treatments ***Other comments*** The study appeared to be unblinded. It was not reported if random allocation was concealed or if blinding had been undertaken The three groups differed at baseline with regards to the dominant site of metastases

continued

Study and design	Participants	Intervention details	Withdrawals/adverse effects	Comments
contd **Venturino *et al.*, 2000**[33] (interim findings published as abstracts by Venturino *et al.*[166] and Simoni *et al.*, 1995[167])	plus leucovorin versus 33 with mitoxantrone plus 5-fluorouracil plus leucovorin With anthracycline: 14 with vinorelbine versus 15 with 5-fluorouracil plus leucovorin versus 17 with mitoxantrone plus 5-fluorouracil plus leucovorin **Palliative hormone therapy** 15 with vinorelbine versus 13 with 5-fluorouracil plus leucovorin versus 16 with mitoxantrone plus 5-fluorouracil plus leucovorin ***Other factors*** **Oestrogen receptor status** Positive: 14 with vinorelbine versus 10 with 5-fluorouracil plus leucovorin versus 11 with mitoxantrone plus 5-fluorouracil plus leucovorin Negative: 5 with vinorelbine versus 5 with 5-fluorouracil plus leucovorin versus 6 with mitoxantrone plus 5-fluorouracil plus leucovorin Unknown: 14 with vinorelbine versus 18 with 5-fluorouracil plus leucovorin versus 16 with mitoxantrone plus 5-fluorouracil plus leucovorin **Median ECOG performance status** 0 (range 0–1) with vinorelbine versus 0 (range 0–2) with 5-fluorouracil plus leucovorin versus 1 (range 0–2) with mitoxantrone plus 5-fluorouracil plus leucovorin **Dominant site of metastases** Soft tissue: 14 with vinorelbine versus 6 with 5-fluorouracil plus leucovorin versus 8 with mitoxantrone plus 5-fluorouracil plus leucovorin Bone: 3 with vinorelbine versus 4 with 5-fluorouracil plus leucovorin versus 2 with mitoxantrone plus 5-fluorouracil plus leucovorin Viscera: 16 with vinorelbine versus 23 with 5-fluorouracil plus leucovorin versus 23 with mitoxantrone plus 5-fluorouracil plus leucovorin			

continued

Results				
Outcome 1: Complete response	**Outcome 2: Partial response**	**Outcome 3: Stable disease**	**Outcome 4: Progressive disease**	**Outcome 5: Overall response (complete + partial response)**
Response was analysed according to the WHO criteria ***Complete response*** 2/33 with vinorelbine versus 1/33 with 5-fluorouracil plus leucovorin versus 1/32 with mitoxantrone plus 5-fluorouracil plus leucovorin	6/33 with vinorelbine versus 9/33 with 5-fluorouracil plus leucovorin versus 6/32 with mitoxantrone plus 5-fluorouracil plus leucovorin	17/33 with vinorelbine versus 15/33 with 5-fluorouracil plus leucovorin versus 16/32 with mitoxantrone plus 5-fluorouracil plus leucovorin	8/33 with vinorelbine versus 8/33 with 5-fluorouracil plus leucovorin versus 9/32 with mitoxantrone plus 5-fluorouracil plus leucovorin	8/33 (24%) with vinorelbine versus 10/33 (30%) with 5-fluorouracil plus leucovorin versus 7/32 (21%) with mitoxantrone plus 5-fluorouracil plus leucovorin
Outcome 6: Median duration of overall response (months)	**Outcome 7: Median time (months) to treatment failure**	**Outcome 8: Overall median survival (months)**	**Outcome 9: Median survival (months) of responding participants (complete + partial response)**	**Outcome 10: Median survival (months) of responding plus stable participants (complete + partial response + stable disease)**
2 months (range 1–9) with vinorelbine (n = 33) versus 2.5 months (range 1–5) with 5-fluorouracil plus leucovorin (n = 33) versus 5.5 months (range 2–7) with mitoxantrone plus 5-fluorouracil plus leucovorin (n = 32)	Time to treatment failure was defined as the interval from the beginning of therapy until disease progression, relapse after initial response, death or treatment withdrawal for any cause ***Median time to treatment failure*** 2 months (range 1–12) with vinorelbine (n = 33) versus 3 months (range 1–10) with 5-fluorouracil plus leucovorin (n = 33) versus 5 months (range 1–11) with mitoxantrone plus 5-fluorouracil plus leucovorin (n = 32)	9.5 months (range 2–24) with vinorelbine (n = 33) versus 9 months (range 1–52) with 5-fluorouracil plus leucovorin (n = 33) versus 9 months (range 2–34) with mitoxantrone plus 5-fluorouracil plus leucovorin (n = 32)	9 months (range 4–17) with vinorelbine (n = 8) versus 11 months (range 6–52) with 5-fluorouracil plus leucovorin (n = 10) versus 10 months (range 5–33) with mitoxantrone plus 5-fluorouracil plus leucovorin (n = 7)	10.5 months (range 2–24) with vinorelbine (n = 25) versus 10.5 months (range 1–52) with 5-fluorouracil plus leucovorin (n = 25) versus 10 months (range 5–34) with mitoxantrone plus 5-fluorouracil plus leucovorin (n = 32)
CNS, central nervous system				

Appendix 7

Included vinorelbine prospective uncontrolled studies

Vinorelbine monotherapy

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Bruno *et al.*, 1995[19] (preliminary results also presented in an abstract by Bruno *et al.*, 1990[367]) ***Country*** Argentina ***Study design*** Phase II ***Objective*** To investigate the therapeutic effect of vinorelbine in women who had received no prior treatment for locally advanced MBC	***Inclusion/exclusion criteria*** Locally ABC or MBC; completed any prior adjuvant chemotherapy 12 months before trial entry (4 weeks for hormonal therapy); defined index lesions; WHO performance status ≤ 2; an expected survival of ≥ 3 months; adequate bone marrow reserve, renal and hepatic function; not > 75 years; no concomitant cancers, brain involvement or leptomeningeal disease; no radiotherapy to the only measurable site of disease ***Number of participants*** 68 (63 evaluable; recruited June 1989–October 1991) ***Age*** Median = 51 years (range 29–72) ***Previous treatment*** 26/63 (41%) received prior adjuvant chemotherapy, 4/63 (6%) received neoadjuvant chemotherapy and 30% received prior hormonal therapy. Prior CMF (*n* = 12), FAC (*n* = 8), others with anthracyclines (*n* = 4), others without anthracyclines (*n* = 5) and unknown treatment (*n* = 1) ***Performance status (WHO/ECOG)*** 0: 33 1: 21 2: 9 ***Stage of disease*** Stage IIIb–IV at entry: 19 (30%)	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis until progressive disease or dose-limiting toxicity Mean dose of vinorelbine was 22.8 mg/m^2/week (76% intensity). Median number of treatments was 8 ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** Response and adverse effects according to WHO criteria. All toxicities and responses were reviewed and discussed by a panel of oncologists. To ensure consistency in recording and reporting results, the trial monitor visited each centre and the study coordinator reviewed all case report forms. The outcome measures were response, adverse effects, progression-free survival (definition given) and overall survival (definition given)	***Withdrawals*** Five participants were excluded (three had absence of measurable disease, one had concomitant radiotherapy on target, and one had another tumour type) ***Severe adverse events*** **Haematological tolerance** Grade 4 anaemia: 3 (4.8%) Grade 3 anaemia: 1 (1.6%) Grade 4 thrombocytopenia: 1 (1.6%) Grade 3 thrombocytopenia: 1 (1.6%) Grade 4 leukopenia: 4 (6.3%) Grade 3 leukopenia: 17 (27.0%) Grade 4 granulocytopenia: 13 (21%) Grade 3 granulocytopenia: 16 (25%) **Non-haematological tolerance** Grade 4 nausea/vomiting: 2 (3.2%) Grade 3 nausea/vomiting: 1 (1.6%) Grade 4 diarrhoea: 2 (3.2%) Grade 3 stomatitis: 2 (3.2%) Grade 3 infection: 3 (4.8%) Grade 3 phlebitis: 4 (6.3%) Grade 3 neuropathy: 1 (1.6%) Grade 4 constipation: 1 (1.6%) Grade 3 constipation: 2 (3.2%) Grade 3 alopecia: 4 (6.3%)	23/63 (36%) achieved partial response 5/63 (8%) achieved complete response Overall response rate = 44% (95% CI, 32 to 56) No change was observed in 8 (13%) participants and progressive disease was observed in 27 (43%) Median duration of response = 17.9 weeks (range 7–52) Median time to progression = 12.9 weeks (range 2–52) Median survival of participants = 50.3 weeks (range 2–188)	***Author's conclusions*** Given its excellent tolerance profile and low morbidity, vinorelbine should be recommended for inclusion in first-line combination chemotherapy regimens ***Other comments*** This study is very similar to the study by Fumoleau *et al.*, 1993[21], although it was conducted in Argentina This was a non-comparative study. Therapeutic effect cannot be determined from this type of study Although there were explicit inclusion and exclusion criteria and the authors state that women were required to have locally ABC and MBC, it was unclear how many participants had locally ABC. Definitions of response and survival were given. Overall response rates were reported for subseries, but not complete and partial responses Preliminary data were presented in an abstract by Bruno *et al.*, 1990[367] (although the recruitment date that was reported in this abstract was May 1989)

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Delgado *et al.*, 1991[20] (data also presented in Canobbio *et al.*, 1989[115] and in an abstract by Boccardo *et al.*, 1989[368]) ***Country*** Italy ***Study design*** Multicentre Phase II (three centres) ***Objective*** To investigate the efficacy and toxicity of vinorelbine in participants with ABC	***Inclusion/exclusion criteria*** Measurable ABC; a WHO performance status ≤ 2; ≤ 75 years of age; a life expectancy of ≥ 3 months; adequate white blood cells, platelet count, renal and hepatic function; no brain metastases or peripheral neuropathy; not previously treated with vinca alkaloids or > one chemotherapy regimen; not with disease localised only at a previously irradiated site ***Number of participants*** 36 (25 evaluable; recruited August 1986–November 1987) ***Age*** Median = 61 years (range 42–75) ***Previous treatment*** Of 26 eligible participants, 13 had received adjuvant chemotherapy (CMF = 10, CMF plus doxorubicin = 1, CMF plus palliative hormonal therapy = 2), three had had adjuvant hormonal therapy, four had had palliative hormonal therapy only and six had no previous medical treatment ***Performance status (WHO)*** Median = 1 (range 0–2) ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis until progressive disease, severe toxicity or refusal by participant ***Concurrent treatment*** Anti-emetic treatment ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects. Therapeutic efficacy was evaluated on the basis of WHO/EORTC/National Cancer Institute criteria	***Withdrawals*** 10 were excluded from analyses as they had previously received chemotherapy for metastatic disease. 26 participants were evaluable for toxicity and 25 for response (one excluded due to early death) ***Severe adverse events*** **Haematological tolerance** Grade 4 granulocytopenia: 3 (11.5%) Grade 3 granulocytopenia: 12 (46%) Grade 4 leukopenia: 1 (3.8%) Grade 3 leukopenia: 8 (30.8%) **Non-haematological tolerance** Grade 3 alopecia: 2 (8%) Grade 3 paraesthesia: 1 (4%) Grade 3 constipation: 2 (8%)	5/25 (20%) achieved complete response 10/25 (40%) achieved partial response Overall response rate = 60% (95% CI, 41 to 79) 5/25 (20%) participants experienced stabilisation and 5/25 (20%) experienced progressive disease Median duration of response = 23 weeks (range 9–58)	***Author's conclusions*** Although the present study was restricted to a small sample, it does suggest that vinorelbine is one of the most effective drugs available in the treatment of ABC ***Other comments*** This was a pilot study with a small sample size and explicit inclusion and exclusion criteria. Participants who had received previous therapy for ABC were initially included in the study, but were excluded from the analysis. It was unclear how many participants had locally ABC and how many had MBC. The duration of follow-up and survival data were also not reported. Criteria used to measure efficacy was reported and sufficient information was presented on a subseries Data were also presented by Canobbio *et al.*, 1989[115] on a smaller sample size (19 participants on first-line therapy), and in an abstract (n = 19) by Boccardo *et al.*, 1989[368]

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Fumoleau *et al.*, 1993[21] (results also presented in abstracts by Delozier *et al.*, 1990[369] and Delozier *et al.*, 1990[370]) ***Countries*** France and Belgium ***Study design*** Multicentre Phase II (24 centres) ***Objective*** To investigate the therapeutic effects of vinorelbine in women who had received no prior chemotherapy for ABC/MBC	***Inclusion/exclusion criteria*** Locally ABC or MBC; completed any adjuvant chemotherapy 12 months before trial entry (4 weeks for hormonal therapy); defined index lesions; WHO performance status ≤ 2; an expected survival of ≥ 3 months; adequate bone marrow reserve, renal and hepatic function; not > 75 years; no concomitant cancers, brain involvement or leptomeningeal disease; no radiotherapy to the only measurable site of disease ***Number of participants*** 157 (145 evaluable; recruited January–December 1989) ***Age*** Median = 58 years (range 32–74) ***Previous treatment*** 96/145 (67%) had had postoperative radiotherapy and 62/145 (43%) had received adjuvant chemotherapy (68% with an anthracycline-based regimen) and 31% had previously received vinca alkaloids ***Performance status (WHO/ECOG)*** 0: 60 1: 54 2: 31 ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis until progressive disease or dose-limiting toxicity Median number of treatments = 9 ***Concurrent treatment*** Not stated (about 185 weeks on Kaplan–Meier curve) ***Duration of follow-up*** Not stated ***Outcome measures*** Response and adverse effects were recorded according to WHO criteria. They were reviewed and discussed by a panel of oncologists. To ensure consistency in recording and reporting, the trial monitor visited each centre and the study coordinator reviewed all case report forms. The outcome measures were response (objective criteria specified in paper), progression-free survival (definition given) and overall survival (definition given)	***Withdrawals*** One participant was lost immediately after inclusion, two were excluded based on an absence of measurable disease, two had clinically evident CNS metastasis, four had a performance status > 2, two had severe hepatic dysfunction and one was aged > 75 years ***Severe adverse events*** **Haematological tolerance** Grade 4 leukopenia: 14 (10%) Grade 3 leukopenia: 63 (44%) Grade 4 granulocytopenia: 52 (36%) Grade 3 granulocytopenia: 52 (36%) Grade 3 thrombocytopenia: 2 (1%) Grade 4 anaemia: 4 (< 3%) Grade 3 anaemia: 3 (2%) **Non-haematological tolerance** Grade 3 nausea/vomiting: 1 (< 1%) Grade 3 alopecia: 2 (1%) Grade 3 stomatitis: 1 (< 1%) Grade 3 infection: 1 (< 1%) Grade 3 fever: 2 (1%) Grade 3 neuropathy: 2 (1.4%) Grade 4 constipation: 2 (1%) Grade 3 constipation: 3 (2%) Grade 3 phlebitis: 4 (4.5%)	50/145 (34%) achieved partial response 10/145 (7%) achieved complete response Overall response rate = 41% (95% CI, 33 to 49). No change was observed in 44 (30%) participants and progressive disease was observed in 41 (28%) Median duration of response = 34 weeks (range 9–141) Median time to progression = 25 weeks Median survival of all participants = 73 weeks Kaplan–Meier curves were presented in the paper	***Author's conclusions*** Our data confirm that vinorelbine has major single-agent antitumour activity as front-line therapy in ABC. Given its excellent tolerance profile and low toxicity, it should be considered for inclusion in first-line combination chemotherapy regimens ***Other comments*** This study is similar to the study by Bruno *et al.*, 1995[19] This was a non-comparative study, and therapeutic effect cannot be determined from this type of study Explicit inclusion/exclusion criteria were reported, although it is unclear how many had locally ABC or MBC. Objective definitions were reported for outcome measures and response rates reported for subseries. Participants were followed-up until they died Sample size calculation was made using the sequential two-step statistical test of Gehan Preliminary results were presented in an abstract by Delozier *et al.*, 1990[369], and results for 157 participants were presented in Delozier *et al.*, 1990[370]

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Garcia-Conde *et al.*, 1994[22] (results were also presented in an abstract by Garcia-Conde *et al.*, 1992[129]) ***Country*** Spain ***Study design*** Phase II ***Objective*** To investigate the therapeutic effect of vinorelbine in women who had received no prior treatment for ABC/MBC	***Inclusion/exclusion criteria*** Locally ABC or MBC; completed any prior adjuvant chemotherapy at least 12 months before trial entry (4 weeks for hormonal therapy); defined index lesions; WHO performance status ≤ 2; an expected survival of ≥ 3 months; adequate bone marrow reserve, renal and hepatic function; not > 75 years; no concomitant cancers, brain involvement or leptomeningeal disease; no radiotherapy to the only measurable site of disease ***Number of participants*** 54 (50 evaluable; recruited January 1990–October 1991) ***Age*** Median = 57 years (range 34–76) ***Previous treatment*** 33/50 (66%) received prior adjuvant chemotherapy, 27 (81%) had received an anthracycline-based regimen, 9/50 (18%) had received prior hormonal therapy ***Performance status (WHO)*** 0: 23 1: 16 2: 11 ***Stage of disease*** Eight (11%) participants had primary and local recurrence and 42% had visceral metastases	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis until progressive disease or dose-limiting toxicity Mean dose of vinorelbine was 20.7 mg/m^2 per week (69% intensity) ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** Response and adverse effects were recorded according to WHO criteria. They were reviewed and discussed by a panel of oncologists. To ensure consistency in recording and reporting, the trial monitor visited each centre and the study coordinator reviewed all case report forms. The outcome measures were response, adverse effects, progression-free survival and overall survival	***Withdrawals*** 53 evaluable for toxicity and 50 for response. Four participants were excluded (two had had adjuvant treatment within the previous year, one had had second-line therapy and one had had an oophorectomy within 1 month) ***Severe adverse events*** **Haematological tolerance** Grade 4 anaemia: 1 (2%) Grade 3 anaemia: 3 (6%) Grade 4 leukopenia: 4 (8%) Grade 3 leukopenia: 25 (47%) Grade 4 granulocytopenia: 23 (43%) Grade 3 granulocytopenia: 15 (28%) Grade 3 thrombocytopenia: 1 (2%) **Non-haematological tolerance** Grade 3 stomatitis: 2 (4%) Grade 3 nausea/vomiting: 1 (2%) Grade 3 fever: 1 (2%) Grade 4 infection: 2 (4%) Grade 3 infection: 1 (2%) Grade 4 constipation: 1 (2%) Grade 3 phlebitis: 1 (2%)	24/50 (48%) achieved partial response 1/50 (2%) achieved complete response Overall response rate = 50% (95% CI, 36 to 64) Median duration of response = 36 weeks (range 14–70) Median time to progression = 19 weeks (range 0–70) Median time to treatment failure = 5 months Median survival of participants = 65 weeks (range 2–105) Kaplan–Meier curve for time to disease progression was presented in the paper	***Author's conclusions*** This study supports the proposition that vinorelbine is a well-tolerated and very active new agent for the management of ABC. Vinorelbine should be considered as a component of combination chemotherapy regimens in first-line treatment ***Other comments*** Similar study to the studies by Bruno *et al.*, 1995[19] and Fumoleau *et al.*, 1993[21] (Delgado as the common author) This was a non-comparative study and therapeutic effect cannot be determined from this type of study Explicit inclusion and exclusion criteria reported, although ≥ one participant appeared to be 76 years of age. It was unclear how many had locally ABC and MBC. Assessment criteria were reported. The overall response rate (% only) was presented according to some disease sites, but not according to the categories reported in the demographic table. Sample size calculation was made using the sequential two-step statistical test of Gehan Data in abstract differed from the paper, although the data seemed to be from the same sample

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Kesselring *et al.*, 1991[23] ***Country*** Brazil ***Study design*** Multicentre Phase II ***Objective*** Not stated (title: Phase II trial of Navelbine in the treatment of ABC in Brazil)	***Inclusion/exclusion criteria*** Untreated measurable ABC ***Number of participants*** 16 (14 evaluable; recruited August 1989–June 1990) ***Age*** Median = 52 years (range 34–68) ***Previous treatment*** Six participants had received prior adjuvant chemotherapy, seven had received prior adjuvant radiotherapy and two had received prior hormonal therapy ***Performance status (ECOG)*** Median = 1 (0–2) ***Stage of disease*** **Sites of disease** Lymph nodes: 6 Liver: 5 Primary tumours: 6 Bone: 4 Lung: 5 Skin: 4 Others: 1	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** 16 evaluable for toxicity and 14 for response ***Severe adverse events*** **Haematological tolerance** Grade 3–4 leukopenia: 3 (18%) **Non-haematological tolerance** Grade 3–4 nausea/vomiting: 1 (6%; resulting in cessation of treatment) Grade 3 phlebitis: 3 (18%)	6/14 (42%) achieved an overall remission (6 achieved partial response and none achieved complete response) Median duration of response = 8 weeks (range 4–12)	***Author's conclusions*** These results have confirmed the high antitumour activity and meaningful toxicity of vinorelbine in ABC. Further Phase III studies in association with other potent antitumour agents must be done to overview the impact on survival ***Other comments*** This was an abstract only. Small sample size and no explicit inclusion/exclusion criteria were presented. It was unclear how many had locally ABC or MBC. No duration of follow-up or survival data were presented. Not enough details were presented to assess the quality of the study Part of a multicentre international trial

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Queisser *et al.*, 1991[24] ***Country*** Germany ***Study design*** Phase II ***Objective*** To evaluate the efficacy and tolerance of oral vinorelbine in women with ABC	***Inclusion/exclusion criteria*** Histologically confirmed and measurable ABC; a life expectancy of ≥ 3 months; a WHO performance status ≤ 2; no neuropathy; adequate polymorphonuclears, platelets and haemoglobin; normal liver and renal function. Participants had to be low risk with positive hormone receptor status of the primary tumour or with a disease-free interval of > 24 months, not pretreated by adjuvant hormonal therapy and showing progressive disease under hormonal treatment. Participants were excluded if they had had previous cytostatic treatment for metastatic disease, except adjuvant chemotherapy with a disease-free interval of ≥ 1 year ***Number of participants*** 17 (15 evaluable) ***Age*** Median = 64 years (range 48–80) ***Previous treatment*** 15/17 (88%) had received prior hormonal therapy ***Performance status (WHO)*** 0: 6 1: 6 2: 5 ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 130 mg orally (in a hard gelatine formulation) per week until progressive disease or refusal by participant Treatment was performed for 3–24 weeks (median = 11 weeks) ***Concurrent treatment*** Anti-emetic treatment if necessary ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects, recorded according to WHO criteria	***Withdrawals*** 15 participants evaluable for response ***Severe adverse events*** **Haematological tolerance** Grade 4 leukopenia: 1 (5.9%) Grade 3 leukopenia: 2 (11.8%) **Non-haematological tolerance** Grade 3 loss of appetite: 1 (5.9%) Grade 3 nausea/vomiting: 3 (17.7%) Grade 3 alopecia: 1 (5.9%) Grade 3 diarrhoea: 1 (5.9%)	Causes for treatment termination were tumour progression in 13 participants and refusal in three Complete and partial remissions were not observed 9/15 (60%) patients showed no change and tumour stabilisation (95% CI, 32.3 to 83.7), and 6/15 (40%) experienced tumour progression Median time to progression = 3 months for those that had no change or stable disease (*n* = 9), 1.7 months for those that had progressive disease and 0.9 months for those that had early progression Kaplan-Meier curve was plotted for time to disease progression (for the three groups)	***Author's conclusions*** The oral route of vinorelbine elicits moderate response as seen by tumour stabilisation, although considerable toxicity was noted. Further trials with vinorelbine in a hard gelatine capsule, in our opinion, cannot be recommended at this point ***Other comments*** Small sample size. Explicit inclusion/exclusion criteria, although the authors state that the study was restricted to participants not pretreated by hormonal therapy while 15 (88%) are reported to have had hormonal pretreatment in a table. Unclear how many participants had locally ABC or MBC. Duration of follow-up and survival data were not reported. Criteria used to measure toxicity and response were reported. Some information was presented on subseries

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Romero *et al.*, 1994[25] ***Country*** Argentina ***Study design*** Phase II ***Objective*** To evaluate the efficacy and toxicity of vinorelbine as first-line chemotherapy for MBC	***Inclusion/exclusion criteria*** Locally ABC or MBC; a life expectancy of > 3 months; measurable lesions; ECOG performance status ≤ 2; adequate bone marrow, renal and liver functions. Participants with progressive disease under primary hormonal therapy were eligible 1 month after last manipulation. No prior chemotherapy for metastatic disease, CNS metastases and hilar enlargement; not pleural effusion or malignant ascites as the only evidence of metastatic disease; minimum interval to relapse of 4 weeks following adjuvant chemotherapy ***Number of participants*** 45 (44 evaluable; recruited August 1991–February 1993) ***Age*** Median = 52 years (range 29–72) ***Previous treatment*** 22 (49%) had received prior adjuvant chemotherapy (19 had FAC and 3 had CMF), 20 (44%) had received prior hormonal therapy (7 adjuvant and 13 metastatic therapy) and 31 (69%) had had adjuvant radiotherapy ***Performance status (ECOG)*** 0: 24 1 or 2: 21 ***Stage of disease*** For 9/45 participants, the dominant site of disease was soft tissue	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis until progressive disease or severe toxicity Mean number of cycles = 12.1 ***Concurrent treatment*** Anti-emetic therapy at the discretion of the attending physician ***Duration of follow-up*** 32 participant years, mean = 9 months (range 1–21) ***Outcome measures*** The outcomes were response (definitions given) and adverse effects, recorded according to WHO criteria. Assessment of chemotherapy-induced phlebitis was based on published criteria, whereas myalgia and asthenia were graded according to Cancer and Leukemia Group B criteria	***Withdrawals*** 45 evaluable for toxicity and 44 for response (one participant refused further treatment after the first course of therapy) ***Severe adverse events*** **Haematological tolerance** Grade 3 anaemia: 3 (7%) Grade 4 leukopenia: 7 (16%) Grade 3 leukopenia: 9 (20%) Grade 4 granulocytopenia: 7 (16%) Grade 3 granulocytopenia: 12 (27%) Grade 4 thrombocytopenia: 1 (2%) **Non-haematological tolerance** Grade 4 infection: 3 (7%) Grade 3 infection: 1 (2%) Grade 3 neuropathy: 1 (2%) Grade 3 constipation: 1 (2%) Grade 3 nausea/vomiting: 1 (2%) Grade 3 stomatitis: 2 (4%) Grade 3 alopecia: 4 (9%)	Three (7%) participants required hospitalisation for sepsis 18/44 participants had overall regression (41%, 95% CI, 26 to 56) 3/44 (7%) achieved complete response 15/44 (34%) achieved partial response No change was observed in 14 (32%) participants and progressive disease in 12 (27%) Time to event was assessed using Kaplan–Meier method Median time to treatment failure for all = 6 months (range 1–15) Median duration of response = 9 months (range 1–15) Median survival duration had not yet been reached 7/19 (37%) participants who had received prior doxorubicin-containing adjuvant chemotherapy, 3/6 (50%) and 4/13 (31%) who had received hormonal therapy as adjuvant or for metastatic disease, respectively, responded to vinorelbine	***Author's conclusions*** Our results demonstrate that, in this setting, vinorelbine has a significant antitumour effect with mild to moderate toxic effects. Future trials should evaluate alternative dosing schedules, efficacy in combination with other agents and possible mechanisms of drug resistance ***Other comments*** Clear inclusion/exclusion criteria reported. Both locally ABC and MBC were included. The criteria to define response and toxicity were given. Details of subseries were clearly presented in a table

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Smith, 1990[26] ***Country*** UK ***Study design*** Phase II ***Objective*** Not stated (title: Navelbine in combination chemotherapy for ABC)	***Inclusion/exclusion criteria*** Untreated participants with ABC ***Number of participants*** 134 (123 evaluable) ***Age*** Not stated ***Previous treatment*** Not stated ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First-line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measure was response	***Withdrawals*** 123 evaluable for response ***Severe adverse events*** Not stated	Response rate = 42% for all eligible participants and 45% for the 123 fully evaluable participants	***Author's conclusions*** Vinorelbine is well tolerated. These results suggest that vinorelbine may be a very effective new agent in combination chemotherapy for ABC ***Other comments*** This is a very brief abstract. As well as reporting results of vinorelbine as a single agent, it also reported that vinorelbine in combination with 5-fluorouracil is being assessed (vinorelbine 30 mg/m^2 on days 1 and 5 plus fluorouracil 750 mg/m^2 on days 1–5, repeated every 21 days) for which the preliminary response rate = 70% in 28 participants. The authors also report that a clinical trial is ongoing with vinorelbine in association with doxorubicin, but that the results are not yet available. Further studies/publications have not been found

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Terenziani et *al.*, 1996[27] ***Country*** Italy ***Study design*** Phase II ***Objective*** To evaluate the efficacy and toxicity of vinorelbine and to investigate its cross-resistance with other current drug treatments for MBC	***Inclusion/exclusion criteria*** Histologically confirmed ABC with measurable metastatic disease; no prior treatment with vinca alkaloids; no brain metastases; no previous radiation therapy to index lesions ***Number of participants*** 57 (53 evaluable (group A = 27, group B = 26); recruited July 1992–December 1993) ***Age*** Median = 52 years (range 31–67) ***Previous treatment*** Group A received no prior chemotherapy (six participants) and none had relapsed in > 12 months since the end of adjuvant chemotherapy (nine had adjuvant CMF, one had FAC and 11 had CMF plus anthracycline) Group B consisted of all other participants (six were relapsing < 12 months from end of adjuvant chemotherapy, nine had received one prior cytotoxic regimen and 11 had had ≥ two previous chemotherapy treatments for metastatic disease) ***Performance status*** Median = 90 (range 80–100) ***Stage of disease*** Not stated	***Line of therapy*** First and second line ***Intervention*** 1) Vinorelbine 30 mg/m^2 on a weekly basis (participants 1–20) 2) Modified to vinorelbine 30 mg/m^2 on days 1 and 8, repeated every 3 weeks (participants 21–57) until progressive disease or severe toxicity ***Concurrent treatment*** Almost all participants received anti-emetic drugs (metoclopramide or dexamethasone) ***Duration of follow-up*** Not explicitly stated (September 1994) ***Outcome measures*** Response (objective criteria specified in paper) and adverse effects recorded according to the South West Oncology Group criteria. The outcome measures were response, adverse effects, progression-free survival (definition given) and overall survival (definition given)	***Withdrawals*** 53 evaluable for response (three participants had no clearly measurable parameters and one refused treatment) ***Severe adverse events*** **For participants with intervention 1** Grade 4 neutropenia: 7 episodes out of 226 administrations Grade 3 neutropenia: 50 episodes out of 226 administrations **For participants with intervention 2** Grade 3 neutropenia: 14 episodes out of 373 administrations	***Group A (first line)*** 13/27 (48%) achieved partial response 3/27 (11%) achieved complete response Overall response rate = 59% (95% CI, 35 to 75) ***Group B (relapse < 12 months after adjuvant chemotherapy and second line)*** 8/26 (31%) achieved partial response 1/26 (4%) achieved complete response Overall response rate = 35% (95% CI, 17 to 56) ***Overall*** 21/53 (40%) achieved partial response (95% CI, 26 to 54) 4/53 (7%) achieved complete response (95% CI, 2 to 18) Overall response rate = 47% (95% CI, 33 to 61) Median time to disease progression = 20 weeks for evaluable participants Median time to maximum tumour shrinkage = 8 weeks (range 3–23) for responders Median duration of the best response = 20 weeks (range 4–56) Median survival of participants = 19 months	***Author's conclusions*** Vinorelbine had clinically significant activity in MBC, and no cross-resistance with prior anthracyclines and CMF treatments. The drug schedule (30 mg/m^2 on days 1 and 8 every 3 weeks) was effective and tolerable ***Other comments*** Although the authors have divided the participants into groups A and B, the results are largely based on the overall sample. Sample of participants with first-line therapy is small (although six participants in group B also had first-line chemotherapy for MBC). Inclusion/exclusion criteria are not extensive. It was not stated how many had ABC or MBC. The performance status scale employed in this study was not described. Data regarding toxicity were not reported in detail, and were only reported according to the administration schedule and not the line of therapy. Objective definitions were provided for outcome measures. Subseries data were reported

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Toussaint *et al.*, 1995[28] ***Country*** France ***Study design*** Case series Phase I/II ***Objective*** To determine the maximum-tolerated dose of vinorelbine and to evaluate the toxicity pattern and antitumour activity in ABC using this administration schedule	***Inclusion/exclusion criteria*** Locally ABC or MBC; prior adjuvant chemotherapy completed ≥ 12 months before trial (palliative chemotherapy or hormonal therapy ≥ 4 weeks); WHO performance status < 2; expected survival ≥ 3 months; adequate bone marrow reserve, renal and hepatic function; not > 70 years; no concomitant cancers, brain involvement or leptomeningeal disease; no radiotherapy to the only measurable site of disease ***Number of participants*** 68 (64 evaluable; recruited February 1990–July 1991) ***Age*** Median = 52 years (range 26–70) ***Previous treatment*** 46/64 (72%) received prior neoadjuvant or adjuvant chemotherapy (35 (55%) with anthracyclines and 20 (32%) also including vinca alkaloids). 30 (47%) received palliative chemotherapy (27 (42%) with anthracycline-containing regimens). 46 (72%) had previous palliative hormonal therapy alone or with chemotherapy ***Performance status (WHO)*** 0: 39 1: 19 2: 6 ***Stage of disease*** 19 participants had locoregional disease (skin = 15, primary tumour = 3, soft tissue = 1)	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 8 mg/m^2 on day 1 followed by 4 days continuous infusion at escalating dose levels (resulting in 30–48 mg/m^2), repeated every 21 or 28 days until progressive disease or toxicity Median number of treatments = 5 ***Concurrent treatment*** Standard heparin prophylaxis ***Duration of follow-up*** Median follow-up = 27 months (range 18–35) ***Outcome measures*** Response and adverse effects recorded according to WHO criteria. The outcome measures were response, adverse effects, progression-free survival (definition given) and overall survival (definition given)	***Withdrawals*** Four participants were excluded (one had brain involvement, three had absence of measurable disease, inadequate bone marrow reserve or > three previous lines of treatment for metastatic disease) ***Severe adverse events*** **Haematological tolerance (cycles)** Grade 3 anaemia: 16 (5%; required blood transfusion in two instances) Grade 4 leukopenia: 41 (14%) Grade 3 leukopenia: 117 (39%) Grade 4 neutropenia: 129 (43%) Grade 3 neutropenia: 73 (24%; at 48 mg/m^2, three participants had grade 3 neutropenia, mucositis and fever) Grade 3 thrombocytopenia: 2 (5%; two participants) **Non-haematological tolerance (cycles)** Grade 3 nausea/vomiting: 2 (< 1%) Grade 4 mucositis: 1 (< 1%) Grade 3 mucositis: 12 (4%) Grade 3 fever: 1 (< 1%) Grade 4 infection: 1 (< 1%) Grade 3 infection: 2 (< 1%) Severe asthenia: 3% Severe anorexia: 1%	***First line*** 9/34 (26%) achieved partial response 2/34 (6%) achieved complete response Overall response rate = 32% ***Second line*** 12/30 (40%) achieved partial response ***Overall*** 21/64 (33%) achieved partial response 2/64 (3%) achieved complete response Overall response rate = 36% (95% CI, 23 to 49) Median duration of complete responses = 3 months (range 2.5–4.5) Median duration of partial responses = 6.5 months (range 2.5–14.5) Median duration of overall response = 6 months (range 2.5–14.5) 20 participants were still alive with disease. Median survival of all participants = 24 months (range 3–37; 28% were still alive) Median survival duration of the 21 participants who achieved a complete or partial response = 21 months	***Author's conclusions*** This trial, while confirming vinorelbine activity in ABC, showed the feasibility of a continuous infusion administration schedule. A decrease of the administered total dose per 3- to 4-week cycle to less than the weekly schedule with the same therapeutic activity suggested a better therapeutic index. The data were also suggestive of a dose–response relationship and a dose-intensity/activity correlation ***Other comments*** Small sample of participants with first-line therapy. Explicit inclusion and exclusion criteria. The study included both ABC and MBC. Criteria used to assess outcomes were reported. Toxicity data by participant were not fully reported and were mainly reported by cycle. Details of subseries were presented

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Twelves *et al.*, 1994[29] ***Country*** UK ***Study design*** Phase II ***Objective*** To determine the efficacy and toxicity of vinorelbine 25 mg/m^2 in participants with ABC	***Inclusion/exclusion criteria*** Histologically-confirmed ABC with at lease one measurable lesion; no prior chemotherapy except adjuvant chemotherapy (with a 6-month disease-free period after treatment); WHO performance status ≤ 2; 18–75 years of age; adequate bone marrow reserve, liver and hepatic function; prior endocrine treatment and radiotherapy were allowed; no neuropathy, brain metastases or a previous history of other malignancy ***Number of participants*** 35 (34 evaluable; recruited April–December 1992) ***Age*** Median = 59 years (range 34–75) ***Previous treatment*** 18/34 (53%) received prior adjuvant endocrine treatment, 3/34 (9%) received adjuvant chemotherapy and 19/34 (56%) received advanced endocrine treatment ***Performance status (ECOG)*** 0: 13 1: 16 2: 5 ***Stage of disease*** 26 participants had multiple measurable/evaluable disease sites (breast/local recurrence = 9, soft tissue = 4)	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on a weekly basis for a maximum of 16 cycles. Some treatments were stopped due to progressive disease, refusal of treatment or physician's discretion Median number of cycles = 10 ***Concurrent treatment*** Most participants received metoclopramide as anti-emetic cover ***Duration of follow-up*** Median = 18.2 months ***Outcome measures*** Response according to Union Internationale Contre le Cancer guidelines. The outcome measures were response, progression-free survival, overall survival and adverse effects (recorded according to WHO criteria)	***Withdrawals*** One participant was excluded (remained on tamoxifen) ***Severe adverse events*** **Haematological tolerance** Grade 4 neutropenia: 11 (32%) Grade 3 neutropenia: 12 (35%) Grade 4 leukopenia: 2 (6%) Grade 3 leukopenia: 16 (47%) Grade 3 anaemia: 1 (3%) **Non-haematological tolerance** Grade 3 nausea/vomiting: 4 (11%) Grade 3 alopecia: 4 (12%) Grade 3 constipation: 2 (6%) Grade 3 diarrhoea: 1 (3%) Grade 4 infection: 1 (3%) Grade 3 infection: 1 (3%) Grade 3 phlebitis: 1 (3%) Severe asthenia (tiredness) was reported in 6% participants and 3.5% of cycles There was one toxic death, attributed to neutropenic sepsis	15/34 (44%) achieved partial response 2/34 (6%) achieved complete response Overall response rate = 50% (95% CI, 34 to 66) 12 (35%) participants had stable disease and 5 (15%) had progressive disease Median duration of response = 5.8 months (range 2.3–9.8) Median time to progression = 4.4 months (range 0.9–> 14.4) Median survival of participants = 9.9 months (range 1.8–> 21.1) The male participant did not respond to vinorelbine Kaplan–Meier methodology was used in the paper	***Author's conclusions*** This study confimed that vinorelbine is highly active and well tolerated as first-line treatment in participants with ABC. These encouraging Phase II data need to be confirmed in Phase III studies supported by QoL data ***Other comments*** Relatively small sample size. One participant in this study was male. Explicit inclusion/exclusion criteria. Not clear how many had locally ABC or MBC. Assessment criteria were referenced. Some details on subseries

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Vogel *et al.*, 1999[30] (results also presented in an abstract by Vogel *et al.*, 1996[371]) ***Country*** USA ***Study design*** Multicentre Phase II ***Objective*** To evaluate the safety and efficacy of vinorelbine as first-line chemotherapy for ABC in women ≥ 60 years old	***Inclusion/exclusion criteria*** ABC; ≥ 60 years of age; no prior chemotherapy for metastatic disease; disease free for ≥ 12 months; radiotherapy had to have been completed ≥ 3 weeks and hormonal therapy ≥ 1 week before study entry; not a Karnofsky performance status < 70; not a life expectancy < 16 weeks; no metastases to the CNS; no second malignancy other than basal cell skin cancer or cervical carcinoma *in situ*; no peripheral neuropathy; adequate liver, kidney and bone marrow function; no other uncontrolled medical condition ***Number of participants*** 56 (recruited March 1994–October 1995) ***Age*** Median = 72 years (range 60–84) ***Previous treatment*** 47/56 (84%) received prior hormonal therapy, 31/56 (55%) received prior radiotherapy, 7 (13%) received anthracycline-based adjuvant chemotherapy and 8 (14%) received non-anthracycline-based adjuvant chemotherapy ***Performance status (Karnofsky)*** 70: 8 80: 14 90: 20 100: 14 ***Stage of disease*** 10 participants had soft tissue as the dominant metastatic site	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on a weekly basis for 13 weeks (every 2 weeks thereafter) until progressive disease or dose-limiting toxicity Median dose intensity = 20.6 mg/m^2/week Median number of doses = 15.5 ***Concurrent treatment*** G-CSFs were used therapeutically if fever and granulocytopenia were present. Analgesics, antibiotics, anti-emetics, anti-diarrhoeals and blood/blood products were permitted as needed ***Duration of follow-up*** Median = 25.5 weeks (range 1–121) ***Outcome measures*** The outcome measures were response and duration of response (objective criteria specified in paper) and adverse effects, recorded according to a modified version of the toxicity scale used by the National Cancer Institute	***Withdrawals*** All participants were evaluable for toxicity and response ***Severe adverse events*** **Haematological tolerance** Grade 4 leukopenia: 4 (7%) Grade 3 leukopenia: 30 (54%) Grade 4 granulocytopenia: 7 (48%) Grade 3 granulocytopenia: 18 (32%) Grade 4 neutropenic fever: 4 (7%) Grade 3 neutropenic fever: 2 (4%) Grade 3 anaemia: 4 (7%) Grade 3 thrombocytopenia: 1 (2%) Four participants were hospitalised due to granulocytopenia and associated fever. One death was considered drug related (the participant was hospitalised for febrile neutropenia, developed sepsis and respiratory failure) **Non-haematological tolerance** Grade 3 asthenia: 4 (7%) Grade 4 fever: 1 (2%) Grade 4 abdominal pain: 1 (2%) Grade 3 abdominal pain: 1 (2%) Grade 3 generalised pain: 3 (5%) Grade 3 chest pain: 2 (4%) Grade 4 nausea: 1 (2%) Grade 3 nausea: 2 (4%) Grade 4 constipation: 1 (2%) Grade 4 vomiting: 1 (2%) Grade 3 vomiting: 1 (2%) Grade 4 diarrhoea: 1 (2%) Two participants withdrew due to adverse effects (one with severe nausea and one due to moderate fatigue)	19/56 (34%) achieved partial response 2/56 (4%) achieved complete response Overall response rate = 38% (95% CI, 24 to 51) 21 (38%) participants had stable disease, which lasted ≥ 6 months in nine (16%) participants Overall success rate (complete and partial response + stable disease ≥ 6 months) = 54% Of the 7 participants who had received anthracycline-based adjuvant therapy, one had a complete and three had partial responses Median duration of response = 9 months Median time to disease progression in all participants = 6 months Kaplan–Meier methodology used in paper	***Author's conclusions*** Vinorelbine offers a promising alternative for the management of ABC in elderly patients who are concerned about the subjective side-effects of cytotoxic chemotherapy. The dose-limiting toxicity is neutropenia. Non-haematological toxicity is minimal. RCTs are warranted to compare the activity of vinorelbine with that of other regimens in elderly participants ***Other comments*** Although there were explicit inclusion and exclusion criteria, the authors waived eligibility criteria for five participants (two with uterine cancer, one with elevated aspartate aminotransferase, one with an inadequate haemoglobin level and one that had received radiotherapy within 3 weeks). It was unclear how many had ABC or MBC. The authors report that survival data were not collected because vinorelbine was used as first-line therapy and survival would have been influenced by subsequent treatment. Response rates were reported for participants who had received previous anthracycline therapy. No other subseries were reported. Participants may have been reported in an earlier paper (Weber *et al.*, 1995[31]). An abstract by Vogel *et al.*, 1996[371] reports preliminary results for 39 participants

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Weber *et al.*, 1995[31] ***Country*** USA ***Study design*** Multicentre Phase II ***Objective*** To evaluate vinorelbine as first- and second-line treatment for ABC in participants who were not resistant to anthracyclines	***Inclusion/exclusion criteria*** ABC; disease free for ≥ 12 months; no cytotoxic therapy for advanced disease; > 18 years of age; measurable disease; Karnofsky performance status > 70; life expectancy > 16 weeks. Prior radiotherapy was acceptable (if measurable disease was outside the radiation portal). No CNS, hepatic or lymphangitic metastases, history of malignancy except basal skin cancer and cervical carcinoma *in situ*; no neuropathy; adequate liver, kidney and bone marrow function ***Number of participants*** 107 (60 first and 47 second line) ***Age*** First line: median = 62.5 years (range 31–85) Second line: median = 64 (range 30–82) ***Previous treatment*** **First line** 46/60 (77%) had been treated with biological agents or hormones, 35/60 (58%) had had radiotherapy and 32/60 (53%) had had chemotherapy **Second line** 34/47 (72%) had been treated with biological agents or hormones, 35/47 (75%) had had radiotherapy and all had had chemotherapy ***Performance status (Karnofsky)*** 70: first line = 12, second line = 13 80: first line = 14, second line = 15 90: first line = 22, second line = 11 100: first line = 12, second line = 8 ***Stage of disease*** Not stated	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 30–35 mg/m^2 on a weekly basis until progressive disease, toxicity or participant refusal ***Concurrent treatment*** G-CSFs were used therapeutically if fever and granulocytopenia were present. Analgesics, antibiotics, anti-emetics, anti-diarrhoeals and blood/blood products were permitted as needed ***Duration of follow-up*** Not stated (Kaplan–Meier curves up to 120 weeks) ***Outcome measures*** The outcome measures were response (objective criteria specified in paper), progression-free survival (definition given), overall survival and adverse effects (recorded according to a modified National Cancer Institute toxicity grading scale)	***Withdrawals*** One participant declined treatment after enrollment and 18 were non-eligible (nine with two prior chemotherapy regimens for advanced disease, six previously treated with an anthracycline for advanced disease and two previously treated with a vinca alkaloid and one had brain metastases) but all were included in the analyses ***Severe adverse events (first line)*** **Haematological tolerance** Grade 4 anaemia: 1 (2%) Grade 3 anaemia: 7 (12%) Grade 4 leukopenia: 7 (12%) Grade 3 leukopenia: 25 (42%) Grade 4 granulocytopenia: 30 (51%) Grade 3 granulocytopenia: 18 (31%) **Non-haematological tolerance** Grade 3 asthenia: 10 (17%) Grade 3 pain: 3 (5%) Grade 3 fever: 2 (3%) Grade 3 abdominal pain: 2 (3%) Grade 3 dyspnoea: 3 (5%) Grade 4 sepsis: 3 (5%) Grade 3 sepsis: 2 (3%) Grade 3 nausea: 2 (3%) Grade 3 constipation: 3 (5%) Grade 3 vomiting: 2 (3%). Nine participants were hospitalised (fever associated with granulocytopenia). Two died of neutropenic sepsis. G-CSFs were used in 15 patients (nine first line)	***First line*** 12/60 (20%) achieved partial response 9/60 (15%) achieved complete response Overall response rate = 35% (95% CI, 23 to 48) 18/60 (30%) had stable disease Median duration of response = 60 weeks for participants with a complete response and 34 weeks for those with complete or partial responses combined Median time to progression = 17 weeks (n = 59) Median time to treatment failure = 20 weeks Median survival duration = 67 weeks Kaplan–Meier methodology was used in the paper ***Second line*** 12/47 (25%) achieved partial response 3/47 (6%) achieved complete response Overall response rate = 32% (95% CI, 20 to 47) Median time to progression = 18 weeks Median time to treatment failure = 8 weeks Median survival duration = 62 weeks ***Overall*** 24/107 (22%) achieved partial response 12/107 (11%) achieved complete response Overall response rate = 34% (95% CI, 25 to 44) Of 69 participants with cancer-related symptoms at entry, 47% of the first-line and 36% of the second-line participants showed improvement (reduction in intensity) in all self-reported baseline symptoms during the first course of treatment. An additional 17% of first-line and 21% of second-line participants showed improvement in some symptoms from baseline and stability in others. Karnofsky performance status scores for responders remained stable or improved throughout the treatment period	***Author's conclusions*** Single-agent vinorelbine was an effective and well-tolerated agent for first- and second-line therapy of ABC. The results of this study confirmed the findings of similar international trials and suggested that vinorelbine should be considered a valid treatment option for participants with ABC and a potential component in future combination regimens for this disease ***Other comments*** Explicit inclusion/exclusion criteria, although the authors report that 18 non-eligible participants were included in the analyses. Dates of recruitment were not presented. It was unclear how many had ABC or MBC. It was not stated how many participants receiving first-line therapy had previously received anthracyclines or vinca alkaloids in a neoadjuvant setting. Participants with complete response also had to have improvement in cancer-related symptoms and improved Karnofsky performance status, which were also required to be stable or improved for stable disease or partial response. Results were presented separately for first- and second-line chemotherapy. No other subseries were presented. Objective criteria were given for outcome measures

Vinorelbine monotherapy *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Winer *et al.*, 1993[32] ***Country*** USA ***Study design*** Phase II ***Objective*** Not stated (title: A US multicenter Phase II trial of oral Navelbine in elderly women with ABC)	***Inclusion/exclusion criteria*** Measurable or evaluable disease; Karnofsky performance status ≥ 70; > 65 years of age; no prior vinca alkaloid or anthracycline in the metastatic setting; disease free for ≥ 12 months from completion of adjuvant therapy ***Number of participants*** 92 (30 evaluable, of which 22 first line; recruited as of March 1993) ***Age*** Not stated ***Previous treatment*** 72 participants had received no prior chemotherapy for metastatic disease and 26 had received one prior chemotherapy regimen in the metastatic setting ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 50 mg/m^2 orally (for participants with decreased marrow reserve) or 80 mg/m^2 orally on a weekly basis ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** 30 evaluable ***Severe adverse events*** **Haematological tolerance** Grade 4 granulocytopenia: 21% Grade 3 granulocytopenia: 22% **Non-haematological tolerance** Grade 4 fever: 3% Grade 3 nausea: 11% Grade 3 vomiting: 13% Grade 3 malaise: 10% Grade 3 asthenia: 6% Grade 3 diarrhoea: 5% There were five adverse experiences requiring discontinuation of therapy and two deaths	***First line*** 5/22 (23%) achieved partial response 2/22 (9%) achieved complete response Overall response rate = 32% ***Second line*** 2/8 (25%) achieved partial response 0/8 (0%) achieved complete response Overall response rate = 25%	***Author's conclusions*** Oral vinorelbine appeared to be an active and well-tolerated agent in elderly women with ABC. Further evaluation of this agent is warranted ***Other comments*** Abstract only of an ongoing study. Some inclusion and exclusion criteria were presented, but no median age, performance status at study entry, duration of follow-up or survival data were presented. Not enough details were presented to assess the quality of the study. The authors report a sample size of 92, but also report that 72 received first-line chemotherapy and 26 received second-line therapy (n = 98)

Vinorelbine combination therapy

Vinorelbine plus doxorubicin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Alvarez *et al.*, 1994[42] ***Country*** Argentina ***Study design*** Case series (Phase II) ***Objective*** To evaluate the use of vinorelbine plus doxorubicin as first-line chemotherapy for ABC	***Inclusion/exclusion criteria*** Participants with ABC ***Number of participants*** 85 (81 evaluable for toxicity, 70 evaluable for response; recruited April 1991–April 1994) ***Age*** Median = 52 years (no range given) ***Previous treatment*** 26 had had previous hormonal therapy, 44 had had previous adjuvant chemotherapy ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response, overall survival and adverse effects (recorded according to WHO criteria)	***Withdrawals*** None stated. No details of patients not evaluable for toxicity or response were given ***Severe adverse events*** Grade 3–4 haematological: 35/81 Grade 3–4 phlebitis: 1 Grade 3–4 infection: 3 Grade 3–4 nausea/vomiting: 3 There were no drug-related deaths	Overall response = 49/70 (70%) Complete response = 4/70 (6%) Partial response = 45/70 (64%)	***Author's conclusions*** Vinorelbine plus doxorubicin was active as first-line therapy in ABC ***Other comments*** ABC was not defined, and might, therefore, have included locally ABC as well as MBC Abstract only, therefore, few details of study. There was a high response rate, but many patients were not accounted for in terms of response evaluation

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Arca *et al.*, 1998[91] ***Country*** Argentina ***Study design*** Case series (Phase II) ***Objective*** Not stated (title: Navelbine plus doxorubicin as first-line chemotherapy in MBC)	***Inclusion/exclusion criteria*** Participants with MBC without previous chemotherapy ***Number of participants*** 76 (73 evaluable for toxicity, 70 evaluable for response; recruited October 1994–September 1996) ***Age*** Median = 56.39 years (no range given) ***Previous treatment*** 22 had had previous hormonal therapy (14 advanced disease, eight adjuvant) ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response, overall survival and adverse effects (recorded according to WHO criteria)	***Withdrawals*** None stated. No details of patients not evaluable for toxicity or response were given ***Severe adverse events*** Grade 3–4 haematological: 41/314 cycles Grade 3–4 phlebitis: 2 Grade 3–4 infection: 3 Grade 3–4 nausea/vomiting: 7 All participants developed alopecia There were no drug-related deaths	Overall response = 48/70 (68%) Complete response = 7/70 (10%) Partial response = 41/70 (58%) Overall survival = 16 months	***Author's conclusions*** Vinorelbine plus doxorubicin was active as first-line therapy in MBC ***Other comments*** Abstract only. No explicit inclusion/exclusion criteria presented. Data on performance status were not presented. However, response rates by site were presented. Not enough details were presented to assess the quality of the study There was an overlapping recruiting period with the study by Bonicatto *et al.*, 1998[90] (also conducted in Argentina). It is possible that some participants may be included in both studies

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Baltali *et al.*, 1996[43] (interim report also reported in Anonymous 1997[372] and Firat *et al.*, 1997[373]) ***Country*** Turkey ***Study design*** Case series (Phase II) ***Objective*** To assess a new schedule of the combination of vinorelbine plus doxorubicin designed to improve tolerance, particularly cardiac	***Inclusion/exclusion criteria*** ABC previously untreated with chemotherapy ***Number of participants*** 37 included (34 evaluated) ***Age*** Median = 47 years (range 30–67) ***Previous treatment*** No chemotherapy for metastatic disease. Other therapies not stated ***Performance status*** 97% had a performance status of 0–1 (name of classification not stated) ***Stage of disease*** 41% had stage IV disease, 76% had two or more organs involved	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 8, repeated every 21 days, for a maximum of eight cycles Patients received 186 cycles (median = 6, range 1–8) ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse events	***Withdrawals*** Not reported. 34/37 patients evaluated for response and tolerance ***Severe adverse events*** – Neutropenia (WHO criteria grades 3–4) in 23.3% of patients (4.1% of courses) – Grade 3 alopecia in 41% of patients – Nausea/vomiting (grade 3 and 4) in 29% of patients (8% of cycles) – Constipation (grade 4) occurred in one patient (0.5% of cycles) – Grade 3 infection occurred in one patient (0.5% of cycles) – No cardiac impairment > grade 2 seen	Overall response rate = 62% (95% CI, 46 to 78) Complete response rate = 32%	***Author's conclusions*** Given its excellent tolerance profile, low morbidity and easy outpatient administration, vinorelbine plus doxorubicin should be recommended as first-line treatment for ABC/MBC ***Other comments*** This abstract was an interim report of an ongoing study. There were too few details to assess the quality of the study

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Bonicatto *et al.*, 1998[90] ***Country*** Argentina ***Study design*** Case series (Phase II) ***Objective*** Not stated (title: Phase II study of a new time schedule. Navelbine plus doxorubicin in ABC: preliminary report)	***Inclusion/exclusion criteria*** Participants with ABC ***Number of participants*** 52 (48 evaluable for toxicity, 47 evaluable for response; treated between February and September 1996) ***Age*** Median = 54.73 years (range 29–70) ***Previous treatment*** 20 had had chemotherapy, 40 had had hormonal therapy ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 5 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days ***Concurrent treatment*** Not stated ***Duration of follow up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects (WHO criteria)	***Withdrawals*** None stated. No details of patients not evaluable for toxicity or response were given ***Severe adverse events*** Grade 3–4 neutropenia: 9/47 Grade 3–4 thrombocytopenia: 1 Grade 3–4 alopecia: 37 Grade 3–4 phlebitis: 1 Grade 3–4 mucositis: 2 3/47 (6.3%) participants were out of protocol for toxicity There were no drug-related deaths	Overall response = 33/47 (70%) Complete response = 5/47 (11%) Partial response = 28/47 (59%)	***Author's conclusions*** Vinorelbine plus doxorubicin on days 1 and 5 was feasible to administer. Moderate/severe mielotoxicity was 20%. This new approach must be compared with standard administration of vinorelbine on days 1 and 8 ***Other comments*** Abstract only from preliminary results. No explicit inclusion/exclusion criteria presented. It was unclear how many had locally ABC or MBC. The authors reported that 48 were evaluable for toxicity, yet presented percentages out of a sample size of 47. Not enough details were presented to assess the quality of the study There was an overlapping recruiting period with the study by Arca *et al.*, 1998[91] (also conducted in Argentina). It is possible that some participants may be included in both studies

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Coppola *et al.*, 1994[44] ***Country*** Argentina ***Study design*** Phase II ***Objective*** Not stated (Title: Vinorelbine-containing regimens in three different schedules for the treatment of ABC)	***Inclusion/exclusion criteria*** Participants with ABC ***Number of participants*** 165 (group A = 76 (73 evaluable for toxicity, 60 evaluable for response), group B = 72 (69 evaluable for toxicity and response), group C = 17 (16 evaluable for toxicity and response); recruited April 1991–October 1993) ***Age*** Group A median = 53 years Group B median = 53 years Group C median = 51 years ***Previous treatment*** Not stated ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First and second line ***Intervention*** **Group A (first line)** Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 21 days **Group B (for those who had progressed or were anthracycline-resistant)** Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitomycin 7 mg/m^2 on day 1, repeated every 28 days **Group C (for those who had progressed or were anthracycline-resistant)** Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitoxantrone 8 mg/m^2 on day 1, repeated every 28 days ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** The authors report that 16 participants abandoned treatment due to toxicity ***Severe adverse events*** Toxicity grade 3–4 was observed in 64/602 courses **Haematological toxicities (grade 3–4)** Group A: 27 Group B: 5 Group C: 8 **Non-haematological toxicities (grade 3–4)** Group A: 10 Group B: 12 Group C: 3 Alopecia = 100% in group A (non-evaluable in groups B and C)	***First line*** **Group A** 5/60 (8%) participants achieved complete response 37/60 (62%) achieved partial response Overall response rate = 42/60 (70%, 95% CI, 58.4 to 81.6) ***Second line*** **Group B** 7 participants achieved complete response 26 achieved partial response **Group C** None achieved complete response 5 participants achieved partial response For groups B and C combined, overall response = 38/89 (42%, 95% CI, 31.8 to 52.2)	***Author's conclusions*** These results encourage us to test vinorelbine in RCTs with polichemotherapy in ABC ***Other comments*** Abstract only. Inclusion and exclusion criteria, performance status at study entry, duration of follow-up and survival data were not presented. Adverse effects were not fully reported. Not enough details were presented to assess the quality of the study Response rates presented for groups B and C were not clear given the number of evaluable participants reported in a table

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Hegg *et al.*, 2001[45] (earlier reports of this study with fewer patients were given in Costa *et al.*, 1996[374] (after 50 patients had been included and when 28 were evaluable for tolerability and 22 for response), Cabral Filho *et al.*, 1997[375] (after 50 patients had been included) and Anelli *et al.*[376] and Hegg *et al.*, 1999[132] (after 51 patients had been included and when 50 were evaluable for tolerability and 43 for response) ***Country*** Brazil ***Study design*** Case series (Phase II) ***Objective*** To assess a new schedule of vinorelbine plus doxorubicin	***Inclusion/exclusion criteria*** Histologically proven MBC with no previous chemotherapy for metastatic disease; measurable disease with defined index lesions; adjuvant therapy with anthracycline ≥ 12 months before trial; other adjuvant chemotherapy ≥ 6 months before; performance status ≤ 2; adequate bone marrow, renal and hepatic function; age ≤ 75 years; expected survival ≥ 3 months ***Number of participants*** 52 (51 evaluable for tolerance and 47 evaluable for response) ***Age*** Not stated, but median = 51 years (range 33–73) from earlier reports ***Previous treatment*** None for MBC 11 (21%) had had adjuvant hormonal therapy and one (2%) had had adjuvant chemotherapy ***Performance status (WHO)*** 0: 26 1: 21 2: 5 ***Stage of disease*** 46% had predominantly visceral involvement	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 8, repeated every 21 days, for a maximum of eight cycles ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated Kaplan-Meier curves were presented that ran up to 220 weeks ***Outcome measures*** The outcome measures were response, time to progression, overall survival and adverse effects (recorded according to WHO criteria) Assessment of response was performed according to WHO criteria after every two cycles of therapy, by repeating those clinical, laboratory or radiological assessments appropriate for defining the extent of the disease at presentation	***Withdrawals*** Not stated, but study ongoing ***Severe adverse events*** Grade 3–4 neutropenia: 49/299 (16.3%) cycles Grade 3-4 anaemia: 5/310 (1.6%) cycles Leukopenia: 24/311 (7.7%) cycles Grade 3–4 reduction in alkaline phosphatase: 3/219 (1.4%) cycles Grade 3 reduction in alanine aminotransferase: 1/232 cycles Grade 3 nausea/vomiting: 16/318 cycles Grade 3 infection: 5/318 (1.6%) cycles Grade 3 stomatitis: 6/317 (1.9%) cycles Grade 3 alopecia: 34 patients Grade 3 phlebitis: 6 patients Grade 3 diarrhoea: 1 patient Grade 3 peripheral neuropathy: 1 patient Grade 4 constipation: 1 patient	Overall response rate = 38/47 (73.1%, 95% CI, 61 to 85.1) when analysed on ITT Complete response rate = 9/47 (19%) Partial response rate = 29/47 (62%) Median response duration = 16 months (range 2–48) Median survival = 22.7 months (range 1–48) Kaplan–Meier curves were presented	***Author's conclusions*** We conclude that the fractionated administration of vinorelbine and doxorubicin was associated with excellent haematological and non-haematological tolerability (especially as regards cardiotoxicity), coupled with high levels of activity comparable to those observed using regimens based on unfractionated administration of treatment ***Other comments*** Full manuscript. Details on inclusion and exclusion criteria. All patients had MBC and no prior chemotherapy. Details were presented on follow-up. The definitions used for response (complete and partial response, stable disease and progressive disease) were presented. All responses and major toxicities were reviewed by a panel of independent oncologists and radiologists. There were some details on subgroups

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Hochster *et al.*, 2001[46] (also reported (vinorelbine versus doxorubicin section only) in Hochster *et al.*, 1994[133] and in a review article by Hochster, 1995[377]) ***Country*** USA ***Study design*** Phase II prospective uncontrolled study (P70-07) ***Objective*** To evaluate the efficacy and safety of vinorelbine combined with doxorubicin or continuous infusion of 5-fluorouracil as initial therapy for ABC This was not a randomised comparative study so vinorelbine plus doxorubicin data have been extracted separately to that of FUN	***Inclusion/exclusion criteria*** Microscopically confirmed, bi-dimensionally measurable ABC; no chemotherapy for ABC; no surgery within 2 weeks or radiotherapy within 3 weeks; adjuvant chemotherapy had to have finished ≥ 12 months before study; no previous anthracycline therapy; no metastatic disease of CNS; no malignancy within 5 years; no clinically significant peripheral neuropathy; no unstable medical condition; no active heart disease, uncontrolled heart disease or history of congestive heart failure; performance status (Karnofsky) < 70; adequate bone marrow and hepatic function. Patients who had received adjuvant anthracycline therapy, had active cardiac disease and were not considered good candidates for doxorubicin or had a left ventricular ejection fraction < 50% were stratified to receive the alternative drug combination FUN ***Number of participants*** 62 (enrolled July 1991–August 1994) ***Age*** Median = 59.5 years (range 30–85) ***Previous treatment*** 36 (58%) had had hormonal therapy, 25 (40%) had had adjuvant chemotherapy (none anthracycline, 39% CMF) ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 3 weeks until disease progression or severe toxicity ***Concurrent treatment*** None. Haematological growth factors were not used prophylactically ***Duration of follow-up*** 25 months after last patient was enrolled ***Outcome measures*** The outcome measures were response (standard objective criteria specified in paper), progression-free survival (standard objective criteria specified in paper), overall survival (standard objective criteria specified in paper) and adverse effects (graded according to modified National Cancer Institute Adverse Events Criteria)	***Withdrawals*** Efficacy and safety parameters were evaluated in all enrolled subjects (ITT analyses) ***Severe adverse events (all grade 3–4)*** Granulocytes: 59 (95%) Leukopenia: 46 (74%) Anaemia: 15 (24%) Alkaline phosphatase: 20 (33%) Aspartate aminotransferase: 3 (5%) Alanine aminotransferase: 3 (5%) Total bilirubin: 2 (3%) Creatinine: 2 (3%) Alopecia: 16 (26%) Asthenia: 8 (13%) Nausea: 5 (8%) Stomatitis: 6 (9%) Vomiting: 4 (6%) Anorexia: 1 (2%) Diarrhoea: 3 (5%) Constipation: 3 (5%) Fever: 6 (10%) Paraesthesia: 3 (5%) Hypesthesia: 2 (3%) Cardiovascular event: 4 (6%) Pain: 2 (3%) Abdominal pain: 1 (2%) Sepsis: 4 (6%) One patient died of neutropenic sepsis	Overall response rate = 34/62 (55%, 95% CI, 42 to 68) Complete response rate = 7 (11%) Partial response rate = 27 (44%) Stable disease rate = 18 (29%) Progressive disease rate = 5 (8%) Not evaluable = 5 (8%) Not reported = 0 Median time to progression = 34 weeks Median time to treatment failure = 32 weeks Median survival = 92 weeks (95% CI, 72 to 128) The 1-year survival rate = 75.5% One participant remained on study as of the data cut-off date of December 1996. The primary reasons for discontinuation in the remaining 117 subjects (including those treated with FUN) were disease progression (n = 57, 49%), symptoms/toxicities/adverse experiences (n = 27, 23%), failure to return or refused treatment (n = 10, 9%), death (n = 8, 7%) and other (n = 15, 13%)	***Author's conclusions*** Vinorelbine plus doxorubicin offered a useful option as initial therapy for ABC. The regimen was associated with predictable but manageable toxicity ***Other comments*** Not completely certain that all patients had MBC rather than some locally ABC. Paper used term ABC rather than MBC. Reference to earlier report in Hochster *et al.*, 1994[133] suggested that the study was of MBC rather than any mix Clear inclusion/exclusion criteria, long follow-up, objective criteria used for assessments and subgroups detailed Multicentre study (13 centres) Seventeen participants (out of the total sample of 118) were enrolled as exceptions to the entry criteria, such as completion of prior therapy within 2 weeks of enrolment (n = 8, 7%), haematological or laboratory abnormality (n = 8, 7%), history of other malignancy (n = 2, 2%) or a combination thereof. Reasons for discontinuation and exceptions to the entry criteria were evenly distributed between the two treatment groups

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Siedlecki *et al.*, 1997[47] (also reported as an abstract by Pawlicki *et al.*, 1996[142]) Ongoing study ***Country*** Poland ***Study design*** Case series (Phase II) ***Objective*** Evaluation of a new schedule of vinorelbine plus doxorubicin	***Inclusion/exclusion criteria*** ABC ***Number of participants*** 37 (recruitment ongoing; 34 evaluable for response and 35 evaluable for toxicity) ***Age*** Median = 57 years (range 34–74). ***Previous treatment*** 26% had had adjuvant chemotherapy (CMF), 29% had had adjuvant hormonal therapy, 23% had had radiotherapy ***Performance status*** 0 or 1 ***Stage of disease*** The disease site was breast in 50% of patients, nine patients had a single involved site	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 8 for a maximum of eight cycles. Duration of cycle not stated ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** None stated ***Severe adverse events*** Grade 4 granulocytopenia: 5.7% Grade 3 granulocytopenia: 20% Grade 3 alopecia: 44% There were no toxic deaths	Overall response rate = 25/34 (73.5%) Complete response rate = 8/34 (23%) Partial response rate = 17/34 (50%) Stable disease rate = 6/34 (17%)	***Author's conclusions*** These preliminary results confirmed the high activity of this vinorelbine plus doxorubicin combination as first-line ABC therapy and the excellent tolerance profile of this new days 1 and 8 schedule allowed an easy outpatient treatment ***Other comments*** Performance status of all patients was 0 or 1, there were no patients with a performance status of 2 Abstract with only few details of study. No definition of ABC, thus unclear if MBC only or included locally ABC Multicentre study

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Smalley *et al.*, 1994[48] ***Country*** USA ***Study design*** Case series (Phase I–II) ***Objective*** To evaluate vinorelbine plus doxorubicin on a days 1 and 4 schedule with G-CSF to prevent neutropenia	***Inclusion/exclusion criteria*** ABC ***Number of participants*** 34 ***Age*** Median = 62 years (range 33–77) ***Previous treatment*** 16 had had adjuvant chemotherapy (four included doxorubicin), 12 had had prior radiotherapy ***Performance status*** Not stated ***Stage of disease*** Definition of ABC not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus doxorubicin 25 mg/m^2 on days 1 and 4 (19 patients were treated with vinorelbine at a reduced dose of 20 mg/m^2) ***Concurrent treatment*** Prophylactic ciprofloxacin to reduce incidence of febrile neutropenia. G-CSF given after cycle 1 to reduce neutropenia – details not given ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** Not stated ***Severe adverse events (toxicity on first cycle)*** Grade 4 neutropenia: 81% Grade 3 neutropenia: 19% Grade 3–4 stomatitis: 1 patient Grade 3–4 vomiting: 3 patients Grade 3–4 nausea: 4 patients Hospitalisation for febrile neutropenia: 7 (21%) There were two treatment deaths during whole study A depressed left ventricular ejection fraction was noted in one patient after four cycles	Overall response rate = 10 (29%, 95% CI, 14 to 44) Complete response occurred in 2 patients Partial response occurred in 8 patients	***Author's conclusions*** Toxicity was significant but could be modified. Further explorations with this two-drug combination are warranted using more aggressive support or utilising different doses or schedules ***Other comments*** Abstract with only few details to assess quality. No definition of ABC given, thus unclear if all patients had MBC

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Spielmann et *al.*, 1994[49] (also reported in Spielmann *et al.*, 1992,[99] Turpin *et al.*, 1991[378] and an interim report by Spielmann *et al.*, 1990,[379] and described in a brief review-type article by Spielmann, 1996[160]) ***Country*** France ***Study design*** Case series (Phase II) prospective uncontrolled study ***Objective*** To investigate the therapeutic effects of a combination of vinorelbine plus doxorubicin as first-line treatment for locally ABC or MBC	***Inclusion/exclusion criteria*** Histologically proven locally ABC or MBC with progressive and measurable disease and defined index lesion; any adjuvant chemotherapy completed ≥ 6 months before and any anthracycline ≥ 12 months before study; any hormonal therapy discontinued ≥ 4 weeks before study; performance status ≤ 2; expected survival ≥ 3 months; adequate bone marrow, renal or hepatic function; age ≤ 70 years; no other cancer, brain involvement or leptomeningeal disease ***Number of participants*** 97 (recruited August 1989–April 1990; 89 evaluable for response and toxicity) ***Age*** Median = 55 years (range 25–70) ***Previous treatment*** 28 (31%) had had hormonal therapy, 27 (30% had had neoadjuvant/adjuvant chemotherapy, 20 (22%) had had prior anthracycline ***Performance status*** 0: 45 (51%) 1: 28 (31%) 2: 16 (18%) ***Stage of disease*** Three patients with locally ABC (stage III)	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 3 weeks ***Concurrent treatment*** None permitted ***Duration of follow-up*** Median = 22.5 months (range 3.7–45.8) ***Outcome measures*** The outcome measures were response (objective WHO criteria and standard statistical methods used and detailed in paper), progression-free survival, overall survival and adverse effects (using WHO criteria)	***Withdrawals*** Eight patients not evaluable. Six were ineligible: one due to illness near start of study and five due to violations of inclusion/exclusion criteria. Two were excluded from the analysis: one due to early death (reason unknown) and one due to protocol violation ***Severe adverse events*** Grade 4 leukopenia: 5 (6%) Grade 3 leukopenia: 9 (10%) Grade 4 neutropenia: 13 (15%) Grade 3 neutropenia: 23 (26%) Grade 4 anaemia: 1 (1%) Grade 3 anaemia: 5 (6%) Grade 4 constipation: 1 (1%) Grade 3 constipation: 2 (2%) Grade 4 mucositis: 2 (2%) Grade 3 mucositis: 9 (10%) Grade 4 cardiac: 3 (4%) Grade 3 cardiac: 1 (1%) Grade 3 alopecia: 56 (63%) Grade 3 nausea/vomiting: 11 (12%) Grade 3 neuropathy: 1 (1%) 50 patients developed fever during treatment and four developed neutropenic sepsis, two of which were fatal. One patient was hospitalised for paralytic ileus (grade 4 constipation). Cardiac toxicity was noted in nine patients (two had received previous anthracycline chemotherapy)	Overall response rate = 66/89 (74%, 95% CI, 65 to 85) Complete response rate = 19 (21%) Partial response rate = 47 (53%) Stable disease rate = 20 (22%) Progressive disease rate = 3 (3%) Median time to first objective response = 1.8 months (range 1–4.5) Median response duration = 12 months (range 2.4–40.5) Median survival = 27.5 months (range 4–46) Kaplan–Meier curves were presented	***Author's conclusions*** The encouraging response rates and duration achieved with this combination of vinorelbine plus doxorubicin under the conditions of this study deserve further RCTs with standard regimens ***Other comments*** The three patients with locally ABC rather than MBC were permitted to have locoregional therapy (surgery and/or radiotherapy). Response duration was calculated from first day of treatment until date of locoregional therapy 17 patients with stage IV disease (n = 14) or stage III disease (n = 3) had no prior therapy Clear inclusion criteria: all MBC and first line except for three patients; long follow-up; objective assessment criteria detailed; subgroups described

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Vorobiof *et al.*, 1997[50] (ongoing evaluation) ***Country*** South Africa ***Study design*** Case series (Phase II), prospective uncontrolled study ***Objective*** To evaluate the efficacy and tolerability of the combination of vinorelbine plus doxorubicin	***Inclusion/exclusion criteria*** ABC with no previous chemotherapy. ABC included MBC and locally ABC ***Number of participants*** 40 (24 patients evaluable for response and tolerability) ***Age*** Median = 47.7 years (range 25–69) ***Previous treatment*** Not stated ***Performance status*** 0–1 ***Stage of disease*** MBC: 77% Locally ABC: 70%	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus doxorubicin 50 mg/m^2 on day 1, repeated every 3 weeks ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** Not reported ***Severe adverse events*** Grade 4 neutropenia: 15% Grade 3 neutropenia: 27% (two patients died due to neutropenia) Grade 3 alopecia: 69% Grade 3 nausea/vomiting: 15% Grade 3 stomatitis: 11.5% Grade 3 phlebitis: 4%	Overall response rate = 54% (95% CI, 34 to 74) Complete response rate = 8% Partial response rate = 46%	***Author's conclusions*** Given the large tumour bulk of local disease in these patients, very good results and tolerance were documented ***Other comments*** Abstract, therefore, very few details of study. No long-term follow-up. Mixed group of MBC and locally ABC

Vinorelbine combination therapy *contd*

Vinorelbine plus epirubicin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Baldini *et al.*, 1998[51] (this study was also reported as an abstract by Tibaldi *et al.*, 1996[380]) ***Country*** Italy ***Study design*** Case series (Phase II) ***Objective*** To investigate the toxicity and activity of the combination epirubicin plus vinorelbine in chemotherapy-naïve patients with MBC	***Inclusion/exclusion criteria*** Histologically confirmed MBC with measurable or evaluable disease; ECOG performance status ≤ 2; no previous chemotherapy or hormonal therapy for metastatic disease; ≥ 6 months since any adjuvant chemotherapy; ≤ 4 weeks since any other hormonal therapy; normal haematology, liver and renal function; no other serious medical condition and no brain metastases ***Number of participants*** 51 (47 evaluated) ***Age*** Median = 68 years (range 36–72) ***Previous treatment*** Nine patients had had non-anthracycline based adjuvant chemotherapy, 13 had had hormonal adjuvant therapy and five had had chemotherapy and hormonal adjuvant ***Performance status (ECOG)*** 0: 27 1: 13 2: 11 ***Stage of disease*** All metastatic: 33 patients (64.7%) had ≥ 2 metastatic sites; 70.6% of patients had visceral disease	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 90 mg/m^2 on day 1, repeated every 21 days (maximum of eight cycles) ***Concurrent treatment*** No prophylatic use of G-CSF, but it was to be used in cases of febrile neutropenia and/or grade 4 neutopenia lasting longer than 72 hours. It was used in 12.6% of courses. Ciprofloxacin and fluconazole used for grade 4 neutropenia ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (assessed according to WHO criteria and performed after three courses of chemotherapy), progression-free survival (WHO criteria), overall survival and adverse effects (WHO criteria)	***Withdrawals*** Four patients were not evaluable for response. Two stopped treatment due to worsening of performance status and two were lost to follow-up ***Severe adverse events (% of courses)*** Grade 3 neutropenia: 16% Grade 4 neutropenia: 70% Grade 3 thrombocytopenia: 1.2% Grade 3 anaemia: 0.8% Grade 4 anaemia: 0.4% Grade 3 nausea/vomiting: 2% Grade 3 mucositis: 5.1% Grade 3 diarrhoea: 1.2% 20/252 courses were delayed due to side-effects, including one case of grade 4 anaemia. One patient was hospitalised due to paralytic ileus and one due to febrile neutropenia	Overall response rate = 33/47 (70.2%, 95% CI, 55.1 to 82.6) Complete response rate = 4/47 (8.5%) Partial response rate = 29/47 (61.7%) Stable disease rate = 11/47 (23.4%) Progressive disease rate = 3/47 (6.4%) Median duration of overall response = 10 months (range 1–21) Median duration of complete response = 11 months (range 6–19) Median duration of partial response = 8 months (range 2–18) Median time to progression = 11 months (range 1–21+) Median overall survival = 23 months (range 2–32) Kaplan–Meier curves were presented up to 30 weeks	***Author's conclusions*** The combination epirubicin plus vinorelbine was feasible in the majority of MBC patients in a multicentre setting, was highly active and was devoid of severe toxicities. RCTs are warranted ***Other comments*** Clear inclusion and exclusion criteria and all patients had MBC with no previous chemotherapy. Follow-up was adequate for assessment of response only. WHO criteria used for assessment. Patient details given by performance status, prior therapy, type of disease, etc Simon's optimal two-stage design for clinical trials was used to calculate sample size and to minimise the expected number of patients to be accrued in case of low activity of the combination Total number of courses was 252 and G-CSF was used in 12% of courses

Vinorelbine combination therapy *contd*

Vinorelbine plus epirubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Cottu *et al.*, 1993[52] ***Country*** France ***Study design*** Case series (Phase II) ***Objective*** Vinorelbine plus epirubicin as first-line chemotherapy in MBC	***Inclusion/exclusion criteria*** MBC with one measurable lesion outside irradiated site; a performance status score of 2 ***Number of participants*** 19 ***Age*** Median = 59 years (range 40–70) ***Previous treatment*** Nine had received adjuvant therapy (seven with anthracyclines) ***Performance status*** 2 ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on days 1 and 8 plus epirubicin 60 mg/m^2 on day 1, repeated every 21 days ***Concurrent treatment*** Patients with grade 3 vomiting received granisetron/ondansetron ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** Not stated ***Severe adverse events*** Grade 3–4 leukopenia: 44/67 evaluable courses Three patients had neutropenic fever Grade 3 vomiting: 2/67 courses	Response rates were not reported Statistical analysis used a group sequential design (triangular test) with an analysis every eight patients. The null hypothesis (H_o) was the lowest acceptable response rate, 50%, and the H_a was the response rate to be reached (70%). Two sequential groups were analysed after three cycles and neither H_o or H_a could be rejected	***Author's conclusions*** The toxicity of this regimen was acceptable and accrual is ongoing ***Other comments*** Ongoing study: accrual and follow-up Reported only as an abstract and, therefore, insufficient details to assess if representative sample, if inclusion/exclusion criteria were explicit and if assessment was objective. All patients had MBC with no previous chemotherapy for metastatic disease, but disease-free interval ranged from 0 to 172 months (median 39.5)

Vinorelbine combination therapy *contd*

Vinorelbine plus epirubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Ezzat *et al.*, 1996[53] ***Country*** Saudi Arabia ***Study design*** Case series (Phase II) ***Objective*** To assess the efficacy of a combination of epirubicin plus vinorelbine as first-line chemotherapy in ABC	***Inclusion/exclusion criteria*** ABC with no previous chemotherapy; performance status of 0–1; ABC included inoperable locally ABC and MBC ***Number of participants*** 28 ***Age*** Not stated ***Previous treatment*** Not stated ***Performance status*** 0–1: 96% (numbers not stated) ***Stage of disease*** Ten participants had locally ABC and 18 MBC; 72% had visceral involvement	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 60–75 mg/m^2 on day 1, repeated every 21 days for a maximum of eight cycles ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** Four patients not accounted for (two had locally ABC and two had MBC) ***Severe adverse events (% of patients)*** WHO grade 3–4 neutropenia: 25% Grade 3 infection: 3.5% Grade 3 nausea/vomiting: 18% Grade 3 constipation: 3.5% Grade 3 alopecia: 67.8%	***MBC patients*** 6/16 responded to therapy 6% had complete response ***Locally ABC*** 6/8 (75%) responded to therapy 5/8 had partial response 1/8 had complete response Overall response rate = 50% (95% CI, 30 to 70)	***Author's conclusions*** Vinorelbine plus epirubicin should be recommended in first-line treatment for ABC/MBC ***Other comments*** Abstract only, therefore, very limited information on study Results did not support conclusion Insufficient information to assess if sample was representative or if inclusion criteria were explicit. ABC and MBC included. Follow-up not stated, but appeared adequate only for response rate. No information on assessment methods or sub-groups. Previous treatment was not stated

Vinorelbine combination therapy *contd*

Vinorelbine plus epirubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Nistico *et al.*, 1999[54] (this study was also reported by Nistico *et al.*, 1997[381] and as interim reports by Nistico *et al.*, 1996,[382] Nistico *et al.*, 1996[383] and Nistico *et al.*, 1995[179]) ***Country*** Italy ***Study design*** Case series (Phase II), prospective uncontrolled study ***Objective*** To explore the effectiveness and tolerability of a weekly regimen of epirubicin plus vinorelbine with G-CSF	***Inclusion/exclusion criteria*** Histologically documented MBC with measurable or assessable lesions; no previous chemotherapy for MBC or adjuvant anthracyclines in the last 2 years; previous maximum dose of doxorubicin of 300 mg/m^2 and of epirubicin of 480 mg/m^2; life expectancy ≥ 3 months; age ≤ 75 years; ECOG performance status ≤ 3; adequate bone marrow, renal, hepatic and cardiac function; no active cardiac disease and left ventricular ejection fraction ≥ 50%; no brain metastases ***Number of participants*** 52 (recruited April 1994–July 1996; all assessable for response and toxicity) ***Age*** Median = 57 years (range 31–71) ***Previous treatment*** Four had had adjuvant hormonal therapy, 17 had had MBC hormonal therapy, 35 had had adjuvant chemotherapy (five with anthracyclines and 30 with CMF) ***Performance status (ECOG)*** 0: 23 1: 18 2: 8 3: 3 ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus epirubicin 25 mg/m^2 once a week for 24 weeks in the absence of progression ***Concurrent treatment*** To help attain high-dose intensity, G-CSF was given in the first 35 patients if neutropenia developed, but prophylactically in the remaining 17 patients. Vomiting was prevented with ondansetron given as premedication and dexamethasone given after chemotherapy ***Duration of follow-up*** Median = 24 months (range 9–40) ***Outcome measures*** The outcome measures were response (WHO criteria and objective criteria reported for duration of response), progression-free survival, overall survival and adverse effects (WHO criteria)	***Withdrawals*** None ***Severe adverse events*** Grade 4 neutropenia: 10% Grade 3 neutropenia: 29% Grade 3 anaemia: 2% Cardiological: 4% Local pain/phlebitis: 13% Alopecia: 27% Asthenia: 13% No episodes of febrile neutropenia or neutropenic sepsis Grade 3 cardiotoxicity included one acute myocardial infarction and one cardiac failure	Overall response = 40/52 (77%, 95% CI, 66 to 88) Complete response rate = 10 (19%) Partial response rate = 30 (58%) Stable disease rate = 12 (23%) Progressive disease = 0 Median response duration = 10 months (range 4–16) Median time to progression = 10 months (range 4–24) Median survival = 31 months 24-month survival rate = 61% Kaplan–Meier curves were presented	***Author's conclusions*** Owing to its effectiveness and tolerability, the weekly regimen of epirubicin plus vinorelbine with G-CSF may represent an acceptable alternative for patients with untreated MBC ***Other comments*** Unusual to have any patients with a performance status of 3 included Clear inclusion and exclusion criteria. All patients had MBC with first-line therapy. Adequate follow-up and objective criteria used for assessment. Differences in response rates between subseries were compared using χ^2 test. Results were not presented, it was merely stated that there was no significant difference

Vinorelbine combination therapy *contd*

Vinorelbine plus epirubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Tabiadon *et al.*, 1998[55] (ongoing study) ***Country*** Italy ***Study design*** Case series (Phase II), prospective uncontrolled study ***Objective*** Vinorelbine plus epirubicin for MBC in patients who have previously received CMF or anthracycline or after hormonal therapy for metastatic disease	***Inclusion/exclusion criteria*** Patients with MBC who had relapsed following adjuvant therapy containing CMF or anthracycline, or after hormonal therapy for metastatic disease ***Number of participants*** 19 (17 evaluable for response and all evaluable for toxicity) ***Age*** Median = 55.3 years (range 33–68) ***Previous treatment*** **Chemotherapy** Adjuvant CMF: 11 Adjuvant anthracycline or CMF: 5 **Hormonal therapy** Adjuvant tamoxifen: 3 Tamoxifen for MBC: 2 ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Epirubicin 80 mg/m^2 on day 1 plus vinorelbine 25 mg/m^2 on days 1 and 8, repeated every 21–28 days ***Concurrent treatment*** G-CSF started whenever neutropenia of at least grade 2 occurred ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response, progression-free survival, overall survival and adverse effects	***Withdrawals*** Two patients not evaluable for response ***Severe adverse events*** Grade 2–3 mucositis: 31.5% Grade 3 alopecia: 89.4% Grade 3–4 neutropenia: 36.8% Cardiotoxicity: 0	Overall response = 13/17 (76.4%) Complete response = 1/17 Partial response = 12/17 Time to progression = 7+ months Survival = 7+ months	***Author's conclusions*** These preliminary data suggest high activity of this schedule with acceptable toxicity in MBC in patients pretreated with anthracycline in adjuvant setting ***Other comments*** Abstract only with few details of methodology

Vinorelbine combination therapy *contd*

Vinorelbine plus epirubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Vici *et al.*, 1999[56] (preliminary data: ongoing study) ***Country*** Italy ***Study design*** Case series (Phase II) prospective uncontrolled study ***Objective*** Specific dose regimen of vinorelbine plus epirubicin as first-line therapy in MBC	***Inclusion/exclusion criteria*** MBC, no previous chemotherapy for MBC ***Number of participants*** 54 (recruited from November 1997; 46 evaluable patients) ***Age*** Median = 61 years (range 25–71) ***Previous treatment*** Hormonal: 25 Adjuvant chemotherapy (CMF): 20 ***Performance status (WHO)*** Median = 1 (range 0–3) ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 5 plus epirubicin 100 mg/m^2 on day 1, repeated every 3 weeks ***Concurrent treatment*** G-CSF 300 g/day was given on days 7–12 of each cycle ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response, progression-free survival, overall survival and adverse effects	***Withdrawals*** One patient refused treatment ***Severe adverse events*** Grade 4 neutropenia: 39% Neutropenic fever: 35% Grade 3 mucositis: 39% Grade 3 anaemia: 12% Grade 3 alopecia: 100% No cardiotoxicity	Overall response in 33/46 (72%) Complete response in 7/46 (15%) Partial response in 26/46 (57%) Median time to progression and median survival not yet reached	***Author's conclusions*** Preliminary data suggested a very high activity of this combination as first-line treatment in MBC, with manageable toxicity ***Other comments*** Abstract, therefore, few details of study. All MBC and first line

Vinorelbine combination therapy *contd*

Vinorelbine plus paclitaxel

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Ibrahim *et al.*, 2001[57] (also reported by Ibrahim *et al.*, 1995[201]) ***Country*** USA ***Study design*** Case series (Phase I) ***Objective*** To determine maximum tolerated doses with and without G-CSF of combination of vinorelbine plus paclitaxel	***Inclusion/exclusion criteria*** Microscopically confirmed MBC with no prior chemotherapy for MBC; bidimensionally measurable disease; performance status of 0–2; life expectancy > 16 weeks; adequate bone marrow, renal and hepatic function; no uncontrolled cardiac disease, metastases to CNS or other malignancy in previous 5 years; no significant peripheral neuropathy not due to MBC ***Number of participants*** 38 (recruited January 1994–January 1995; 25 without G-CSF, 13 with G-CSF) ***Age*** Without G-CSF: median = 47 years (range 34–72) With G-CSF: median = 55 years (range 36–73) ***Previous treatment*** **Adjuvant chemotherapy** Without G-CSF: 20 With G-CSF: 6 **Prior anthracycline** Without G-CSF: 17 With G-CSF: 5 ***Performance status*** **Without G-CSF** 0–1: 24 2: 1 **With G-CSF** 0–1: 8 2: 5 **Stage of disease** All MBC	***Line of therapy*** First line ***Intervention*** The starting doses were paclitaxel 175 mg/m^2 plus vinorelbine 36 mg/m^2 (on day 1?) every 3 weeks. In the without G-CSF group, the doses were reduced to vinorelbine 25 mg/m^2 plus paclitaxel 150 mg/m^2. In the with G-CSF group, vinorelbine could range from 25 to 46 mg/m^2 and paclitaxel could be reduced to 150 mg/m^2 ***Concurrent treatment*** Premedication included dexamethasone, diphenylhydramine and cimetadine, and prophylactic G-CSF in some patients ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects (using the National Cancer Institute grading system)	***Withdrawals*** None ***Severe adverse events (number of cycles (%))*** **Without G-CSF** Grade 3–4 granulocytopenia: 135 (72%) Grade 3–4 neutropenic fever: 14 (7%) Hospitalisations: 17 (9%) Grade 3–4 sensory: 7 (4%) Grade 3–4 myalgia: 6 (3%) Grade 3–4 fatigue: 21 (11%) Grade 3–4 pelvic pain: 3 (2%) Grade 3–4 diarrhoea: 2 (1%) Grade 3–4 stomatitis: 1 (1%) Grade 3–4 bone pain: 1 (1%) **With G-CSF** Grade 3–4 granulocytopenia: 25 (23%) Grade 3–4 neutropenic fever: 1 (1%) Hospitalisations: 0 (0%) Grade 3–4 sensory: 7 (6%) Grade 3–4 myalgia: 1 (1%) Grade 3–4 fatigue: 13 (12%) Grade 3–4 bone pain: 1 (1%)	***Without G-CSF*** Overall response = 40% Complete response = 1 Partial response = 9 Stable disease = 12 Progressive disease = 3 (12%) Median time to progression = 17 weeks (range 6–56) ***With G-CSF*** Overall response = 61% Complete response = 2 Partial response = 6 Stable disease = 3 Progressive disease = 2 (15%) Median time to progression = 31 weeks (range 9–41)	***Author's conclusions*** Vinorelbine plus paclitaxel could be safely administered concomitantly and were well tolerated ***Other comments*** Phase I study only. Clear inclusion/exclusion criteria, all MBC with no prior chemotherapy, follow-up not clear, assessment methods not stated, no disease subgroups

Vinorelbine combination therapy *contd*

Vinorelbine plus paclitaxel *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Martin, 1999[58] ***Country*** Spain ***Study design*** Case series (Phase II) ***Objective*** Vinorelbine plus paclitaxel in MBC in patients previously treated (as adjuvant or for metastatic) with anthracyclines	***Inclusion/exclusion criteria*** MBC; previously treated (as adjuvant or for metastatic) with anthracyclines ***Number of participants*** 50 (17 first line, 18 second line and 15 third or fourth line) ***Age*** Median = 54 (range 28–78) ***Previous treatment*** Anthracyclines (anthracycline for MBC in 19 patients, as adjuvant in 21, as both in 10) ***Performance status*** Not stated ***Stage of disease*** All patients had at least one metastatic site (mean = 2, range 1–5). 35 participants had visceral involvement	***Line of therapy*** First or second line or greater ***Intervention*** Vinorelbine 30 mg/m^2 plus paclitaxel 135 mg/m^2 on day 1 every 3 weeks ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects (using common toxicity criteria)	***Withdrawals*** None reported ***Severe adverse events*** One patient died of pneumonia during neutropenia. The other main toxicities were: Neutropenic fever: 18% Grade 2–3 peripheral neuropathy: 18% Grade 2–3 arthralgia/ myalgia: 44% Grade 2 alopecia: 94%	***First line*** Overall response rate = 59% ***Second line*** Overall response rate = 50% ***Third or fourth line*** Overall response rate = 40% ***All patients (n = 50)*** Overall response rate = 50% (95% CI, 35.5 to 64.5) Complete response = 6 Partial response = 19 ***Patients treated previously with anthracyclines*** Overall response rate = 9/19 (47%)	***Author's conclusions*** 1-day paclitaxel plus vinorelbine was safe, easy to administer and active in patients with MBC who had had prior anthracycline therapy. Refractoriness to anthracyclines apparently did not affect response to this regimen ***Other comments*** This study did **not** appear to be the same as that reported in Martin *et al.*, 2000.[59] Later paper had 56 patients but fewer patients treated as first line (15 versus 17) and fewer treated with adjuvant anthracycline (17 versus 21) or for MBC (17 versus 19) Abstract only, therefore, limited details to assess quality of study

Vinorelbine combination therapy *contd*

Vinorelbine plus paclitaxel *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Martin *et al.*, 2000[59] ***Country*** Spain ***Study design*** Case series (multicentre (two sites) Phase II study) ***Objective*** Vinorelbine plus paclitaxel in MBC in patients previously treated (as adjuvant or for metastatic) with anthracyclines	***Inclusion/exclusion criteria*** Histologically proven MBC; previously treated (as adjuvant or for metastatic) with anthracyclines; Karnofsky performance status ≥ 70; life expectancy ≥ 2 months; adequate bone marrow, renal and hepatic function; no previous therapy with paclitaxel or vinorelbine; no previous high-dose chemotherapy with stem cell support ***Number of participants*** 56 (recruited July 1996–September 1997; 54 evaluable for response and toxicity – 15 first line, 22 second line and 17 third line) ***Age*** Median = 53 years (range 27–78) ***Previous treatment*** Anthracyclines (anthracycline for MBC in 17 patients, as adjuvant only in 17, as both in 20) ***Performance status (Karnofsky)*** 100: 11 80–90: 29 70: 14 ***Stage of disease*** All patients had at least one metastatic site	***Line of therapy*** First, second or third line **Intervention** Vinorelbine 30 mg/m^2 plus paclitaxel 135 mg/m^2 on day 1 every 3 weeks ***Concurrent treatment*** Premedication with dexamethasone (20 mg), cimetidine (200 mg) and dexchlorpheniramine (5 mg) or another antihistamine drug just prior to paclitaxel administration ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (assessed after at least three cycles by two independent assessors), progression-free survival and adverse effects (using National Cancer Institute common toxicity criteria grading)	***Withdrawals*** Two excluded: one due to previous paclitaxel therapy and one had no metastatic disease ***Severe adverse events*** Grade 4 neutropenia: 28% Grade 3 neutropenia: 12% Grade 3 anaemia: 2 patients Grade 3 thrombocytopenia: 2 patients Grade 3 peripheral neuropathy: 2% Grade 3 arthralgia/myalgia: 4% Grade 3 nausea/vomiting: 2% Grade 3 local phlebitis: 4% Grade 3 asthenia: 4% Nine patients (20%) had dose reduced due to febrile neutropenia. There were no toxic deaths due to neutropenic infection	***First line*** Overall response rate = 10/15 (67%) ***All patients (n = 54)*** Overall response rate = 46% (95% CI, 33 to 60) Complete response = 6 Partial response = 19 Stable disease (> 6 months) = 6 ***Second line*** Overall response rate = 9/22 (41%) ***Third line*** Overall response rate = 6/17 (35%) ***Anthracycline-refractory patients*** Overall response rate = 6/13 (46%)	***Author's conclusions*** The combination of paclitaxel plus vinorelbine on 1 day every 3 weeks was active in patients with MBC with prior anthracycline exposure. The regimen was safe, well tolerated and convenient for the patient ***Other comments*** This study did **not** appear to be the same as that reported in Martin, 1999.[58] Earlier paper had 50 patients but had more patients treated as first line (17 versus 15) and more treated with adjuvant anthracycline (21 versus 17) or for MBC (19 versus 17). Both studies conducted at the same centre, therefore, there was possibly some overlap of patients There were clear inclusion and exclusion criteria. There was no survival time, independent assessment of response or subgroup details. Toxicity and demographic data were only presented for the group as a whole and not according to first-, second- or third-line therapy

Vinorelbine combination therapy *contd*

Vinorelbine plus paclitaxel *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Romero Acuna *et al.*, 1999[60] (also reported as an abstract by Romero Acuna *et al.*, 1998[384] and as an earlier interim report (abstract) by Romero Acuna *et al.*, 1997[385]) ***Country*** Argentina ***Study design*** Case series (Phase I) ***Objective*** To evaluate efficacy and toxicity of a combination of vinorelbine plus paclitaxel as first-line chemotherapy in MBC	***Inclusion/exclusion criteria*** Histologically confirmed MBC with no prior chemotherapy for MBC; bidimensionally measurable disease; performance status (ECOG) of 0–2; life expectancy > 3 months; adequate bone marrow, renal and hepatic function. Those with progressive disease on hormone therapy had to have completed hormone treatment 4 weeks before. Previous adjuvant chemotherapy had to be completed ≥ 4 weeks before. No prior vinorelbine or paclitaxel; no CNS metastases, hilar enlargement, pleural effusion or malignant ascites as only evidence of metastatic disease; no history of alcohol abuse or peripheral neuropathy; no hypertension or heart condition ***Number of participants*** 49 (recruited August 1995–August 1997; 45 evaluable for response) ***Age*** Median = 52 years (range 31–75) ***Previous treatment*** Hormonal adjuvant: 11 (22%) Hormonal MBC: 4 (8%) Adjuvant chemotherapy (FAC): 22 (44%) Adjuvant chemotherapy (CMF): 7 (14%) ***Performance status (ECOG)*** 0: 23 1: 23 2: 3 ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on days 1 and 8 plus paclitaxel 135 mg/m^2 on day 1 every 4 weeks ***Concurrent treatment*** Premedication with dexamethasone 20 mg, diphenylhydramine 50 mg and ranitidine 50 mg No patient received G-CSF or antibiotics ***Duration of follow-up*** 53 patient-years, mean = 13 months (range 1–27) ***Outcome measures*** The outcome measures were response (objective criteria stated in paper and all responses reviewed by an independent panel of experts) and adverse effects (according to WHO and Cancer or Leukaemia Group B criteria)	***Withdrawals*** Four patients not evaluable for response but all included in analysis of toxicity. Two died and one withdrew due to adverse events. One patient refused treatment after first cycle ***Severe adverse events (number of patients (%))*** Grade 4 leukopenia: 15 (32%) Grade 3 leukopenia: 30 (61%) Grade 4 granulocytopenia: 35 (71%) Grade 3 granulocytopenia: 11 (22%) Grade 4 thrombocytopenia: 2 (4%) Grade 3 anaemia: 6 (12%) Grade 4 infection: 8 (16%) Grade 3 infection: 1 (2%) Grade 3 constipation: 1 (2%) Grade 3 nausea/vomiting: 1 (2%) Grade 3 alopecia: 42 (86%) Phlebitis: 2 (12%) A total of eight case of febrile neutropenia occurred. Of these, three were in patients with massive liver involvement, two of whom died and one required antibiotics and hospitalisation. Following this, patients with liver metastases were excluded. The other five cases of febrile neutropenia also required hospitalisation	Objective response = 27/45 (60%, 95% CI, 46 to 74) Complete response = 3/45 (7%) Partial response = 24/45 (53%) Stable disease = 12/45 (27%) Progressive disease = 6 (13%) Median time to progression = 7 months Median survival = 17 months Kaplan–Meier methods used	***Author's conclusions*** The combination of vinorelbine plus paclitaxel showed significant activity as first-line chemotherapy for patients with MBC. Myelosuppression was the dose-limiting side-effect, whereas neurotoxicity was mild to moderate ***Other comments*** There were clear inclusion and exclusion criteria, all had MBC with no prior chemotherapy, follow-up was clear, assessment methods were stated and subgroups were described

Vinorelbine combination therapy *contd*

Vinorelbine plus paclitaxel *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Vici *et al.*, 2000[61] (earlier report when only 33 patients recruited given by Vici *et al.*, 1998[386] and Vici *et al.*, 1997[387]) ***Country*** Italy ***Study design*** Case series (Phase II) ***Objective*** To investigate the activity and toxicity of vinorelbine plus paclitaxel as first-line therapy in ABC	***Inclusion/exclusion criteria*** Histologically confirmed ABC; WHO performance status ≤ 3; measurable or evaluable disease; adequate bone marrow, renal and hepatic function; previous adjuvant chemotherapy permitted but not with vinca alkloids or taxanes; any adjuvant chemo-therapy must have been completed ≥ 6 months before and hormonal therapy ≥ 4 weeks before ***Number of participants*** 43 (41 evaluable for response, 42 evaluable for toxicity; recruited October 1995–January 1997) ***Age*** Median = 53 years (range 29–71) ***Previous treatment*** Hormonal adjuvant: 10 Hormonal ABC: 8 Adjuvant chemotherapy: 22 (12 CMF, 10 anthracyclines) ***Performance status*** Median = 1 (range 0–3) ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus paclitaxel 150 mg/m^2 on day 1, repeated every 3 weeks ***Concurrent treatment*** G-CSF 300 µg/day on days 7–12 of each cycle Premedication and anti-emetic treatment consisted of dexamethasone plus ranitidine 12 and 6 hours before treatment, followed by orphenadrine and ranitidine 1 hour before chemotherapy; tropisetron was given immediately before chemotherapy ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (assessed by two observers and using WHO criteria), progression-free survival, overall survival and adverse effects (evaluated using National Cancer Institute common toxicity criteria)	***Withdrawals*** One patient lost to follow-up after first cycle and one removed from study due to hepatotoxicty after the first drug administration ***Severe adverse events (% of 42 patients)*** Grade 4 neutropenia: 21% Grade 3 neutropenia: 21% Grade 4 leukopenia: 5% Grade 3 leukopenia: 17% Grade 4 hepatotoxicity: 2% Grade 3 alopecia: 100% Grade 3 anaemia: 4%	Complete response = 2/41 (5%) Partial response = 18/41 (18%) Overall response rate = 49% (95% CI, 34 to 64) Stable disease = 12/41 (29%) Progressive disease = 9/41 (22%) Median time to response = 2 months Median time to progression = 7 months (range 3–35) Median survival = 22 months (range 3–35) Kaplan–Meier methods used	***Author's conclusions*** Simultaneous infusion of vinorelbine plus paclitaxel was a well-tolerated and active regimen in MBC, with overall results similar to those reported with more toxic regimens. Furthermore, it may be a good option in patients with anthracycline contraindications ***Other comments*** There were standard, clear inclusion and exclusion criteria, but it was unclear how many had locally advanced disease. All had first-line treatment and objective assessment criteria were used. Subgroups were not applicable

Vinorelbine combination therapy *contd*

Vinorelbine plus mitroxantrone

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Ferrero *et al.*, 1995[62] (*n* = 41; an earlier group of patients from this study appeared to have been published separately as an abstract by Ferrero *et al.*, 1993[388] (*n* = 33). This second publication included only MBC patients, whereas Ferrero *et al.*, 1995[62] also included locally ABC) ***Country*** France ***Study design*** Case series (Phase II) uncontrolled study ***Objective*** To assess the efficacy and toxicity of the combination of vinorelbine plus mitoxantrone as first-line therapy for MBC	***Inclusion/exclusion criteria*** **Ferrero *et al.*, 1995**[62] MBC or locally ABC with no previous chemotherapy for ABC; aged ≥ 18 and ≤ 75 years; performance status ≤ 2; values for laboratory parameters not outside range acceptable for chemotherapy; cardiac function normal (left ventricular ejection fraction ≥ 50% as assessed by echocardiography or isotope methods); adjuvant chemotherapy completed > 1 year prior to study and any hormonal therapy had to be stopped before the study; life expectancy > 3 months **Ferrero *et al.*, 1993**[388] MBC with evaluable disease, with no previous chemotherapy for MBC; aged ≥ 18 and ≤ 75 years; performance status ≤ 2; adjuvant chemotherapy completed > 1 year prior to study ***Number of participants*** **Ferrero *et al.*, 1995**[62] 41 (37 evaluable for response, all evaluable for toxicity; recruited March 1991–April 1993) **Ferrero *et al.*, 1993**[388] 33 (32 evaluable for response, all evaluable for toxicity) ***Age*** **Ferrero *et al.*, 1995**[62] Median = 63 years (range 35–75) **Ferrero *et al.*, 1993**[388] Median = 60 years (range 35–75) ***Previous treatment*** **Ferrero *et al.*, 1995**[62] Adjuvant chemotherapy: 14 (34%; 12 (29%) with anthracyclines, two with CMF) Adjuvant hormonal therapy: 10 (24%) Hormonal therapy for MBC: 26 (65%)	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitoxantrone 12 mg/m^2 on day 1 every 21 days until disease progression or toxicity ***Concurrent treatment*** **Ferrero *et al.*, 1995**[62] Anti-emetics given at clinician's discretion **Ferrero *et al.*, 1993**[388] None stated ***Duration of follow-up*** **Ferrero *et al.*, 1995**[62] Approximately 30 months from Kaplan–Meier curves presented **Ferrero *et al.*, 1993**[388] Not stated ***Outcome measures*** **Ferrero *et al.*, 1995**[62] The outcome measures were response, progression-free survival, overall survival and adverse effects **Ferrero *et al.*, 1993**[388] The outcome measures were response (assessed after at least two courses) and adverse effects	***Withdrawals*** **Ferrero *et al.*, 1995**[62] Four patients were not evaluable for efficacy, although they were included in the safety analysis **Ferrero *et al.*, 1993**[388] One patient was not evaluable for efficacy, not clear if included in the safety analysis ***Severe adverse events*** **Ferrero *et al.*, 1995**[62] Grade 4 neutropenia: 12 (29%) Grade 3 neutropenia: 5 (12%) Grade 4 leukopenia: 4 (10%) Grade 3 leukopenia: 6 (15%) Grade 3 anaemia: 1 (2%) Grade 3 nausea/vomiting: 2 (5%) Grade 3 mucositis: 1 (2%) Grade 3 constipation: 2 (5%) Grade 3 alopecia: 4 (10%) Two patients developed febrile septicaemia, one requiring hospitalisation and one requiring antibiotic treatment. There were no deaths or cardiac problems due to toxicity **Ferrero *et al.*, 1993**[388] One patient received only one course of therapy due to grade 4 neutropenia with septicaemia. Grade 3 and 4 neutropenia reported for 9 and 7%, respectively	**Ferrero *et al.*, 1995**[62] Objective response = 19/37 (51%, 95% CI, 45 to 74) Complete response = 5 (13%) Partial response = 14 (37%) Stable disease = 11 (30%) Progressive disease = 7 (19%) 15/19 responded after third cycle Median time to progression = 9 months (range 2–24) Median overall survival = 14 months (range 1–26) Kaplan–Meier methods used **Ferrero *et al.*, 1993**[388] Overall response = 56% Complete response = 8 (25%) Partial response = 10 (31%) Stable disease = 7 (22%) Progressive disease = 7 (22%)	***Author's conclusions*** **Ferrero *et al.*, 1995**[62] Good tolerability offered patients greater QoL in the few months of survival gained **Ferrero *et al.*, 1993**[388] Vinorelbine plus mitoxantrone in non-pretreated MBC showed similar response rates as regard to classical combinations, however, toxicity was less important, particularly regarding alopecia and nausea/vomiting ***Other comments*** It is uncertain if participants reported by Ferrero *et al.*, 1993[388] and those reported by Ferrero *et al.*, 1995[62] were the same group. Although the first group was smaller, the number with adjuvant chemotherapy was greater. The information from both studies were, therefore, reported The full manuscript published by Ferrero *et al.*, 1995[62] is in French

continued

Vinorelbine combination therapy *contd*

Vinorelbine plus mitroxantrone *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
contd **Ferrero et *al.*, 1995**[62] (*n* = 41; an earlier group of patients from this study appeared to have been published separately as an abstract by Ferrero *et al.*, 1993[388] (*n* = 33). This second publication included only MBC patients, whereas Ferrero *et al.*, 1995[62] also included locally ABC)	**Ferrero et *al.*, 1993**[388] Adjuvant chemotherapy: 16 (13 with anthracyclines) ***Performance status*** **Ferrero et *al.*, 1995**[62] 0: 11 1: 27 2: 3 **Ferrero et *al.*, 1993**[388] Median = 1 (range 0–2) **Stage of disease** Not stated				**Ferrero et *al.*, 1995**[62] Objective response criteria were used. Unknown if it was a representative sample. Inclusion criteria were specified. Patients had either MBC or locally ABC. Follow-up was adequate and details of subgroups (and results) were included **Ferrero et *al.*, 1993**[388] No details of whether objective response criteria were used. Unknown if it was a representative sample. Inclusion criteria were specified. Patients had MBC and were first line only. Follow-up was unknown. Details of subgroups (and results) were included

Vinorelbine combination therapy *contd*

Vinorelbine plus mitroxantrone *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Frasci et *al.*, 1995[63] (ongoing study) ***Country*** Italy ***Study design*** Case series (Phase I–II) ***Objective*** To assess efficacy and tolerability of vinorelbine plus mitoxantrone when G-CSF used to reduce myelosuppression	***Inclusion/exclusion criteria*** Histologically proven locally ABC or MBC; aged 18–75 years; WHO performance status ≤ 2; estimated life expectancy ≥ 8 weeks; leukocyte count > 3000/l, platelets ≥ 100,000/l, serum creatinine ≤ 1.5 mg/dl and serum bilirubin ≤ 2 mg/dl; no cancer therapy for previous 8 weeks and no significant cardiac morbidity ***Number of participants*** 43 (23 were receiving at least second-line chemotherapy) ***Age*** Mean = 54 years (range 32–74) ***Previous treatment*** 23 patients had received previous chemotherapy for metastatic disease. Details of chemotherapy or adjuvant therapy not given. 8/23 metastatic pretreated patients had received a prior anthracycline ***Performance status (ECOG)*** 0–1: 29 2: 14 ***Stage of disease*** 11 with locally ABC, 32 with MBC. Dominant site of metastases was visceral in 16 participants	***Line of therapy*** First, second or subsequent line ***Intervention*** The starting dose intensity was mitoxantrone 3 mg/m^2/week plus vinorelbine 15 mg/m^2/week without G-CSF support. There were three different schedules for mitoxantrone: total dose on day 1; divided between days 1 and 8; divided between days 1, 8 and 15. Vinorelbine was administered once a week. The dose was escalated by 1 mg/m^2/week for mitoxantrone and by 5 mg/m^2/week for vinorelbine. Dose-escalation continued until dose-limiting toxicity occurred ***Concurrent treatment*** G-CSF was administered from dose level 2 ***Duration of follow-up*** Approximately 30 months (from Kaplan–Meier curves) ***Outcome measures*** The outcome measures were response (partial response defined as a > 50% reduction in the sum of the products of the greatest diameters of measurable lesions), progression-free survival, overall survival and adverse effects	***Withdrawals*** All patients were evaluable for toxicity. 41/43 patients (18 first line) received at least two courses of intervention and were evaluable for response ***Severe adverse events*** Five different dosage levels were used. There were nine participants treated with the first dose, 12 with the second, 12 with the third, six with the fourth and four with the fifth Grade 3 leukopenia occurred in 12–27% of courses, the incidence increasing approximately as the dose increased. Grade 4 leukopenia did not occur at the lowest dose but then increased from 2 to 10% of courses as the dose increased. Grades 3 and 4 thrombocytopenia occurred from the third dose level, grade 3 at about 10% and grade 4 increasing from 2 to 10%. Grade 3 anaemia occurred in 4% of the fourth dose level courses and in 6% of the fifth dose level	***First line*** Overall response rate = 12/18 (67%) Details of complete and partial responses not given Median time to disease progression = 15 months (Kaplan–Meier methods used) ***Second line*** Overall response rate = 9/23 (39%) Median time to disease progression = 5.5 months ***All patients*** Overall response rate = 51% (range 35–67) Complete response = 5 Partial response = 16 Median time to disease progression = 9.5 months	***Author's conclusions*** G-CSF support allowed us to achieve a high dose intensity of mitoxantrone plus vinorelbine. Weekly administration of mitoxantrone was recommended to achieve the maximum dose level ***Other comments*** Small sample size was, therefore, unlikely to be a representative sample. Inclusion criteria were explicit. Patients had locally ABC and MBC and first- and second-line therapy, therefore, not a homogenous group. Follow-up was not complete. Methods for assessment were not stated but definitions of response were reported. Multiple logistic analysis was performed to detect factors that were independently associated with clinical response

Vinorelbine combination therapy *contd*

Vinorelbine plus mitroxantrone *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Gladieff *et al.*, 1996[64] ***Country*** France ***Study design*** Case series (Phase II) ***Objective*** To assess the efficacy and toxicity of the combination of vinorelbine plus mitoxantrone for ABC in elderly women	***Inclusion/exclusion criteria*** Aged > 70 years; performance status ≤ 2; histologically proven MBC that was measurable and evaluable and not subject to hormonal or radiotherapy; normal haematology, renal function and cardiac ejection fraction; adjuvant chemotherapy completed > 1 year before and the total dose of anthracycline received must have been ≤ 300 mg/m^2 ***Number of participants*** 25 (recruited January 1991–May 1993; 23 patients were included in evaluation of response and toxicity) ***Age*** Median = 73.5 years (range 70–82) ***Previous treatment*** 18 patients had had adjuvant therapy: 16 hormonal and two anthracycline-based chemotherapy. 16 had had hormonal therapy during the metastatic phase ***Performance status*** ≤ 2 for whole group ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 20 mg/m^2 on days 1 and 8 plus mitoxantrone 10 mg/m^2 on day 1, every 21 days (maximum of ten cycles) ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response, progression-free survival, overall survival and adverse effects	***Withdrawals*** Two withdrawals due to death near the beginning of the first treatment cycle ***Severe adverse events*** Neutropenia occurred in 25% of cycles, which was grade 3–4 in 42% of cases. No cases of febrile neutropenia. Two cycles were associated with grade 3 thrombocytopenia, but this was asymptomatic	Overall response = 5/23 (22%, standard error 10%) Stable disease in two patients Median time to progression = 13 months (range 5–36) Median survival = 17 months (range 3–38) 1-year survival = 43.8% (95% CI, 23.4 to 66.4)	***Author's conclusions*** This combination was well tolerated in elderly women, but the best results could be achieved by increasing delivered dose intensity ***Other comments*** Full manuscript in French Small sample size, clear inclusion criteria, follow-up of at least 1 year, no assessments methods or subgroup details

Vinorelbine combination therapy *contd*

Vinorelbine plus mitroxantrone *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Llombart-Cussac *et al.*, 1998[65] (an earlier report on this study published as an abstract by Spiellman *et al.*, 1994[389]) ***Country*** France ***Study design*** Case series (Phase II) prospective uncontrolled study ***Objective*** Vinorelbine plus mitoxantrone in MBC patients who had received previous adjuvant anthracycline	***Inclusion/exclusion criteria*** Histologically proven MBC and progressive disease with one measurable lesion; completed one adjuvant anthracycline regimen ≥ 3 months previously; no prior chemotherapy for MBC; performance status ≤ 2; life expectancy ≥ 12 weeks; normal ventricular ejection fraction; adequate bone marrow, renal and liver function; aged > 18 years; no previous vinorelbine therapy; no brain involvement, leptomeningeal disease, concomitant cancer or other serious medical illnesses ***Number of participants*** 72 (recruited October 1991–December 1994; 69 assessable for toxicity and 65 assessable for response) ***Age*** Median = 54 years (range 27–78) ***Previous treatment*** Hormonal: 42 (61%) – 18 adjuvant, eight for MBC and 16 both Radiotherapy: 54 (78%) – 49 adjuvant Adjuvant doxorubicin: 24 (35%) Adjuvant epirubicin: 45 (65%) Anthracycline-containing neoadjuvant: 3 ***Performance status*** Median = 1 (range 0–2) ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus mitoxantrone 10 mg/m^2 (except for the first six patients who received 12 mg/m^2) on day 1, repeated every 3 weeks ***Concurrent treatment*** G-CSF only allowed as curative treatment of febrile neutropenia ***Duration of follow-up*** Up to 48 months from Kaplan–Meier curves ***Outcome measures*** The outcome measures were response (using WHO criteria), progression-free survival, overall survival and adverse effects (using WHO criteria)	***Withdrawals*** Three patients provided no data from first cycle (one patient had symptomatic brain lesion, one had an initial subnormal ventricular ejection fraction and one was lost to follow-up during the first cycle) and a further four were not assessable for response (no measurable lesion at baseline) ***Severe adverse events*** Grade 4 granulocytopenia: 12 (17%) Grade 3 granulocytopenia: 20 (29%) Grade 4 anaemia: 2 (3%) Grade 3 anaemia: 3 (4%) Grade 3 thrombocytopenia: 3 (4%) Grade 4 infection: 2 (3%) Grade 3 infection: 2 (3%) Grade 3 nausea/vomiting: 3 (4%) Grade 3 stomatitis: 1 (1%) Grade 3 constipation: 1 (1%) Grade 3 alopecia: 1 (1%) Grade 4 cardiac: 3 (4%) Grade 3 cardiac: 4 (6%) Of the six patients given mitoxantrone 12 mg/m^2, three had febrile neutropenia. Over the study as a whole, there were 12 hospital admissions for febrile neutropnia involving nine patients. There were no infection-related deaths	Overall response = 32/65 (49%, 95% CI, 37 to 63) When analysed on an ITT basis = 32/69 (46%, 95% CI, 34 to 59) Complete response = 4/65 (6%) Patial response = 28/65 (43%) Stable disease = 17/65 (26%) Progressive disease = 16/65 (25%) Median duration of response = 7 months (range 2.6–27) Median survival (Kaplan–Meier method) = 19 months (range 2–48) After a median time (of the study) of 3 years, six patients were alive	***Author's conclusions*** Vinorelbine plus mitoxantrone combination was an active regimen with low toxic complications when cumulative doses of mitoxantrone were limited to 70 mg/m^2. Further studies are warranted ***Other comments*** Clear standard inclusion and exclusion criteria. All patients had MBC and were undergoing first-line therapy. Follow-up was 3 years, WHO criteria were used for response and adverse effects and subgroups were described

Vinorelbine combination therapy *contd*

Vinorelbine plus docetaxel

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Bonneterre *et al.*, 1998[66] ***Country*** France ***Study design*** Case series (Phase II) ***Objective*** Dose-finding study in MBC	***Inclusion/exclusion criteria*** Histologically proven MBC; measurable or evaluable disease; no previous chemotherapy for metastatic disease; any neoadjuvant and/or adjuvant chemotherapy completed ≥ 12 months prior to entering study; performance status of ≤ 2; aged ≤ 75 years; normal haematological, hepatic and renal function ***Number of participants*** Six patients received lower dose and nine patients received higher dose. It was unclear if the total number of patients was 15 or less ***Age*** Not stated ***Previous treatment*** Not stated ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 20 mg/m^2 on days 1 and 8 plus docetaxel 60 or 75 mg/m^2 on day 8 ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The only outcome measure was adverse effects	***Withdrawals*** None ***Severe adverse events*** **60 mg/m^2 docetaxel combination** Grade 4 neutropenia: 52% Febrile neutropenia: 5% One patient had dose-limiting toxicity at first cycle (febrile neutropenia requiring antibiotics and/or hospitalisation) **75 mg/m^2 docetaxel combination** Grade 4 neutropenia: 37% Febrile neutropenia: 15% Three patients had dose-limiting toxicity (febrile neutropenia requiring antibiotics and/or hospitalisation) at first cycle and one patient died of septic shock after second cycle	No other results reported	***Author's conclusions*** Further patients to be accrued at the 75 mg/m^2 docetaxel dose level ***Other comments*** No efficacy data Ongoing study. No information to determine how representative the sample was, particularly none on previous adjuvant therapy or previous anthracycline exposure

Vinorelbine combination therapy *contd*

Vinorelbine plus docetaxel *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
De Paz *et al.*, 1999[67] ***Country*** Spain ***Study design*** Case series (Phase II) ***Objective*** To assess tolerability of the combination of vinorelbine plus docetaxel	***Inclusion/exclusion criteria*** MBC with measurable or evaluable disease ***Number of participants*** 34 (16 as first line and 18 as second or third line) ***Age*** Mean = 53.1 years (range 24–76) ***Previous treatment*** 32 patients had received previous anthracycline-containing regimens (94%) – 18 as adjuvant therapy, five as adjuvant and first line for MBC and nine as first line only ***Performance status*** Not stated ***Stage of disease*** Of all patients, mean number of metastatic sites = 2 (range 1–4). 18/34 (52.9%) had visceral disease	***Line of therapy*** First, second or third line ***Intervention*** Vinorelbine 30 mg/m^2 plus docetaxel 70 mg/m^2 on day 1 every 3 weeks ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** Not stated ***Severe adverse events*** Grade 3–4 neutropenia: 24 cycles (15.6%) Neutropenic fever: 19 cycles (12.3%) Hypersensitivity reactions: 5 cycles (3.3%) Grade 3 alopecia: 97 cycles (63.3%)	***First line*** Overall response rate = 11/16 (68.8%) Complete response rate = 3/16 (18.7%) ***Second line*** Overall response rate = 8/18 (44.0%) Complete response rate = 1/18 (5.5%) ***All patients*** Overall response rate = 55.9% Complete response = 4 (11.8%) Partial response = 15 (44.1%) ***Patients with previous anthracycline-containing regimens*** Overall response rate = 17/32 (53.1%)	***Author's conclusions*** A combination of vinorelbine plus docetaxel chemotherapy was feasible with tolerable toxicity and attractive activity in MBC ***Other comments*** Abstract only, therefore, reporting not detailed. Could not tell if sample was representative, or how explicit inclusion and exclusion criteria were. A mix of patients received first-, second- or even third-line therapy. Follow-up was unknown, but study is ongoing. There was no blinding of assessors or report of assessment methods or criteria. There was no information on risk factors for first-line subgroup

Vinorelbine combination therapy *contd*

Vinorelbine plus docetaxel *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Fumoleau *et al.*, 1997[68] (interim findings also reported by Fumoleau *et al.*, 1996[390,391]) ***Country*** France ***Study design*** Case series (Phase I) ***Objective*** To determine the dose-limiting toxicities and the recommended dose for further Phase II trials. A secondary objective was to define the major pharmacokinetic parameters in order to assess potential interactions between the two drugs when administered in combination	***Inclusion/exclusion criteria*** Evaluable and/or measurable MBC with no previous chemotherapy for advanced disease; previous adjuvant chemotherapy allowed if 1-year interval between end of adjuvant chemotherapy and entry into study; performance status (ECOG) ≤ 2; normal haematological, liver and renal function ***Number of participants*** 29 (recruitment started June 1994) ***Age*** Not stated ***Previous treatment*** Not stated ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line for MBC ***Intervention*** Vinorelbine 20 or 22.5 mg/m^2 i.v. on days 1 and 5 followed by docetaxel 60–100 mg/m^2 i.v on day 1, repeated every 3 weeks ***Concurrent treatment*** 3 days of corticosteroid premedication (oral dexamethasone) and diosime 500 mg (to stabilise capillary endothelium) on day before first infusion until end of therapy ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** None reported ***Severe adverse events*** **Docetaxel 60 mg/m^2 plus vinorelbine 20 mg/m^2 (three patients, 18 cycles)** Grade 4 neutropenia: 4 patients **Docetaxel 75 mg/m^2 plus vinorelbine 20 mg/m^2 (six patients, 34 cycles)** Grade 4 neutropenia: 4 patients Grade 4 febrile neutropenia: 9% of cycles **Docetaxel 75 mg/m^2 plus vinorelbine 22.5 mg/m^2 (four patients, 19 cycles)** Grade 4 neutropenia: 2 patients Grade 4 febrile neutropenia: 37% of cycles Grade 3–4 mucositis: 2 patients Dose-limiting toxicity (febrile neutropenia > 3 days and/or grade 4 neutropenia > 7 days and/or grade 3 non-haematological toxicity): 3 patients **Docetaxel 85 mg/m^2 plus vinorelbine 20 mg/m^2 (ten patients, 43 cycles)** Grade 4 neutropenia: 5 patients Grade 4 febrile neutropenia: 11% of cycles Grade 3–4 mucositis: 1 patient Dose-limiting toxicity: 1 patient **Docetaxel 100 mg/m^2 plus vinorelbine 20 mg/m^2 (six patients, 28 cycles)** Grade 4 neutropenia: 4 patients Grade 4 febrile neutropenia: 11% of cycles Grade 3–4 mucositis: 1 patient Dose-limiting toxicity: 4 patients	***At all dose levels*** Overall response rate = 66% ***Docetaxel 85 mg/m^2 plus vinorelbine 20 mg/m^2*** Overall response rate = 80% ***Docetaxel 75 mg/m^2 plus vinorelbine 20 mg/m^2*** Overall response rate = 67%	***Author's conclusions*** Based on the results of the trial, the recommended dosage regimen for the docetaxel plus vinorelbine combination in Phase II studies was docetaxel 75–85 mg/m^2 on day 1 plus vinorelbine 20 mg/m^2 on days 1 and 5, every 3 weeks ***Other comments*** The current recommended dose of vinorelbine used in combination therapy is 25–30 mg/m^2 This was a dose-finding study with a small sample size, which means that there were not many participants within each dosage group. The response rate of 11 participants with liver metastases were reported, but it was not stated how many subseries analysis were undertaken in total. No baseline demographic details of included participants were reported Inclusion and exclusion criteria were reported, however, no information was given on assessment methods and the length of follow-up was not reported

Vinorelbine combination therapy *contd*

Vinorelbine plus docetaxel *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Kornek *et al.*, 2001[69] (also interim reports (abstracts only) published by Penz *et al.*, 2000[392], Kornek *et al.*, 2000[393] and Kornek *et al.*, 1999[135]) ***Country*** Austria ***Study design*** Case series (Phase II) prospective uncontrolled study ***Objective*** To investigate the efficacy and tolerance of vinorelbine plus docetaxel with or without G-CSF in patients with MBC	***Inclusion/exclusion criteria*** Histologically confirmed, progressive, bi-dimensionally measurable MBC; aged ≤ 75 years; WHO performance status ≤ 3; expected survival time > 12 weeks; adequate bone marrow, renal and hepatic function; maximum of one previous chemotherapy for MBC allowed, which was to have been completed ≥ 4 weeks before study; adjuvant therapy must have been completed 1 year before first-line chemotherapy; bone lesions as only site of MBC not eligible; no CNS metastases, no previous or second invasive malignancy ***Number of participants*** 57 (recruited February 1998–March 1999; all assessable for response and toxicity; 42 first line, 15 second line) ***Age*** Median = 59 years (range 36–75) ***Previous treatment*** Hormonal: 31 (12 adjuvant, eight MBC, 11 both) Radiotherapy: 37 (23 adjuvant, eight MBC, six both) Adjuvant chemotherapy: 23 Chemotherapy for MBC: 11 Both adjuvant and MBC chemotherapy: four Chemotherapy for MBC + both adjuvant and MBC chemotherapy: 15 (ten anthracycline, five CMF) ***Performance status*** 0: 22 1: 1 2: 12 ***Stage of disease*** Not stated	***Line of therapy*** First or second line ***Intervention*** Vinorelbine 30 mg/m^2 on days 1 and 15 plus docetaxel 30 mg/m^2 on days 1, 8 and 15, repeated every 4 weeks ***Concurrent treatment*** G-CSF 5 µg/kg/day depending upon absolute granulocyte count on day of scheduled chemotherapy administration ***Duration of follow-up*** Median follow-up time = 18 months (range 13–26) ***Outcome measures*** The outcome measures were response (objective criteria detailed in paper, and all responses confirmed by an independent panel of oncologists and radiologists), progression-free survival (objective criteria detailed in paper), overall survival (objective criteria detailed in paper) and adverse effects (according to WHO criteria)	***Withdrawals*** Treatment was discontinued prematurely in three cases due to progressive peripheral neuropathy. Two additional patients withdrew for personal reasons after four and five courses, respectively ***Severe adverse events*** **All patients (*n* = 57)** Grade 4 leukopenia: 9 (16%) Grade 3 leukopenia: 21 (37%) Grade 4 neutropenia: 18 (32%) Grade 3 neutropenia: 18 (32%) Grade 4 thrombocytopenia: 1 (2%) Grade 3 thrombocytopenia: 1 (2%) Grade 3 anaemia: 1 (2%) Grade 4 infection: 1 (2%) Grade 3 infection: 3 (5%) Grade 3 nausea/vomiting: 2 (4%) Grade 3 stomatitis: 1 (2%) Grade 3 alopecia: 18 (32%) Grade 3 peripheral neuropathy: 1 (2%) Grade 3 skin/nail alterations: 1 (2%) One patient required packed red blood cell transfusion for severe anaemia. Nineteen patients (33%) developed infection, four of whom required hospitalisation and i.v. antibiotics	***First line*** Overall response = 27/42 (64.3%, 95% CI, 48.1 to 78.4) Complete response = 8/42 (19%) Partial response = 19/42 (45.3%) Stable disease = 11/42 (26.2%) Progressive disease = 4/42 (9.5%) Median duration of response = 8 months Median time to progression = 12 months (range 2.5–19+) Median survival = > 19.5 months ***Second line*** Overall response = 8/15 (53.3%) Complete response = 3/15 (20%) Partial response = 5/15 (33.3%) Stable disease = 4/15 (26.6%) Progressive disease = 3/15 (20%) Median time to progression = 9.8 months (range 2–23+) Median survival (Kaplan–Meier method) = 15.2 months	***Author's conclusions*** The results suggest that docetaxel plus vinorelbine with or without G-CSF was an effective and fairly well-tolerated regimen for the treatment of ABC ***Other comments*** Clear, standard inclusion and exclusion criteria. First- and second-line therapy mixed together, but response data for first line were reported separately. Adequate follow-up, but median survival in first-line group not yet reached. Objective criteria. Subgroups described, but patient characteristics and toxicity data were only reported for group as a whole (i.e. not separately for first-/second-line chemotherapy)

Vinorelbine combination therapy *contd*

FUN

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Dieras *et al.*, 1996[70] (also reported in an abstract by Spielmann *et al.*, 1992[99]. Interim reports of study by Dieras *et al.*, 1990[394] and Dieras *et al.*, 1991[122]) ***Country*** France ***Study design*** Case series (Phase II). Group-sequential design, uncontrolled study ***Objective*** To assess the efficacy and safety profile of the combination of FUN as first-line therapy for MBC	***Inclusion/exclusion criteria*** Histologically proven MBC; no prior chemotherapy for MBC; measurable disease; WHO performance status < 3; aged < 70 years; expected survival > 8 weeks; no major organ dysfunction (bone marrow or liver); no simultaneous radiotherapy on other sites or concurrent hormonal therapy permitted ***Number of participants*** 63 (recruited January 1989–January 1992) ***Age*** Median = 55 years (range 32–69) ***Previous treatment*** 40/63 patients had had adjuvant chemotherapy – 34 (54%) with anthracyclines and six with vinca alkaloids 20/63 (32%) had had hormonal therapy as adjuvant, first line for MBC or both ***Performance status (WHO)*** 0: 12 1: 42 2: 9 ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on days 1 and 5 plus 5-fluorouracil 750 mg/m^2 for 5 days consecutively, repeated every 21 days Median vinorelbine dose = 17 mg/m^2/week (86% intensity) ***Concurrent treatment*** None stated ***Duration of follow-up*** Responses confirmed ≥ 4 weeks after first assessment. Long-term = 36+ months from Kaplan–Meier curves ***Outcome measures*** The outcome measures were response (assessed with reference to an index lesion identified and defined at the beginning of treatment), progression-free survival, overall survival and adverse effects (according to WHO criteria)	***Withdrawals*** All 63 patients were evaluated for efficacy and toxicity ***Severe adverse events*** Grade 4 leukopenia: 19 (30.2%) Grade 3 leukopenia: 30 (47.6%) Grade 4 neutropenia: 50 (79.4%) Grade 3 neutropenia: 7 (11.1%) Grade 4 thrombocytopenia: 1 (1.6%) Grade 3 thrombocytopenia: 2 (3.2%) Grade 4 anaemia: 1 (1.6%) Grade 3 anaemia: 2 (3.2%) Grade 4 stomatitis: 11 (17.5%) Grade 3 stomatitis: 13 (20.5%) Grade 4 nausea/vomiting: 1 (1.6%) Grade 3 nausea/vomiting: 3 (4.8%) Grade 3 diarrhoea: 1 (1.6%) Grade 4 infection: 1 (1.6%) Grade 3 infection: 7 (11.1%) Grade 3 alopecia: 23 (36.5%) Grade 3 neuropathy: 1 (1.6%) Grade 3 constipation: 4 (6.3%) Nine episodes of neutropenic fever required patient hospitalisation for i.v. antibiotics One patient died 5 days after completion of the first course due to multiple toxicities	Using a triangular test after inclusion of 63 patients, the results allowed for rejection of the null hypothesis (a response rate < 50%) with a significance level of 0.042 Overall response rate = 40/63 (64%) Complete response = 8 Partial response = 32 Stable disease = 13 (20%) Progressive disease = 10 (16%) Median response duration = 12.3 months Median progression-free survival = 8.3 months Median survival = 23 months for all patients and 28.1 months for patients with a complete response Kaplan–Meier methods were used	***Author's conclusions*** The FUN combination was an active and tolerable regimen for the treatment of first metastatic progression of breast cancer. It provided an alternative regimen for patients who had previously received anthracycline-based adjuvant therapy or in whom anthracyclines could be used ***Other comments*** Inclusion and exclusion criteria were detailed and sample appeared to be representative. All patients had MBC with no chemotherapy. Follow-up allowed calculation of median survival. Information on subgroups was adequate

Vinorelbine combination therapy *contd*

FUN *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Hochster *et al.*, 2001[46] (also appears to have been reported (FUN group only) by Vogel *et al.*, 1995[395] as a preliminary analysis as an abstract) ***Country*** USA ***Study design*** Phase II prospective uncontrolled study (P70-07) ***Objective*** To evaluate the efficacy and safety of vinorelbine combined with doxorubicin or continuous infusion of 5-fluorouracil as initial therapy for ABC This was not a randomised comparative study so FUN data have been extracted separately to that of vinorelbine plus doxorubicin	***Inclusion/exclusion criteria*** Microscopically confirmed, bidimensionally measurable ABC; no chemotherapy for ABC; no surgery within 2 months or radiotherapy within 3 weeks; adjuvant chemotherapy completed ≥ 12 months before study; no metastatic disease of CNS, malignancy within 5 years, clinically significant peripheral neuropathy, unstable medical condition, uncontrolled heart disease or history of congestive heart failure; performance status (Karnofsky) < 70; adequate bone marrow and hepatic function; only patients who were unsuitable candidates for doxorubicin or had left ventricular ejection fraction of < 50% were stratified to receive FUN (the remaining patients received vinorelbine plus doxorubicin) ***Number of participants*** 56 (enrolled July 1991–August 1994) ***Age*** Median = 56.0 years (range 30–80) ***Previous treatment*** Hormonal: 35 (63%) Adjuvant chemotherapy: 40 (71%) – 30 (54%) with anthracycline, eight (14%) with CMF and two (4%) with other) ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on days 1 and 5 plus 5-fluorouracil 750 mg/m^2 on days 1–5, every 3 weeks, until disease progression or severe toxicity ***Concurrent treatment*** None. Haematological growth factors were not used prophylactically ***Duration of follow-up*** 25 months after last patient was enrolled (Kaplan–Meier curves) ***Outcome measures*** The outcome measures were response (standard objective criteria specified in paper), progression-free survival (standard objective criteria specified in paper), overall survival (standard objective criteria specified in paper) and adverse effects (graded according to modified National Cancer Institute Adverse Events Criteria)	***Withdrawals*** Efficacy and safety parameters were evaluated in all enrolled subjects (ITT analyses) ***Severe adverse events*** Grade 3–4 granulocytes: 49 (88%) Grade 3–4 leukopenia: 35 (62%) Grade 3–4 anaemia: 9 (17%) Grade 3–4 alkaline phosphatase: 18 (34%) Grade 3–4 aspartate aminotransferase: 7 (13%) Grade 3–4 alanine aminotransferase: 4 (8%) Grade 3–4 total bilirubin: 6 (11%) Grade 3–4 creatinine: 2 (4%) Grade 3–4 alopecia: 2 (4%) Grade 3–4 asthenia: 4 (7%) Grade 3–4 nausea: 4 (7%) Grade 3–4 stomatitis: 18 (32%) Grade 3–4 vomiting: 3 (5%) Grade 3–4 diarrhoea: 6 (11%) Grade 3–4 constipation: 2 (4%) Grade 3–4 fever: 7 (12%) Grade 3–4 paraesthesia: 1 (2%) Grade 3–4 hypesthesia: 1 (2%) Grade 3–4 cardiovascular event: 4 (4%) Grade 3–4 sepsis: 2 (4%) One patient died of neutropenic sepsis. One subject died due to dehydration and diarrhoea	Overall response = 25/56 (45%, 95% CI, 31 to 59) Complete response = 3 (5%) Partial response = 22 (39%) Stable disease = 18 (32%) Progressive disease = 11 (20%) Not evaluable = 0 (0%) Not reported = 2 (4%) Median time to progression = 32 weeks Median time to treatment failure = 30 weeks Median survival = 53 weeks (95% CI, 47 to 64) 1-year survival rate = 50.2% Kaplan–Meier methods used One participant remained on study as of the data cut-off date of December 1996. The primary reasons for discontinuation in the remaining 117 subjects (including those treated with vinorelbine plus doxorubicin) were disease progression (n = 57, 49%), symptoms/toxicities/adverse experiences (n = 27, 23%), failure to return or refused treatment (n = 10, 9%), death (n = 8, 7%) and other (n = 15, 13%) 17 participants (out of the total sample of 118) were enrolled as exceptions to the entry criteria, such as completion of prior therapy within 2 weeks of enrolment (n = 8, 7%), haematological or laboratory abnormality (n = 8, 7%), history of other malignancy (n = 2, 2%) or a combination thereof. Reasons for discontinuation and exceptions to the entry criteria were evenly distributed between the two treatment groups	***Author's conclusions*** FUN offers a useful option as initial therapy for ABC. Regimen was associated with predictable but manageable toxicity. A lower dose of 5-fluorouracil should be used to reduce the risk of stomatitis. Efficacy was lower than that achieved with vinorelbine plus doxorubicin in a similar patient group, which may be due to the fact that the patients treated with FUN in this study were those who had relapsed after receiving previous aggressive anthracycline-based adjuvant therapy ***Other comments*** Not clear if all patients had MBC (stage IV) or whether some had locally ABC (stage III). Paper used term ABC (stages III and IV) rather than MBC Clear inclusion and exclusion criteria, long follow-up, objective criteria used for assessments and subgroups detailed

Vinorelbine combination therapy *contd*

Vinorelbine plus 5-fluorouracil plus leucovorin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Kornek *et al.*, 1998[71] (this study appears to have been reported twice before (interim reports) by Kornek *et al.*, 1996[152] and Kornek *et al.*, 1996[134]) ***Country*** Austria ***Study design*** Case series (Phase II) ***Objective*** To investigate the efficacy and tolerability of vinorelbine, 5-fluorouracil, L-isomer leucovorin and G-CSF in ABC	***Inclusion/exclusion criteria*** Histologically confirmed ABC (locally advanced or MBC); bidimensionally measurable disease; aged ≤ 75 years; WHO performance status ≤ 2; life expectancy of ≥ 12 weeks; adequate bone marrow, renal and hepatic function; prior radiotherapy and maximum of one palliative chemotherapy with or without hormonal therapy permitted as long as completed ≥ 4 weeks prior to study; osteoblastic bone lesions as only metastases; CNS metastases or prior or second invasive malignancy excluded ***Number of participants*** 53 (recruited August 1994–October 1996; all evaluable for response and toxicity) ***Age*** Median = 55 years (range 29–75) ***Previous treatment*** Hormonal adjuvant: 21 Hormonal for metastatic disease: 19 Chemotherapy adjuvant: 20 Chemotherapy for metastatic disease: 16 (12 anthracyclines, four other) ***Performance status (WHO)*** 0: 14 1: 32 2: 7 ***Stage of disease*** Except for 13 patients (12 of whom had second-line chemotherapy), all had multiple metastases involving two or more organs	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 40 mg/m^2 on days 1 and 14 plus 5-fluorouracil 400 mg/m^2 plus L-leucovorin 100 mg/m^2 on days 1–5, every 4 weeks ***Concurrent treatment*** G-CSF 5 µg/kg/day on days 6–10 (note earlier abstracts say days 6–12) ***Duration of follow-up*** For all patients, median follow-up time was 14 months (range 12–26) ***Outcome measures*** The outcome measures were response (objective criteria specified in paper; confirmed by at least two principal investigators), progression-free survival, overall survival and adverse effects (WHO criteria)	***Withdrawals*** None ***Severe adverse events*** Dose-limiting toxicity was myelosuppression Grade 4 leukopenia: 3 (6%) Grade 3 leukopenia: 11 (21%) Grade 4 neutropenia: 4 (8%) Grade 3 neutropenia: 15 (28%) Grade 3 thrombocytopenia: 3 (6%) Grade 3 anaemia: 4 (8%) Grade 4 infection: 1 (2%) Grade 3 infection: 1 (2%) Grade 3 nausea/vomiting: 1 (2%) Grade 3 stomatitis: 3 (6%) Grade 3 alopecia: 1 (2%) Two patients were hospitalised due to sepsis and four patients required packed red blood cell transfusion for anaemia	***First line*** Overall response rate = 22/37 (59%) Complete response rate = 5/37 (13%) Partial response rate = 17/37 (46%) Stable disease = 10/37 (27%) Progressive disease = 5/37 (14%) Median time to response = 2 months Median duration of response = 9.5 months (range 4–21) Median time to progression = 10.5 months (range 2–23) Median survival time not yet reached (> 13 months (range 1.5–26+)) ***All patients*** Overall response rate = 47% (*n* = 53, 95% CI, 33 to 61) Complete response rate = 5/53 (9%) Partial response rate = 20/53 (38%) Stable disease for > 3 months = 19 (36%) Progressive disease = 9 (17%) Median duration of response = 9.5 months (range 4–12) Median time to treatment failure = 9 months (range 2–23) Median survival time not yet reached ***Second line*** Complete response rate = 0/16 (0%) Partial response rate = 3/16 (19%) Stable disease = 9/16 (56%) Progressive disease = 4/16 (25%) Duration of response in three responders was 6, 11.5 and 14.5 months (median = 10.6 months) Median time to progression = 7 months (range 2–19) Median survival time not yet reached (> 11 months (range 3.5–24+))	***Author's conclusions*** Our data suggested that the combination of vinorelbine plus 5-fluorouracil plus L-leucovorin and G-CSF is an effective first-line regimen for treatment of ABC ***Other comments*** Although not conclusive that all three Kornek publications were of the same group of patients (no cross referencing in publications), the same regimen, same research group and progressively increasing sample size indicates they were Clear inclusion and exclusion criteria, locally ABC and MBC mixed, follow-up continued for survival, objective criteria used for response and subgroups detailed

Vinorelbine combination therapy *contd*

Vinorelbine plus 5-fluorouracil plus leucovorin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Nole *et al.*, 1997[72] ***Country*** Italy ***Study design*** Case series (Phase I–II) ***Objective*** To investigate the therapeutic effect of a combination of vinorelbine plus 5-fluorouracil plus folinic acid as first-line treatment in patients with MBC	***Inclusion/exclusion criteria*** Histologically proven MBC; no prior chemotherapy for MBC; measurable or evaluable disease; ECOG performance status of 0–2; aged > 18 years; expected survival ≥ 3 months; reasonable bone marrow, renal and hepatic function; no severe uncontrolled morbidities; no second malignancies ***Number of participants*** 49 (39 into Phase II study) ***Age*** **Phase II** Median = 51 years (range 35–71) ***Previous treatment*** **Phase II** 21 had had previous adjuvant chemotherapy, 13 of them with anthracycline, and 13 had had prior hormone therapy with tamoxifen ***Performance status (ECOG)*** **Phase II** 0–1: 34 2: 5 ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** **Phase I study** Vinorelbine starting dose 25 mg/m^2 (n = 3) or 30 mg/m^2 (dose level 2, n = 3) on days 1 and 3 plus 5-fluorouracil 350 mg/m^2 plus folinic acid 100 mg/m^2 on days 1–3, repeated every 21 days. The vinorelbine dose was escalated in 5 mg/m^2 steps until dose-limiting toxicity when it was reduced by 20% for the rest of the treatment period **Phase II study** Vinorelbine 25 mg/m^2 plus 5-fluorouracil plus folinic acid (administered as above) ***Concurrent treatment*** Dexamethasone as an anti-emetic ***Duration of follow-up*** Median = 15 months (range 4–31) ***Outcome measures*** The outcome measures were response (objective WHO assessment criteria specified and documented by two investigators), progression-free survival, overall survival and adverse effects (National Cancer Institute common toxicity grading criteria)	***Withdrawals*** None stated, however, three patients were reported as being ineligible: one refused treatment after first cycle (Phase I) and two had only unmeasurable bone disease (Phase II) ***Severe adverse events*** Grade 3 granulocytopenia: 2/39 Grade 4 granulocytopenia: 29/39 Four patients were hospitalised for granulo-cytopenic complications Non-haematological toxicity was recorded for 42 (included patients from a Phase I study), therefore, following data might not be derived from the 39 patients for whom demography is described Grade 3 injection-site reaction: 3/42 Grade 3 constipation: 4/42 Grade 3 stomatitis: 1/42 Grade 3 peripheral neuropathy: 1/42	**Phase II** Overall response rate = 24/39 (62%, 95% CI, 47 to 77) Complete response rate = 7/39 (18%) Partial response rate = 17/39 (44%) Stable disease = 9/39 (23%) Progressive disease = 6/39 (15%) Median response duration = 10 months (range 6–24+) Median time to progression = 8 months (range 2–24+) Median survival time not yet reached (12-month survival rate = 78%, Kaplan–Meier methods used) **Patients pretreated with anthracycline (adjuvant)** Partial response rate = 6/13 (46%) Complete response rate = 1/13 (18%) Stable disease = 4/13 (31%)	***Author's conclusions*** This effective combination chemotherapy vinorelbine plus 5-fluorouracil plus folinic acid was comparable to other first-line regimens in terms of efficacy and was subjectively well tolerated ***Other comments*** Clear inclusion and exclusion criteria and all participants had MBC and were first line. The follow-up continues. Objective criteria were used for assessment of response, and details of subseries were clearly presented Adverse event data were confused by inclusion of data from patients who did not enter the main trial Demographic data were only presented for Phase II study

Vinorelbine combination therapy *contd*

FAN

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Dieras et *al.*, 1996[73] ***Country*** France ***Study design*** Case series (Phase II) uncontrolled study ***Objective*** To assess the efficacy of a FAN combination as first-line therapy in ABC	***Inclusion/exclusion criteria*** Measurable disease; performance status of 0–2; adjuvant chemotherapy completed > 6 months before; white blood cells > 3000/l, platelets > 100,000/l, creatinine < 1.25 mg/dl and glutamate oxaloacetic transaminase < 1.25 IU/l unless liver metastases ***Number of participants*** 82 (70 evaluable for response) ***Age*** Median = 55 years (range 31–72) ***Previous treatment*** 42 (51%) patients had neoadjuvant or adjuvant chemotherapy (66% of which had anthracyclines) ***Performance status*** All had a performance status of 0–2 ***Stage of disease*** All patients had at least one metastatic site, and 77% had visceral disease	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus doxorubicin 20 mg/m^2 on days 1 and 8 plus 5-fluorouracil 250 mg/m^2 on days 1–15 ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (as reviewed by an independent board), progression-free survival, overall survival and adverse effects	***Withdrawals*** 12/82 patients not evaluable for response and not accounted for ***Severe adverse events*** Grade 3–4 neutropenia: 83% Grade 3–4 febrile neutropenia: 6 (7.3%) Grade 3–4 mucositis: 29%	Overall response rate = 44/70 (63%, 95% CI, 51 to 74) Complete response = 4 Partial response = 40 Stable disease = 16 Progressive disease = 10 Median time to first response = 57 days (range 25–169) Median time of progression-free survival and median time of overall survival not yet reached	***Author's conclusions*** This trial confirmed the high activity of vinorelbine-based regimens in the treatment of poor prognosis ABC with a 63% overall response rate ***Other comments*** Unclear if sample was representative of a 'poor prognosis' group referred to in author's conclusions. Clear inclusion criteria (although brief due to abstract) and all patients at same disease and treatment stage. Follow-up adequate for response only – long-term follow-up continues

Vinorelbine combination therapy *contd*

FAN *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Goss *et al.*, 1997[74] ***Country*** Canada ***Study design*** Case series (two parallel Phase I studies) ***Objective*** To assess the maximum tolerated dose and recommended dose of a FAN combination	***Inclusion/exclusion criteria*** Histologically proven MBC with no chemotherapy for MBC and no previous anthracycline at all; life expectancy ≥ 12 weeks; performance status (ECOG) ≤ 2; aged ≥ 18 years; acceptable haematological, hepatic and renal function; cardiac ejection fraction ≥ 50%; no uncontrolled blood pressure, cardiac problems, active infection, or previous cancer (except *in situ* cervical cancer, curatively treated non-melanomatous skin cancer or cancer of the colon) for > 5 years prior to diagnosis of breast cancer; no unstable hypercalcaemia or severe psychiatric or mental disability; no significant neuropathy if brain metastases ***Number of participants*** 26 enrolled in the FAN regimen and 12 in the SUPERFAN ***Age*** **FAN** Median = 60.3 years (range 41–71) **SUPERFAN** Median = 64.2 years (range 51–73) ***Previous treatment*** **FAN** Chemotherapy: 5 Hormonal: 23 Radiotherapy: 17	***Line of therapy*** First line ***Intervention*** **FAN** 5-fluorouracil 500 mg/m^2 plus doxorubicin 50 mg/m^2 on day 1 plus escalating doses of vinorelbine (15, 20, 25 and 30 mg/m^2) on days 1, 8 and 15, every 3 weeks **SUPERFAN** 5-fluorouracil 340 mg/m^2 plus folinic acid 200 mg/m^2 on days 1–5 plus doxorbicin 40 mg/m^2 on day 1 plus escalating doses of vinorelbine (15, 20, 25 and 30 mg/m^2) on days 1 and 5, every 4 weeks Maximum dose of doxorubicin was 400 mg/m^2 ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (using standard WHO criteria) and adverse effects	***Withdrawals*** **FAN** All evaluable for toxicity and 21 evaluable for response **SUPERFAN** 12 evaluable for toxicity and nine evaluable for response ***Severe adverse events*** After initial patients, starting dose of vinorelbine was reduced to 15 mg/m^2 and treatment on day 15 removed **FAN** Maximum tolerated dose of vinorelbine defined as 25 mg/m^2. Neutropenia was the dose-limiting toxicity, including two cases of febrile neutropenia (grade 3) Grade 3 leukopenia: 4 (15%) Grade 4 leukopenia: 2 (8%) Grade 4 granulocytopenia: 7 (27%) Grade 4 vomiting: 2 (8%) Grade 3 vomiting: 1 (4%) Grade 4 hypotension: 1 (4%) Grade 3 hypotension: 1 (4%) Grade 4 infection: 1 (4%) Grade 4 dyspnoea: 1 (4%) Grade 3 allergy: 1 (4%) Grade 3 diarrhoea: 1 (4%) Grade 3 dysphagia: 1 (4%) Grade 3 dry mouth: 1 (4%) Grade 3 heartburn: 1 (4%) Grade 3 cortical : 1 (4%) Grade 3 ocular: 1 (4%) Grade 3 flu-like symptoms: 2 (8%) Grade 3 anorexia: 2 (8%) Grade 3 nausea: 6 (23%) Grade 3 stomatitis: 4 (15%)	***FAN*** Overall response = 10/21 (48%) Complete response = 3/21 (12%) Partial response = 7/21 (33%) Stable disease = 9/21 (43%) Progressive disease = 2/21 (9%) ***SUPERFAN*** Overall response = 2/9 (22%) Complete response = 0/9 (0%) Partial response = 2/9 (22%) Stable disease = 6/9 (67%) Progressive disease = 1/9 (11%)	***Author's conclusions*** The limited response data from our study implied that combining vinorelbine with more toxic agents might not enhance response rates, defeating the advantage of tolerability, especially in elderly patients ***Other comments*** Clear inclusion and exclusion criteria reported. All patients had MBC and were first line. Follow-up and assessment criteria were unclear. Subgroups were described

continued

Vinorelbine combination therapy *contd*

FAN *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
contd **Goss et *al.*, 1997**[74]	**SUPERFAN** Chemotherapy: 4 Hormonal: 10 Radiotherapy: 6 ***Performance status (ECOG)*** **FAN** 0: 5 1: 11 2: 10 **SUPERFAN** 0: 5 1: 4 2: 3 ***Stage of disease*** All MBC		Grade 3 alopecia: 9 (35%) Grade 3 local toxicity: 3 (12%) Grade 3 constipation: 3 (12%) Grade 3 other neurological adverse events: 2 (8%) **SUPERFAN** Only two patients were treated with 20 mg/m^2 vinorelbine and both experienced severe toxicity Grade 4 granulocytopenia: 1 (8%) Grade 4 leukopenia: 1 (8%) Grade 4 thrombocytopenia: 1 (8%) Grade 4 stomatitis: 1 (8%) Grade 4 deep vein thrombosis: 1 (8%) Grade 4 dyspnoea: 1 (8%) Grade 4 pneumonitis: 1 (8%) Grade 4 hyperglycaemia: 1 (8%) Grade 4 diarrhoea: 2 (17%) Grade 3 flu-like symptoms: 1 (8%) Grade 3 anorexia: 1 (8%) Grade 3 nausea: 1 (8%) Grade 3 constipation: 1 (8%) Grade 3 cortical: 1 (8%) Grade 3 stomatitis: 4 (33%) Grade 3 febrile neutropenia: 2 (17%)		

Vinorelbine combination therapy *contd*

Vinorelbine and cyclophosphamide and 5-fluorouracil

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Ardavanis *et al.*, 1998[75] (interim findings also published as an abstract by Ardavanis *et al.*, 1997[396]) ***Country*** France ***Study design*** Case series (Phase II) uncontrolled study ***Objective*** To assess the efficacy and tolerance of a combination of vinorelbine plus cyclophosphamide plus 5-fluorouracil for the treatment of ABC	***Inclusion/exclusion criteria*** Histologically proven metastatic, locoregionally advanced or relapsing disease; measurable or evaluable disease; progression after initial manipulation; no previous chemotherapy for metastatic disease; WHO performance status < 3; adequate renal, liver and medullary function; haemoglobin > 10.5 g/dl and platelets > 100 x 10^9/l ***Number of participants*** 45 (43 evaluated, but only 38 of these met the inclusion criterion for no previous chemotherapy for metastatic disease (first line)) ***Age*** Median = 57 years (range 34–77) ***Previous treatment*** Hormonal adjuvant: 16 (37%) Hormonal metastatic: 12 (28%) Chemotherapy adjuvant: 23 (53%) Chemotherapy metastatic: 5 (1%) Almost one-quarter exposed to adjuvant anthracyclines ***Performance status (WHO)*** 0: 14% 1: 58% 2: 27% ***Stage of disease*** Stage III or IV % not stated	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 3 plus cyclophosphamide 600 mg/m^2 plus 5-fluorouracil 750 mg/m^2 on days 1–3, repeated every 21 days for six cycles. The doses were modified if there was a severe fall in white blood cells or platelets, or if serious mucositis, constipation, neuropathy or febrile aplasia developed. Maintenance vinorelbine-based therapy was then instituted ***Concurrent treatment*** Anti-HT_3-based anti-emetic plus freezing casque applied to prevent alopecia ***Duration of follow-up*** Median = 28 months (range 12–36) ***Outcome measures*** The outcome measures were response, progression-free survival, overall survival and adverse effects	***Withdrawals*** Not stated ***Severe adverse events*** Grade 4 neutropenia: 19 (44%) Grade 3 constipation: 1 (2%) Grade 3 mucositis: 3 (7%) Grade 4 alopecia: 1 (2%) Grade 3 alopecia: 4 (9%)	***First line*** Complete response = 4/38 (11%) Partial response = 15/38 (39%) Overall response = 19/38 (50%) Stable disease = 13/38 (34%) Progressive disease = 6/38 (16%) Median time to progression = 10.5 months % patients progression-free at 26 months unclear Overall survival not calculated ***All patients*** Complete response = 5/43 (12%) Partial response = 17/43 (39%) Overall response 22/43 (51%) Stable disease = 14/43 (33%) Progressive disease = 7/43 (16%) Median time to progression not stated Overall survival not calculated 61% of all evaluable patients were alive at 26 months and, of these, 35% were progression-free. These figures included the five patients who had previously received chemotherapy for advanced disease	***Author's conclusions*** The combination of vinorelbine plus cyclophosphamide plus 5-fluorouracil presented an interesting therapeutic index. It may be proposed as an alternative for the treatment of ABC, notably in the elderly and compromised patients ***Other comments*** No details of why two patients were not evaluable Unclear how representative the sample was. Inclusion and exclusion criteria were explicit, although those with and without previous chemotherapy for metastatic disease were included. There were no details of assessment techniques. Clear breakdown of different subpopulations were included. Follow-up continues

Vinorelbine combination therapy *contd*

Vinorelbine and cyclophosphamide and 5-fluorouracil *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Turpin et *al.*, 1999[76] ***Country*** France ***Study design*** Case series (Phase II) ***Objective*** To evaluate the combination of vinorelbine plus 5-fluorouracil plus cylophosphamide in ABC	***Inclusion/exclusion criteria*** Histologically proven locally advanced or MBC; bidimensionally measurable or evaluable progressive disease; adjuvant therapy completed ≥ 6 months previously; ≥ 2 weeks since surgery; radiotherapy completed 3 weeks before study; hormone therapy completed 2 weeks before study; aged 18–75 years; performance status ≤ 2; expected survival > 3 months; adequate renal and liver function; not limited to bone metastases; no peripheral neuropathy ***Number of participants*** 60 (recruited June 1992–April 1994; 59 evaluable for toxicity and 56 evaluable for response) ***Age*** Median = 54 years (range 33–74) ***Previous treatment*** Adjuvant chemotherapy: 42% Adjuvant hormonal therapy: 42.2% Immunotherapy: 1.7% ***Performance status*** 0: 37 1: 19 2: 4 ***Stage of disease*** Unclear how many patients had MBC or locally ABC	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 8 plus cyclophosphamide 500 mg/m^2 on day 1 plus 5-fluorouracil 500 mg/m^2 on days 1 and 8, repeated every 21 days for a maximum of eight cycles ***Concurrent treatment*** Folinic acid 200 mg/m^2 after administration of 5-fluorouracil ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (WHO grades), progression-free survival, overall survival and adverse effects (WHO criteria)	***Withdrawals*** One patient was not evaluable for toxicity due to having received chemotherapy for MBC. Four patients were not evaluable for response: one withdrew due to toxicity after first course, one suffered non-toxic death after first course, one rejected protocol after first course and one was lost to follow-up ***Severe adverse events*** Grade 4 neutropenia: 5% Grade 3 neutropenia: 35% Grade 3 nausea/vomiting: 4 patients Grade 3 constipation: 3 patients Grade 3 alopecia: 1 patient	***Locally ABC and MBC together*** Overall response = 27/60 (45%, 95% CI, 32.4 to 57.6) Complete response = 4/60 (6.7%, 95% CI, 0 to 13) Partial response = 23/60 (38.3%, 95% CI, 22.5 to 54.1) Stable disease = 15/60 (25%) Progressive disease = 14/60 Number not evaluable for response = 4/60 (6.7%) Median overall survival = 66.4 weeks (range 3+–80+) Median time to response = 26.7 weeks (range 15.1–75.1+) Duration of complete response = 45.4 weeks (range 20.3–45.4+) Duration of partial response = 37.4 weeks (range 13–36+)	***Author's conclusions*** This schedule achieves good levels of response without the use of an anthracycline ***Other comments*** Results for locally ABC and MBC together Clear inclusion and exclusion criteria except that it did not explicitly say that patients had not had chemotherapy for MBC. Follow-up long but not complete. Objective criteria for response. Details of subgroup muddled Participants were recruited from three centres

Vinorelbine combination therapy *contd*

Vinorelbine plus cyclophosphamide plus epirubicin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Braud *et al.*, 1999[77] (interim report of ongoing study) ***Country*** France ***Study design*** Case series (Phase II) ***Objective*** To assess the efficacy and toxicity of the combination of vinorelbine plus epirubicin plus cyclophospahamide in patients with MBC and no prior chemotherapy	***Inclusion/exclusion criteria*** Patients with MBC and no prior chemotherapy ***Number of participants*** 20 (19 evaluable) ***Age*** Not stated ***Previous treatment*** Not stated ***Performance status*** Not stated ***Stage of disease*** 6/20 patients had synchronous metastases. Median number of metastases = 2 (range 1–4)	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 on days 1 and 3 plus epirubicin 30 mg/m^2 plus cyclophosphamide 350 mg/m^2 on days 1–3 every 21 days. After six cycles, doses were reduced by 30%. Maximum number of cycles was 12. Median number of cycles was six (range 2–12) ***Concurrent treatment*** Prophylactic G-CSF given if required ***Duration of follow-up*** Not stated ***Outcome measures*** Evaluation planned for every three cycles	***Withdrawals*** None stated, 19/20 patients were evaluable ***Severe adverse events*** Grade 3–4 neutropenia was the most common, which required G-CSF in three patients	Complete response = 4/19 Partial response = 11/19 Overall response rate = 79%	***Author's conclusions*** Preliminary results were promising, with a high response rate. Longer follow-up is required to assess survival, with more patients ***Other comments*** Abstract only and little information on inclusion and exclusion criteria, and no information on assessment methods Ongoing study, started recruitment in June 1997

Vinorelbine combination therapy *contd*

Vinorelbine plus cyclophosphamide plus epirubicin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Esteban *et al.*, 2000[78] ***Country*** Spain ***Study design*** Case series (Phase II) prospective uncontrolled study ***Objective*** To determine the activity and toxicity of the combination of vinorelbine plus epirubicin plus cyclophosphamide	***Inclusion/exclusion criteria*** Histologically proven locally ABC or MBC with measurable disease; no chemotherapy for MBC; any adjuvant chemotherapy completed ≥ 3 months before; no anthracycline or vinorelbine; Karnofsky performance status ≥ 50; adequate bone marrow, renal and hepatic function; aged ≥ 75 years; patients with osseous metastases only eligible if lytic lesions present; exclusion if other cancer, brain involvement or pre-existing cardiac disease ***Number of participants*** 59 (recruited April 1996–March 1998; 56 evaluable for toxicity and 55 evaluable for response) ***Age*** Median = 53 years (range 35–70) ***Previous treatment*** Radiotherapy: 24 (20 adjuvant, four palliative) Hormone therapy: 43 (24 adjuvant, 19 palliative) Adjuvant chemotherapy (CMF): 21 ***Performance status (Karnofsky)*** Median = 70 (range 50–100) ***Stage of disease*** All MBC and first line	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus epirubicin 30 mg/m^2 plus cyclophosphamide 400 mg/m^2 on days 1 and 8, repeated every 28 days ***Concurrent treatment*** The use of G-CSF was permitted in the presence of grade 4 neutropenia with fever or documented infection ***Duration of follow-up*** Up to 119 weeks from Kaplan–Meier curves ***Outcome measures*** The outcome measure were response (criteria of International Union Against Cancer; assessable for response if at least one full course of regimen), progression-free survival, overall survival and adverse effects (WHO criteria)	***Withdrawals*** Three were not eligible due to having only local disease and receiving the regimen as neoadjuvant therapy. One further patient not eligible for response due to only receiving one course of therapy ***Severe adverse events*** Grade 4 anaemia: 1 (2%) Grade 3 anaemia: 3 (5%) Grade 4 leukopenia: 6 (11%) Grade 3 leukopenia: 10 (18%) Grade 4 neutropenia: 10 (18%) Grade 3 neutropenia: 10 (18%) Grade 4 thrombocytopenia: 1 (2%) Grade 3 thrombocytopenia: 2 (3%) Grade 4 mucositis: 1 (2%) Grade 3 mucositis: 2 (4%) Grade 3 nausea/vomiting: 2 (4%) Grade 3 alopecia: 26 (54%) Toxicity in the study reflected the need for some dose reduction, especially regarding cyclophosphamide One patient had reversible precordial pain and electrocardiogram alterations during third cycle attributable to vinorelbine, which led to discontinuation of vinorelbine	Overall response = 28/55 (51%, 95% CI, 37 to 63) Complete response = 5/55 (9%) Partial response = 23/55 (41%) Stable disease = 25/55 (45%) Progressive disease = 2/55 (4%) Median duration of response = 54 weeks Median time to progression = 47 weeks (range 35–59) Median survival = 90 weeks (range 62–119; using Kaplan–Meier methodology)	***Author's conclusions*** This combination at these doses and treatment schedule appeared to have acceptable tolerability, but there was no apparent improvement in therapeutic efficacy when compared with other regimens used as first-line treatment in ABC ***Other comments*** Author's conclusion about comparability with other regimens was not based on any direct comparative data Standard inclusion and exclusion criteria, and all patients had MBC and were first line. Follow-up adequate to calculate survival and objective criteria were used. Description of subgroups Multicentre trial

Vinorelbine combination therapy *contd*

Vinorelbine and cisplatin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Audhuy *et al.*, 1998[79] ***Country*** France ***Study design*** Case series (Phase II) ***Objective*** Vinorelbine plus cisplatin in MBC	***Inclusion/exclusion criteria*** MBC ***Number of participants*** 19 (16 analysed) ***Age*** Mean = 56 years (range 33–73) ***Previous treatment*** Adjuvant chemotherapy with anthracyclines or anthracenedione in six patients; adjuvant hormonal therapy in nine patients ***Performance status*** 0: 7 1: 7 2: 2 ***Stage of disease*** Metastatic (one to > three sites)	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 on days 1 and 5 plus cisplatin 100 mg/m^2 on day 1, every 3 weeks ***Concurrent treatment*** None reported ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response, progression-free survival and adverse effects	***Withdrawals*** None stated ***Severe adverse events*** Dose of vinorelbine had to be reduced to 25 mg/m^2 and that of cisplatin to 80 mg/m^2 due to febrile neutropenia or infection in three patients Grade 3 neutropenia: 6 patients Grade 4 neutropenia: 4 patients Hospitalisation was required for one patient due to febrile neutropenia	Overall response rate = 71% (range 48–95) Complete response = 1/14 Partial response = 9/14 Median overall progression-free survival = 7.3 months (range 1.6–15.2+)	***Author's conclusions*** These data confirmed that the combination of vinorelbine plus cisplatin in MBC with visceral disease (13 patients) was effective in first-line treatment and deserves further RCTs against standard regimens ***Other comments*** Study only reported as an abstract, thus difficult to assess Unclear how authors drew conclusions about visceral disease, given sample size was very small Follow-up was adequate to detect response rates only

Vinorelbine combination therapy *contd*

Vinorelbine and cisplatin *contd*

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Hochster *et al.*, 1997[80] (ongoing study: recruitment continues) ***Country*** USA ***Study design*** Case series (Phase II) ***Objective*** Vinorelbine plus cisplatin in ABC	***Inclusion/exclusion criteria*** Histologically proven locally ABC or MBC; ECOG performance status ≤ 2; adequate organ function ***Number of participants*** 24 (23 eligible; 20 patients first line (19 evaluable), three second line) ***Age*** Median = 49 years (range 32–67) ***Previous treatment*** Adjuvant chemotherapy = 9 Radiotherapy = 8 No details of chemotherapy received as first line in the three patients receiving study treatment as second line ***Performance status (ECOG)*** Median = 0 ***Stage of disease*** 13 MBC, 10 locally ABC (nine evaluable for response)	***Line of therapy*** First line in 20 patients and second line in three ***Intervention*** Vinorelbine 30 mg/m^2 on days 1 and 8 plus cisplatin 75 g/m^2 on day 1, repeated every 3 weeks ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response and adverse effects	***Withdrawals*** For one participant, it was too early for response ***Severe adverse events*** Grade 4 leukopenia: 2 Grade 3 leukopenia: 4 Grade 4 neutropenia: 7 Grade 3 neutropenia: 4 Grade 3 nausea/vomiting: 1	***MBC first line*** Overall response = 6/10 Complete response = 1/10 Partial response = 5/10 ***Locally ABC first line*** Overall response = 8/9 Complete response = 2/9 Partial response = 6/9 ***MBC second line*** Overall response = 2/3 Complete response = 1/3 Partial response = 1/3 ***All patients (n = 22)*** Overall response = 16/22 (73%) Complete response = 4/22 Partial response = 12/22 Stable disease = 4/22	***Author's conclusions*** Combined vinorelbine plus cisplatin therapy was highly active in locally ABC and MBC, without the dose-limiting neurotoxicity seen with a cisplatin plus paclitaxel combination ***Other comments*** Ongoing study Abstract, thus only few details. Mix of ABC/MBC and first and second line. Follow-up only adequate for response

Vinorelbine combination therapy *contd*

Vinorelbine plus gemcitabine

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Haider *et al.*, 1999[81] ***Country*** Austria ***Study design*** Case series (Phase II) prospective uncontrolled study ***Objective*** To investigate the efficacy and tolerability of gemcitabine plus vinorelbine and G-CSF in ABC	***Inclusion/exclusion criteria*** Histologically diagnosed locally ABC or MBC; aged ≤ 75 years; WHO performance status ≤ 2; expected survival time of > 12 weeks; adequate bone marrow, renal and liver function; prior radiotherapy, hormonal therapy and maximum of one chemotherapy for ABC permitted; patients with osteoblastic bone lesions as site of disease, CNS metastases and coexisting invasive malignancies were excluded ***Number of participants*** 60 (recruited April 1996–August 1997; 45 first line, 15 second line) ***Age*** Median = 58 years (range 29–75) ***Previous treatment*** Hormonal for MBC: 21 Radiotherapy for MBC: 5 Adjuvant chemotherapy: 19 (details not stated) Chemotherapy for MBC: 5 Adjuvant and MBC chemotherapy: 10 Chemotherapy for MBC + both adjuvant and MBC chemotherapy: 15 (five CMF, ten anthracycline-containing regimen) ***Performance status (WHO)*** 0: 21 1: 24 2: 15 ***Stage of disease*** Not stated	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 40 mg/m^2 on days 1 and 21 plus gemcitabine 1000 mg/m^2 on days 15 and 21, repeated every 5 weeks ***Concurrent treatment*** G-CSF was administered at 5 µg/kg/day on days 2–6 and 22–26 during each cycle ***Duration of follow-up*** Median = 15 months (range 12–28) ***Outcome measures*** The outcome measures were response (primary endpoint: overall, complete and partial responses, stable disease and progressive disease were defined objectively), progression-free survival, overall survival and adverse effects (according to WHO criteria)	***Withdrawals*** None. All evaluable for both efficacy and toxicity ***Severe adverse events*** (for all 60 participants) Grade 4 leukopenia: 1 (2%) Grade 3 leukopenia: 7 (12%) Grade 4 neutropenia: 2 (3%) Grade 3 neutropenia: 9 (15%) Grade 3 anaemia: 2 (3%) Grade 3 nausea/vomiting: 2 (5%) Grade 3 constipation: 2 (3%) Infection in nine patients but none required hospitalisation. Treatment discontinued due to drug-related toxicity in four patients	***First line*** Overall response = 25/45 (55.5%, 95% CI, 40 to 70.3) Complete response = 5/45 (11.1%) Partial response = 20/45 (44.4%) Stable disease = 12/45 (26.7%) Progressive disease = 8/45 (17.8%) Median time to progression = 9.5 months (range 1.5–28) Median survival > 14.0 months (not yet reached) ***Second line*** Overall response = 6/15 (40%) Complete response = 0 (0%) Partial response = 6 (40%) Stable disease = 5 (33%) Progressive disease = 4 (27%) Median time to progression = 7.0 months (range 2–23) Median survival = 12.2 months (Kaplan–Meier methods used)	***Author's conclusions*** The data suggested that gemicitabine plus vinorelbine and G-CSF was an effective and tolerable first- as well as second-line combination regimen for the treatment of ABC ***Other comments*** Inclusion and exclusion criteria detailed. ABC and MBC were mixed as well as first and second line. Objective criteria clearly detailed. First- and second-line demography and toxicity data merged. Follow-up continues

Vinorelbine combination therapy *contd*

Vinorelbine plus ifosfamide

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Leone *et al.*, 1996[82] (also reported as an abstract by Leone *et al.*, 1996[397] and by Leone *et al.*, 1995[398]) ***Country*** Argentina ***Study design*** Case series (Phase II) prospective, uncontrolled trial ***Objective*** To evaluate the efficacy and toxicity of the combination of ifosfamide plus vinorelbine as first-line chemotherapy in MBC	***Inclusion/exclusion criteria*** Histologically confirmed MBC; bidimensionally measurable disease; no chemotherapy for MBC; no prior vinorelbine or ifosamide; life expectancy > 3 months; ECOG performance status ≤ 2; adequate bone marrow, renal and hepatic function; only bone metastases allowed as long as measurable on X-ray; hormonal or adjuvant chemotherapy completed 4 weeks before study; no CNS metastases; no hilar enlargement, pleural effusion or malignant ascites as only evidence of metastatic disease; no peripheral neuropathy, active ischaemic heart disease, myocardial infarction within previous 6 months or uncontrolled hypertension ***Number of participants*** 45 (recruited August 1993–August 1995; 43 evaluable for response and toxicity (two did not start therapy)) ***Age*** Median = 53 years (range 30–73) ***Previous treatment*** Hormone therapy: 15 (nine adjuvant, six palliative) Adjuvant chemotherapy: 17 (ten FAC, seven CMF) ***Performance status (ECOG)*** 0: 20 1: 21 2: 4 ***Stage of disease*** All MBC and first line	***Line of therapy*** First line ***Intervention*** Vinorelbine 35 mg/m^2 on days 1 and 15 (during first cycle only, vinorelbine given as 17.5 mg/m^2 on days 8 and 22) plus ifosamide 2 g/m^2/day for 3 days, repeated every 28 days ***Concurrent treatment*** Mesna 400 mg/m^2 i.v. immediately before and 4 hours after ifosamide and 800 mg/m^2 orally 8 hours after ***Duration of follow-up*** Mean = 14 months (range 2–24), total 52 patient-years ***Outcome measures*** The outcome measures were response (objective criteria detailed in paper; all responses reviewed independently by two or more investigators), progression-free survival, overall survival and adverse effects (WHO criteria)	***Withdrawals*** Two patients did not start therapy (one due to development of psychiatric disorder and one due to worsening of performance status as a result of CNS metastasis) ***Severe adverse events*** Grade 3 anaemia: 2 (5%) Grade 4 leukopenia: 2 (5%) Grade 3 leukopenia: 13 (30%) Grade 4 granulocytopenia: 9 (21%) Grade 3 granulocytopenia: 12 (28%) Grade 3 thrombocytopenia: 1 (2%) Grade 4 infection: 3 (7%) Grade 3 infection: 1 (2%) Grade 3 peripheral neuropathy: 2 (5%) Grade 3 constipation: 2 (5%) Grade 3 nausea/vomiting: 2 (5%) Grade 3 stomatitis: 1 (2%) Grade 3 alopecia = 24 (56%) Grade 3 phlebitis: 3 (14%) Three patients (7%) developed febrile neutropenia that required hospitalisation and treatment with antibiotics and G-CSF. These treatments were not given prophylactically in the study	Overall response = 25/43 (58%, 95% CI, 43 to 73) Complete response = 6/43 (14%) Partial response = 19/43 (44%) Stable disease = 10/43 (23%) Progressive disease = 8/43 (19%) Median time to treatment failure = 12 months (range not stated) Median survival = 19 months (range not stated; Kaplan–Meier methods used)	***Author's conclusions*** Ifosamide plus vinorelbine was an active combination against MBC with moderate toxicity, and deserves further evaluation ***Other comments*** Inclusion and exclusion criteria were clear and standard. All patients had MBC and were first line. Good follow-up and objective criteria used for assessment. Details of subgroups given

Vinorelbine combination therapy *contd*

Vinorelbine plus mitomycin C

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Kornek *et al.*, 1996[83] (also reported as Scheithauer *et al.*, 1994.[148] Note that the earlier report included 45 patients recruited January 1993–July 1994, whereas the later one included 55 patients recruited October 1992–July 1994. In other respects, the populations appeared to be the same) ***Country*** Austria ***Study design*** Phase II prospective uncontrolled study ***Objective*** To evaluate the efficacy and tolerability of vinorelbine plus mitomycin C and G-CSF in advanced ABC	***Inclusion/exclusion criteria*** Histologically confirmed progressive, bidimensionally measurable, locally ABC or MBC; aged ≤ 75 years; WHO performance status < 2; expected survival > 12 weeks; adequate bone marrow, renal and hepatic function; prior chemotherapy for MBC permitted as long as no more than one regimen; prior radiotherapy or hormonal therapy permitted; all therapy completed ≥ 4 weeks before study; those with bone metastases only, CNS metastases or a second malignancy were excluded ***Number of participants*** 55 (all evaluable for response and toxicity) ***Age*** Median = 59 years (range 35–75) ***Previous treatment*** Hormonal adjuvant: 21 Hormonal MBC: 18 Chemotherapy adjuvant: 22 Chemotherapy MBC: 14 (nine anthracyclines, five other) ***Performance status (WHO)*** 0: 19 1: 36 ***Stage of disease*** Nine patients had locally ABC and 46 had MBC	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 50 mg/m^2 every 3 weeks in the first 36 patients, but then, due to toxicity, reduced to 40 mg/m^2 every 3 weeks, plus mitomycin C 15 mg/m^2 every 6 weeks. Treatment continued until complete or partial response or stable disease for a total of six courses ***Concurrent treatment*** G-CSF 5 µg/kg/day on days 2–7 following each cytotoxic drug administration. Ondansetron 8 mg and dexamethasone 8 mg given as premedication ***Duration of follow-up*** Median = 20 months (range 12–33). Median follow-up for participants with locally ABC = 18 months (range 13.5–28.0) ***Outcome measures*** The outcome measures were response (objective criteria detailed in paper; response confirmed by two principal investigators), progression-free survival (objective criteria detailed in paper), overall survival (objective criteria detailed in paper) and adverse effects (WHO criteria)	***Withdrawals*** All patients evaluable ***Severe adverse events*** Grade 4 leukopenia: 8 (14%) Grade 3 leukopenia: 6 (11%) Grade 4 neutropenia: 9 (16%) Grade 3 neutropenia: 10 (18%) Grade 4 thrombocytopenia: 2 (4%) Grade 3 thrombocytopenia: 4 (7%) Grade 3 anaemia: 2 (4%) Grade 4 infection: 1 (2%) Grade 3 infection: 3 (5%) Grade 3 nausea/vomiting: 4 (7%) Grade 3 diarrhoea: 1 (2%) Grade 3 stomatitis: 3 (5%) Grade 3 alopecia: 5 (9%) Grade 3 phlebitis: 3 (5%) Grade 3 peripheral neurotoxicity: 3 (5%) Grade 3 constipation: 5 (9%) Grade 4 pulmonary toxicity: 1 (2%) Grade 3 pulmonary toxicity: 5 (9%) Three patients were hospitalised and treated with antibiotics for sepsis. Pulmonary toxicity required a bronchodilator with or without glucocorticoids. One patient required respiratory support. Seven patients discontinued therapy due to acute lung toxicity, three due to progressive or severe neurotoxicity, one due to intercurrent septicaemia and two due to negative compliance	***MBC first line*** Complete response = 9/32 (28%) Partial response = 15/32 (47%) Stable disease = 7 (22%) Progressive disease = 1 (3%) Overall response rate = 24 (75%) Median duration of response = 10.8 months (range 3.5–22+) Median time to progression = 12.0 months (range 2–24+) Median survival = > 15.5 months ***Locally ABC first line*** All nine patients were rated as responsive (two complete and seven partial) and eight underwent surgery with curative intent. Only 1/8 patients who underwent surgery developed (supraclavicular lymph node) recurrence 11.5 months after initiation of therapy, and the ninth patient who refused surgery died of systemic disease progression 13 months after study entry ***Second line*** Overall response = 7/14 (50%) Complete response = 1/14 Partial response = 6/14 Stable disease = 5/14 Progressive disease = 1/14 Median duration of response = 4.5 months (range 3–15) Median time to progression = 6.0 months (range 2–22) Median survival = 11.5 months ***All patients (including 14 MBC patients having second-line therapy and nine with locally ABC)*** Overall response = 73% (95% CI, 59 to 84) Complete response = 12/55 (22%) Partial response = 28/55 (51%) Stable disease = 13 (24%) Progressive disease = 2 (4%)	***Author's conclusions*** The results indicated that vinorelbine plus mitomycin C and G-CSF had an excellent anti-tumour activity in ABC. Overall toxicity was low ***Other comments*** Performance status only 1 or 0 eligible to enter into study (most studies included 0–2) Toxicity only presented for sample population as a whole (and not according to those who received first-line chemotherapy) Subseries included response according to first- or second-line chemotherapy, vinorelbine dosage (50 or 40 mg/m^2) and locally ABC or MBC

Vinorelbine combination therapy *contd*

Vinorelbine plus trastuzumab

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Burstein *et al.*, 2001[84] ***Country*** USA ***Study design*** Case series (Phase II) uncontrolled study ***Objective*** To determine the response rate and toxicity profile of trastuzumab administered concurrently with weekly vinorelbine in women with human epidermal growth factor receptor 2 (HER2)-overexpressing MBC	***Inclusion/exclusion criteria*** Women with +2 or +3 HER2-overexpressing MBC; aged ≥ 18 years; both patients who had or had not received previous chemotherapy for MBC were eligible to enter the study; patients could have had adjuvant therapy; patients were not permitted to have received vinorelbine or trastuzumab before; performance status (ECOG) of 0–2; absence of other serious illness; adequate cardiac, hepatic function and haematology (details specified in full paper) ***Number of participants*** 40 (19 received vinorelbine plus trastuzumab as first line for MBC) ***Age*** Median = 50 years (range 28–70) for all 40 patients ***Previous treatment*** No chemotherapy for MBC: 19 (48%) No chemotherapy at all: 7 Chemotherapy for MBC: 10 (25%) Adjuvant chemotherapy: 12 (30%) Both adjuvant chemotherapy and chemotherapy for MBC: 11 (28%) Anthracycline-based chemotherapy: 8 (20%) Taxane-based chemotherapy: 6 (15%) Both anthracycline- and taxane-based chemotherapy: 15 (38%) Non-anthracycline-based, non-taxane-based therapy: 4 (10%) ***Performance status*** Not stated ***Stage of disease*** +2 HER2: 10 (25%) +3 HER2: 30 (75%) 35 (87%) had more than one metastatic site	***Line of therapy*** First and second line ***Intervention*** Vinorelbine 25 mg/m^2 weekly plus trastuzumab 2 mg/m^2 (except for first dose of 4 mg/m^2) weekly, administered on the same day. The vinorelbine dose, but not the trastuzumab one, could be adjusted if there were signs of toxicity ***Concurrent treatment*** G-CSF was to be permitted if treatment delays of > 2 weeks were occurring due to neutropenia or febrile neutropenia ***Duration of follow-up*** 100+ weeks. Median time on study = 27 weeks (Kaplan–Meier curves) ***Outcome measures*** The outcome measures were response, progression-free survival, overall survival and adverse effects	***Withdrawals*** 27 due to progressive disease, four withdrew consent and four had changes in left ventricular ejection fraction. All patients enrolled were included in an ITT analysis ***Severe adverse events (number of patients (%))*** Grade 3 white blood cells: 13 (33%) Grade 3 absolute neutrophil count: 13 (33%) Grade 4 white blood cells: 2 (5%) Grade 4 absolute neutrophil count: 4 (10%) Grade 3 low haemoglobin: 1 (3%) Grade 3 thrombosis: 1 (4%) Grade 3 pancreatitis: 1 (3%) Grade 3 fatigue: 2 (5%)	***First line*** Overall response rate = 16/19 (84%) Time to progression median = 34 weeks Overall survival median not yet reached (Kaplan–Meier methods used) ***All patients*** Overall response rate = 30/40 (75%) Complete response rate = 3/40 (8%) Partial response rate = 27/40 (68%) Stable disease for > 6 months = 2 (5%) Progressive disease = 8 (20%) ***+3 HER2*** Overall response rate = 24/30 (80%) ***+2 HER2*** Overall response rate = 6/10 (60%)	***Author's conclusions*** Trastuzumab in combination with vinorelbine was highly active in women with HER2-overexpressing ABC and was well tolerated ***Other comments*** Study originally designed to include only patients who had received chemotherapy for MBC. Based on initial activity and toxicity, inclusion expanded to include those with no previous chemotherapy for MBC Demographic data were presented for whole study group and not always just for the 19 patients receiving vinorelbine plus trastuzumab as first line for MBC Statistical tests: log-rank, Fisher's exact test and CIs were calculated using standard methods Mix of first- and second-line therapy, follow-up acceptable for response, but not long enough to reach median survival yet. Details of assessment methods not given

Vinorelbine combination therapy *contd*

Vinorelbine plus 5-fluorouracil plus cisplatin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Nole *et al.*, 2001[85] (interim results of this study also reported as an abstract by Nole *et al.*, 1999[399]) ***Country*** Italy ***Study design*** Case series (Phase II) ***Objective*** To investgate a multi-agent regimen for patients for whom anthracyclines and/or taxanes may not be suitable	***Inclusion/exclusion criteria*** Histologically proven, measurable or evaluable MBC; aged 18–70 years; ECOG performance status ≤ 2; expected survival ≥ 3 months; adequate bone marrow, renal and hepatic function; no severe uncontrolled morbidities; no second malignancies ***Number of participants*** 100 (recruited January 1997–April 1999; 96 evaluable for response (four had only evaluable bone disease) and all assessable for toxicity; 48 first line, 52 second line) ***Age*** **First line** Median = 50 years (range 27–69) **Second line** Median = 50 years (range 23–72) ***Previous treatment*** **First line** Adjuvant chemotherapy: 30 (21 anthracyclines) **Second line** Adjuvant chemotherapy: 42 (15 anthracyclines) MBC chemotherapy: 52 (32 anthracyclines, 7 CMF, 18 taxanes) ***Performance status*** **First line** 0: 32 1: 16 **Second line** 0: 23 1: 29 **Stage of disease** All MBC	***Line of therapy*** First and subsequent line ***Intervention*** Vinorelbine 20 mg/m^2 on days 1 and 3 plus cisplatin 60 mg/m^2 on day 1 and 5-fluorouracil 200 mg/m^2/day (number of days not stated), repeated every 3 weeks ***Concurrent treatment*** None stated ***Duration of follow-up*** Median = 10.2 months (range 1–26.3+) ***Outcome measures*** The outcome measures were response (WHO standard objective criteria detailed in paper; response assessed by two investigations ≥ 6 weeks apart), progression-free survival, overall survival and adverse effects (according to National Cancer Institute common toxicity criteria)	***Withdrawals*** Four patients had only evaluable bone disease ***Severe adverse events*** **First line (*n* = 48)** Grade 4 leukopenia: 1 Grade 3 leukopenia: 5 Grade 4 granulocytopenia: 8 Grade 3 granulocytopenia: 12 Grade 3 anaemia: 2 Grade 4 thrombocytopenia: 1 **All patients (*n* = 100)** Grade 3 fatigue: 1 Grade 3 fever: 1 Grade 3 photosensitivity: 1 Grade 3 hand and foot: 1 Grade 3 nausea: 4 Grade 4 diarrhoea: 1 Grade 3 diarrhoea: 2 Grade 3 stomatitis: 4 Grade 3 epigastric pain: 1 11 patients (11%) had right diaphragmatic supraelevation due to right phrenic nerve axonal injury. Eight patients had venous thrombo-embolism that required treatment with low-molecular weight heparin	***First line*** Overall response = 30/45 (66%) Complete response = 2/45 (5%) Partial response = 28/45 (61%) Stable disease = 11/45 (25%) Progressive disease = 4/45 (9%) Median time to progression = 8 months (range 0.7–21.4) Median survival not reached (Kaplan–Meier methods used) ***Second or subsequent line*** Overall response = 23/51 (45%) Complete response = 2/51 (4%) Partial response = 21/51 (41%) Stable disease = 20/51 (39%) Progressive disease = 8/51 (16%) Median time to progression = 5.6 months (range 1.2–24.7) Median survival = 14.3 months (range 7.8–35.4; Kaplan–Meier methods used) ***All patients*** Overall response = 53/96 (55%) Complete response = 4/96 (4%) Partial = 49/96 (51%) Stable disease = 31/96 (32%) Progressive disease = 12/96 (13%) Median time to progression = 6.8 months (range 0.3–24.7) Median survival not reached (Kaplan–Meier methods used)	***Author's conclusions*** Vinorelbine plus 5-fluorouracil plus cisplatin represented a valid and acceptable alternative to other chemotherapy regimens when anthracyclines were contraindicated or when patient's preference led to a choice of a combination of cytotoxics which did not cause significant alopecia yet preserved relevant antitumour efficacy ***Other comments*** Performance status only 0 or 1 Unclear how long 5-fluorouracil was given for in each cycle Standard inclusion and exclusion criteria. All MBC but some first and some second line, although data separated. Objective criteria and subgroups described, but non-haematological toxicity only presented for group as a whole (data for first-line chemotherapy not presented separately). Follow-up continuing

Vinorelbine combination therapy *contd*

Vinorelbine plus 5-fluorouracil and epirubicin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Guler *et al.*, 2000[86] ***Country*** Turkey ***Study design*** Case series (multicentre Phase II study) ***Objective*** To evaluate the efficacy and toxicity of the combination of vinorelbine plus epirubicin plus 5-fluorouracil as first-line therapy in MBC	***Inclusion/exclusion criteria*** MBC ***Number of participants*** 52 (recruited May 1997–May 1999; 50 evaluable for efficacy and toxicity) ***Age*** Median = 48 years (range 34–68) ***Previous treatment*** 21 (40%) had had adjuvant chemotherapy with anthracyclines ***Performance status*** Not stated ***Stage of disease*** 69% had multiple metastases	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus epirubicin 35–40 mg/m^2 plus 5-fluorouracil 350 mg/m^2 on days 1 and 8, repeated every 3 weeks for a maximum of six to eight cycles ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response, progression-free survival, overall survival and adverse effects	***Withdrawals*** Two patients not accounted for ***Severe adverse events*** Grade 3–4 neutropenia: 15% Grade 3 nausea/vomiting: 5% Grade 3 alopecia: 18% Local phlebitis (grade not stated): 28%	Complete response = 7/50 (14%) Partial response = 28/50 (56%) Overall response = 70% Stable disease = 12/50 (12%) ***Survival analyses in 31 patients*** Median progression-free survival = 7 months (range 2–22) Median survival = 14 months (range 5–32+)	***Author's conclusions*** Vinorelbine plus epirubicin plus 5-fluorouracil combination was an effective and safe combination in the treatment of MBC ***Other comments*** Abstract only, thus limited details All MBC and first line. No details of methods of assessment or subgroups. Follow-up appears to continue

Vinorelbine combination therapy *contd*

Vinorelbine plus mitoxantrone and carboplatin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Kakolyris *et al.*, 1999[87] ***Country*** Greece ***Study design*** Case series (Phase II) ***Objective*** To evaluate the efficacy and toxicity of a combination of vinorelbine plus mitoxantrone plus carboplatin in MBC	***Inclusion/exclusion criteria*** Histologically proven, bidimensionally measurable MBC; bone metastases not considered evaluable; only adjuvant hormonal therapy permitted; aged 18–75 years; WHO performance status ≤ 2; expected survival ≤ 3 months; adequate bone marrow, renal, hepatic and cardiac function; no second malignancies; no brain metastases, peripheral neuropathy, severe infection or malnutrition ***Number of participants*** 50 (recruited October 1993–November 1996; all evaluable for response and toxicity) ***Age*** Median = 64 years (range 40–75) ***Previous treatment*** Adjuvant hormonal: 16 (32%) Adjuvant chemotherapy: 17 (34%) Radiotherapy: 26 (21 adjuvant, five palliative) ***Performance status (WHO)*** 0: 35 1: 15 ***Stage of disease*** All MBC	***Line of therapy*** First line ***Intervention*** Vinorelbine 30 mg/m^2 plus mitoxantrone 12 mg/m^2 on day 1 plus carboplatin 250 mg/m^2 on day 2, repeated every 3 weeks. Initially vinorelbine was to be given on day 8 also, but this was dropped after first four patients due to toxicity ***Concurrent treatment*** Anti-emetic therapy with dexamethasone and ondansetron. Patients who developed grade 3–4 neutropenia in first cycle were given G-CSF 150 g/m^2 in subsequent cycles ***Duration of follow-up*** Median follow-up = 26 months (range 2–38) ***Outcome measures*** The outcome measures were response (according to Union Internationale Contre le Cancer criteria; response to last 4 weeks for confirmation), progression-free survival, overall survival and adverse effects (WHO criteria)	***Withdrawals*** None stated ***Severe adverse events*** Grade 4 neutropenia: 20 (40%) Grade 3 neutropenia: 9 (18%) Grade 4 thrombocytopenia: 8 (16%) Grade 3 thrombocytopenia: 3 (6%) Grade 3 anaemia: 7 (14%) Grade 3 nausea/vomiting: 3 (6%) Four patients had febrile neutropenia requiring hospitalisation and treatment with antibiotics and G-CSF	Overall response = 28/50 (56%, 95% CI, 42 to 70) Complete response = 4/50 (8%) Partial response = 24/50 (48%) Stable disease = 12/50 (24%) Progressive disease = 10/50 (20%) Median duration of response = 6 months (range 1.5–33) Median time to progression = 7 months (range 3–38) Median survival (Kaplan–Meier method) = 26 months (range 2–38) 1-year survival: 76% 2-year survival: 57%	***Author's conclusions*** This three-drug regimen was effective and well tolerated for the treatment of MBC ***Other comments*** 70% had a performance status of 0 Standard inclusion and exclusion criteria and all MBC and first line. Objective criteria were used and details of subgroups were given

Vinorelbine combination therapy *contd*

Vinorelbine plus mitoxantrone and cisplatin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Wendling *et al.*, 1995[88] ***Country*** France ***Study design*** Case series (Phase II) ***Objective*** Vinorelbine plus mitoxantrone plus cisplatin as first-line treatment in MBC	***Inclusion/exclusion criteria*** Evaluable MBC; no chemotherapy for MBC; aged 18–75 years; performance status ≤ 2 ***Number of participants*** 25 ***Age*** Median = 57 years (range 36–70) ***Previous treatment*** Adjuvant chemotherapy: 16 (12 anthracycline) ***Performance status*** Not stated ***Stage of disease*** Not stated	***Line of therapy*** First line ***Intervention*** Vinorelbine 25 mg/m^2 plus mitoxantrone 12 mg/m^2 on day 1 plus cisplatin 25 mg/m^2 on days 1–3 ***Concurrent treatment*** G-CSF used for 35% of courses ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (assessed after at least two courses) and adverse effects	***Withdrawals*** Five patients not evaluable for response. Number evaluable for toxicity not stated ***Severe adverse events*** Grade 4 neutropenia: 10% Grade 3 neutropenia: 20% Grade 4 thrombocytopenia: 10% Grade 3 thrombocytopenia: 30% Grade 3 alopecia: 6%	Overall response = 16/20 (75%) Complete response = 5/20 (25%) Partial response = 11/20 (55%)	***Author's conclusions*** This regimen showed a good response rate. However, haemato-logical toxicity was severe, especially thrombocytopenia after four courses ***Other comments*** Abstract only, thus very limited details All patients had MBC and were first line 5/20 not evaluable for response, which is a high proportion to have 'lost'

Vinorelbine combination therapy *contd*

Vinorelbine plus doxorubicin plus methotrexate plus leucovorin

Study and design	Participants	Intervention details and outcome measures	Withdrawals/severe adverse events	Results	Comments
Subramanyan *et al.*, 1999[89] ***Country*** USA ***Study design*** Case series (Phase I and II), prospective uncontrolled study ***Objective*** To determine the maximum tolerated dose and toxicity of vinorelbine when used in combination with doxorubicin plus methotrexate plus leucovorin rescue in women with MBC	***Inclusion/exclusion criteria*** Histologically documented MBC with at least one measurable or evaluable lesion; no chemotherapy for MBC; relapsed after at least one prior course of hormonal therapy; no more than 250 mg/m^2 total lifetime exposure to doxorubicin and prior radiotherapy to no more than 25% of marrow-containing bones; aged > 18 years; ECOG performance status ≤ 2; adequate bone marrow, renal, hepatic, cardiac and pulmonary function; no active cardiac disease, other major medical illness or pregnancy ***Number of participants*** 23 (recruited October 1993–July 1996; all patients evaluable for toxicity and 22 evaluable for response) ***Age*** Median = 49 years (range 32–65) ***Previous treatment*** Adjuvant hormonal: 6 MBC hormonal: 5 Adjuvant chemotherapy: 7 ***Performance status*** All 0–1 ***Stage of disease*** 20 patients had measurable disease (stage IV). One patient had stage II breast cancer with a separate primary lung cancer, which was not diagnosed until after completion of the study	***Line of therapy*** First line ***Intervention*** Starting dose levels of vinorelbine 20 mg/m^2 plus doxorubicin 40 mg/m^2 plus methotrexate 100 mg/m^2 on day 1 plus leucovorin 10 mg/m^2 for six doses starting on day 2 Dose of vinorelbine increased by 5 mg/m^2 if at least three patients completed the 21-day course with no dose-limiting toxicity. Maximum dose of vinorelbine used was 30 mg/m^2. Doxorubicin 50 and 60 mg/m^2 were also used with 25 mg/m^2 vinorelbine in some patients ***Concurrent treatment*** None stated ***Duration of follow-up*** Not stated ***Outcome measures*** The outcome measures were response (ECOG criteria), progression-free survival, overall survival and adverse effects (National Cancer Institute common toxicity criteria)	***Withdrawals*** One patient was not included in the analyses of response because they had a chest wall nodule that was not found to be benign on excision at the end of treatment. It was unknown if patient had stage IV disease that responded to chemotherapy or the mass was simply residual fibrotic tissue (no evidence of disease) Out of the 22 patients included in the ITT analysis of response, one was found (during a resection 1 year later) to have stage II disease with a primary lung cancer ***Severe adverse events*** At the third dose level (vinorelbine 30 mg/m^2 plus doxorubicin 40 mg/m^2 plus methotrexate 100 mg/m^2), there were two cases of dose-limiting toxicity due to neutropenia, one due to grade 3 nausea/vomiting, one due to grade 3 fatigue, one due to grade 3 arm pain and one due to grade 3 malaise At the fourth dose level (vinorelbine 25 mg/m^2 plus doxorubicin 40 mg/m^2 plus methotrexate 100 mg/m^2), one of five patients developed grade 4 nausea/vomiting All patients treated with doses of doxorubicin above 40 mg/m^2 developed dose-limiting neutropenia Neutropenic fever occurred in 6/94 of courses	Overall response = 8/22 (36%) Complete response = 3/22 (14%) Partial response = 5/22 (23%) Stable disease = 5/22 (23%) Progressive disease = 8/22 (36%) Also two with evaluable (but not measurable) disease showed some improvement ***Patients with measurable disease (n = 20)*** Complete response = 15% (95% CI, 3 to 38) Partial response = 25% (95% CI, 9 to 49) Overall response = 40% (95% CI, 19 to 64) Estimated median survival from start of therapy using Kaplan–Meier method = 25 months	***Author's conclusions*** Response rates observed with this regimen suggested that this combination might not be more effective than the combination of vinorelbine plus doxorubicin ***Other comments*** Inclusion criteria regarding radiotherapy of marrow bones and requirement to have relapsed after hormonal therapy were unusual, and median age younger than most studies Number of patients with prior hormonal therapy did not correspond with inclusion criterion that all patients should have had at least one hormonal regimen Numbers that responded did not add up to 22 Only 22 (and not 23) patients were included in the ITT analysis: two patients were found not to have stage IV disease Inclusion and exclusion criteria were clear except that about hormonal therapy. All patients had MBC with no chemotherapy. Follow-up was unclear, objective criteria were reported and there were limited subgroup details

HER2, human epidermal growth factor receptor 2

Appendix 8

Included economic evaluations for vinorelbine

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Brown *et al.*, 2000[34] (also included data from Brown *et al.*, 2000,[403] Cameron, 2000,[183] Brown and Hutton, 2000,[404] Brown *et al.*, 2000,[405] Anderson and Cox, 2000[406] and Leonard and Anderson, 2000[407]) ***Research question*** A CUA of docetaxel versus paclitaxel versus vinorelbine estimating the costs and QoL for management of ABC patients ***Type of economic evaluation*** CUA ***Country/currency*** UK/£ sterling ***Cost year*** 1997 ***Perspective*** UK NHS ***Study population*** Patients with ABC whose disease progressed following first-line chemotherapy ***Interventions (including comparator)*** Docetaxel, vinorelbine or paclitaxel	***Source of effectiveness data*** For docetaxel, three Phase III RCTs for patients with ABC were used to estimate response and adverse event rates. For paclitaxel, one Phase III RCT was used for response rates, and weighted averages from several Phase II trials were used for adverse event rates. For vinorelbine, the only published Phase III RCT was used for both response and adverse event rates ***Source of cost data*** Cost data were taken from the NHS, National Trust Hospital Surveys and the UK *Monthly Index of Medical Specialities*. Costs were discounted at 6%	***Valuation for clinical outcomes or benefits*** Response rate, time to progression, median survival and rate of grade 4 febrile neutropenia with hospitalisation Utilities for the model were derived using the standard gamble method from proxy utilities provided by 30 oncology nurses in the UK ***Estimation of costs*** Resource use was based on estimates of UK oncologists. It was assumed that chemotherapy was given in 3-weekly cycles: the taxanes once every 3 weeks and vinorelbine once weekly The costs included in the analysis were those related to: the acquisition and administration of chemotherapy; concomitant medication for palliative care and the treatment of adverse events; physician and nurse visits; laboratory testing; hospitalisation and home care ***Modelling*** An updated version of the Hutton *et al. Pharmacoeconomics* 1996 decision analysis model (using Markov process) was used to simulate the experiences (associated costs and outcomes) of patients undergoing treatment for ABC from onset of salvage chemotherapy to death	***Clinical outcome/benefits*** Effectiveness measures used in the base-case analysis were: – Response rates (28% with paclitaxel, 41.7% with docetaxel and 16% with vinorelbine) – Time to progression (21 weeks with paclitaxel, 24 weeks with docetaxel and 12 weeks with vinorelbine) – Median survival (46 weeks with paclitaxel, 56 weeks with docetaxel and 36 weeks with vinorelbine) – Rate of grade 4 neutropenia (7.0% with paclitaxel, 7.3% with docetaxel and 0% with vinorelbine) ***Benefit*** The estimated QALY values were 0.48 for vinorelbine, 0.73 for docetaxel and 0.65 for paclitaxel. Translated into days, this means that vinorelbine produces 175 days of good quality life, docetaxel produces 266 days and paclitaxel produces 237 days ***Costs*** The average patient costs were found to be £4268 for vinorelbine, £7817 for docetaxel and £7645 for paclitaxel ***Synthesis of costs and benefits*** The incremental cost per QALY for docetaxel was £14,500 compared with vinorelbine and £1990 compared with paclitaxel (i.e. it was less cost-effective relative to vinorelbine) ***Statistical analysis*** None reported	***Sensitivity analysis*** Various sensitivity analyses were undertaken and did not change the findings appreciably. Under every scenario, docetaxel was more expensive than paclitaxel and vinorelbine, except where cost of progressive disease increased to £300 per 3-week period, when docetaxel became dominant compared with paclitaxel. Docetaxel was always more expensive and more effective than vinorelbine at a cost/QALY of between £12,790 and £15,095 ***Appropriateness*** The sensitivity analysis was appropriate, although additional analysis around the clinical assumptions (particularly involving the Phase II data) would have been useful	***Author's conclusions*** The CERs were within the range of generally acceptable technologies. Patients managed with docetaxel had improved QoL in comparision to these alternative chemotherapies and a longer survival ***Magnitude and direction of result*** 1 (for vinorelbine versus paclitaxel or docetaxel) ***Implications for practice*** The results of this study support the use of docetaxel in the management of ABC ***Comments*** This study was based on a Markov model and concluded that docetaxel is cost-effective when compared with both paclitaxel and vinorelbine. The study employed sensitivity analysis to confirm the robustness of the model to alternative assumptions. Nevertheless, there are significant weaknesses in the analysis (some of which are acknowledged by the authors). Firstly, the effectiveness data were not derived from a head-to-head comparison. Rather, individual arms of RCTs were used, which negates some of the properties of an RCT. In addition, some of the data employed in the analysis were taken from Phase II trials and may be open to bias, which was not accounted for in the model The study also used median survival rather than mean survival which would have been more appropriate. Given that the clinical trial had been completed, mean survival data may have been available. If not, median survival could have been adjusted using statistical techniques to more accurately reflect likely mean survivals Expert opinion was used to derive the resource use estimates. Clearly, this is not the best method of measurement and is open to bias (for instance, estimates may reflect ideal rather than actual levels of resource use) Patients' utility values were ascertained from a sample of nurses and the authors acknowledged that the use of patient-derived utilities would have strengthened the analysis The analysis used appropriate techniques, but could have addressed some of the issues above. Given the relative proximity of the cost/QALY figure (of docetaxel versus vinorelbine) to the authors threshold (£20,000–30,000) and the large degree of uncertainty surrounding the estimates, the conclusions should be interpreted with caution The economic evaluation was sponsored by Aventis (manufacturer of docetaxel)

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Launois *et al.*, 1996[36,189] ***Research question*** To determine the cost-effectiveness of docetaxel, paclitaxel and vinorelbine as second-line treatment in patients with MBC ***Type of economic evaluation*** CEA and CUA ***Country/currency*** France/FF ***Cost year*** 1993 ***Perspective*** Healthcare system and patient ***Study population*** Patients with MBC treated with second-line drugs ***Interventions (including comparator)*** Vinorelbine, docetaxel and paclitaxel	***Source of effectiveness data*** Multiple trials. Data for docetaxel are based on results from the drug registration master file, i.e. pooling of three Phase II trials (NN 1995) recently published (Ten Bokkel *et al.*, 1994;[408] Valero *et al.*, 1995;[409] Ravdin *et al.*, 1995[410]). For paclitaxel, interim results of the BMTSG trial were used (Nabholtz *et al.*, 1993[411]; FDA 1993[412]). Vinorelbine data were taken from one non-controlled trial (Degardin *et al.*, 1994[182]) that evaluated the efficacy and tolerability of vinorelbine in refractory advanced/and/or MBC ***Source of cost data*** Direct medical costs were calculated using a standard cost method (defined as the product of a standard quantity and standard price). Standard quantities were derived from a retrospective study in five hospitals. Standard costs were based on national accounting costs by diagnosis-related groups	***Valuation for clinical outcomes or benefits*** Type of response (complete response, partial response, no change, disease progression) and the nature of toxicity/adverse reactions HRQoL using the standard gamble method (via a survey of 20 nurses/non-patients) ***Estimation of costs*** Second-line treatment; follow-up assessment of responders; management of toxicity of metastatic complications; third-line treatment; palliative end-of-life treatment ***Modelling*** Markov model	***Clinical outcome/benefits*** **Clinical outcomes** Overall responses were 57.1% for docetaxel, 28.9% for paclitaxel and 16.0% for vinorelbine, durations of response were 28, 28 and 21 weeks, respectively, and times to progression were 21, 18 and 12.9 weeks, respectively. The main toxicities were as follows: febrile neutropenia occurred in 17.9, 2.0 and 3.0% of patients treated with docetaxel, paclitaxel and vinorelbine, respectively; arthralgia was found in 16.0% and severe neurotoxicities in 6.0% of patients treated with paclitaxel only; severe fluid retention was found in docetaxel patients only, leading to interrupted treatment in 1.9% and no interruption of treatment in 2.9% ***Benefits*** **Progression-free survival** 0.473 years or 173 days with docetaxel, 0.398 years or 145 days with paclitaxel and 0.271 years or 99 days with vinorelbine. After quality adjustment, the results were 125 days with docetaxel, 103 days with paclitaxel and 68 days with vinorelbine ***Costs*** **Treatment and follow-up** FF61,300 with docetaxel, FF26,900 with vinorelbine and FF53,600 with paclitaxel **Treatment-related complications** FF20,700 with docetaxel, FF22,700 with vinorelbine and FF19,200 with paclitaxel **Disease-related complications** FF168,400 with docetaxel, FF207,600 with vinorelbine and FF178,300 with paclitaxel **Total costs** FF250,400 with docetaxel; FF257,200 with vinorelbine and FF251,100 with paclitaxel **Synthesis of costs and benefits** NA because docetaxel was the dominant treatment **Statistical analysis** NA	***Sensitivity analysis*** Sensitivity analysis included variations in response rates, median time to progression, median duration of response, adverse event rates and costs. These restricted the range of possibilities to the results of the clinical trials that had been published When the least favourable values for the time to progression, median response time and response rate seen in Phase II trials with docetaxel were used, docetaxel was still dominant over vinorelbine in all situations. Vinorelbine was more expensive and less effective Overall, the results obtained with reference to paclitaxel appeared to be robust. Although the order of the different strategies could be reversed, docetaxel appeared to be more effective in all cases. Moreover, while docetaxel was more expensive, the additional cost per extra unit of efficacy remained acceptable ***Appropriateness*** Sensitivity analyses appeared to be appropriate but only included effectiveness data. The costs were, therefore, open to uncertainties	***Author's conclusions*** Vinorelbine and paclitaxel were dominated strategies with a lower effectiveness (progression-free days both adjusted or not adjusted for QoL) and a greater cost than docetaxel Although the incremental costs for vinorelbine were higher when compared with paclitaxel and the incremental utility was favourable for paclitaxel compared to vinorelbine, the authors do not discuss the significance of these differences ***Magnitude and direction of result*** Vinorelbine versus docetaxel: matric score C Vinorelbine versus paclitaxel: matrix score C? ***Implications for practice*** Vinorelbine and paclitaxel were inferior to docetaxel, since, overall, they were less effective than docetaxel, whereas the projected costs per patient treated were higher ***Comments*** Comparison between docetaxel and both other drugs were clear and robust. Comparison between vinorelbine and paclitaxel was not clear. The effectiveness data were not derived from a head-to-head comparison and study populations may, therefore, have varied in terms of prognosis. Cost results might not apply outside the French setting. Only direct medical costs were considered in the analysis

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Leung et *al*, 1999[37,413] ***Research question*** A CUA was performed to create a rank order on the basis of effectiveness, QoL and economic consideration of using paclitaxel, docetaxel or vinorelbine in the treatment of patients with anthracycline-resistant breast cancer ***Type of economic evaluation*** CUA ***Country/currency*** Canada/Can$ ***Cost year*** 1999 ***Perspective*** Societal (Canadian) Canadian healthcare system ***Study population*** Participants with MBC (anthracycline-resistant) who received treatment with either docetaxel, vinorelbine or paclitaxel in 1996 and 1997	***Source of effectiveness data*** Measures of effectiveness required for the decision model were obtained from multiple RCTs (Phase III),[38,414,415] and only one arm was used from each trial ***Source of cost data*** Cost estimates were derived from a retrospective chart review. Patients were identified through the database of the Department of Pharmaceutical Services. Individuals must have relapsed within 12 months after anthracycline-based adjuvant therapy or must have had disease progression after treatment with anthracyclines (alone or in combination) for metastatic disease. Costs included acquisition, preparation and administration of chemotherapy; premedications; laboratory tests; hospitalisation; clinic visits; management of adverse effects or complications and all related physician fees	***Valuation for clinical outcomes or benefits*** For disease progression, the measures of effectiveness required for the decision model were toxic death rates, treatment-limiting toxicity rates and tumour response rates The HRQoL values measured in the analysis were based on preferences for certain health outcomes compared with perfect health. These utilities were determined using the time trade-off technique. Utility data were obtained from 25 healthy oncology care providers. 25 breast cancer patients were also interviewed to obtain utility scores for comparison The following assumptions regarding the 'number of cycles' for each branch were used for the decision model: – toxic deaths were rare but were assumed to occur after one cycle of chemotherapy because toxic deaths are often due to hypersensitivity (this was not applicable for vinorelbine because the occurrence rate was zero) – where treatment was discontinued due to toxicity, it was assumed that an average of three cycles of chemotherapy were given before severe toxicity occurred (again not applicable to vinorelbine)	***Clinical outcomes/ benefits*** **Clinical outcomes** Response rates: 21% with paclitaxel, 30% with docetaxel and 16% with vinorelbine Discontinuation due to toxicity: 4% with paclitaxel, 4.4% with docetaxel and 0% with vinorelbine Toxic deaths: 0.40% with paclitaxel, 2% with docetaxel and 0% with vinorelbine Time to progression (weeks): 16.8 with paclitaxel, 19 with docetaxel and 12 with vinorelbine ***Benefits*** Each of the three drugs led to a similar duration of quality-adjusted progression-free survival using healthy volunteers (37.2 days with paclitaxel, 33.6 days with docetaxel and 38.0 days with vinorelbine). The quality-adjusted progression-free survival using breast cancer patients were 39.8 days with paclitaxel, 33.2 days with docetaxel and 35.0 days with vinorelbine ***Costs*** The estimated mean costs per cycle for each study drug were Can$503 (95% CI, 453 to 641) for 180 cycles with vinorelbine, Can$2653 (95% CI, 2363 to 3053) for 138 cycles with docetaxel and Can$1680 (95% CI, 1574 to 1976) for 139 cycles with paclitaxel. The favourable economic profile of vinorelbine was primarily due to the lower acquisition cost of the drug, the shorter administration time, minimal premedications and the better toxicity profile. The mean overall treatment cost for each strategy for vinorelbine was Can$3259 per patient, compared with Can$6039 and Can$10,090 for paclitaxel and docetaxel, respectively ***Synthesis of costs and benefits*** The utility in days was transformed to years for the CUA. The average cost per quality-adjusted progression-free year was Can$59,096 for paclitaxel, Can$110,072 for docetaxel and Can$31,220 for vinorelbine	***Sensitivity analysis*** Sensitivity analysis included: – an evaluation of alternative choices of subsequent therapy – substitution of the utility scores from 25 breast cancer patients for those measures in healthy volunteers – for each taxane, variation of the number of cycles before treatment-limiting toxicity occurred from one to six cycles – reanalysis of the baseline results, using the upper and lower 95% CI limits for the response rates and treatment costs ***Appropriateness*** Ranges were justified and seemed to be appropriate. It was not clear what type of sensitivity analysis was performed	***Author's conclusions*** Palliative chemotherapy with vinorelbine in anthracycline-resistant MBC patients had economic advantages over taxanes and provided at least equivalent quality-adjusted progression-free survival. These benefits were largely related to its lower drug acquisition costs and better toxicity profile ***Magnitude and direction of result*** Matrix score G ***Implications for practice*** Vinorelbine was more cost-effective because it improved quality-adjusted progression-free survival with reduced cost, compared with the two taxanes. Therefore, an incremental cost-effectiveness analysis would be consistent with a situation of economic dominance (i.e. lower cost with at least equal benefit) ***Comments*** Vinorelbine did not have the longest quality-adjusted progression-free survival according to the 25 patients with breast cancer. Data for costing were derived from patients notes. No information was given regarding the validation of this information Supported in part by an unrestricted educational grant from Glaxo-Wellcome Canada Inc. TreeAge software (version 2.6.7.) was used to build the model. Although the response rates were taken from three RCTs, the advantages of randomisation were lost because data from only one arm were used

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
contd **Leung *et al*, 1999**[37,413] ***Interventions (including comparator)*** Vinorelbine, docetaxel or paclitaxel monotherapy	The data from the chart review were derived from 88 patients who had received paclitaxel (n = 34), docetaxel (n = 29) or vinorelbine (n = 25). Patients who received vinorelbine had a higher median number of metastatic sites and had received a slightly greater cumulative dose of anthracycline previously The cost of drugs and supplies were estimated from pharmacy order catalogues (1998). Costs of laboratory tests and diagnostic imaging were obtained from the relevant departments. The cost of daily hospitalisation was Can$521/day as reported by the Ontario Hospital Association (1996) for a teaching hospital. The cost of oncologist fees were obtained from the Schedule of Benefits Future costs and benefits were not discounted due to the short time involved	– for responders with symptomatic improvement, it was assumed that six cycles of paclitaxel or docetaxel would be given and vinorelbine responders would continue treatment until the time of disease progression, which was estimated to occur after nine doses – it was assumed that at least three cycles would be needed to determine the lack of response to either of the taxanes, and at least six cycles would be needed to assess response with vinorelbine ***Estimation of costs*** The total cost for all patients was divided by the total number of cycles to obtain a mean 'cost per cycle' for each agent ***Modelling*** Decision analysis model	***Statistical analysis*** Not stated A sensitivity analysis was used to test the impact on the overall results following the discontinuation of treatment after one and six cycles		from each trial. It would be clearer to view these data as originating from three separate cohorts. The assumptions under 'Clinical data for the model' were not part of a sensitivity analysis. It was not clear which effectiveness data were used for the period of 'subsequent chemotherapy or hormonal therapy'

continued

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
Silberman et *al.*, 1999[35] ***Research question*** To estimate the relative cost-effectiveness of four chemotherapeutic options currently used to treat patients with anthracycline- and paclitaxel-resistant MBC ***Type of economic evaluation*** CUA ***Country/currency*** USA/US$ ***Cost year*** 1998 ***Perspective*** Not stated ***Study population*** A hypothetical cohort of patients with anthracycline- and paclitaxel-resistant MBC receiving capecitabine, continuous infusion 5-flourouracil, gemcitabine or vinorelbine ***Interventions (including comparator)*** Vinorelbine, 5-fluorouracil, capecitabine and gemcitabine	***Source of effectiveness data*** Response rates and toxicity for capecitabine were obtained from the registration trial, and for other therapies these data were obtained from the literature and discussions by a panel of North American oncologists (modified Delphi approach) ***Source of cost data*** Health Care Financing Administration's 1998 reimbursements for professional and facility fees and average wholesale price for drugs Costing was conducted retrospectively	***Valuation for clinical outcomes or benefits*** Response rates (method of valuation not stated) and adverse effects (method of valuation not stated) QALMs for disease progression were calculated by adjusting progression-free survival months for treatment-associated toxicities and modes of delivery. Penalty scores for toxicities and modes of delivery (resulting in diminution in QoL months) were assigned on the basis of oncology nurses' responses to a modified standard gamble questionnaire ***Estimation of costs*** Only direct costs of treatment toxicity management were considered in the analysis. The time measured was from initiation of therapy to disease progression. Discounting was not stated ***Modelling*** A Markov model was used to evaluate HRQoL and health-related direct costs of therapy (no further details)	***Clinical outcomes/benefits*** Response rates and toxicity incidence were not stated Expected QALMs ranged from 2.92 to 3.49 (intervention not stated, no further details) ***Costs*** Expected total per patient cost of treatment and toxicity management was $4668–9586 (intervention not stated, no further details) ***Synthesis of costs and benefits*** Capecitabine was the most cost-effective therapy with a CER of $1436 and a marginal CER of $687 per QALM with 5-fluorouracil as the reference therapy ***Statistical analysis*** No details provided	***Sensitivity analysis*** Multiple sensitivity analyses were carried out that showed that, compared to capecitabine therapy, vinorelbine or gemcitabine were either more expensive as well as less efficacious or exorbitantly expensive (no further details provided) ***Appropriateness*** Difficult to make any comments without further details of the model, costs, effectiveness data and analyses used	***Author's conclusions*** An analysis of the results suggested that capecitabine is a cost-effective alternative to 5-fluorouracil, gemcitabine and vinorelbine because it is well priced, administered orally and demonstrates a toxicity profile that is managed inexpensively ***Magnitude and direction of result*** Insufficient data to give a matrix score ***Implications for practice*** None stated ***Comments*** Difficult to make many comments about the structure and quality of the evaluation because the details are only presented in abstract form and mainly concentrate on capecitabine. Vinorelbine was only included as a comparator to capecitabine The source of the effectiveness was not considered to be very robust (reported to be obtained from a literature review, with no further details, and a Delphi panel). The costs considered were limited. Only a short time-frame was used. It would have been useful to add a lifetime analysis (e.g. survival, life-years gained or QALY) or justify why this was not performed

Appendix 9

Ongoing and planned vinorelbine RCTs

Therapy	Patient population	Treatment schedule	Status at time of review
Vinorelbine plus epirubicin versus epirubicin alone[400]	Anthracycline-naive patients with ABC (n = 350) Scandinavian multicentre trial	Vinorelbine i.v. 25 mg/m^2 on days 1 and 8 plus epirubicin 90 mg/m^2 on day 1, repeated every 3 weeks versus epirubicin 90 mg/m^2 on day 1, repeated every 3 weeks	Recruitment completed; report expected first quarter of 2001. Protocol published as Ejlersten, 1996[400]
TOPIC 2: vinorelbine plus epirubicin versus doxorubicin plus cyclophosphamide	Patients with operable (≥ 3 cm) early breast cancer (n = 400) UK 30-centre trial	Vinorelbine 25 mg/m^2 on days 1 and 8 plus epirubicin 60 mg/m^2 on day 1, repeated every 3 weeks versus doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 on day 1, repeated every 3 weeks	Recruitment ongoing. Protocol published as Smith, 2000[401]
Vinorelbine plus epirubicin versus FEC	Patients with high-risk node-positive breast cancer stage III N0–N2, aged < 65 years, who had had no previous treatment other than complete resection of breast cancer with axillary node dissection (n = 640)	Vinorelbine plus epirubicin, dose not stated, repeated every 21 days for six cycles versus epirubicin plus 5-fluorouracil plus cyclophosphamide, dose not stated, repeated every 21 days for six cycles	Presented as an abstract (Kerbrat, 1997[402]), but no results presented

Appendix 10

Forest plots of vinorelbine prospective uncontrolled studies

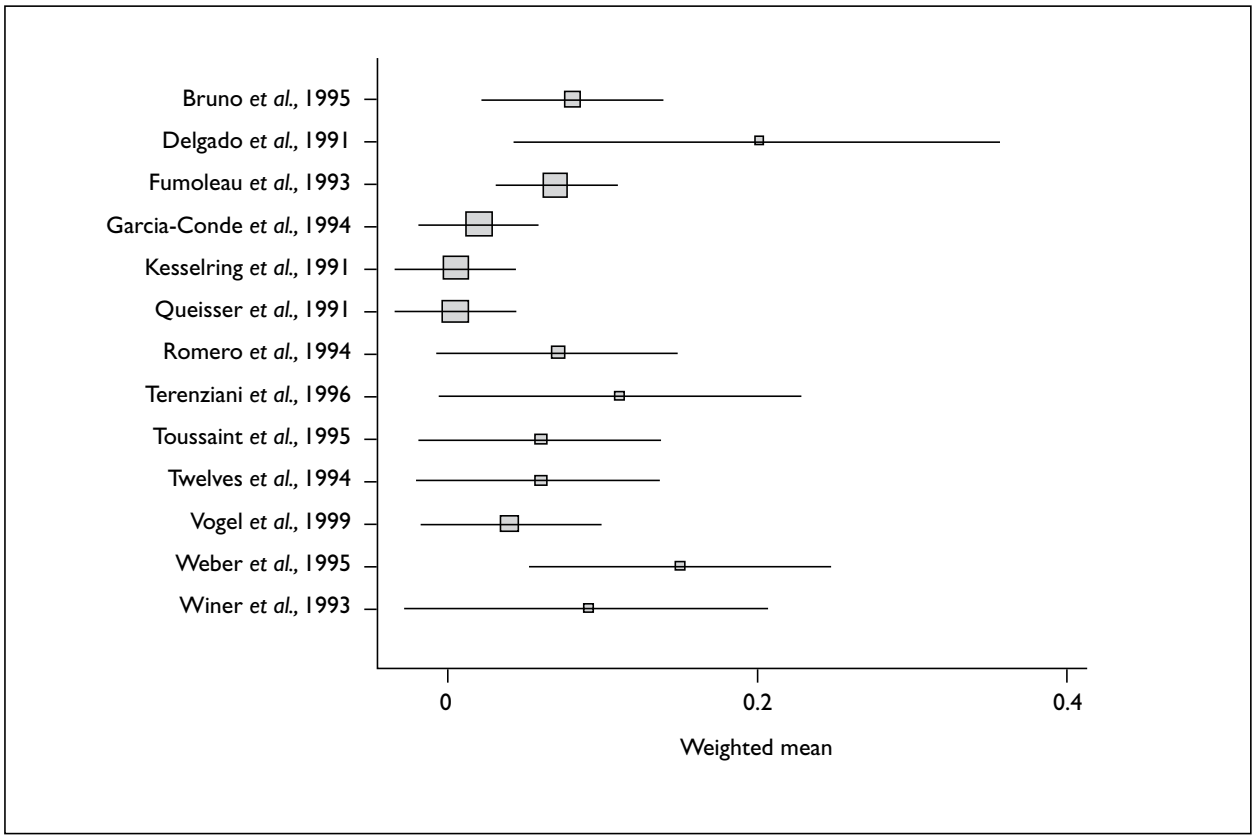

FIGURE 20 *Forest plot of vinorelbine monotherapy: complete tumour response*

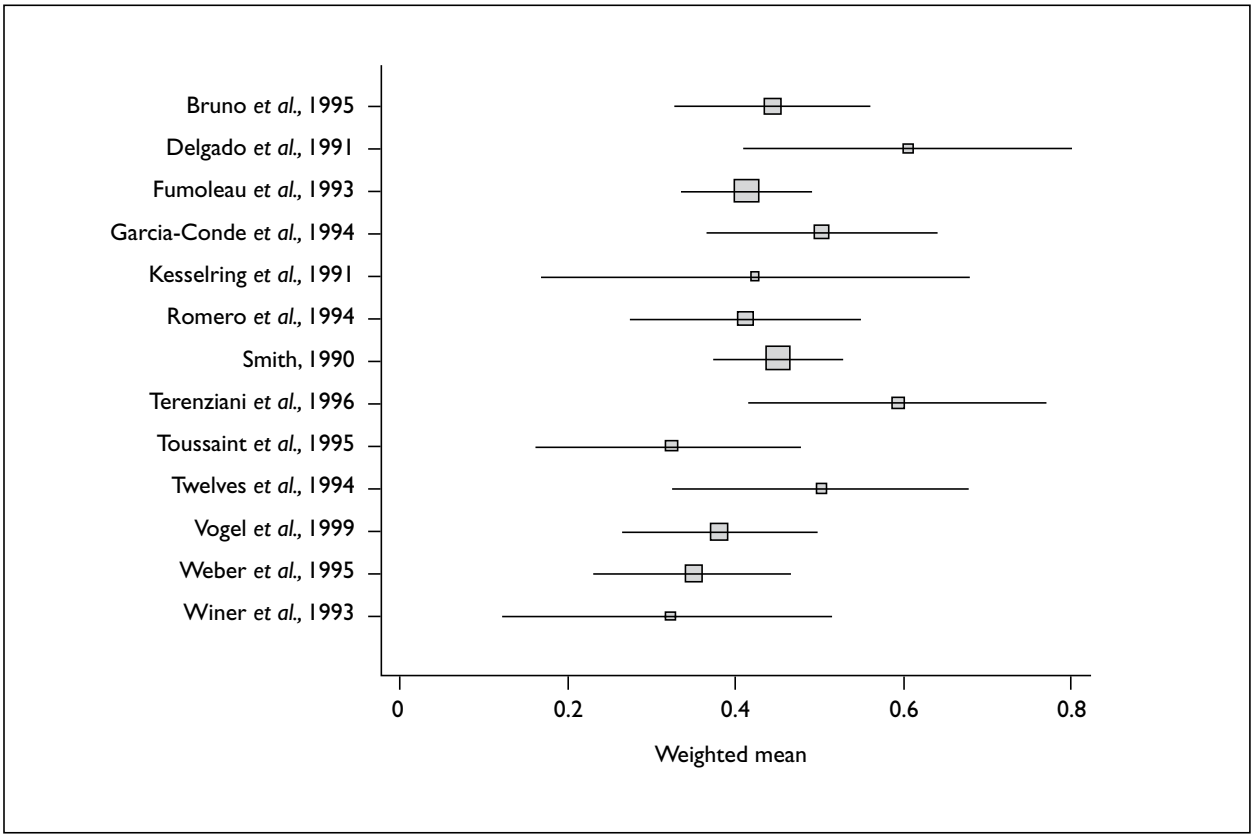

FIGURE 21 *Forest plot of vinorelbine monotherapy: overall tumour response*

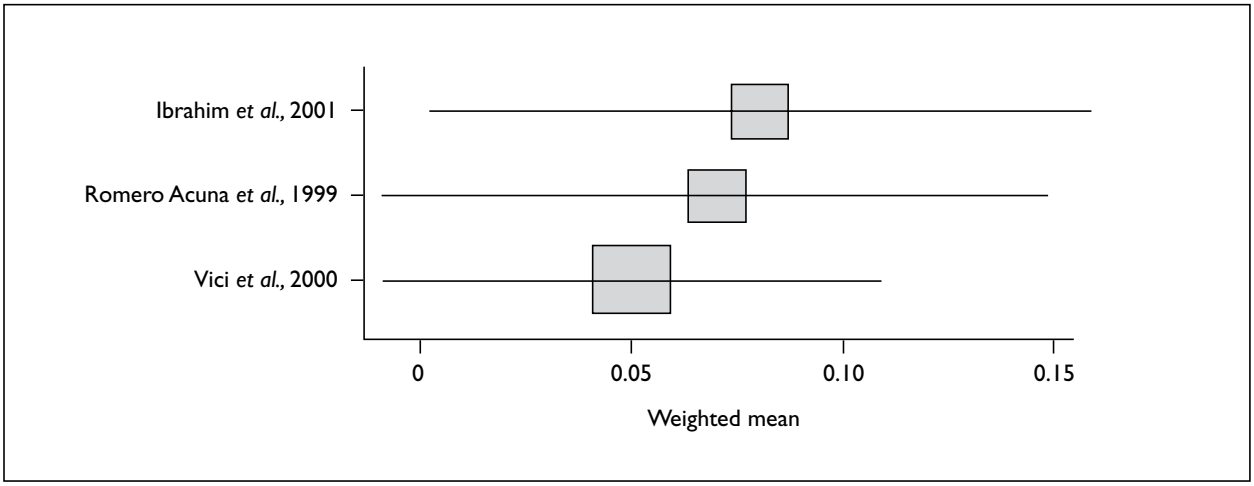

FIGURE 22 *Forest plot of vinorelbine plus paclitaxel: complete tumour response*

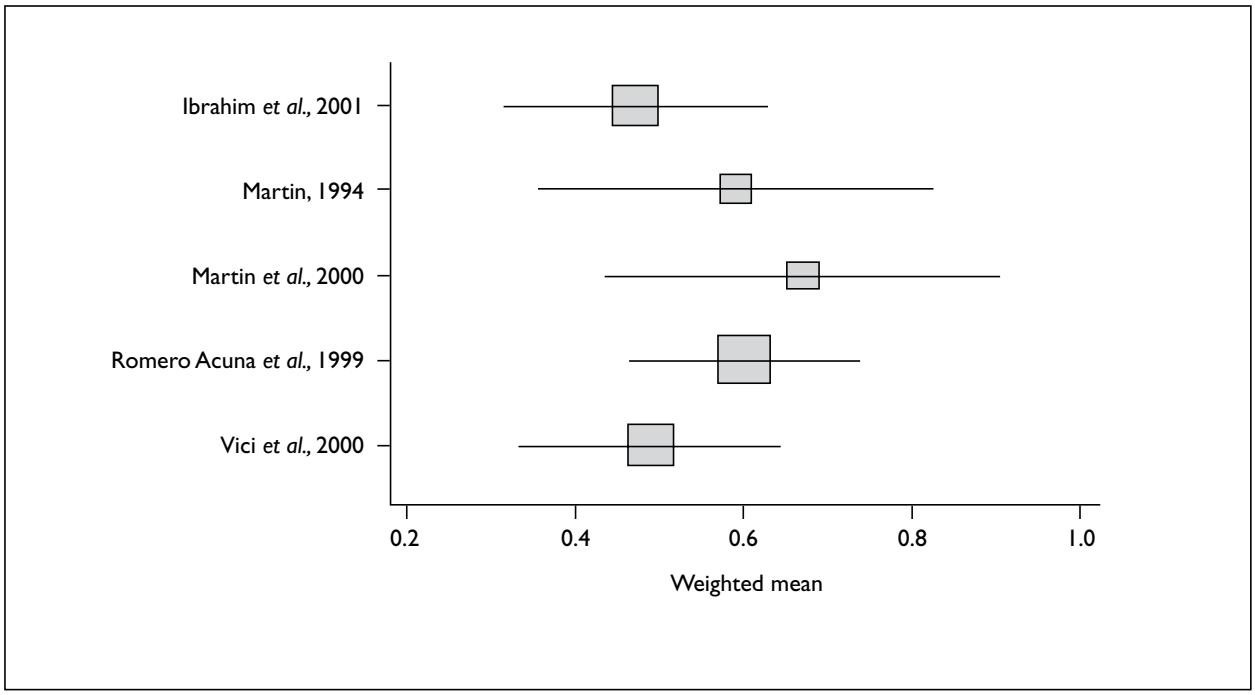

FIGURE 23 *Forest plot of vinorelbine plus paclitaxel: overall tumour response*

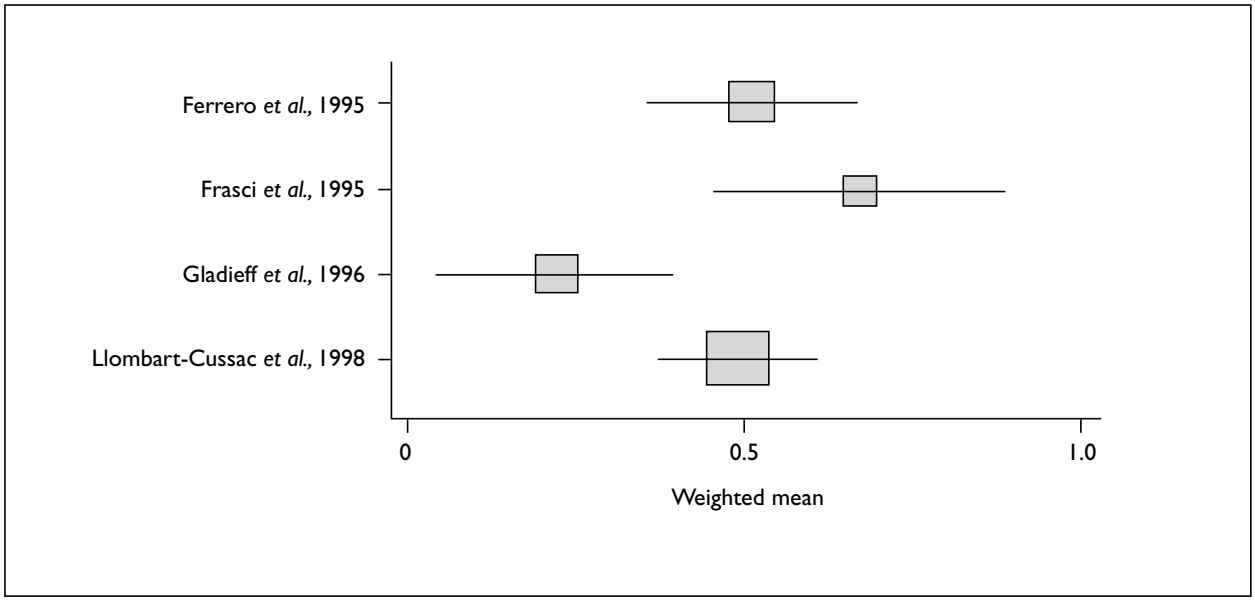

FIGURE 24 *Forest plot of vinorelbine plus mitoxantrone: overall tumour response*

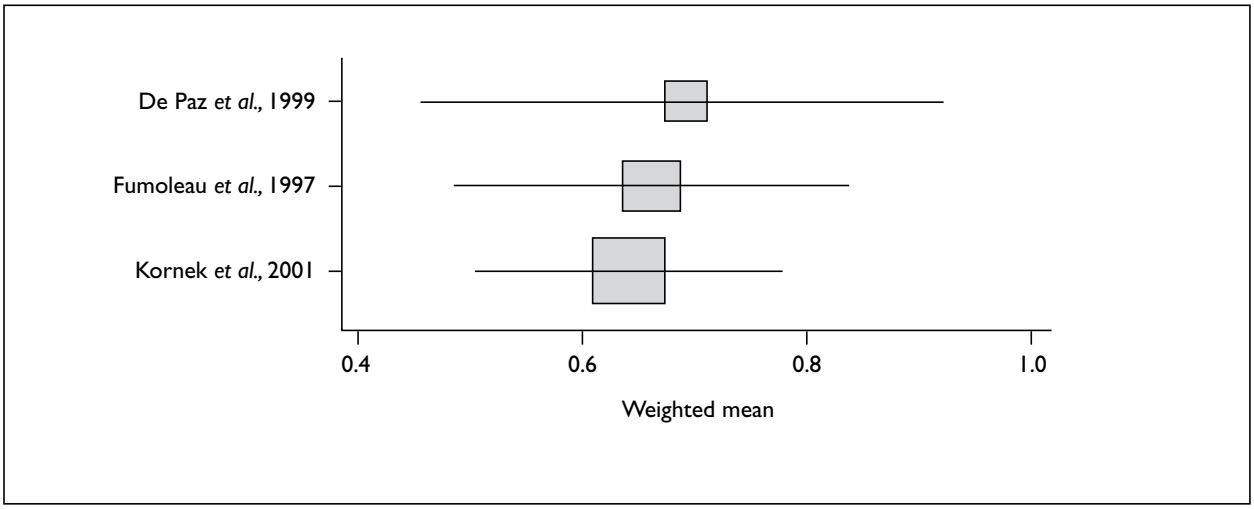

FIGURE 25 *Forest plot of vinorelbine plus docetaxel: overall tumour response*

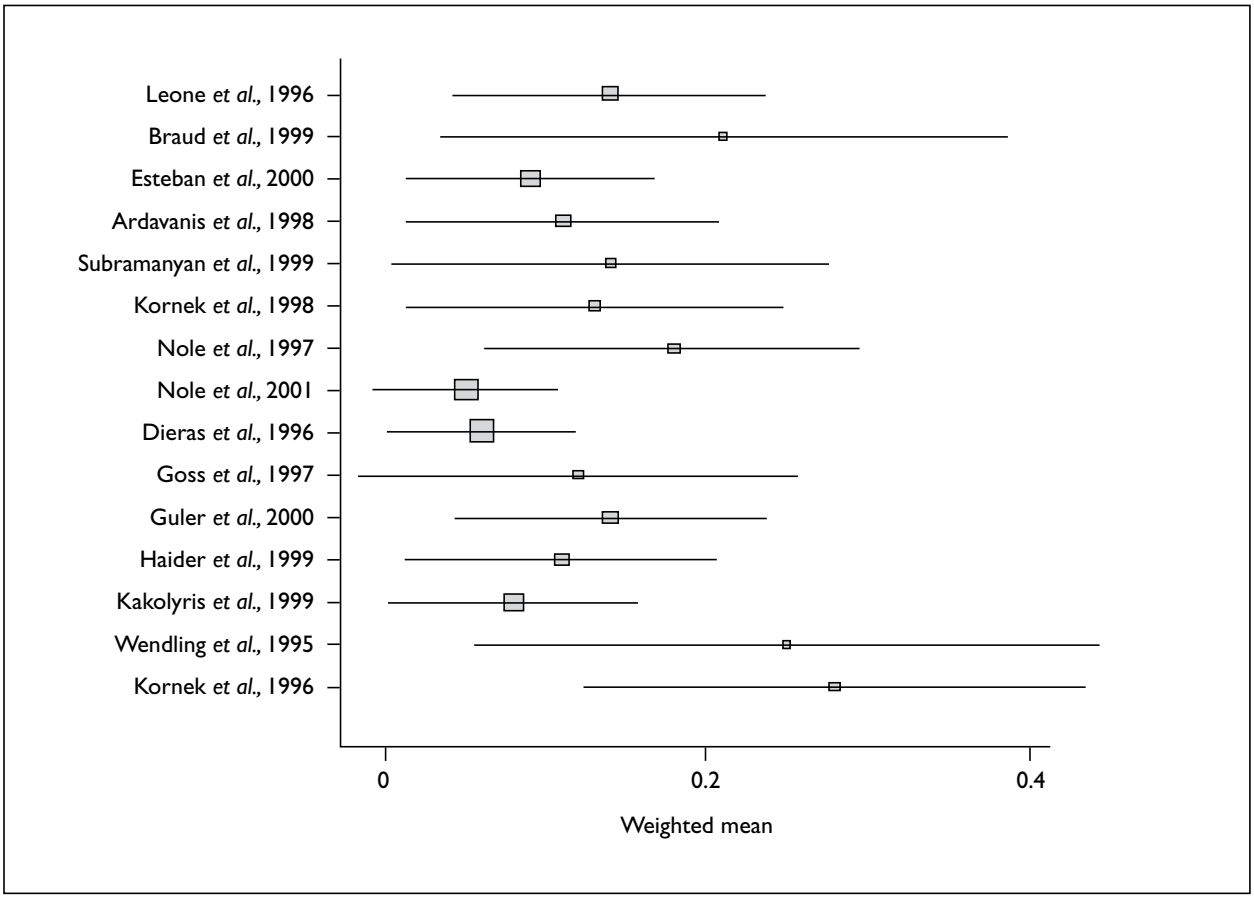

FIGURE 26 *Forest plot of vinorelbine plus all other combinations: complete tumour response*

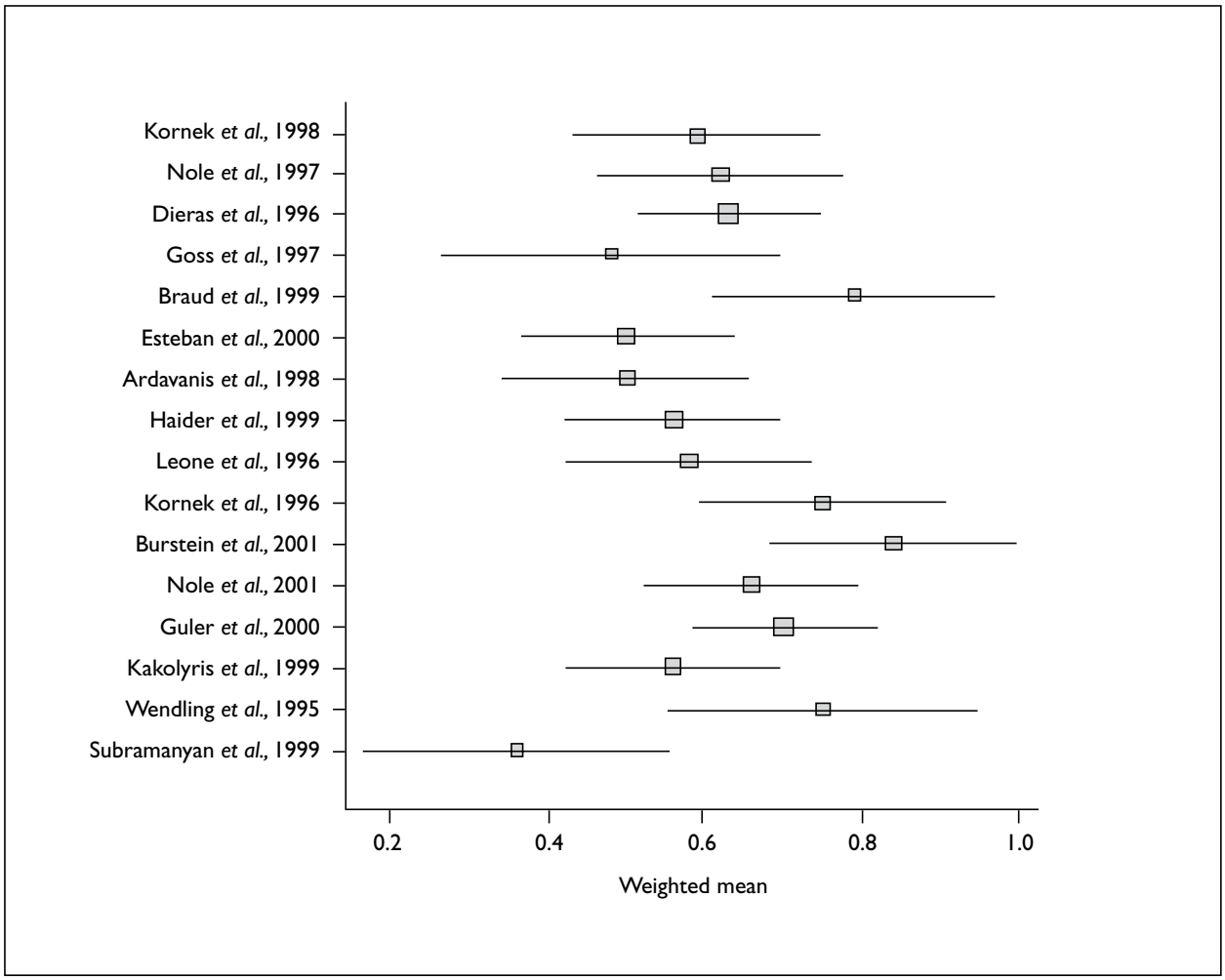

FIGURE 27 *Forest plot of vinorelbine plus all other combinations: overall tumour response*

Appendix 11

Levels of evidence based on those developed by members of the NHS R&D Centre for Evidence-Based Medicine[184]

Grade	Level of evidence	Therapy
A	1a	Systematic review (with homogeneity) of RCTs
	1b	Individual RCT (with narrow CI)
	1c	All or none*
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low-quality RCT, e.g. < 80% follow-up)
	2c	"Outcomes" research
	3a	Systematic review (with homogeneity) of case–control studies
	3b	Individual case–control study
C	4	Case series (and poor-quality cohort and case–control studies†)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

* *Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it*

† *A poor-quality cohort study is one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both cases and controls and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. A poor-quality case–control study is one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both cases and controls and/or failed to identify or appropriately control known confounders*

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We look forward to hearing from you.

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