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Rapid review

A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer

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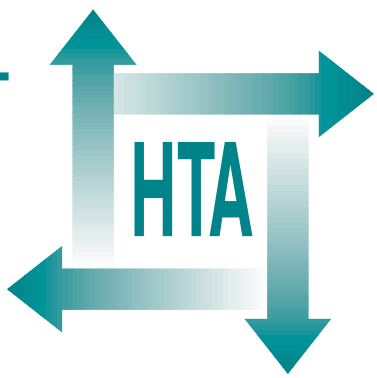
Health Technology Assessment
NHS R&D HTA Programme



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A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer

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Expiry date: This report is likely to be out of date after July 2000, when the results of the ICON3 trial are mature. An update of this report has been planned for June 2001.

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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

Adjuvant treatment Treatment used in addition to the main treatment, usually radiotherapy or chemotherapy given after surgery.

Advanced disease Locally advanced and metastatic disease.

Anthracycline refractory Patients who have never responded to anthracycline therapy.

Anthracycline resistant Patients, who, at some point in their therapy have stopped responding to anthracyclines.

Arthralgia Pain in the joints or in a single joint.

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

Carcinoma A cancerous growth.

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, paticularly through the use of radiotherapy, but who may also use chemotherapy.

Combination chemotherapy 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.

Cost–utility analysis Estimates of the additional cost per quality-adjusted life-year (QALY) saved or gained.

Cross-over Cross-over trials are generally used in chronic benign conditions where outcomes are reversible, allowing completion of various trial periods. In this review, when patients "cross over" to the other arm of the study, this represents a failure of the allocated treatment, not a planned cross-over at the end of a defined treatment period. In this situation, analysis is based on intention-to-treat according to the treatments allocated at randomisation.

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

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

Debulking Removal by surgery of a substantial proportion of cancer tissue. Optimal debulking refers to the removal of the largest possible amount of a tumour while limiting damage to normal tissue; interval debulking refers to the surgical removal of tumour after chemotherapy, aimed at further reducing its bulk.

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

FIGO International Federation of Gynaecology and Obstetrics. FIGO defines staging in gynaecological cancer and collates information about treatment and survival from a group of collaborating European centres (including some in the UK).

continued

Glossary *contd*

First-line treatment 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.

Gynaecology The branch of medicine that deals with the female reproductive organs.

Heterogeneous Of differing origins or different types.

Histological grade The 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 year of life saved or gained.

Locally advanced disease (breast) Disease that has infiltrated the skin or chest wall or disease that has matted, 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 Less than 50% but greater that 25% tumour regression for all measurable lesions for at least 4 weeks with no new lesions appearing.

Measurable lesion Lesion that can be unidimensionally or bidimensionally measured by physical examination, echography, radiography or computed tomographic scan.

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

Menopause The end of menstruation; this usually occurs naturally at around the age of 50.

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

Metastases/metastatic cancer Cancer that has spread to a site distant from the original site.

Myalgia Muscle pain.

Neo-adjuvant treatment Treatment given before the main treatment; usually chemotherapy or radiotherapy given before surgery.

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

Objective or overall response A complete or partial response.

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

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

Partial response At least 50% decrease in tumour size for more than 4 weeks without an increase in the size of any area of known malignant disease or the appearance of new lesions.

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 that defines appropriate action.

Quality of life (QoL) An individual's overall appraisal of his or her situation and subjective sense of well-being.

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

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

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

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

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

Second-line or salvage chemotherapy Reserved for patients who do not respond or who relapse after first-line treatment.

Second-line treatment Used in advanced (usually metastatic) disease after relapse or failure following first-line treatment. The main intervention is systemic treatment with the intent to palliate the disease.

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

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

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

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

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

Utilities Preferences with risk.

Values Preferences without risk or uncertainty.

List of abbreviations

A	unspecified anthracycline or doxorubicin*
AC	anthracycline (doxorubicin), cyclophosphamide*
ALT	alanine aminotransferase
AOC	advanced ovarian cancer*
AST	aspartate aminotransferase
ATd	anthracycline (doxorubicin), docetaxel*
ATp	anthracycline, paclitaxel*
BMT	bone marrow transplantation*
C	cyclophosphamide*
CAP	cyclophosphamide, doxorubicin, cisplatin
CI	confidence interval
CMF	cyclophosphamide, methotrexate, fluorouracil*
CMFP	cyclophosphamide, methotrexate, fluorouracil, prednisone
Con	combined control*
CP	cyclophosphamide, platinum*
DRG	diagnosis-related group
ECOG	Eastern Cooperative Oncology Group
ER	oestrogen receptor*
FAC	fluorouracil, anthracycline, cyclophosphamide
FUN	fluorouracil, navelbine*
G-CSF	granulocyte colony-stimulating factor
ITT	intention-to-treat
LYG	life-years gained
M	mitomycin*
MtF	methotrexate, fluorouracil*
MV	mitomycin, vinblastine*
NA	not applicable*
NNT	number needed to treat
NRR	National Research Register
ns	not statistically significant
P	unspecified platinum or carboplatin or cisplatin*
PFLYG	progression-free life-years gained
PS	performance status
QALY	quality-adjusted life-year
QoL	quality of life
Q-TWIST	quality time spent without symptoms and toxicity
RCT	randomised controlled trial
RR	relative risk
Td	docetaxel*
Tp	paclitaxel*
TpP(CAP)	paclitaxel, carboplatin (CAP control)*
TpP(P)	paclitaxel, carboplatin (carboplatin control)*
ULN	upper limit of normal

*Used only in figures and tables

Aim of assessment

Research questions

The following questions were addressed:

How effective is **paclitaxel** (Taxol®), compared with other standard chemotherapeutic regimens, as a **first-line** treatment of advanced **breast** cancer in terms of response, progression-free survival, overall survival, adverse effects and quality of life?

How effective is **docetaxel** (Taxotere®), compared with other standard chemotherapeutic regimens, as a **first-line** treatment of advanced **breast** cancer in terms of response, progression-free survival, overall survival, adverse effects and quality of life?

How effective is **paclitaxel**, compared with other standard chemotherapeutic regimens, as a **second-line** treatment of advanced **breast** cancer in terms of response, progression-free survival, overall survival, adverse effects and quality of life?

How effective is **docetaxel**, compared with other standard chemotherapeutic regimens, as a **second-line** treatment of advanced **breast** cancer in terms of response, progression-free survival, overall survival, adverse effects and quality of life?

How effective is **paclitaxel**, compared with other standard chemotherapeutic regimens, as a **first-line** treatment of **ovarian** cancer in terms of response, progression-free survival, overall survival, adverse effects and quality of life?

What are the cost implications of the use of taxanes as above?

Executive summary

Research question

The aim of this systematic review was to bring together the most recent reliable data to elucidate the following areas of uncertainty: (1) the use of paclitaxel (Taxol®) and docetaxel (Taxotere®) as first- and second-line treatment of advanced breast cancer; and (2) the use of paclitaxel as first-line treatment of ovarian cancer. Adjuvant chemotherapy was not considered in this review.

Methods

This systematic review was conducted in accordance with the NHS Centre for Reviews and Dissemination's Guidelines for Conducting Systematic Reviews. All randomised controlled trials (RCTs) and economic evaluations on the effectiveness of paclitaxel and docetaxel as first- or second-line treatments for breast cancer, or paclitaxel as first-line treatment for ovarian cancer, were considered. The main outcomes were progression-free survival, overall survival, quality of life and economic evaluation.

The body of evidence

The searches identified 2250 articles relating to the taxanes. After independent assessment against the inclusion criteria by two reviewers, it was agreed that 213 references were to be obtained. Of these: 100 were trials listed in the National Research Register, the authors of which were contacted; 13 were reviews and background information; 32 appeared to be economic assessments; and the remaining 68 appeared to be reports of RCTs. Many were duplicate publications. On examination of the obtained papers and reports, those selected for review were as shown in *Table A*.

Results

There was considerable heterogeneity in the populations investigated, intervention and control regimens, and outcomes assessed. Some studies were available only as conference abstracts or presentations, limiting the amount of information that could be extracted.

Breast cancer

First-line treatment

Paclitaxel Four randomised controlled Phase III trials were identified: EORTC, TITGANZ, E1193 and CA139-278. A total of 1974 patients were included. Of these, the EORTC, E1193 and TITGANZ trials evaluated single-agent paclitaxel, and the E1193 and CA139-278 trials evaluated combination paclitaxel/anthracycline. There were no economic evaluations for first-line treatment of breast cancer. Information about the EORTC trial has been removed from this

TABLE A *The body of evidence reviewed*

Review question			No. RCTs (no. patients)	No. economic evaluations
Cancer	**Level of treatment**	**Chemotherapy**		
Breast	First-line	Paclitaxel	4[a] (1545)	0
		Docetaxel	1[b] (429)	0
	Second-line	Paclitaxel	1 (81)	7[c]
		Docetaxel	4 (1092)	6
Ovarian	First-line	Paclitaxel	4[a] (3746)	13[c]

[a] *Data from published papers substituted for original data from manufacturer's confidential submission (1 study)*
[b] *Phase III trial that does not specifically mention randomisation*
[c] *One study not presented in this report at request of manufacturer*

document because it was obtained from a paper that has been submitted for publication and is not yet available for public comment (expected publication date February 2000). Where possible, consistent information from an interim report and meeting abstracts has been substituted.

Quality of trials The TITGANZ trial was analysed on an intention to treat basis and gave details on length of follow-up: 26 months. The EORTC and E1193 trials allowed cross-over to alternate treatment and the TITGANZ trial recommended treatment with epirubicin on progression. Patients crossing over in this way were violating the randomisation; however, no details were given concerning whether or not such patients were censored.

Median progression-free survival:

- Single-agent paclitaxel: The median progression-free survival in the paclitaxel arm ranged from 4 months (EORTC) to 5.9 months (E1193). In no trial was this greater than the control arm. In the EORTC trial, the anthracycline group had significantly longer progression-free survival (7.5 months versus 4.0 months, $p = 0.0001$).
- Combination paclitaxel/anthracycline: The median progression-free survival in the paclitaxel plus anthracycline arms ranged from 8 months (E1193) to 8.3 months (CA139-278). In both trials this was significantly greater than the control arm (E1193: 8 months versus 6 months, $p = 0.003$; CA139-278 8.3 months versus 6.2 months, $p = 0.034$).

Median overall survival:

- Single-agent paclitaxel: The median length of overall survival in the paclitaxel arm ranged from 17.3 months (TITGANZ) to 22.2 months (E1193). In no trial was this significantly different to control.
- Combination paclitaxel/anthracycline: The median length of overall survival for patients in the paclitaxel/anthracycline combination arm ranged from 22 months (E1193) to 22.7 months (CA139-278). Patients in the paclitaxel/anthracycline arm survived for significantly longer than control (22.7 months versus 18.3 months, $p = 0.02$) in one trial (CA139-278) but not in the other (E1193) (22 versus 18.9 months, $p = 0.24$), although the difference was comparable.
- E1193 trial: Survival in the single-agent paclitaxel and the combined paclitaxel/anthracycline arms was similar (22.2 versus 22 months).

Quality of life Quality of life was evaluated in three of the studies: TITGANZ, E1193 and CA139-278. There were no significant differences between paclitaxel and control in any of the trials in terms of overall quality of life, although differences were apparent on some subscales. These did not appear to follow a consistent pattern across the trials.

Docetaxel One Phase III trial of docetaxel as a first-line treatment for advanced breast cancer was identified. This was available only as a conference abstract and randomisation was not specifically mentioned. Consequently, the results should be treated with caution. Although a combination of docetaxel and doxorubicin produced a greater overall response than doxorubicin and cyclophosphamide combined, there were no long-term results such as progression-free or overall survival.

Second-line treatment

Paclitaxel One randomised controlled Phase II trial was identified: CA139-047. A total of 81 patients were included. Patients had previously received chemotherapy. There were seven economic evaluations.

Quality of trial It is not clear whether this trial was analysed on an intention to treat basis and no details were given on length of follow-up. However, the authors stated that most of the patients were alive at the time of analysis. Only two patients responded in the mitomycin control arm. Cross-over to alternate treatment was allowed. More than half the patients in the control arm crossed over to the paclitaxel arm; none crossed the other way. No details were given about whether such patients were censored. In none of the economic evaluations was the estimation of benefits based on a direct clinical comparison.

Median progression-free survival The median progression-free survival in the paclitaxel arm was 3.5 months. This was significantly longer than the mitomycin control arm (1.6 months, $p = 0.026$).

Median overall survival The median length of overall survival in the paclitaxel arm was 12.7 months, compared with 8.4 months in the mitomycin arm.

Quality of life Quality of life was not reported.

Economic evaluation The only economic evaluation that compared paclitaxel with control (mitomycin) was submitted in confidence and has been removed from this report. Six economic evaluations

involved comparisons of paclitaxel and docetaxel, which are given below.

Docetaxel Four randomised controlled Phase III trials were identified: 303 Study, 304 Study, Scand and Bonneterre. A total of 1092 patients were included. One of these was a preliminary report of a study before completion of accrual (Bonneterre). Patients in the 303 Study had previously received chemotherapy involving alkylating agents; those in the other three had received anthracyclines. There were six economic evaluations on docetaxel.

Quality of trials The 303 and 304 Studies were analysed on an intention to treat basis; the Scand trial excluded a single patient. The length of follow-up ranged from 11 months (Scand) to 23 months (303 Study). At least two-thirds of the participants in these trials had died. The Scand study recommended cross-over to alternate treatment on objective signs of disease progression. Patients crossing over in this way were violating the randomisation; however, no details were given concerning whether or not such patients were censored. In the economic analyses, there were no direct comparisons for the estimation of benefits.

Median progression-free survival The median progression-free survival in the docetaxel arm ranged from 4.75 months (304 Study) to 7 months (Bonneterre). Patients in the docetaxel arms of the 304 and Scand studies had significantly longer progression-free survivals than controls (4.75 months versus 2.75 months, $p = 0.001$; 6.3 months versus 3 months, $p = 0.001$).

Median overall survival The median overall survival in the docetaxel arm ranged from 10.4 months (Scand) to 15 months (303 Study). Patients in the docetaxel arms of the 304 Study survived for significantly longer than the mitomycin plus vinblastine arm (11.4 months versus 8.7 months, $p = 0.03$).

Quality of life Quality of life was evaluated in two of the trials: the 303 and 304 Studies. There were no significant differences between docetaxel and control in either of these trials in terms of global health status, although differences were apparent on some subscales. These did not appear to follow a consistent pattern across the trials.

Economic evaluations All six of these involved comparisons of paclitaxel and docetaxel, where the range of cost–utility ratios for incremental quality-adjusted life-years (QALYs) gained was £1990–£2431. In addition, three analyses compared docetaxel and vinorelbine. The cost–utility ratio for incremental QALYs gained was £14,050 in the only one of these carried out in the UK.

Ovarian cancer

First-line treatment

Paclitaxel Four randomised controlled Phase III trials were identified: GOG111, GOG132, OV10 and ICON3. A total of 3746 patients were included. ICON3 evaluated the effectiveness of paclitaxel combined with carboplatin; the others evaluated a paclitaxel/cisplatin combination. There were 13 economic analyses, one of which was submitted in confidence and has been removed from this document.

Quality of trials All the studies were analysed on an intention to treat basis. The median length of follow-up ranged from 18 months (ICON3) to 37 months (GOG111). The ICON3 trial was reported only 6 months after accrual was completed, at which time over two-thirds of the patients were alive. All the studies allowed cross-over to alternate treatment. In the economic analyses, the estimation of benefits was based on a direct clinical comparison in only eight out of 13 studies.

Median progression-free survival The median progression-free survival in the paclitaxel/platinum arm ranged from 14.1 months (GOG132) to 18 months (GOG111). Patients in the GOG111 and OV10 trials had significantly greater median progression-free survivals with paclitaxel/platinum than controls (18 months versus 13 months, $p < 0.001$; 16.5 months versus 11.8 months, $p = 0.001$).

Median overall survival The median length of overall survival in the paclitaxel/platinum arm ranged from 26.6 months (GOG132) to 38 months (GOG111). Patients in the GOG111 and OV10 trials had significantly greater median overall survivals with paclitaxel/platinum than controls (38 months versus 24 months, $p < 0.001$; 35 months versus 25 months, $p = 0.001$).

Quality of life Quality of life was not reported.

Economic analysis Nine were cost-effectiveness and three were cost–utility analyses. The range of incremental costs per life-year gained (£7173–£12,417) found in two UK studies is within the range reported for all studies comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin

(£3960–£13,360). The two UK studies used carboplatin rather than cisplatin in their analyses. In the cost–utility analyses, the range of incremental cost per QALY gained was £5273–£11,269.

Summary of evidence on effectiveness

The ranges of median progression-free and overall survivals found in the RCTs are given in *Table B*.

Conclusions

For the first-line treatment of breast cancer, the evidence suggests a potential advantage of paclitaxel and anthracycline over control. However, this evidence is not robust. There are ongoing, multicentre randomised controlled Phase III trials, one comparing epirubicin and paclitaxel versus epirubicin and cyclophosphamide (ABO1) and another comparing doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide (EORTC) in the treatment of women with metastatic breast cancer. These trials should provide a clearer picture of the role of paclitaxel.

Both paclitaxel and docetaxel are licensed for use as second-line treatment for breast cancer. The evidence to support the use of paclitaxel in this context is not strong. There has been only one small trial and the cost-effectiveness of paclitaxel compared with mitomycin has not been proved.

There is a slightly greater body of evidence to support the use of docetaxel as a second-line treatment of advanced breast cancer, especially among women who are resistant to anthracyclines. In two trials there was an advantage in overall survival compared with control. However, there were no differences in quality of life. In addition, docetaxel was found to be of similar effectiveness to doxorubicin, so it may be useful in the treatment of women for whom anthracyclines are contraindicated. In three studies comparing docetaxel to vinorelbine, the one UK study found the cost per QALY gained of docetaxel was £14,050. Docetaxel was found to have highly favourable cost-effectiveness ratios in comparison with paclitaxel (incremental cost per QALY gained £1990– £2431). These studies are weakened by the lack of direct comparison data.

Paclitaxel is licensed and recommended for use as first-line treatment for ovarian cancer. The best available evidence supports its use in combination with platinum in this context, with two trials showing significant improvement in overall survival. This treatment combination was also found to have potentially acceptable

TABLE B *Summary of effectiveness evidence*

Review question			Range (mo) of median progression-free survival or median time to treatment failure (control)	Range (mo) of median overall survival (control)
Cancer	**Level of treatment**	**Chemotherapy**		
Breast	First-line	Paclitaxel	4.0–5.9[a] (6.0–7.5)	17.3–22.2 (13.9–18.9)
		Paclitaxel + anthracycline	8.0–8.3[b] (6.0–6.2)	22.0–22.7[c] (18.3–18.9)
	Second-line	Paclitaxel	3.5[d] (1.6)	12.7[e] (8.4)
		Docetaxel	4.7–7.0[f] (2.7–5.0)	10.4–15[g] (8.7–14)
Ovarian	First-line	Paclitaxel	14.1–18[h] (11.8–16.4)	26.6–38[h] (25–30.2)

[a] *Control significantly better than paclitaxel in 1/3 trials*
[b] *Paclitaxel plus anthracycline significantly better than control in 2/2 trials*
[c] *Paclitaxel plus anthracycline significantly better than control in 1/2 trials*
[d] *Paclitaxel significantly better than control in 1/1 trial*
[e] *Paclitaxel significantly better than control in 1/1 trial*
[f] *Docetaxel significantly better than control in 2/4 trials*
[g] *Docetaxel significantly better than control in 1/4 trials*
[h] *Paclitaxel plus platinum significantly better than control in 2/4 trials*

cost-effectiveness ratios (cost per QALY gained £5273–£11,269). As the results of the ICON3 trial mature, they may be able to demonstrate for which subgroups of women this treatment is more or less appropriate. The mature results of this trial will also add to our understanding of the comparative costs and benefits of cisplatin and carboplatin. In addition, when complete and mature, the SCOTROC Phase III comparison of paclitaxel/carboplatin versus docetaxel/carboplatin as first-line chemotherapy in ovarian cancer should provide information on the comparative merits of these two taxanes.

This review is based on currently available evidence, which favours docetaxel in the second-line treatment of advanced breast cancer and paclitaxel in the first-line treatment of ovarian cancer. However, the evidence is not robust for any indication. There are several relevant trials in progress, which will need to be taken into consideration once they are suitably mature. Further recommendations for primary research are premature before the final results of ongoing research are published in full. Updating this systematic review is the most pertinent recommendation at this stage.

Chapter 1
Background

Breast cancer is the leading cause of cancer deaths among women, killing 13,000 per annum in England and Wales;[1] ovarian cancer is the fourth most common cause of cancer deaths in women[2] (see *Table 1*[3]).

Breast cancer

The aetiology of breast cancer is unclear, although it is likely that hormonal factors play a major role. Risk factors include age of early menarche and late menopause, and later age of first full-term pregnancy.[4] A family history of breast cancer is also an important factor,[4] suggesting a genetic basis for the condition.

Breast cancer is usually detected by a woman discovering a lump in her breast or through mammographic screening.[4] Tumour cells are frequently distributed throughout the body via the blood and lymphatic systems and may develop into secondary tumours or metastases. Common sites of metastases include the lung, liver, bone and brain. Staging is based on tumour size (T), the presence of axillary nodes (N) and the presence of metastases (M) (see appendix 1).

The prognosis for women who develop metastases is poor and metastatic disease is often considered incurable.[5] For most of these patients, treatment provides only temporary control of cancer growth. The goals of treatment are to relieve symptoms with as few side-effects as possible and to extend the duration of high-quality life.[6]

Current treatment options for metastatic breast cancer include endocrine therapy, anthracyclines (e.g. doxorubicin, epirubicin), cyclophosphamide, methotrexate, fluorouracil, mitomycin, mitoxantrone and the taxanes.[7]

Ovarian cancer

The natural history of ovarian cancer is inconsistent.[8] Again, hormonal factors may play a part its aetiology, with reduced ovulation, pregnancy and early menopause associated with reduced risk.[2] There appears to be an inherited predisposition to develop ovarian cancer in about 5–10% of these patients;[8] more than 80% of these are linked to the BRCA1 gene.[8]

The biology of the tumour has a strong influence on survival.[4] Ovarian cancer is not easily identified because the most common symptoms of persistent abdominal distension, pain and pressure in the pelvis can be attributed to a number of causes. In the majority of patients, the disease has progressed to a late stage before it is diagnosed. The FIGO system is used to stage ovarian cancer (see appendix 1).

The two most important prognostic factors for epithelial ovarian cancer are the FIGO stage at diagnosis and the size of residual disease after surgery.[9] When ovarian cancer is diagnosed early (Stage I), surgery alone can lead to survival rates of over 80% at 5 years.[2] Unfortunately, about three-quarters of patients are at Stages II–IV at the time of diagnosis.[2] Five-year survival in European countries that report to FIGO has increased from 27% in 1958–1962 to 42% in 1990–1992.[2] However, an overall survival of only 30% has been cited for the UK.[8,9]

Surgery is currently the first intervention used to treat ovarian cancer, but in most women the disease is too far advanced by the time of diagnosis for complete removal of the tumour to be possible.[10] Consequently, survival time is likely to be improved by appropriate chemotherapy after expert surgery.[2]

The recent consensus statement on standard practice recommended that standard

TABLE 1 *Incidence and deaths from breast and ovarian cancers in the UK (derived from Cancer Research Campaign data[3])*

	No. registrations 1993	Incidence rate 1995 (%)	No. deaths 1996
Breast cancer	30,495	27	13,760
Ovarian cancer	5,337	5	4,580

chemotherapy for patients with ovarian cancer should include a platinum compound. In general the preferred analogue is carboplatin[11] and, for the majority of women with ovarian cancer, the recommended chemotherapy should comprise a combination of paclitaxel with a platinum compound (either cisplatin or carboplatin).[11] This is echoed by the Royal College of Physicians Joint Council for Clinical Oncology recommendation of a combination of paclitaxel and platinum as first-line treatment for ovarian cancer.[12]

The results of four systematic meta-analyses[13] in which cisplatin and carboplatin were compared demonstrated no obvious advantage of one compound over the other in terms of survival.

The taxanes

The taxanes are class of anticancer drugs, originally derived from the bark of the Pacific yew, *Taxus brevifolia*. Paclitaxel (Taxol®, Bristol-Myers Squibb) was identified as the active constituent in 1971. Docetaxel (Taxotere®, Aventis) is a semi-synthetic taxoid produced from the needles of *Taxus baccata*. Paclitaxel and docetaxel have similar mechanisms of action. Cells exposed to taxanes cannot form a mitotic spindle.[14] This interferes with cell division and leads to cell death.

Chemotherapy may be used in the treatment of a range of cancers as **first-line** treatment – initial systemic therapy following surgery (if appropriate) – and as **second-line** treatment if the disease persists or relapses. **Adjuvant** therapy refers to chemotherapy after initial treatment by surgery or radiotherapy, which is administered to destroy any cancer cells that have spread.

Paclitaxel (Taxol)

Paclitaxel is currently indicated for both breast and ovarian cancer in:

- the treatment of metastatic carcinoma of the breast in patients who have failed or are not candidates for standard anthracycline-containing therapy
- the primary treatment of carcinoma of the ovary, in combination with cisplatin, in patients with advanced disease or residual disease (> 1 cm) after initial laparotomy
- the secondary treatment of metastatic carcinoma of the ovary after failure of standard platinum-containing therapy
- there is also an indication for paclitaxel in non-small cell lung carcinoma.

Docetaxel (Taxotere)

Docetaxel is currently indicated in:

- the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic therapy; previous chemotherapy should have included an anthracycline or an alkylating agent.

Current recommendations

Breast cancer

There was insufficient evidence to include studies of taxane treatment in the 1996 NHS Executive guidance for purchasers of breast cancer services.[1] However, it was concluded that a wide variety of therapeutic regimens are used in metastatic disease and that a review of randomised controlled trials (RCTs) revealed no clearly superior regimen.[1] The recent meta-analysis of polychemotherapy in breast cancer[15] concentrated on early disease and hence did not include taxanes. In 1997, the Scottish Health Purchasing Information Centre[5] reported that the taxanes had some effect on secondary disease and may be useful for palliation. However, it concluded that "the cost effectiveness of the taxanes ... is **unproven**" (current authors' emphasis).

Ovarian cancer

A number of reports have evaluated the effectiveness of the taxanes in the treatment of ovarian cancer. In 1996, a Development and Evaluation Committee report recommended the use of paclitaxel as a first-line chemotherapeutic agent in the treatment of ovarian cancer.[16] This recommendation was to be reviewed after 12–18 months.

Additionally, the Trent Development and Evaluation Committee evaluated the use of paclitaxel and cisplatin as a first-line treatment in ovarian cancer and recommended "that paclitaxel should be available for patients within national controlled trials ... and for other patients at the discretion of clinicians".[17] Subsequently, this decision was supported in a supplementary document.[18]

An earlier Development and Evaluation Committee report investigated the second- and third-line use of paclitaxel in advanced ovarian cancer. The authors concluded that there was insufficient evidence to recommend "the use of paclitaxel for second-line chemotherapy after standard platinum chemotherapy has failed".[19] However, "the use of paclitaxel for third-line chemotherapy (by heavily pre-treated patients), when other chemotherapy agents

have failed" was considered "beneficial but high cost".[19]

The role of chemotherapy, including paclitaxel, in the treatment of ovarian cancer was discussed in the recent NHS Executive guidelines for commissioning cancer services for gynaecological cancers.[2] It was recommended that paclitaxel plus carboplatin should be standard therapy for women with advanced ovarian cancer. It was advised that this recommendation should be reviewed when the results of the ICON3 trial are mature.

Projected unit cost

Paclitaxel

NHS list price excluding VAT:

- 30 mg vial £124.79
- 100 mg vial £374.00.

Recommended dosage:

- first-line ovarian cancer 135 mg/m^2
- second-line breast cancer 175 mg/m^2.

Assuming an average body surface area of 1.75 m^2, required dose for:

- ovarian cancer = 236.25 mg/m^2 can be given from 2 × 100 mg vials and 2 × 30 mg vials
- breast cancer = 306.25 mg/m^2 can be given from 3 × 100 mg vials and 1 × 30 mg vial.

Total cost per cycle:

- ovarian cancer = £997.58
- breast cancer = £1246.79.

This costing does **not** include any premedication or other medication required to manage adverse events (e.g. granulocyte colony-stimulating factor (G-CSF) for neutropenia).

Docetaxel

The following estimated costs of docetaxel per patient were taken from the manufacturer's submission.[20]

NHS list price excluding VAT:

- 20 mg vial £175
- 80 mg vial £575.

Other information:

- Recommended dosage 100 mg/m^2
- dose can be given from 2 × 80 mg vials
- total cost per cycle = 2 × £575 = £1150
- average number of cycles of docetaxel received by a breast cancer patient = 4
- total cost of treatment per patient = £1150 × 4 = £4600.

Costing does **not** include any premedication or other medication required to manage adverse events (e.g. G-CSF for neutropenia).

Licensed indications, contraindications and warnings

Paclitaxel

Therapeutic indications:

- ovarian carcinoma: (1) primary treatment of carcinoma of the ovary, in combination with cisplatin, in patients with advanced disease or residual disease (> 1 cm) after initial laparotomy; and (2) secondary treatment of metastatic carcinoma of the ovary after failure of standard platinum-containing therapy
- breast carcinoma: treatment of patients with metastatic carcinoma of the breast who have failed or are not candidates for standard anthracycline-containing therapy.

Recommended dosage:

- primary treatment of ovarian carcinoma: a combination regimen consisting of paclitaxel 135 mg/m^2 administered over 24 hours followed by cisplatin 75 mg/m^2, with a 3-week interval between courses
- secondary treatment of ovarian and breast carcinoma: paclitaxel 175 mg/m^2 administered over a period of 3 hours with a 3-week interval between courses.

Subsequent doses of paclitaxel should be administered according to individual patient tolerance. This agent should not be readministered until the neutrophil count is ≥ 1.5 × 10^9/l and the platelet count is ≥ 100 × 10^9/l. Patients who develop severe neutropenia (neutrophil count < 0.5 × 10^9/l for ≥ 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses.

All patients must be premedicated with corticosteroids, antihistamines and H_2 antagonists prior to the administration of paclitaxel.

Contraindications

Paclitaxel is contraindicated in:

- patients with severe hypersensitivity reactions to this agent or to any other component of the formulation, especially polyethoxylated castor oil
- pregnancy and lactation.
- patients with baseline neutrophils < 1.5×10^9/l.

Special warnings and special precautions for use
Paclitaxel should be administered under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Significant hypersensitivity reactions may occur, so appropriate supportive equipment should be available. *Table 2* provides the toxicities of paclitaxel.

Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists.

Taxol should be given **before** cisplatin when used in combination.

Hypersensitivity reactions Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in < 1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine mediated. In the case of severe hypersensitivity, paclitaxel should be discontinued immediately; symptomatic therapy should then be initiated and the patient should not be rechallanged with the drug.

Haematological Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to a level ≥ 1.5×10^9/l and the platelets improve to a level ≥ 100×10^9/l.

Cardiovascular Rarely, severe cardiac conduction abnormalities have been reported. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with this agent. Hypotension, hypertension and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of the paclitaxel infusion, is recommended. Severe cardiovascular events have been observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

Neurological Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is unusual. In severe cases, a dose reduction of 20% is recommended for all subsequent courses of paclitaxel.

Liver impairment There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe liver impairment.

Paclitaxel is not recommended for patients with severely impaired hepatic function.

Other Paclitaxel contains dehydrated alcohol (396 mg/ml), therefore consideration should be given to possible central nervous system and other effects.

Special care should be taken to avoid the intra-arterial injection of paclitaxel. In animal studies investigating local tolerance, severe tissue reactions occurred following intra-arterial administration.

Docetaxel

Therapeutic indications
Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.

The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should be administered only under the supervision of a physician who is qualified in the use of anticancer chemotherapy.

Recommended dosage
The recommended dosage of docetaxel monotherapy is 100 mg/m^2, administered as a 1-hour infusion every 3 weeks. A premedication consisting of an oral corticosteroid, such as dexamethasone, 16 mg/day for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Contraindications
Docetaxel is contraindicated in:

- patients who have a history of severe hypersensitivity reactions to the drug or to polysorbate 80

- patients with a baseline neutrophil count of < 1500 cells/ml
- pregnant or breast-feeding women
- patients with severe liver impairment because no data are available for this condition.

Special warnings and special precautions for use

Table 2 provides a summary of the toxicities of docetaxel. A premedication consisting of an oral corticosteroid such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Severe hypersensitivity reactions characterised by hypotension or bronchospasm or generalised rash/erythema have occurred in 5.3% of patients receiving docetaxel.

Haematological Neutropenia is the most frequent adverse reaction of docetaxel. Neutrophil nadirs occur at a median of 7 days but this interval may be shorter in heavily pretreated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving docetaxel. Patients should be retreated with docetaxel when neutrophils recover to a level of ≥ 1500 cells/ml. In severe neutropenia (< 500 cells/ml for 7 days or more) during a course of docetaxel therapy, a reduction in dose for subsequent courses or the use of appropriate symptomatic measures is recommended.

Hypersensitivity reactions Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes after the initiation of infusion of docetaxel, so facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and institution of the appropriate therapy. Patients who have developed severe hyposensitivity reactions should not be rechallanged with docetaxel.

Cutaneous reactions Localised skin erythema of the extremities (palms of the hands and soles of the feet), with oedema followed by desquamation, has been observed. Severe symptoms such as eruptions preceding desquamation, which lead to the interruption or discontinuation of docetaxel treatment, were reported in 5.9% of patients. Bullous epidermolysis has not been observed.

Fluid retention A premedication consisting of an oral corticosteroid such as dexamethasone 16 mg/day (e.g. 8 mg twice daily) for 3 days, starting 1 day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Patients with severe fluid retention, such as pleural effusion, pericardial effusion or ascites, should be monitored closely.

Liver impairment In patients treated with docetaxel who have serum transaminase levels (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)) greater than 1.5 times the upper limit of normal (ULN) concurrent with serum alkaline phosphatase levels greater than 2.5 times the ULN, there is a higher risk of developing severe adverse reactions such as toxic death, and including sepsis and gastrointestinal haemorrhage (which can be fatal), febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. The recommended dose of docetaxel in patients with elevated liver function test levels is 75 mg/m^2 and liver function tests should be conducted at baseline and before each cycle. For patients with serum bilirubin levels > ULN and/or ALT and AST levels > 3.5 times the ULN concurrent with serum alkaline phosphatase levels > 6 times the ULN, no dose reduction can be recommended and docetaxel should not be used unless strictly indicated.

Neurological The development of severe peripheral neurotoxicity has been observed in 4.1% of patients and requires a dose reduction.

Other Contraceptive measures must be taken during and for at least 3 months after cessation of therapy.

Chemotherapy used in breast and ovarian cancer

Table 3 provides a summary of some of the chemotherapeutic agents used in the treatment of breast and ovarian cancers, their toxicities and their mode of administration.

TABLE 2 *Toxicity of taxoids in recommended dosages (derived from Eisenhauer and Vermorken[21])*

Adverse effect	Paclitaxel		Docetaxel
	3 h	24 h	1 h
Neutropenia	+	++	++
Hypersensitivity reaction	+	+	+
Hair loss	++	++	++
Mucositis	–	+	+
Cardiac arrhythmia	+	+	–
Arthralgia/myalgia	+	+	–
Neurosensory	+[a]	+[a]	±
Cumulative oedema	–	–	+
Skin/nails	–	–	+

[a] *Dose related and also more prominent when paclitaxel is given over 3 h*

+, moderate; ++, severe; –, absent; ±, mild

TABLE 3 *Summary of chemotherapeutic agents*

Drug	Mode of action	Toxicity/side-effects	Administration
Carboplatin	Binds to DNA; forms interstrand cross-links and intrastrand adducts	Myelosuppression, especially thrombocytopenia Nausea and vomiting Side-effects less severe than with cisplatin	i.v. over 15–60 min
Cisplatin	Binds to DNA; forms interstrand cross-links and intrastrand adducts	Severe nausea and vomiting Nephrotoxicity Myelotoxicity Ototoxicity Peripheral neuropathy Hypomagnesaemia Visual disturbance	Pretreatment hydration mandatory i.v. over 6–8 h
Cyclophos-phamide	Metabolite alkylates to DNA	Myelosuppression Haemorrhagic cystitis Nausea and vomiting Alopecia Cardiomyopathy (rare) "Allergic" interstitial pneumonitis	p.o. or i.v. over 5–15 min Increased fluid intake advised
Docetaxel	Promotes microtubule assembly and arrests cell cycle in G_2 and M phases	Hypersensitivity Fluid retention	Premedication with dexamethasone p.o. for 5 d i.v. over 1 h
Doxorubicin	Cytotoxic, anthracycline antibiotic Intercalation to DNA double helix Topoisomerase II-mediated DNA damage Production of oxygen free radicals, which cause damage to DNA and cell membranes	Nausea and vomiting Myelosuppression Alopecia Mucositis Cumulative cardiac toxicity Dose-related acute ECG changes Severe tissue damage if extravasated	i.v. over 2–3 min

continued

TABLE 3 *Summary of chemotherapeutic agents*

Drug	Mode of action	Toxicity/side-effects	Administration
Fluorouracil	Antimetabolite: prevents normal cell division	Toxicity unusual but may include: Myelosuppression Mucositis Nausea and vomiting Diarrhoea Dermatological toxicity Cerebellar syndrome	i.v. over 4 h
Methotrexate	Antimetabolite: inhibits the enzyme dihydrofolate reductase	Myelosuppression Mucositis Pneumonitis	p.o., i.v., i.m., i.t. Folinic acid after administration helps to prevent mucositis and myelosuppression
Mitomycin	Cytotoxic antibiotic	Delayed bone marrow toxicity Lung fibrosis Renal damage	Administered at 6-weekly intervals
Paclitaxel	Promotes microtubule assembly and arrests cell cycle in G_2 and M phases	Hypersensitivity Myelosuppression Peripheral neuropathy Cardiac conduction defects with arrhythmias Alopecia Myalgia/arthralgia	Premedication with corticosteroid, antihistamine and histamine H_2-receptor antagonist 3-h or 24-h infusion
Vinblastine	Vinca alkaloid Reversible inhibition of mitosis Binds to microtubule protein, ultimately inhibiting formation of mitotic spindles	Peripheral or autonomic neuropathy Abdominal pain Constipation Myelosuppression Alopecia Severe local irritation	i.v. over 1 min
Vinorelbine	Vinca alkaloid Reversible inhibition of mitosis Binds to microtubule protein, ultimately inhibiting formation of mitotic spindles	Peripheral or autonomic neuropathy Abdominal pain Constipation Myelosupression Alopecia	i.v.

Chapter 2

Methods

Search strategy and bibliographic databases used

The following databases were searched for relevant literature (see appendix 2 for strategy):

- MEDLINE
- EMBASE
- Cochrane Controlled Trials Register
- National Research Register (NRR)
- CancerLIT.

The National Institute for Clinical Excellence approached the manufacturers (Bristol-Myers Squibb and Aventis) for submissions presenting clinical and economic evaluations of the taxanes.

The researchers and groups identified by the NRR were contacted for further information on their studies (appendix 3).

Other contacts included the Cochrane Breast Cancer Group and the Cochrane Gynaecological Cancer Group (appendix 3). Not all groups contacted responded to our request for information.

Inclusion and exclusion criteria

Interventions:

- taxanes
  - paclitaxel (Taxol, Bristol-Myers Squibb) used either alone or in combination with other drugs as part of a chemotherapy regimen
  - docetaxel (Taxotere, Aventis) used either alone or in combination with other drugs as part of a chemotherapy regimen
- other standard chemotherapy regimens
  - for ovarian cancer these include non-platinum drugs such as cyclophosphamide, doxorubicin (Adriamycin), and platinum (cisplatin and carboplatin), either alone or in combination[10]
  - standard chemotherapy used in advanced breast cancer includes CMF (cyclophosphamide, methotrexate and fluorouracil),[5] anthracyclines (epirubicin, doxorubicin), mitozantrone and mitomycin.

The use of taxanes as part of high-dose regimens with autologous stem cell support was not considered. Trials comparing different taxane regimens only (in terms of dose, period of administration or combination) were not included.

Participants:

(See appendix 1 for definition of stages.)

- women with ovarian cancer
  - early (FIGO Stage I)
  - advanced (FIGO Stages II–IV)
- people with breast cancer
  - locally advanced (Stages II–III)
  - metastatic (Stage IV)
  - recurrent (second-line treatment).

Outcomes:

- overall response (complete response + partial response)
- progression-free survival
- overall survival
- symptom relief
- quality of life (QoL)
- adverse events
- cost per quality-adjusted life-year (QALY)
- cost per progression-free life-year
- incremental cost per QALY
- incremental cost per progression-free life-year.

Design:

- RCTs comparing a taxane with a standard chemotherapy regimen
- economic evaluations.

Trials comparing only different doses or periods of infusion of taxanes were not included.

Phase II trials in which randomisation was employed were considered for inclusion.

All obtained titles and abstracts were independently assessed for inclusion by two reviewers (DLS and MSM or KSK) using a prescreen form (appendix 4). Any discrepancies were resolved by discussion and full articles obtained where possible.

Data extraction strategy

The data were extracted into an Access database (see appendix 5), which was checked by a second reviewer.

Some of the studies included Kaplan–Meier curves. When raw data were not presented, numbers of patients surviving were estimated from these graphs.

Quality assessment strategy

One reviewer assessed the quality of the studies by using the rating system set out in the NHS cancer guidance reports[1,2,22,23] as follows:

- Grade I (strong evidence): RCT or review of RCTs
  - IA: calculation of sample size and accurate and standard definition of outcome variables
  - IB: accurate and standard definition of outcome variables
  - IC: none of the above
- Grade II (fairly strong evidence): prospective study with comparison group (non-RCT or good observational study)
  - IIA: calculation of sample size, accurate, standard definitions of outcome variables and adjustment for the effects of important confounding variables
  - IIB: one of the above
- Grade III (weak evidence): retrospective study
  - IIIA: comparison group, calculation of sample size and accurate standard definition of outcome variables
  - IIIB: two of the above criteria
  - IIIC: none of the above
- Grade IV (weak evidence): cross-sectional study

A second reviewer checked the quality assessments.

Analysis

Response rates, progression-free survival and overall survival rates were analysed using the Cochrane Collaboration's Metaview 4.0.3 software. Relative risks (RRs) were calculated.

In quantifying the effectiveness of cancer treatment, survival analyses are preferable to simple proportions because the outcomes are time dependent.[24] Ideally, data synthesis in these reviews should also be based on time-to-event analysis. This requires meta-analyses using individual patient data.[25] Such analyses could not be conducted in the short time frame of this rapid review.

The cross-over design provides a useful alternative to the parallel comparison because, to achieve the same amount of precision in estimating the response, a smaller sample size is required.[26,27] However, cross-over trials are ideally suited for chronic benign conditions where the outcomes are reversible.[28] Under these circumstances the various periods of a cross-over trial can be completed. In this overview, when patients are 'crossed over' to the other arm of the study, this represents allocated treatment failure, not a planned cross-over at the end of a defined treatment as is the case in cross-over trials. "Cross-over" frequently occurs during cancer chemotherapy trials and trials were not excluded because of this problem. However, for the purpose of this review, the analysis was based on intention-to-treat (ITT) according to treatments allocated at randomisation.

Where the authors discussed differences in, for example, the median time to progression, the statistics presented in the primary study are given in the tables. Often, data had to be extrapolated from survival curves to generate RRs. Where this approach was used it has not been possible to estimate variances. Because of the above limitations to analyses, caution has been used in generating inferences.

Synthesis

Results of data extraction and assessment of study validity are presented in structured tables and also as a narrative description. In addition, the results are presented as RR plots (without pooling). Both beneficial and adverse effects have been discussed in the light of study quality. The heterogeneity of studies has been assessed by clinical judgements of differences regarding: (1) patients, (2) interventions, (3) outcomes, (4) costs and (5) quality. Because of the heterogeneity of included studies, quantitative syntheses were not undertaken.

All economic analyses in first-line ovarian cancer and in advanced breast cancer were reviewed. Their quality was assessed by using the Drummond checklist.[29] The studies were scored on the following dimensions:

1. well-defined question
2. comprehensive description of alternatives
3. effectiveness established

4. all important and relevant costs and consequences for each alternative identified
5. costs and consequences measured accurately
6. costs and consequences valued credibly
7. costs and consequences adjusted for differential timing
8. incremental analysis of costs and consequences
9. sensitivity analyses to allow for uncertainty in estimates of cost or consequences
10. study results/discussion include all issues of concern to users.

These grades were used:

+, item properly addressed
–, item not properly addressed
±, item partially addressed
?, unknown.

The main focus was on studies originating in the UK.

Confidentiality

The National Institute for Clinical Excellence has been requested by Bristol-Myers Squibb to remove from this report all information that they submitted as commercially in confidence. The relevant sections of this document have been removed and are clearly noted. Where possible this information has been replaced by trial details that are in the public domain.

The Institute's Appraisal Committee had access to the full report when drawing up their recommendations relating to the use of taxanes for breast and ovarian cancer.

Chapter 3

Results

The searches identified 2250 articles related to the taxanes. After independent assessment against the inclusion criteria by two reviewers, it was agreed that 213 references were to be obtained. Of these, 100 were trials listed in the NRR, the authors of which were contacted, 13 were reviews and background information, 32 were economic evaluations, and the remaining 68 appeared to be reports of relevant RCTs. On closer examination, 47 studies were rejected (see appendix 6).

Table 4 shows the selected studies, broken down according to the review questions. The number of studies includes duplicate publications. No RCTs evaluating the effectiveness of docetaxel as adjuvant or first-line treatment of breast cancer were found.

TABLE 4 *Selection of studies*

	No. trials	No. economic evaluations
Paclitaxel as first-line treatment for ovarian cancer	4[a]	13[b]
Docetaxel as first-line treatment for breast cancer	1[c]	0
Paclitaxel as first-line treatment for breast cancer	4[a]	0
Docetaxel as second-line treatment for breast cancer	4	6
Paclitaxel as second-line treatment for breast cancer	1	7[b]

[a] *Data from published papers substituted for original data from manufacturer's confidential submission (1 study)*
[b] *One study not presented in this report at request of manufacturer*
[c] *Phase III trial that does not specifically mention randomisation*

Chapter 4

Breast cancer

The effectiveness of paclitaxel as first-line treatment for advanced breast cancer

Description of included trials

Ten publications were identified that evaluated the effectiveness of paclitaxel as a first-line treatment for advanced breast cancer. These pertained to four Phase III trials: EORTC;[30–33] TITGANZ;[34–37] E1193[38] and CA139-278[39] (*Table 5*). Only the results of the TITGANZ trial have been published in journals. An article detailing the EORTC trial is awaiting publication. However, the results from this are not presented in this version of the report as they are not yet available for public comment; results taken from the two meeting abstracts and interim report have been substituted where possible. Details of the Intergroup E1193 and CA139-278 trials have been taken from meeting abstracts and presentations.

All four were randomised controlled Phase III trials. The TITGANZ trial had power calculations and accurate and standard definitions of outcome variables. Insufficient details were given in the EORTC, E1193 and CA139-278 abstracts and meeting presentations to assess the quality of these trials properly. Only the EORTC and TITGANZ trials were said to have been analysed on an ITT basis; the TITGANZ trial defined what was meant by this. Both the EORTC and the E1193 trials allowed cross-over to alternate treatment on progression. The TITGANZ trial recommended treatment with epirubicin (an anthracycline) on progression; the number, if any, so treated was not mentioned. Patients crossing over to alternate treatment violate the randomisation unless progression is independently verified by blind external assessors. Unless this is the case, such participants should be counted as treatment failures and censored from analysis. Crossing over to alternate treatment on progression, no matter how well validated, cannot be considered as a randomised trial of second-line treatment. Consequently, the cross-over parts of the EORTC and E1193 trials have not been considered.

Only the TITGANZ trial stated the median length of follow-up. More than half the participants in the CA139-278 trial still survived at the time of this analysis; consequently, any overall survival data should be treated with caution.

All the included trials required participants to have undergone no previous chemotherapy for advanced disease, although adjuvant chemotherapy was permitted (*Table 6*). Consequently, these trials looked at the use of paclitaxel outside its licensed indications. The EORTC trial specified that adjuvant therapy had to have finished 3 months previously; the other trials specified a 6-month delay. All but the TITGANZ trial specifically excluded previous treatment with anthracyclines.

Three of the trials included a paclitaxel-only arm (EORTC, E1193 and TITGANZ). Both the EORTC and TITGANZ trials used paclitaxel 200 mg/m^2 administered as a 3-hour infusion (*Table 7*). The E1193 trial used 175 mg/m^2 given as a 24-hour infusion. Two trials included a paclitaxel plus 50 mg/m^2 doxorubicin arm. The TITGANZ trial used paclitaxel 220 mg/m^2 given as a 3-hour infusion; the E1193 trial used 150 mg/m^2 of paclitaxel with G-CSF support. No information was given about length of infusion. Both the EORTC and the E1193 trials allowed cross-over to alternate treatment on discovery of progressive disease. With the exception of the TITGANZ trial, all included an anthracycline in the control groups (usually doxorubicin). Only the TITGANZ trial gave details of premedication and prophylactic medication. It is unclear whether prophylactic G-CSF was permitted in all arms of the E1193 trial.

There was variation between the trials in terms of included patients. The details for the EORTC trial are taken from a report[30] that included only 331 participants. The proportions of women who were oestrogen receptor positive were: the TITGANZ trial, around 38%; and the E1193 trial, about 45%. Women who are not oestrogen receptor positive have a worse prognosis. A greater

TABLE 5 *Design of included trials*

Trial: source	Quality	Design	Accrual dates	No. randomised	ITT	No. evaluated	Cross-over	Median length of follow-up	No. patients surviving (%)
EORTC: interim report, meeting abstract[30,32,33]	I	Randomised Multicentre Non-blinded	Aug 1993 – May 1996	Tp: 166 A: 165	Not defined	Evaluable for toxicity: 327 Evaluable for response to first-line chemo-therapy: 299	Cross-over on demonstrated disease progression If cross-over without documented progression then counted as treatment failure	Not stated	Not stated
TITGANZ: published reports[34–37]	IA	Randomised Power calculations Outcomes defined Multicentre Open label	Sep 1993 –	Tp: 107 CMFP: 102	All randomised patients	Tp: 107 CMFP: 102	No cross-over but patients whose disease progressed were recommended to receive epirubicin No. not stated	26 mo	Tp: 30 CMFP: 20
E1193: meeting abstract and presentation[38]	IC	Randomised Multicentre Non-blinded	Jul 1994 – Feb 1997	Tp: 245 A: 248 ATp: 245		Analysable: Tp: 229 A: 224 ATp: 230		Not stated	Not stated
CA139-278: meeting abstract and presentation[39]	IB	Randomised Power calculations Multicentre Open label	Nov 96 – Apr 97	ATp: 134 FAC: 133		Evaluable for response: ATp: 128 FAC: 131		Not stated	ATp: 56 FAC: 42

ITT, intention to treat; Tp; paclitaxel; A, anthracycline (doxorubicin); ATp, anthracycline, paclitaxel; FAC, fluorouracil, anthracycline, cyclophosphamide; CMFP, cyclophosphamide, methotrexate, fluorouracil, prednisone

TABLE 6 *Comparison of inclusion criteria*

Trial	Disease	Previous treatment
EORTC	Histologically or cytologically proven adenocarcinoma of the breast Metastatic disease with measurable lesions WHO PS 0–2	Prior hormone therapy, radio- or immunotherapy permitted but this had to be stopped on study entry Prior adjuvant therapy permitted if at least 3 mo previously No exposure to anthracyclines or taxanes No chemotherapy for advanced disease
TITGANZ	Metastatic breast cancer Measurable or evaluable disease ECOG PS 0–2	Prior radiotherapy permitted if at least 4 wk previously Prior adjuvant therapy permitted if at least 6 mo previously No chemotherapy for advanced disease
E1193	Histologically confirmed recurrent or metastatic breast cancer Measurable or evaluable disease ECOG PS 0–2	Prior adjuvant therapy permitted if at least 6 mo previously No prior systemic anthracycline-, anthracene- or taxane-containing chemotherapy No chemotherapy for overt metastatic disease
CA139-278	Measurable disease ECOG PS 0–2	Prior hormone therapy, radio- or immunotherapy permitted Prior adjuvant therapy permitted if at least 6 mo previously No prior anthracyclines or taxanes No chemotherapy for overt metastatic disease

PS, performance status; ECOG, Eastern Cooperative Oncology Group

TABLE 7 *Comparison of interventions*

Trial	Intervention	Control A	Control B	Control C
EORTC	Tp: paclitaxel (200 mg/m^2), 3-h infusion, 7 x 3-wk cycles Standard antihypersensitivity premedication	A: doxorubicin (75 mg/m^2), 7 x 3-wk cycles Premedication of dexamethasone and 5-HT antagonist	–	Cross-over on progression or within 4 wk of receiving 7th cycle
TITGANZ	Tp: paclitaxel (200 mg/m^2), 3-h infusion, 8 x 3-wk cycles Premedication with dexamethasone 2 x 20 mg, diphenhydramine 50 mg, cimetidine 300 mg Antiemetics permitted	CMFP: cyclophosphamide (100 mg/m^2) + methotrexate (40 mg/m^2) + fluorouracil (600 mg/m^2) + prednisone, 6 x 4-wk cycles Antiemetics permitted	–	Patients whose disease progressed while receiving first-line therapy were recommended to receive epirubicin 90 mg/m^2 i.v. every 3 wk
E1193	Tp: paclitaxel (175 mg/m^2), 24-h infusion, 3-wk cycles	A: doxorubicin (60 mg/m^2), 8 x 3-wk cycles	ATp: doxorubicin (50 mg/m^2) + paclitaxel (150 mg/m^2), 8 x 3-wk cycles Prophylactic G-CSF	–
CA139-278	ATp: doxorubicin (50 mg/m^2) + paclitaxel (220 mg/m^2), 3-h infusion; 8 x d 1, d 2, 3-wk cycles	FAC: fluorouracil (500 mg/m^2), anthracycline (50 mg/m^2), cyclophosphamide (500 mg/m^2), 8 x 3-wk cycles	–	–

proportion of women in the CA193-278 trial were fully active than in the other studies. More than half the women in the E1193 trial had three or more metastatic sites, compared with about a third in the EORTC trial. There was also variation in previous treatments (*Table 8*). Less than half the women in the CA139-278 and TITGANZ trials had received radiotherapy, compared with three-quarters of those in the EORTC trial. Previous adjuvant chemotherapy ranged from 21% in one arm of the TITGANZ trial to 46% in an arm of the CA139-278 trial. Prior hormone therapy ranged from 34% in the CA139-278 trial to 77% in the TITGANZ trial.

It was not possible to assess the quality of the E1193 or CA139-279 studies. The trials varied both in terms of the interventions and controls used. Finally, there were major differences between the participants included in the studies. The dissimilarities make pooling inappropriate.

Results

Single-agent paclitaxel versus control

Overall response rates Overall response rates (complete response plus partial response) were presented for the two relevant trials (E1193 and TITGANZ; *Figure 1* (insufficient data were available to allow the EORTC trial to be presented)). For paclitaxel, these ranged from 25% for (EORTC) to 34% (E1193). In all of these, more patients in the control arm than in the paclitaxel arm showed an overall response. This difference was statistically significant in the EORTC trial, which compared paclitaxel and doxorubicin (25% versus 41%, $p = 0.004$).

Progression-free survival Kaplan–Meier curves were presented for the TITGANZ trial only.

The median time to progression was similar for paclitaxel and CMFP in the TITGANZ trial (5.3 months (95% confidence interval

TABLE 8 *Comparison of participants*

Trial: source	Median age (yr)	ER status (%)	PS (%)	Secondary spread (%): dominant site of disease	No. metastatic sites (%)	Median disease-free interval	Previous treatment (%)
EORTC: from interim report[30] based on 235 patients	Tp: 56; A: 55		***WHO 0*** Tp: 43; A: 39 ***WHO 1*** Tp: 45; A: 44 ***WHO 2*** Tp: 10; A: 7	***Soft tissue only*** Tp: 8; A: 17 ***Bone*** Tp: 17; A: 13 ***Single visceral*** Tp: 62; A: 53 ***Multiple visceral*** Tp: 13; A: 17	***1 site*** Tp: 34; A: 25 ***2 sites*** Tp: 39; A: 42 ***3 sites*** Tp: 27; A: 34	***Median time between diagnosis and relapse (mo)*** Tp: 40; A: 44	***Prior radiotherapy*** Tp: 83; A: 77 ***Prior adjuvant chemotherapy*** Tp: 30; A: 30 ***Prior hormone therapy*** Tp: 77; A: 75
TITGANZ	Tp: 54; CMFP: 54	***Positive*** Tp: 40; CMFP: 37	***ECOG 0*** Tp: 31; CMFP: 40 ***ECOG 1*** Tp: 60; CMFP: 48 ***ECOG 2*** Tp: 9; CMFP: 12	***Skin/soft tissue only*** Tp: 7; CMFP: 14 ***Bone ± skin/soft tissue*** Tp: 18; CMPF: 16 ***Visceral ± bone ± skin/soft tissue*** Tp: 75; CMFP: 71		***Time since diagnosis > 3 yr (%)*** Tp: 53; CMFP: 50	***Prior adjuvant chemotherapy*** Tp: 21; CMFP: 33 ***Adjuvant radiotherapy*** Tp: 39; CMFP: 48 ***Prior hormone therapy*** Tp: 72; CMFP: 77
E1193	Tp: 56; A: 58; ATp: 56	***Positive*** Tp: 47; A: 45; ATp: 44	***ECOG 0, 1*** Tp: 78; A: 83; ATp: 80	***Visceral*** Tp: 70; A: 60; ATp: 61	***At least 3*** Tp: 52; A: 52; ATp: 47	***1–24 mo (%)*** Tp: 34; A: 32; ATp: 36	***No previous treatment*** Tp: 40; A: 43; ATp: 40 ***Adjuvant CT*** Tp: 31; A: 31; ATp: 32
CA139-278	ATp: 50; FAC: 50		***ECOG 0*** ATp: 55; FAC: 47 ***ECOG 1*** ATp: 38; FAC: 46 ***ECOG 2*** ATp: 7; FAC: 7	***Visceral*** ATp: 64; FAC: 68 ***Bone*** ATp: 11; FAC: 8 ***Soft tissue only*** ATp: 25; FAC: 24	***Lung*** ATp: 38; FAC: 42 ***Liver*** ATp: 28; FAC: 39 ***Bone*** ATp: 37; FAC: 36 ***Soft tissue*** ATp: 70; FAC: 65	***Median time from diagnosis (mo)*** ATp: 20.7; FAC: 22.5	***Prior radiotherapy*** ATp: 44; FAC: 43 ***Prior adjuvant therapy*** ATp: 44; FAC: 46 ***Prior hormone therapy*** ATp: 34; FAC: 37 ***No prior therapy*** ATp: 28; FAC: 26

ER, oestrogen receptor

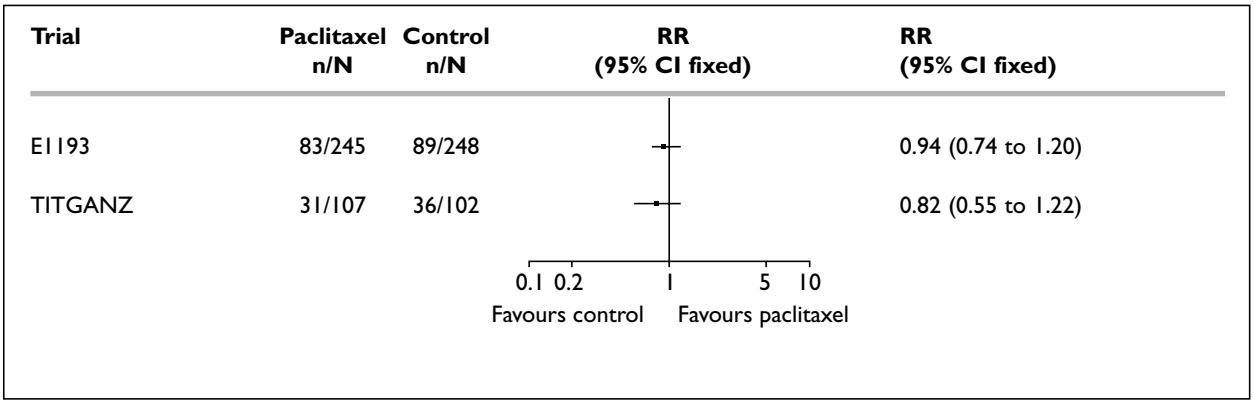

FIGURE 1 *Single-agent paclitaxel as first-line treatment of breast cancer: overall response rates*

(CI): 4.1 to 6.4) versus 6.4 months (95% CI: 5.2 to 7.8), $p = 0.25$) (*Table 9*). The median time to treatment failure was similar for paclitaxel and doxorubicin in the E1139 trial (5.9 months versus 6 months respectively, $p = 0.35$) (*Table 9*).

Figure 2 illustrates the estimates of progression-free survival rates at 6, 12, 18, 24, 30 and 36 months for the TITGANZ trial. The estimates of percentage survival are extrapolated from the Kaplan–Meier curves. These allow the generation of RR point esimates but not their CIs.

At 12 and 18 months, only five women in each arm survived without progression. By 36 months there was only one progression-free survivor, in the paclitaxel group.

Overall survival Kaplan–Meier curves were presented for the TITGANZ trial only.

The median lengths of survival ranged from 17.3 months in the TITGANZ trial to 22.2 months in E1139, although it is not clear whether E1139 was analysed on an ITT basis (*Table 9*). There were no significant differences between the arms of the trials in median length of overall survival.

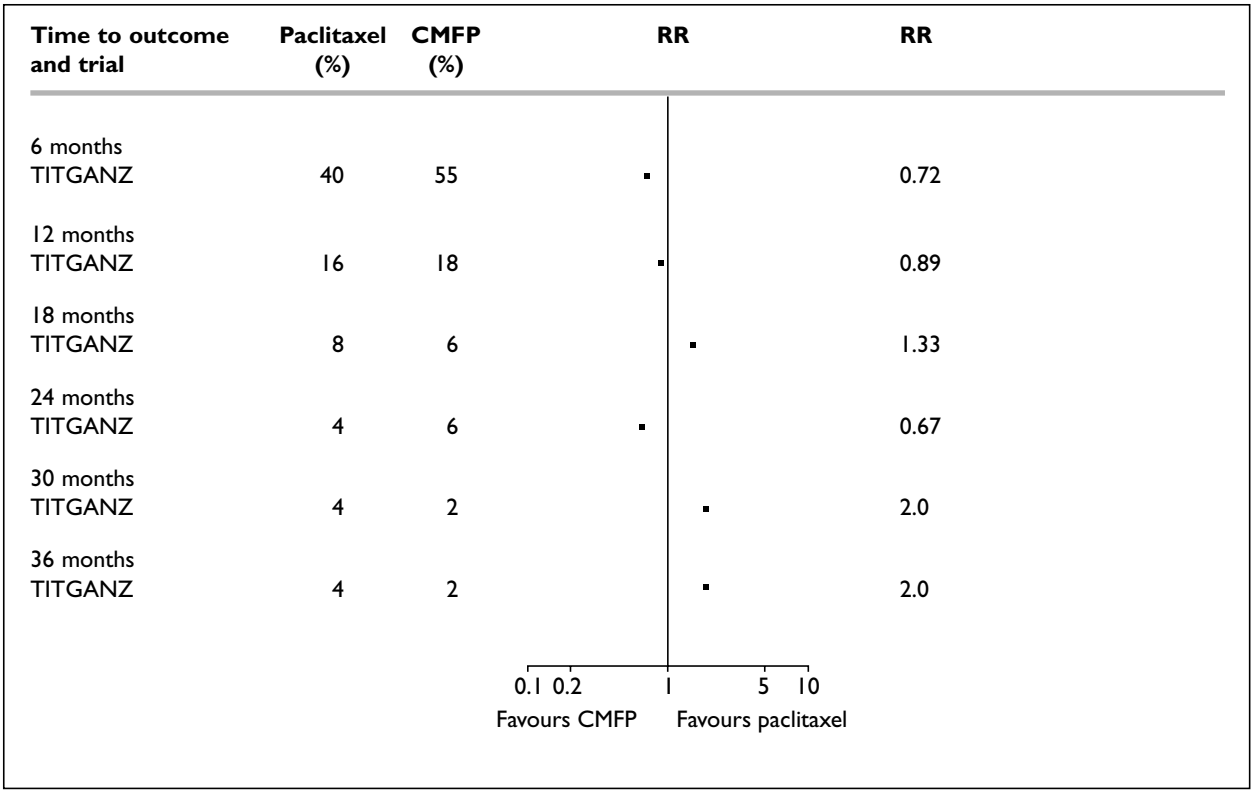

FIGURE 2 *Single-agent paclitaxel as first-line treatment for breast cancer: progression-free survival*

TABLE 9 *Median survival times in first-line treatment for breast cancer*

Trial	Median progression-free survival (mo)	Median time to treatment failure (mo)	Median length of survival (mo)
EORTC	Tp: 4.0 A: 7.5 p = 0.0001		
E1193		Tp: 5.9 A: 6 p = 0.35[a]	Tp: 22.2 A: 18.9 p = 0.24[a] (Unclear if ITT)
TITGANZ	Tp: 5.3 (95% CI: 4.1 to 6.4)[b] CMFP: 6.4 (95% CI: 5.2 to 7.8)[b] p[c] = 0.25		Tp: 17.3 (95% CI: 12.5 to 21.4)[b] CMFP: 13.9 (95% CI: 11.4 to 16.5)[b] p[c] = 0.068

[a] *No details of tests used*
[b] *CIs estimated using Brookmeyer and Crowley method*
[c] *Mantel–Cox logrank test*

Figure 3 illustrates the estimates of overall survival rates at 6, 12, 18, 24, 20 and 36 months for the TITGANZ trial, which are extrapolated from the Kaplan–Meier curves. These allow the generation of RR point esimates but not their CIs.

By 36 months, only two patients in each arm survived.

Paclitaxel plus anthracycline versus control

Overall response rates Overall response rates (complete response plus partial response) were presented for both trials that compared paclitaxel plus doxorubicin with control (CA139-278 65%; E1193 47%; *Figure 4*). In both trials, more women in the paclitaxel plus doxorubicin arm responded; this difference was statistically

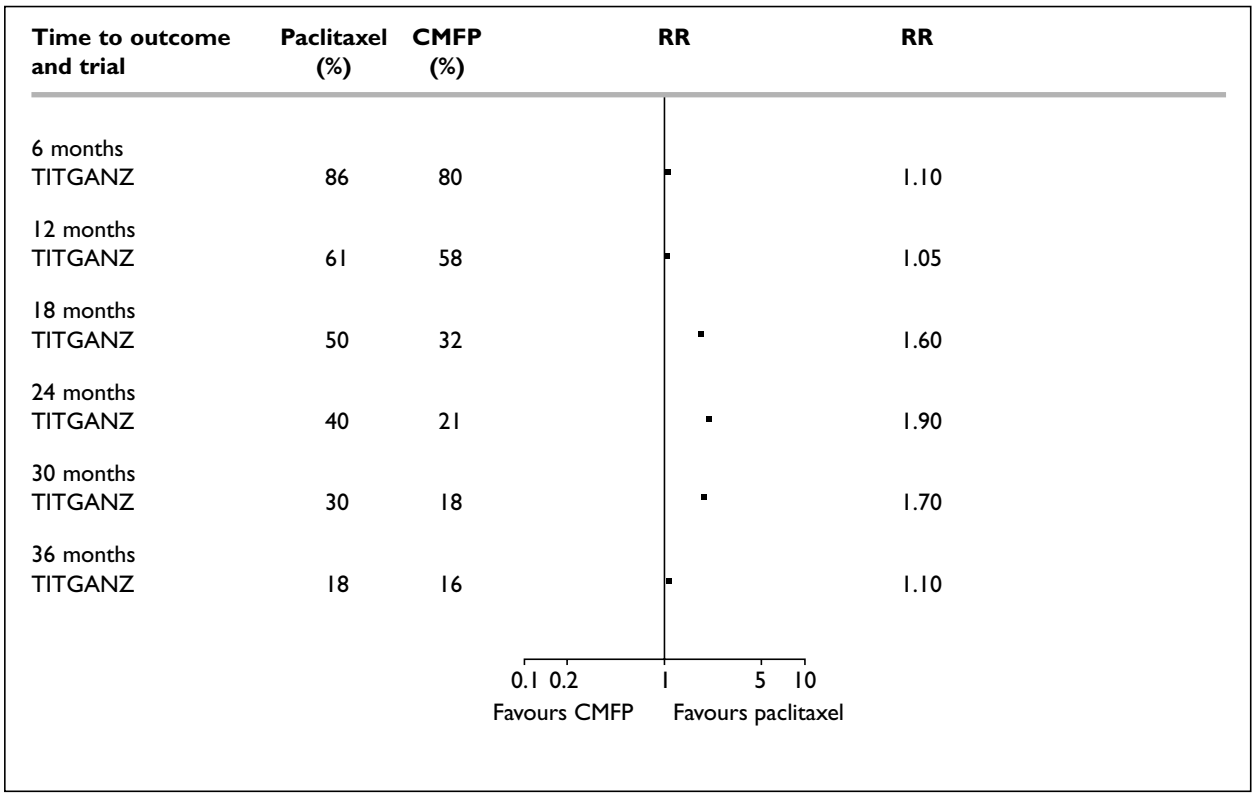

FIGURE 3 *Single-agent paclitaxel as first-line treatment for breast cancer: overall survival*

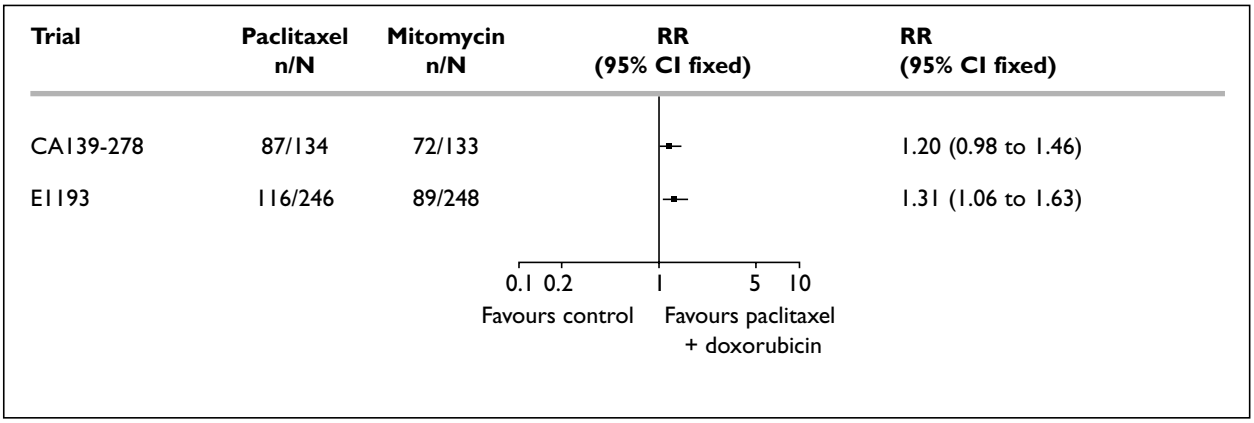

FIGURE 4 *Combined paclitaxel/anthracycline as first-line treatment for breast cancer: overall response rates*

significant in the E1193 trial, which compared paclitaxel plus doxorubicin with doxorubicin alone (47% versus 36%, RR = 1.31 (95% CI: 1.06 to 1.63), NNT = 9).

Neither trial reported time to or duration of response.

Progression-free survival Kaplan–Meier curves were not presented for either trial.

The median time to progression reported in the CA139-278 study was significantly longer for the paclitaxel plus doxorubicin arm than for the FAC arm (*Table 10*): 8.3 months (95% CI: 7.2 to 9.0) versus 6.2 months (95% CI: 5.8 to 7.6). The median time to treatment failure in E1193 was also significantly longer for the paclitaxel plus doxorubicin arm than for doxorubicin alone (8 months versus 6 months, $p = 0.003$).

Overall survival Kaplan–Meier curves were not presented for either trial.

In both trials, patients in the paclitaxel plus doxorubicin group survived longer than the control group. This difference was statistically significant in CA139-278 (paclitaxel plus doxorubicin: 22.7 months; FAC: 18.3 months; $p = 0.02$).

Comparing paclitaxel alone with paclitaxel plus other

The E1193 trial allowed single-agent paclitaxel to be compared with paclitaxel in combination with doxorubicin. The median time to treatment failure was significantly longer with the drug combination (8 months versus 5.9 months, $p = 0.05$). There was no significant difference in the median length of survival (22.2 months for single agent, 22 months for combination).

Compliance

Details of numbers of patients completing all cycles and the reasons for early discontinuation were patchy. In the CA139-278 trial, patients in

TABLE 10 *Median survival times in first-line treatment for breast cancer*

Trial	Median progression-free survival (mo)	Median time to treatment failure (mo)	Median length of survival (mo)
E1193		ATp: 8 A: 6 $p = 0.003$[a]	ATp: 22 A: 18.9 $p = 0.24$[a] (Unclear if ITT)
CA139-278[39]	ATp: 8.3 (95% CI: 7.2 to 9.0) FAC: 6.2 (95% CI: 5.8 to 7.6) p[b] = 0.034		ATp: 22.7 (95% CI: 20.2 to ?) FAC: 18.3 (95% CI: 16.1 to 21.8) p[b] = 0.02

[a] *No details of tests used*
[b] *Stratified logrank* p
?, data missing from article

TABLE 11 *Treatment received*

Trial	Completing all cycles (%)	Median number of cycles (range)	Reasons for early discontinuation (%)	
			Disease progression	Adverse events or refusal
EORTC	Not available			
TITGANZ	Tp: 48 CMFP: 52			
E1193	No details			
CA139-278	ATp: 65 FAC: 50	ATp: 8 (1–8) FAC: 8 (1–8)	ATp: 15 FAC: 34	ATp: 11 FAC: 10

TABLE 12 *Haematological adverse events*

Adverse event	EORTC (%) (*n* = 327[32])	TITGANZ (%) RR (95% CI) (*n* = Tp: 107; CMFP: 102)	E1193 (%) RR (95% CI) (*n* = Tp: 241; ATp: 242; A: 241)	CA139-278 (%) RR (95% CI) (*n* = ATp: 131; FAC: 133)
Neutropenia	Tp: 40 A: 85	Tp: 68 CMFP: 74 0.93 (0.78 to 1.10)		ATp: 47 FAC: 20 2.33 (1.59 to 3.42)
Febrile neutropenia	Tp: 7 A: 20			ATp: 29 FAC: 16 1.84 (1.14 to 2.95)
Infections		Tp: 1 CMFP: 7 0.14 (0.02 to 1.09)	Tp: 9 ATp: 12 A: 4 Tp vs. A: 2.2 (1.06 to 4.55) ATp vs. Tp: 1.36 (0.57 to 2.43) ATp vs. A: 2.89 (1.44 to 5.79)	ATp: 2 FAC: 0 5.08 (0.25 to 104.7)
Thrombo-cytopenia		Tp: 1 CMFP: 12 0.08 (0.01 to 0.60)	Tp: 2 ATp: 16 A: 5 Tp vs. A: 0.42 (0.15 to 1.16) ATp vs. Tp: 9.07 (3.53 to 23.44) ATp vs. A: 3.24 (1.74 to 6.03)	
Leucopenia		Tp: 29 CMFP: 66 0.44 (0.32 to 0.61)		
Granulo-cytopenia			Tp: 79 ATp: 57 A: 66 Tp vs. A: 1.19 (1.07 to 1.34) ATp vs. Tp: 0.36 (0.24 to 0.53) ATp vs. A: 0.86 (0.75 to 1.00)	

the FAC arm were more likely to discontinue because of disease progression (*Table 11*).

Adverse events

The study reports were not consistent in the way adverse events were reported. The percentages of patients experiencing grade 3/4 toxicity for each trial are given in this report.

Haematological adverse events

The proportion of participants experiencing neutropenia in the paclitaxel arms of the trials ranged

from 40% to 68% (47% when in combination with anthracycline) (*Table 12*). More patients in the doxorubicin than the paclitaxel arm of the EORTC trial suffered neutropenia (85% versus 40%) and febrile neutropenia (20% versus 7%). In the CA139-278 trial, more patients treated with paclitaxel plus anthracycline than those treated with FAC suffered neutropenia (47% versus 20%, RR = 2.33 (95% CI: 1.59 to 3.42)) and febrile neutropenia (29% versus 16%, RR = 1.84 (95% CI: 1.14 to 2.95)).

Other infections were not common in the paclitaxel groups (range 1–9% in paclitaxel-only arms; 2–12% in paclitaxel combinations). In the E1193 trial, more patients treated with paclitaxel, either alone or in combination, developed infections compared with patients treated with doxorubicin alone (9% versus 4%, RR = 2.2 (95% CI: 1.06 to 4.55) and 12% versus 4%, RR = 2.89 (95% CI: 1.44 to 5.97) respectively).

Thrombocytopenia was rare in patients treated with paclitaxel alone (1–2%) but occurred in 16% of patients treated with paclitaxel plus doxorubicin in E1193. Significantly more patients treated with CMFP than with paclitaxel in the TITGANZ trial experienced thrombocytopenia (12% versus 1%; RR = 0.08 (95% CI: 0.01 to 0.60)) and leucopenia (66% versus 29 %; RR = 0.44 (95% CI: 0.32 to 0.61)). Significantly more women treated with paclitaxel plus doxorubicin in the E1193 trial suffered thrombocytopenia than those treated with paclitaxel or doxorubicin alone (RR = 9.07 (95% CI: 3.53 to 23.44) and RR = 3.24 (95% CI: 1.74 to 6.03) respectively).

Significantly more patients treated with single-agent than combined paclitaxel experienced granulocytopenia in the E1193 trial (79% versus 57%; RR = 0.36 (95% CI: 0.24 to 0.53)).

TABLE 13 *Gastrointestinal adverse events*

Adverse event	**EORTC (%) (*n* = 327[32])**	**TITGANZ (%) RR (95% CI) (*n* = Tp: 107; CMFP: 102)**	**CA139-278 (%) RR (95% CI) (*n* = ATp: 131; FAC: 133)**
Vomiting		Tp: 1[a] CMFP: 8 0.12 (0.02 to 0.94)	ATp: 6 FAC: 14 0.45 (0.20 to 1.00)
Stomatitis	Tp: 1 A: 15		ATp: < 1 FAC: < 1 1.02 (0.06 to 16.06)
Diarrhoea			ATp: 2 FAC: 0 5.11 (0.25 to 105.51)
[a] *Nausea and vomiting*			

TABLE 14 *Neurological adverse events*

Adverse event	**EORTC (%) RR (95% CI) (*n* = 327[32])**	**TITGANZ (%) RR (95% CI) (*n* = Tp: 107; CMFP: 102)**	**E1193 (%) RR (95% CI) (*n* = Tp: 241; ATp: 242; A: 241)**
Neurosensory	Tp: 9 A: 0		Tp: 3[a] ATp: 10 A: 2 Tp vs. A: 1.4 (0.45 to 4.35) ATp vs. Tp: 3.68 (1.55 to 8.71) ATp vs. A: 4.78 (1.85 to 12.32)
Peripheral neuropathy		Tp: 10 CMFP: 0 21.94 (1.31 to 367.48)	
[a] *Includes neuromotor*			

TABLE 15 *Cardiovascular adverse events*

Adverse event	EORTC (%) (*n* = 327[32])	E1193 (%) RR (95% CI) (*n* = ATp: 242; A: 241)
Congestive heart failure	Tp: 0 A: 4	
Cardiac death		Tp: < 1 A: 3 ATp: < 1 ATp vs. A: 0.33 (0.03 to 3.17)
Cardiotoxicity		Tp: 4 ATp: 9 A: 9 Tp vs. A: 0.45 (0.22 to 0.94) ATp vs. Tp: 2.31 (1.07 to 4.99) ATp vs. A: 1.00 (0.57 to 1.75)

Gastrointestinal adverse events

Gastrointestinal events reported in the TITGANZ and CA139-278 trials were rare in the paclitaxel arms (*Table 13*). Nausea and/or vomiting were more frequent in the control arms of the TITGANZ trial (RR = 0.12 (95% CI: 0.02 to 0.94)). Stomatitis was also more common among patients treated with doxorubicin rather than paclitaxel in the EORTC trial (15% versus 1%).

*Neurological adverse events (***Table 14***)*

More patients in the paclitaxel than the doxorubicin arm of the EORTC trial suffered from neurosensory adverse events (9% versus 0%). Significantly more patients treated with paclitaxel plus doxorubicin than either single-agent paclitaxel or doxorubicin experienced neurosensory and neuromotor adverse events (10% versus 3%; RR = 3.68 (95% CI: 1.55 to 8.71) and 10% versus 2%; RR = 4.78 (95% CI: 1.85 to 12.32) respectively). More patients in the paclitaxel arm than the CMFP arm of the TITGANZ trial suffered peripheral neuropathy (10% versus 0%, RR = 21.94 (95% CI: 1.31 to 367.48)).

Cardiovascular adverse events

Cardiovascular adverse events were reported only in the EORTC and E1193 trials. These were more frequent in patients treated with anthracyclines than with paclitaxel (*Table 15*). In the E1193 trial, significantly more patients treated with doxorubicin alone or in combination with paclitaxel experienced cardiac adverse events than those receiving single-agent paclitaxel (9% versus 4%, RR = 0.45 (95% CI: 0.22 to 0.94) and 9% versus 4%, RR = 2.31 (95% CI: 1.07 to 4.99) respectively).

Other adverse events

Most other adverse effects were rare (*Table 16*). However, the majority of patients treated with paclitaxel in the TITGANZ trial suffered alopecia (76% compared with 25% in the CMFP arm, RR = 3.09 (95% CI: 2.16 to 4.41)). Arthralgia and myalgia occurred significantly more frequently in the paclitaxel arm than in the control arms of the TITGANZ and CA139-278 trials (20% versus 1%, RR = 20.02 (2.74 to 146.11) and 8% versus 0%, RR = 21.32 (95% CI: 1.26 to 360.12)).

Quality of life

QoL was evaluated in three studies (TITGANZ, E1193 and CA139-278; *Table 17*). There were no significant differences between paclitaxel and controls in any of these trials in terms of overall QoL, although differences were apparent on some subscales. These did not reach significance in the TITGANZ trial.

Discussion

Paclitaxel is not licensed for the first-line treatment of advanced breast cancer. Patients should have received previous first-line treatment with an anthracycline or an alkylating agent before commencing on paclitaxel. Notwithstanding this, the effectiveness of paclitaxel as a first-line treatment for advanced breast cancer was reviewed.

Single-agent paclitaxel

Of the three RCTs, none found single-agent paclitaxel superior to control in terms of response; in one trial (EORTC) significantly more women responded to doxorubicin than to paclitaxel. The median length of progression-

TABLE 16 *Other adverse events*

Adverse event	EORTC (%) (*n* = 327[32])	TITGANZ (%) RR (95% CI) (*n* = Tp: 107; CMFP: 102)	E1193 (%) RR (95% CI) (*n* = Tp: 241; ATp: 242; A: 241)	CA139-278 (%) RR (95% CI) (*n* = ATp: 131; FAC: 133)
Alopecia		Tp: 76 CMFP: 25 3.09 (2.16 to 4.41)		
Mucositis		Tp: 3 CMFP: 6 0.48 (0.12 to1.86)		
Toxic death			Tp: 1 A: 2 ATp: 1 ATp vs. A: 0.5 (0.13 to 1.97)	
Arthralgia/ myalgia	Tp: 4 A: 0	Tp: 20 CMFP: 1 20.02 (2.74 to146.11)		ATp: 8 FAC: 0 21.32 (1.26 to 360.12)

free survival was significantly longer in the doxorubicin control than in the paclitaxel arm of one trial (EORTC); no significant differences were found in the other two. Survival curves were presented for only one trial (TITGANZ); these generally showed few differences between paclitaxel and control in terms of progression-free and overall survival. However, more women in the CMFP group survived progression free at 6 months, whereas more women in the paclitaxel arm survived overall at 2 years. There were no significant differences in the median length of survival for the three trials.

Haematological side-effects were relatively frequent but gastrointestinal adverse effects were rare. Neurological adverse events were significantly more frequent in the paclitaxel group but cardiovascular adverse events were more common in anthracycline-containing regimens. Alopecia was present in the majority of patients treated with paclitaxel in one trial. Arthralgia and myalgia were significantly more common in those treated with paclitaxel. Three of the trials investigated QoL; none found a significant difference between paclitaxel and control.

The TITGANZ study was a high-quality RCT. However, insufficient details were given in the EORTC and E1193 abstracts and meeting presentations to assess their quality properly. The E1193 and EORTC trials allowed cross-over on progression and the TITGANZ trial recommended that patients who progressed should receive epirubicin. It was not clear from the available information whether the E1193 trial distinguished between early and late cross-overs and patients who did not cross over in the survival analysis; analysis was on an ITT basis. No mention was made in the TITGANZ trial concerning whether any patients did receive epirubicin and, if so, how many.

Although superficially similar, the EORTC and E1193 trials differed in terms of paclitaxel administration (200 mg/m^2 given as a 3-hour infusion compared with 175 mg/m^2 over 24 hours respectively) and in the dose of doxorubicin (75 mg/m^2 compared with 60 mg/m^2). The TITGANZ trial used a dose of 200 mg/m^2. These doses differ from the recommended dose of 175 mg/m^2 given over 3 hours for paclitaxel in advanced breast cancer. This, however, is specified for second-line treatment

Of these two trials, one (E1193) included anthracyclines in the control arm; one (TITGANZ) did not. Consequently the survival curves of the TITGANZ trial should not be generalised to the E1193 trial. Anthracyclines are the standard first-line treatment for advanced breast cancer.

Taken together, there is little evidence that single-agent paclitaxel is superior to control in terms of response, progression-free survival or overall survival in the first-line treatment of metastatic breast cancer.

Paclitaxel plus anthracycline

Two RCTs evaluated the effectiveness of paclitaxel combined with an anthracycline (E1193 and CA139-278). The response rate of paclitaxel

TABLE 17 *Quality of life*

Quality factor	TITGANZ[a]	E1193[b]	CA139-278
Overall QoL	Tp: 2.2 CMFP: –3.7 *p* = 0.07	Global FACT-B Tp: –2.9 A: –1.8 ATp: –2.8	ATp = FAC
Physical well-being	Tp: 1.9 CMFP: –4.3 *p* = 0.08		FAC greater
Mood	Tp: 4.2 CMFP: 1.1 *p* = 0.49		
Pain	Tp: –0.4 CMFP: 3.5 *p* = 0.35		FAC greater
Nausea/vomiting	Tp: –2.5 CMFP: –5.3 *p* = 0.07		ATp greater
Appetite	Tp: 1.8 CMFP: –3.6 *p* = 0.24		
QoL by physician	Tp: 1 CMFP: –2.5 *p* = 0.25		
Sexual functioning			FAC greater
Fatigue			FAC greater
Insomnia			FAC greater
Diarrhoea			FAC greater
Role			ATp = FAC
Emotional			ATp = FAC
Cognitive			ATp = FAC
Social			ATp = FAC

[a] *Difference in 16-wk (paired) Global FACT-B QoL and baseline (paired) Global FACT-B QoL*
[b] *Average changes in QoL relative to baseline*

plus doxorubicin was statistically superior to doxorubicin alone in the E1193 trial. No survival curves were presented. However, in both trials, patients in paclitaxel/anthracycline combination survived significantly longer without progression than control arms. In a comparison of single-agent and combined paclitaxel (E1193), patients treated with the latter had longer, median progression-free survivals.

Although they were both Phase III RCTs, insufficient details were given in the E1193 or CA139-278 abstracts and meeting presentations to assess their quality properly. The drug combination used in the CA139-278 trial involved a higher dose of paclitaxel than in the E1193 trial (220 mg/m^2 compared with 150 mg/m^2). The control used in the E1193 trial was single-agent doxorubicin (60 mg/m^2); the CA139-278 trial used FAC (a combination of fluorouracil, anthracycline (50 mg/m^2; type not specified) and cyclophosphamide). A larger proportion of participants in the E1193 trial had received no previous treatment.

These results suggest that paclitaxel combined with an anthracycline is more effective than either single-agent paclitaxel or doxorubicin. However, the quality of these trials is uncertain.

Summary: paclitaxel as first-line treatment for advanced breast cancer

Four RCTs were identified that investigated the first-line use of paclitaxel in breast cancer. A total of 1545 patients were included. None of the trials found single-agent paclitaxel to be superior to control in terms of median progression-free survival. However, paclitaxel combined with doxorubicin was significantly superior to controls, including single-agent doxorubicin. The median length of survival in the paclitaxel plus doxorbicin arm was 8.3 months compared with 6.2 months in the FAC control ($p = 0.034$). The median time to treatment failure was also greater for paclitaxel plus doxorubicin than for single-agent doxorubicin (8 months versus 6 months, $p = 0.003$). There were no significant differences between paclitaxel and control in terms of overall QoL.

The effectiveness of docetaxel as first-line treatment for advanced breast cancer

Description of included trial

Only one Phase III study was identified that evaluated the effectiveness of docetaxel as a first-line treatment for advanced breast cancer (TAX306; *Table 18*).[40] This was the subject of a conference abstract; no further details have been located.

This was a Phase III trial; the abstract does not state whether it was randomised. No power calculations or accurate and standard definitions of outcome variables were provided.

The TAX306 trial required participants to have undergone no previous chemotherapy for advanced disease, but adjuvant chemotherapy was permitted (*Table 19*).

This trial compared doxorubicin (50 mg/m^2) plus docetaxel (75 mg/m^2) to doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2), both regimens given in 3-week cycles (*Table 20*). Prophylactic colony-stimulating factors or antibiotics were not given unless after a prior neutropenic complication.

Details of the included participants are given in *Table 21*. These were not broken down by intervention in the abstract; the authors state there was no imbalance.

Results

Overall response rates

Participants treated with docetaxel plus doxorubicin had significantly greater overall response rates than those treated with doxorubicin plus cyclophosphamide (60% versus

TABLE 18 *Design of included trial*

Trial	Quality	Accrual dates	No. entered	ITT	No. treated	Median length of follow-up
TAX306[40]	No details available	Jun 1996 – Mar 1998	ATd: 215 AC: 214	Yes	ATd: 213 AC: 210	1 yr
ATd, doxorubicin + docetaxel; AC, doxorubicin + cyclophosphamide						

TABLE 19 *Inclusion criteria*

Trial	Disease	Previous treatment
TAX306	Metastatic breast cancer	Anthracycline naive

TABLE 20 *Intervention*

Trial	Intervention	Control
TAX306	ATd: doxorubicin (50 mg/m^2) + docetaxel (75 mg/m^2), 3-wk cycle	AC: doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2), 3-wk cycle

TABLE 21 *Participants*

Trial	Median age (yr)	PS	Secondary spread (%)	Median disease-free interval (mo)	Previous treatment (%)
TAX306	53	Median Karnofsky PS: 90	***Extent of disease*** 3 organs: 41 Visceral: 63 Bone: 52	25	Adjuvant chemotherapy: 42

47%, $p = 0.008$ (from abstract)). Complete responses occurred in 11% of the docetaxel plus doxorubicin and 8% of the doxorubicin plus cyclophosphamide groups. Progressive disease was found in 8% of the docetaxel plus doxorubicin and 18% of the doxorubicin plus cyclophosphamide groups.

Progression-free survival

No details were given in the abstract concerning progression-free survival rates.

Overall survival

No details were given in the abstract of overall survival rates.

Compliance

Fifteen per cent of the docetaxel plus doxorubicin and 14% of the doxorubicin plus cyclophosphamide groups discontinued treatment because of toxicity. The median numbers of cycles received were eight and seven respectively.

Adverse events

Only grade 3–4 toxicities are reported here.

Haematological adverse events

Neutropenia was common in both arms of the trial (*Table 22*).

TABLE 22 *Haematological adverse events*

	TAX306 (%) (*n* = ATd: 215; AC: 214)
Neutropenia	ATd: 82 AC: 69
Febrile neutropenia	ATd: 6 AC: 2
Infection	ATd: 1 AC: < 1

Gastrointestinal adverse events

Gastrointestinal events were rare (*Table 23*).

TABLE 23 *Gastrointestinal adverse events*

	TAX306 (%) (*n* = ATd: 215; AC: 214)
Diarrhoea	ATd: 2 AC: < 1

Neurological adverse events

There were no neurosensory adverse events in either arm of the trial.

Cardiovascular adverse events

Clinical heart failure was found in 2% of the docetaxel plus doxorubicin group and in 4% of the doxorubicin plus cyclophosphamide group. There was a decrease of 30 points from baseline in the left ventricular ejection fraction in 2% of the docetaxel plus doxorubicin group and in 5% of the doxorubicin plus cyclophosphamide group.

Other adverse events

Severe oedema was reported in 1% of participants in the docetaxel plus doxorubicin group; overall, oedema was reported in 31% of this group. There was one toxic death in the docetaxel plus doxorubicin group compared with three in the doxorubicin plus cyclophosphamide group.

Quality of life

QoL was not assessed.

Discussion

Only one Phase III trial was found that evaluated the effectiveness of docetaxel as first-line treatment for metastatic breast cancer. This was available only as a conference abstract, so details are scant. It is not stated whether this was in fact an RCT. Consequently, the findings should be treated with extreme caution. In addition, it appears to be an early report (median follow-up of 1 year) and no survival figures are given.

There does appear to be a significantly greater response rate among participants treated with

docetaxel plus doxorubicin. However, there is no information regarding long-term outcomes such as progression-free or overall survival.

Summary: docetaxel as first-line treatment for advanced breast cancer

A single Phase III trial evaluated the effectiveness of docetaxel as first-line treatment for breast cancer. This was available only as a conference abstract and it is not clear whether the trial was randomised. No long-term results were available.

The effectiveness of paclitaxel as second-line treatment for advanced breast cancer

Description of included trial

Only two reports were identified that evaluated the effectiveness of paclitaxel as a second-line treatment for advanced breast cancer. These both relate to the same trial, CA139-047 (*Table 24*). One is a report submitted by the manufacturer,[41] the second is a journal article.[42]

This was a randomised, controlled Phase II trial. Power calculations and accurate and standard definitions of outcome variables were provided. Patients were permitted to cross over to the alternate arm on disease progression; more than half the patients in the mitomycin arm crossed over compared with none in the paclitaxel arm. Such patients should be censored from further analyses (see above).

The CA139-047 trial required participants to have undergone previous chemotherapy for advanced disease, either one cycle of chemotherapy for metastatic disease or two cycles, if one was adjuvant chemotherapy (*Table 25*). The permissible cytotoxic drugs were not specified.

The trial compared paclitaxel (175 mg/m^2) administered as a 3-hour infusion in a 3-week cycle to mitomycin (12 mg/m^2) given as a slow bolus injection in a 6-week cycle (*Table 26*).

Details of the included participants are given in *Table 27*.

Overall response rates

None of the patients in the CA139-047 trial showed a complete response; consequently,

TABLE 24 *Design of included trial*

Trial: source	Quality	Design	Accrual dates	No. randomised	ITT	No. evaluable	No. crossing over	Median length of follow-up	No. participants surviving (%)
CA139-047: trial report;[41] journal article[42]	IA	Randomised Open label Non-blinded	Apr 1992 – Dec 1993	Tp: 41 M: 40	Unclear	72 evaluable	Tp → M: 0 M → Tp: 22	Not stated	55 (68)

M, mitomycin

TABLE 25 *Inclusion criteria*

Trial	Disease	Previous treatment
CA139-047	Histologically proven breast cancer Metastatic progression Measurable tumour site WHO PS 0–2	Prior treatment with one (metastatic) or two (adjuvant and metastatic disease) regimens of chemotherapy before study entry

TABLE 26 *Intervention*

Trial	Intervention	Control
CA139-047	Tp: paclitaxel (175 mg/m^2) 3-h infusion 3-wk cycle	M: mitomycin (12 mg/m^2) Slow bolus injection 6-wk cycle

TABLE 27 *Participants*

Trial	Median age (yr)	ER status (%)	PS (%)	Secondary spread (%)	Median disease-free interval (mo)	Previous treatment (%)
CA139-047	Tp: 52; M: 52.5	***Positive*** Tp: 54; M: 48	***ECOG 0*** Tp: 39; M: 45 ***ECOG 1*** Tp: 51; M: 40 ***ECOG 2*** Tp: 10; M:15	***Extent of disease*** Soft tissue: Tp: 51; M: 48 Bone: Tp: 56; M: 43 Liver: Tp: 59; M: 60 Lung Tp: 34; M: 45 ***Dominant site of disease*** Soft tissue only: Tp: 7; M: 0 Bone ±soft tissue: Tp: 12; M: 5 Visceral ± bone ± soft tissue: Tp: 80; M: 95	***Median time from diagnosis*** Tp: 48.2; M: 53.5	***Prior chemotherapy*** Metastatic only: Tp: 49; M: 48 Metastatic + adjuvant: Tp: 51; M: 53 Anthracycline: Tp: 98; M: 98 Vinca alkaloid: Tp: 24; M: 38

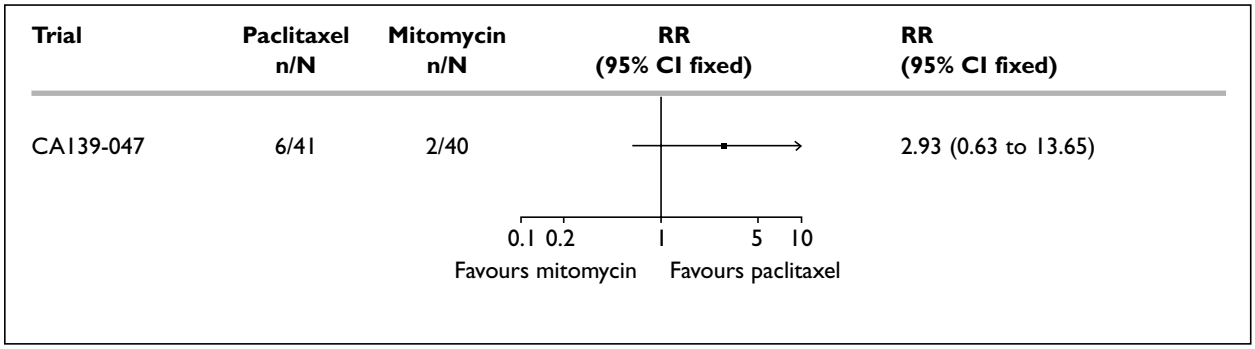

FIGURE 5 *Paclitaxel as second-line treatment for breast cancer: overall response rate*

overall response was based on partial response only (*Figure 5*). Although more patients in the paclitaxel arm responded, the difference between arms was not statistically significant (RR = 2.93 (95% CI: 0.63 to 13.65)).

Progression-free survival (Table 28)

The scales on the Kaplan–Meier curves presented do not allow estimates of progression-free survival at given points. Patients in the paclitaxel arm, compared with those receiving mitomycin, had a significantly longer duration of disease control (3.5 months (95% CI: 1.8 to 5.0) versus 1.6 months (95% CI: 1.5 to 2.8), $p = 0.026$). The duration of disease control in patients who crossed over from mitomycin to paclitaxel was 2.2 months (95% CI: 1.7 to 3.5).

Overall survival

The median length of survival in the paclitaxel arm was also longer than that in the mitomycin arm (12.7 months versus 8.4 months). The authors state that most of the patients were alive at the time of analysis[42] and comment that the cross-over design could mask the impact of paclitaxel on survival.

Compliance

Twenty-two patients crossed over from the mitomycin to the paclitaxel arm. Five discontinued therapy because of adverse reactions.

Adverse events

Adverse events were reported for about half the participants. Only grades 3–4 toxicities are reported here.

Haematological adverse events (Table 29)

More than 60% of the patients in the paclitaxel arm suffered neutropenia, compared with 3% in the mitomycin arm (RR = 23.61, (95% CI: 3.35 to 166.19)). Anaemia and leucopenia

TABLE 28 *Median survival times*

Trial	Median duration of disease control (mo)	Median length of survival (mo)
CA139-047	Tp: 3.5 (95% CI: 1.8 to 5.0)[a] M: 1.6 (95% CI: 1.5 to 2.8) p[b] = 0.026	Tp: 12.7 M: 8.4 p[b] = 0.15
CA139-047 cross-over	M → Tp: 2.2 (95% CI: 1.7 to 3.5)	

[a] *CIs calculated using Brookmeyer and Crowley method*
[b] *logrank test*

TABLE 29 *Haematological adverse events*

Adverse event	CA139-047 (%) RR (95% CI) (*n* = Tp: 38; M: 39)
Neutropenia	Tp: 61 M: 3 23.61 (3.35 to 166.19)
Febrile neutropenia	Tp: 3 M: 0 3.08 (0.13 to 73.26)
Infection	Tp: 3 M: 0 3.08 (0.13 to 73.26)
Thrombocytopenia	Tp: 3 M: 20 0.13 (0.02 to 0.98)
Leucopenia	Tp: 21 M: 5 4.11 (0.93 to 18.10)
Anaemia	Tp: 27 M: 8 2.05 (0.55 to 7.62)

TABLE 30 *Gastrointestinal adverse events*

Adverse event	CA139-047 (%) (*n* = Tp: 38; M: 39)
Nausea/vomiting	Tp: 3 M: –

TABLE 31 *Neurological adverse events*

Adverse event	CA139-047 (%) (*n* = Tp: 38; M: 39)
Peripheral neuropathy	Tp: 4 M: –

occurred in 27% and 21% of patients in the paclitaxel arm respectively. There was no significant difference between the arms in either case.

Gastrointestinal adverse events

Gastrointestinal events were rare. Nausea and vomiting occurred in only 3% of the paclitaxel group (*Table 30*).

Neurological adverse events

Peripheral neuropathy was reported in 4% of patients in the paclitaxel arm (*Table 31*).

Cardiovascular adverse events

No cardiovascular adverse events were reported.

Other adverse events

Arthralgia/myalgia occurred in 11% of the patients treated with paclitaxel; this was not significantly different from the incidence among patients receiving mitomycin (*Table 32*).

Quality of life

QoL was not assessed.

TABLE 32 *Other adverse events*

Adverse event	CA139-047 (%) RR (95% CI) (*n* = Tp: 38; M: 39)
Mucositis	Tp: 1 M: – 3.08 (0.13 to 73.26)
Arthralgia/myalgia	Tp: 11 M: 5 1.54 (0.27 to 8.71)
Anorexia	Tp: 0 M: 5 0.21 (0.01 to 4.14)
Hospitalisation	Tp: 16 M: 23 0.68 (0.27 to 1.74)

Discussion

Only one RCT was found that evaluated the effectiveness of paclitaxel as a second-line treatment for metastatic breast cancer. Only two patients in the mitomycin control arm responded; most crossed over to the paclitaxel arm. Because this was an open-label trial, a variety of factors may have influenced the patients' decision to cross from mitocycin to paclitaxel treatment. Those treated with paclitaxel had a significantly greater duration of disease control than those in the control arm.

Haematological side-effects were relatively frequent but gastrointestinal adverse effects were rare. Peripheral neuropathy was significantly more frequent in the paclitaxel group.

The sample size was small, although it was based on power calculations. However, more than half the patients in the mitomycin arm crossed over to paclitaxel on treatment failure. This is, in effect, a violation of randomisation and such patients should be censored from analyses. Consequently, long-term results such as survival cannot be compared because most participants received paclitaxel.

Summary: paclitaxel as second-line treatment for advanced breast cancer

A single, small Phase II trial evaluated the effectiveness of paclitaxel as a second-line treatment for breast cancer. Only two patients in the mitomycin control arm responded; more than half the mitomycin arm crossed over to the paclitaxel arm. This trial provides very weak evidence that paclitaxel is an effective second-line treatment for metastatic breast cancer.

The effectiveness of docetaxel as second-line treatment for advanced breast cancer

Description of included trials

Thirteen publications were identified that evaluated the effectiveness of docetaxel as a second-line treatment for advanced breast cancer. These all pertained to four randomised controlled Phase III trials: 303 Study,[43–47] 304 Study,[48–52] Bonneterre[53] and Scand[54] (*Table 33*). With the exception of the Bonneterre trial, for which only a meeting abstract is available, these studies have been published in journals.

All four were randomised, controlled Phase III trials. The 303 Study, 304 Study and Scand trial had power calculations and accurate and standard definitions of outcome variables; no details were given in the Bonneterre abstract. About two-thirds of the participants in the 303 Study, the 304 Study and the Scand trial had died; consequently, the data were adequately mature for reliable analysis. The Bonneterre abstract contained preliminary results only and stated that accrual was ongoing. The literature searches did not identify any further articles dealing with this trial. The Scand study allowed cross-over to alternate treatment on progression. Response rate, time to progression, time to treatment failure, and survival on an ITT principle (including all randomised patients) were analysed in both the 303 Study and the 304 Study. The Scand study excluded one randomised patient from the "ITT" analyses of response, time to progression and overall survival. No such details were given in the Bonneterre abstract.

All the included trials required participants to have undergone previous chemotherapy (*Table 34*). Three trials – 304 Study, Scand and Bonneterre – specified that anthracycline should have been given; the 303 Study specifically excluded anthracycline therapy but specified previous alkylating agent chemotherapy. All but the Bonneterre study specifically excluded previous taxane therapy.

All of the trials had docetaxel (100 mg/m^2) given as a 1-hour infusion as the experimental condition; the control conditions were all different (*Table 35*). The 303, 304 and Scand studies included premedication of the docetaxel group; this was not mentioned in the Bonneterre abstract. The 303 and 304 Studies allowed prophylactic antiemetic premedication; this was not given in the Scand trial. The 303 Study, the 304 Study and the Scand trial did not allow the prophylactic administration of colony-stimulating factors. No details were given in the Bonneterre abstract.

The differences in the inclusion criteria influenced the patient mix of these trials. Consequently, the patients involved in the 303 Study were resistant to alkylating chemotherapy, whereas those in the other trials were resistant to anthracyclines. Participants in the 304 Study were more likely to have received both adjuvant and advanced chemotherapy than those in the Scand study.

The differences between the studies made pooling inappropriate (*Table 36*). It was not possible to assess the quality of the Bonneterre study and

TABLE 33 *Design of included trials*

Trial: source	Quality	Design	Accrual dates	No. randomised	ITT	No. evaluated	Criteria for cross-over	No. crossing over	Median length of follow-up	No. participants surviving (%)
303 Study: journal articles[43–47]	IA	Randomised Power calculations Outcomes defined Multicentre Non-blinded	July 1994 – Jan 1997	Td: 161 A: 165	All randomised patients	Assessable: met inclusion criteria; no on-study deviation; received at least 2 cycles of treatment; at least 1 complete tumour assessment after baseline Td: 148 A: 147	No cross-over	Patients withdrawn before progression not to receive other anti-tumour therapy until progression documented, unless considered necessary by investigator	23	Td: 59 (37) A: 27 (16)
304 Study: journal articles[48–52]	IA	Randomised Power calculations Outcomes defined Multicentre Non-blinded	July 1994 – Feb 1997	Td: 203 MV: 189	All randomised patients	Assessable: met inclusion criteria; no on-study deviation; received at least 2 cycles of treatment; at least 1 complete tumour assessment after baseline D: 179 MV: 171	No cross-over	Patients withdrawn before progression not to receive other anti-tumour therapy until progression documented, unless considered necessary by investigator	19	Td: 66 (33) MV: 51 (27)
Scand: journal article[54]	IA	Randomised Power calculations Outcomes defined Multicentre Open label	Dec 1994 – Oct 1997	Td: 143 MtF: 140[a]	All randomised patients except one	Eligible: met all inclusion criteria receiving ≥ 1 cycle Td: 136 MtF: 131	Crossover recommended if objective signs of disease progression	Td → MtF: 48 MtF → D: 74	11	99 (35%)
Bonneterre: meeting abstract[53]	I	Randomised Multicentre Open label	Ongoing?	Td: 46 FUN: 45	Td: 46 FUN: 45				No details	No details

[a] *1 patient excluded from effectiveness analysis because of misclassification at enrolment*

Td, docetaxel; A, anthracycline (doxorubicin); MV, mitomycin + vinblastine; FUN, fluorouracil + navelbine; MtF, methotrexate + fluorouracil

TABLE 34 *Comparison of inclusion criteria*

Trial	Disease	Previous treatment
303 Study	Histologically or cytologically confirmed metastatic breast cancer Measurable or evaluable disease Karnofsky PS > 60	Previous alkylating agent chemotherapy (e.g. CMF), either adjuvant or for advanced disease No more than one previous line of chemotherapy for metastatic disease No previous treatment with anthracyclines, anthracenes or taxoids
304 Study	Histologically or cytologically confirmed metastatic breast cancer Measurable or evaluable disease Karnofsky PS > 60	Previous anthracycline chemotherapy for advanced disease or relapse within last 12 mo of anthracycline adjuvant therapy No more than one previous line of chemotherapy for metastatic disease No previous treatment with mitomycin, vinca alkaloids or taxoids
Scand	Histologically proven primary breast cancer Measurable or evaluable lesions WHO PS 0–2	Previous anthracycline chemotherapy for advanced disease or relapse within last 12 mo of anthracycline adjuvant therapy No more than one previous line of chemotherapy for metastatic disease No previous treatment with taxanes
Bonneterre	Metastatic breast cancer	Prior anthracycline chemotherapy

CMF, cyclophosphamide, methotrexate, fluorouracil

TABLE 35 *Comparison of interventions*

Trial	Intervention	Comparison	Cross-over
303 Study	Td: docetaxel (100 mg/m^2), 1-h infusion, up to 7 x 3-wk cycles Premedication: oral dexamethasone 2 x 8 mg for 5 d Usual antiemetic premedication No prophylactic G-CSF	A: doxorubicin (75 mg/m^2), up to 7 x 3-wk cycles Usual antiemetic premedication No prophylactic G-CSF	None
304 Study	Td: docetaxel (100 mg/m^2), 1-h infusion, up to 10 x 3-wk cycles Premedication: oral dexamethasone 2 x 8 mg for 5 d Usual antiemetic premedication No prophylactic G-CSF	MV: mitomycin (12 mg/m^2) + vinblastine (6 mg/m^2), bolus injection M: 42-d cycle,V: 21-d cycle, up to 10 cycles Usual antiemetic premedication No prophylactic G-CSF	None
Scand	Td: docetaxel (100 mg/m^2), 1-h infusion, at least 6 x 3-wk cycles Premedication: oral dexamethasone or betamethasone 2 x 8 mg for 5 d No prophylactic antiemetics No prophylactic G-CSF	MtF: methotrexate (200 mg/m^2) + fluorouracil (600 mg/m^2), at least 6 cycles, d 1 and 8 of 3-wk cycle Urinary alkalisation ($NaHCO_3$) Leucovorin 4 x 15 mg for 2 d No prophylactic antiemetics No prophylactic G-CSF	On progression if appropriate
Bonneterre	Td: docetaxel (100 mg/m^2), 3-wk cycles	FUN: fluorouracil (750 mg/m^2) + navelbine (25 mg/m^2)	

TABLE 36 *Comparison of participants*

Trial: source	Median age (yr)	ER status (%)	PS	Secondary spread (%): dominant site of disease	No. metastatic sites (%)	Median disease-free interval (mo)	Previous treatment (%)
303 Study	Td: 52; A: 52		***Median Karnofsky*** Td: 90; A: 90	***Soft tissue only*** Td: 9; A: 12 ***Bone*** Td: 55; A: 63 ***Viscera*** Td: 75; A: 76 ***Liver*** Td: 43; A: 40	***1 site*** Td: 22; A: 19 ***2 sites*** Td: 34; A: 38 ***≥ 3 organs*** Td: 44; A: 43	***Time from first diagnosis to first relapse*** Td: 27; A: 25	***Adjuvant only*** Td: 51; A: 42 ***Advanced disease only*** Td: 43; A: 49 ***Resistance to last chemotherapy*** Primary: Td: 10; A: 14 Secondary: Td: 37; A: 36 Not resistant: Td: 53; A: 50
304 Study	Td: 51; MV: 52		***Median Karnofsky*** Td: 90; MV: 90	***Soft tissue only*** Td: 8; MV: 10 ***Bone*** Td: 57; MV: 65 ***Viscera*** Td: 75; MV: 73 ***Liver*** Td: 50 MV: 47	***1 site*** Td: 23; MV: 21 ***2 sites*** Td: 37; MV: 27 ***≥ 3 sites*** Td: 39; MV: 52	***Time from first diagnosis to first relapse*** Td: 18; MV: 18	***Adjuvant only*** Td: 17; MV: 21 ***Advanced only*** Td: 49; MV: 50 ***Resistance to last chemotherapy*** Primary: Td: 23; MV: 21 Secondary: Td: 34; MV: 34 Not resistant: Td: 43; MV: 44
Scand	Td: 50; MtF: 51	***Positive*** Td: 35; MtF: 31	***WHO 0 (%)*** Td: 32; MtF: 27 ***WHO 1 (%)*** Td: 57; MtF: 57 ***WHO 2 (%)*** Td: 12; MtF: 16	***Visceral*** Td: 73; MtF: 69 ***Liver*** Td: 51; MtF: 41 ***Bone*** Td: 46; MtF: 39 ***Soft tissue*** Td: 48; MtF: 50	***1 organ*** Td: 35; MtF: 38 ***2+ organs*** Td: 40; MtF: 33	***Median disease-free interval*** Td: 18.7; MtF: 16.9	***Adjuvant only*** Td: 17; MtF: 12 ***Advanced only*** Td: 82; MtF: 86 ***Both*** Td: 1; MtF: 1 ***None*** MtF: 1
Bonneterre	54.3		***Median*** 1 (scale not stated)	***Liver*** 70 ***Bone*** 45 ***Lung*** 25 ***Skin and soft tissue*** 20	***1 site*** 30 ***2 sites*** 31 ***≥ 3 sites*** 37	***Median time from diagnosis*** 35	

preliminary results only were presented. Although the trials all investigated the same experimental intervention, different controls were used. The 303 Study included patients who had not been previously treated with anthracyclines; patients in the other studies had deteriorated since anthracycline treatment.

Synthesis

Overall response

The median time to response was presented only for the 303 Study (*Table 37*). Patients in the docetaxel arm responded significantly more quickly than those in the doxorubicin arm ($p = 0.007$). There was no statistical analysis of the duration of response for the Bonneterre trial.

Overall response rates (complete response plus partial response) were presented for all four trials: 303 Study, 304 Study, Bonneterre and Scand (*Figure 6*). The response to docetaxel ranged from 30% (304 Study) to 54% (Bonneterre). The response rate of docetaxel was superior to doxorubicin (48% versus 33%, RR = 1.43 (95% CI: 1.10 to 1.88), NNT = 7), to mitomycin plus vinblastine (30% versus 12%, RR = 2.58 (95% CI: 1.65 to 4.03), NNT = 5) and to methotrexate plus fluorouracil (43% versus 21%, RR = 2.04 (95% CI: 1.40 to 2.98), NNT = 5). The preliminary results of the Bonneterre study showed no significant difference between the conditions.

Progression-free survival

Kaplan–Meier curves were presented for three of the trials: 303 Study, 304 Study and the Scand trial. The median time to progression reported in the 304 Study was significantly longer for the docetaxel arm than the mitomycin plus vinblastine arm (19 weeks versus 11 weeks; $p = 0.001$). In addition, the median time to progression was longer for docetaxel than methotrexate plus fluorourocil in the Scand study (25.2 weeks versus 12 weeks, $p = 0.001$). The time to progression was similar for the docetaxel and doxorubicin arms of the 303 Study (26 weeks versus 21 weeks, $p = 0.45$). The Bonneterre study reported a time to disease progression of 28 weeks for docetaxel and 20 weeks for fluorouracil and navelbine; no statistics were given.

Figure 7 illustrates the estimates of progression-free survival rates at 24-weekly intervals obtained from these analyses. The 1-year estimate for the Scand trial has been entered at 48 weeks. These estimates have been extrapolated from the Kaplan–Meier curves. These allow the generation of RR point estimates but not their CIs.

At 2 and 3 years, in the Scand trial, none of the docetaxal group was progression free, compared with two patients in the methotrexate plus fluorouracil group.

Overall survival (Figure 8)

Kaplan–Meier curves were presented for three of the trials: 303 Study, 304 Study and Scand.

The median survival for patients in the docetaxel arm of the 304 Study was significantly longer than for those in the mitomycin plus vinblastine arm (11.4 months versus 8.7 months, $p = 0.01$). There was no difference between the arms in the 303 Study (docetaxel 15 months, doxorubicin 14 months, $p = 0.39$). Patients in the docetaxel

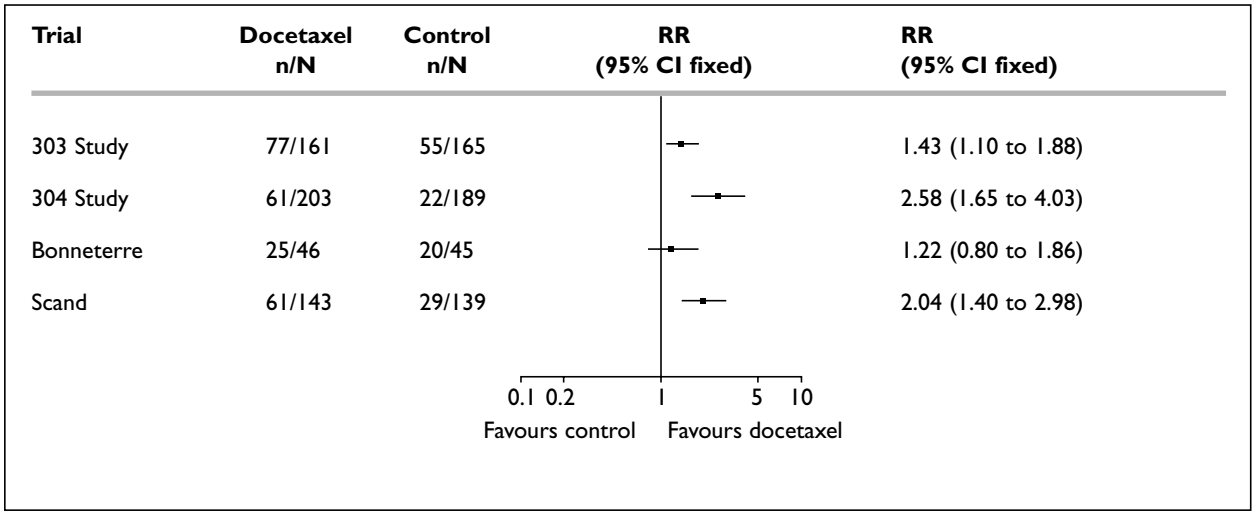

FIGURE 6 *Docetaxel as second-line treatment for breast cancer: overall response rates*

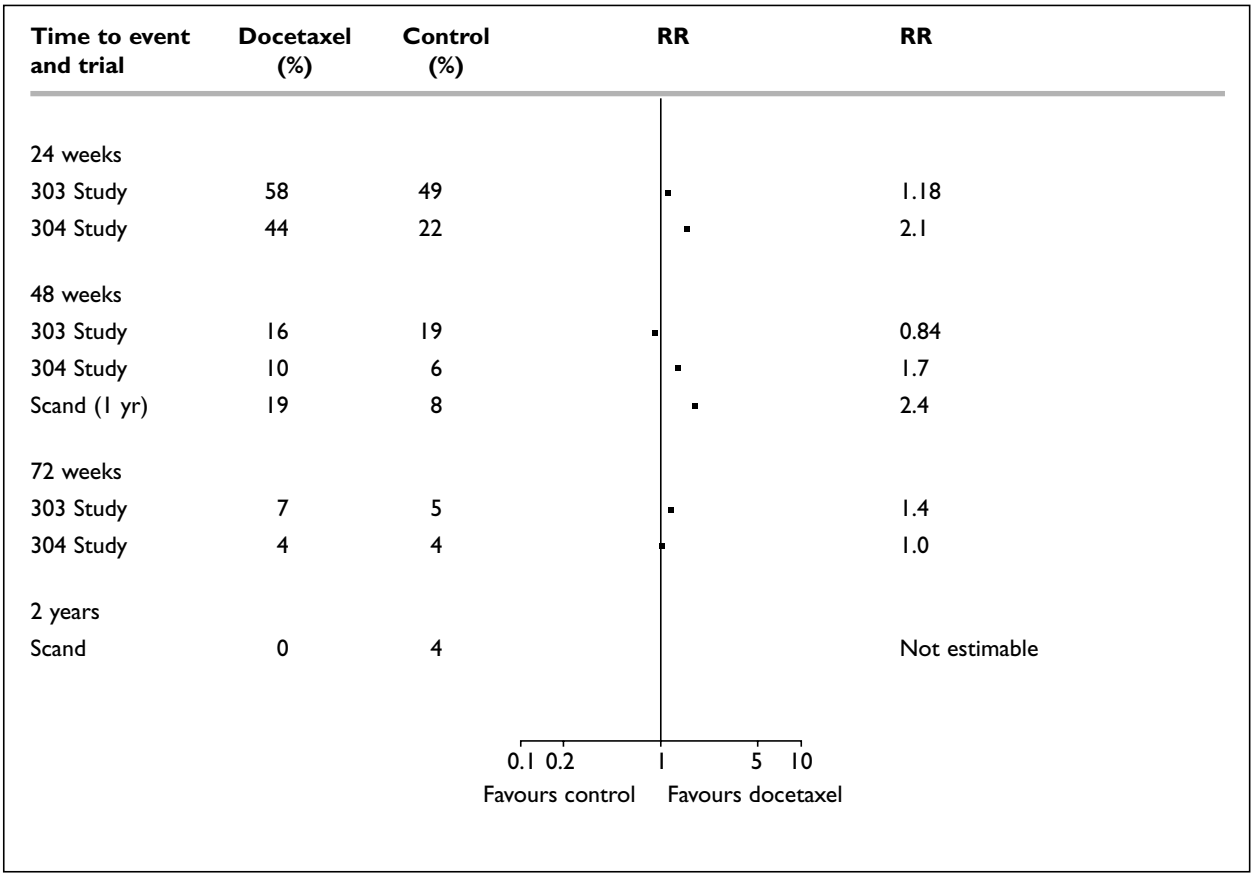

FIGURE 7 *Docetaxel as second-line treatment for breast cancer: progression-free survival*

and methotrexate plus fluorouracil arms of the Scand trial survived for similar times (10.4 months and 11 months respectively); however, most of the latter crossed over to docetaxel on disease progression.

Figure 8 shows the estimates of overall survival, which are extrapolated from Kaplan–Meier curves. These allow the generation of RR point estimates but not their CIs. It is important to note that many of the patients in the Scand trial had crossed over to alternative treatment.

Compliance (*Table 38*)

The numbers of patients completing all cycles specified by the protocol were given for the 303 and 304 Studies. Few completed all cycles; the median number of cycles of docetaxel completed across all trials was six. This was generally slightly more than in the control group. In the Scand trial, 14 patients continued with treatment but there are no details about which group they belonged to or whether they had crossed over. None of the studies was blinded so there may have been different pressures to continue with treatment or cross-over, depending on the treatment arm.

Adverse events

The reports were not consistent in the way that adverse events were reported. The percentages of patients experiencing grade 3–4 toxicities for each trial are given here.

Haematological adverse events

The proportion of participants experiencing neutropenia in the docetaxel arms of the trials ranged from 78% to 94% (*Table 39*). The 303, 304 and Scand studies did not allow the prophylactic administration of colony-stimulating factors.

Significantly more patients in the docetaxel arm (93%) than in the mitomycin plus vinblastine arm (62%) of the 304 Study suffered from neutropenia (RR = 1.49 (95% CI: 1.32 to 1.67)). Less than 10% of patients in the docetaxel arms experienced febrile neutropenia (range 6–9%). This was significantly more prevalent in the doxorubicin arm of the 303 Study (RR = 0.46 (95% CI: 0.22 to 0.98)), but significantly less so in the mitomycin plus vinblastine arm of the 304 Study (RR = 16.8, (95% CI: 2.27 to 124.83)). A greater proportion of patients suffered serious infections in the docetaxel

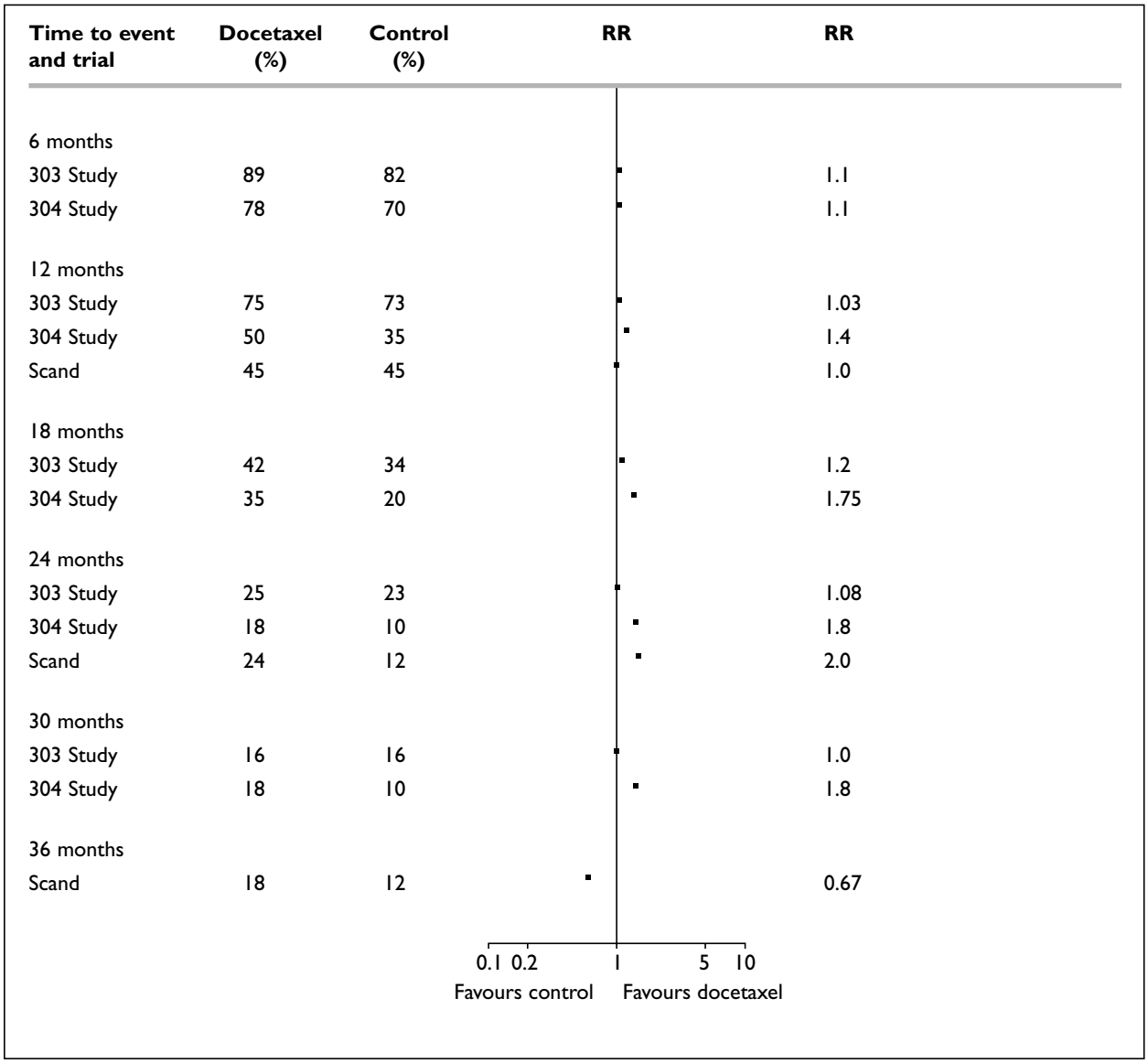

FIGURE 8 *Docetaxel as second-line treatment for breast cancer: overall survival*

arms of the 304 Study and the Scand trial compared with controls (RR = 10.3 (95% CI: 2.45 to 43.14) and RR = 4.5 (95% CI: 2.17 to 9.33)) respectively. Thrombocytopenia was rare in the docetaxel group (range 1–4%) and significantly less frequent than controls in the 303 and 304 Studies (RR = 0.17 (95% CI: 0.04 to 0.75) and RR = 0.34 (95% CI: 0.16 to 0.74) respectively). Leucopenia was reported in the Scand trial only; more than three-quarters of the participants in the docetaxel arm were affected, significantly more than in the methotrexate plus fluorouracil arm (RR = 2.73 (95% CI: 1.76 to 4.24)).

Gastrointestinal adverse events

Gastrointestinal events were relatively rare in the docetaxel arm: nausea (range 3.1–6.0%), vomiting (range 2.5–3.1%); stomatitis (range 5–9%); diarrhoea (range 7.5–10.7%); and constipation (0.5%). With the exception of diarrhoea, these were more frequent in the doxorubicin arm of the 303 Study (*Table 40*). Prophylactic antiemetics were allowed in the 303 and 304 Studies but not in the Scand trial.

Neurological adverse events

Five per cent of the patients in the docetaxel arms of these studies suffered from neurosensory or neuromotor adverse events or from peripheral neuropathy. Such events were significantly less likely to occur in the control groups but the CIs are very wide (*Table 41*).

Cardiovascular adverse events

None of the patients in the docetaxel arms reported cardiological adverse events (*Table 42*).

TABLE 37 *Median survival times in second-line treatment for breast cancer*

Trial	Median time to response (wk)	Median duration of response (mo)	Median time to treatment failure (wk)	Median time to progression	Median length of survival (mo)
303 Study	Td: 12 A: 23 p^a = 0.007		Td: 22 A: 18 p^b = 0.10 p^c = 0.01	Td: 26 wk A: 21 wk p^b = 0.45 p^c = 0.09	Td: 15 A: 14 p^b = 0.39 p^c = 0.41
304 Study			Td: 16 MV: 10 p^b = 0.0003 p^c = 0.0002	Td: 19 wk MV: 11 wk p^b = 0.001 p^c = 0.0001	Td: 11.4 MV: 8.7 p^b = 0.01 p^c = 0.03
Scand				Td: 6.3 mo MtF: 3 mo p^b = 0.001	Td: 10.4 MtF: 11
Bonneterre		Td: 8 FUN: 6		Td: 7 mo FUN: 5 mo	

[a] *Chi squared*
[b] *logrank test*
[c] *Wilcoxon test*

TABLE 38 *Treatment received*

Trial	Completing all cycles (%)	Median no. cycles (range)	Reasons for early discontinuation (%)					
			Disease progression	Adverse events	Withdrew consent	Death	Protocol violation	Other
303 Study	Td: 46 A: 34 p = 0.027	Td: 7 (1–11) A: 6 (1–7)	Td: 30 A: 36	Td: 12 A: 16	Td: 3 A: 7	Td: 3 A: 2	Td: 1 A: 1	Td: 5 A: 4
304 Study	Td: 12 MV: 7	Td: 6 (1–12) MV: 4 (1–12)	Td: 51 MV: 65	Td: 14 MV: 10	Td: 9 MV: 6	Td: 5 MV: 4	Td: 1 MV < 1	Td: 7 MV: 6
Scand		Td: 6 (1–20) MtF: 4 (1–19)	Td: 49 MtF: 80	Td: 21 MtF: 3	Td: 9 MtF: 3	Td: 6 MtF: 4	Td: 1 MtF < 1	Td: 7 MtF: 4
Bonneterre		Td: 6 (1–11) FUN: 4 (1–9)						

More patients in the doxorubicin arm of the 303 Study discontinued treatment because of cardiac toxicity than in the docetaxel arm (RR = 0.03 (95% CI: 0.00 to 0.55)).

Other adverse events

Most other adverse effects were rare (*Table 43*). However, the majority of patients suffered alopecia (74–91% of patients in the docetaxel arms) and the incidence of asthenia ranged from 12% to 16%. Significantly more asthenia was found among patients treated with docetaxel than with mitomycin plus vinblastine or with methotrexate plus fluorouracil (RR = 2.49 (95% CI: 1.32 to 4.69) and RR = 5.67 (95% CI: 1.70 to 18.91) respectively).

There was a higher incidence of severe fluid retention in the docetaxel compared with the mitomycin plus vinblastine arm of the 304 Study, but the CIs are very wide.

TABLE 39 *Haematological adverse events*

Adverse event	**303 Study (%) RR (95% CI) (*n* = Td: 159; A: 163)**	**304 Study (%) RR (95% CI) (*n* = Td: 200; MV: 187)**	**Scand (%) RR (95% CI) (*n* = Td: 134; MtF: 135)**	**Bonneterre (%) RR (95% CI) (*n* = Td: 46;FUN: 45)**
Neutropenia	Td: 94 A: 89 1.05 (0.98 to 1.13)	Td: 93 MV: 62 1.49 (1.32 to 1.67)		Td: 78 FUN: 65 1.21 (0.93 to 1.58)
Febrile neutropenia	Td: 6 A: 12 0.46 (0.22 to 0.98)	Td: 9 MV: < 1 16.8 (2.27 to 124.83)		Td: 9 FUN: 9 1.37 (0.68 to 2.76)
Infections	Td: 2.5 A: 4.3 0.59 (0.17 to 1.96)	Td: 11 MV: 1 10.3 (2.45 to 43.14)	Td: 26 MtF: 3 4.50 (2.17 to 9.33)	
Thrombocytopenia	Td: 1.3 A: 7.5 0.17 (0.04 to 0.75)	Td: 4.1 MV: 12.0 0.34 (0.16 to 0.74)	Td: 3 MtF: 6 0.50 (0.16 to 1.63)	
Leucopenia			Td: 77 MtF: 16 2.73 (1.76 to 4.24)	
Anaemia			Td: 2 MtF: 2 1.01 (0.21 to 4.90)	

TABLE 40 *Gastrointestinal adverse events*

Adverse event	**303 Study (%) RR (95% CI) (*n* = Td: 159; A: 163)**	**304 Study (%) RR (95% CI) (*n* = Td: 200; MV: 187)**	**Scand (%) RR (95% CI) (*n* = Td: 134; MtF: 135)**
Nausea	Td: 3.1 A: 14.1 0.22 (0.09 to 0.57)	Td: 4.5 MV: 2.1 2.1 (0.66 to 6.72)	Td: 6.0 MtF: 11 0.51 (0.23 to 1.17)
Vomiting	Td: 3.1 A: 12.3 0.26 (0.10 to 0.67)	Td: 2.5 MV: 2.7 0.94 (0.28 to 3.18)	
Stomatitis	Td: 5 A: 12.3 0.41 (0.19 to 0.90)	Td: 9.0 MV: 0.5 16.8 (2.27 to 124.8)	Td: 9 MtF: 5 1.71 (0.70 to 4.23)
Diarrhoea	Td: 10.7 A: 1.2 8.71 (2.05 to 37.1)	Td: 7.5 MV: 0 29.0 (1.7 to 481.2)	Td: 10 MtF: 10 1.0 (0.5 to 2.02)
Constipation		Td: 0.5 MV: 3.2 0.16 (0.02 to 1.28)	

Quality of life

QoL was reported only in the 303 and 304 Studies. Mean changes in QoL scores from baseline were calculated (*Table 44*) but the data were presented only graphically. The global health status was not different between the arms in either study.

TABLE 41 *Neurological adverse events*

Adverse event	303 Study (%) RR (95% CI) (*n* = Td: 159; A: 163)	304 Study (%) RR (95% CI) (*n* = Td: 200; MV: 187)	Scand (%) RR (95% CI) (*n* = Td: 134; MtF: 135)
Neurosensory	Td: 5.0 A: 0 17.43 (1.01 to 299.4)	Td: 5.0 MV: 0.5 9.53 (1.21 to 72.34)	
Neuromotor	Td: 5.0 A: 0 17.43 (1.01 to 299.4)		
Peripheral neuropathy			Td: 5 MtF: 1 7.0 (0.87 to 56.15)

TABLE 42 *Cardiovascular adverse events*

Adverse event	303 Study (%) RR (95% CI) (*n* = Td: 159; A: 163)	304 Study (%) RR (95% CI) (*n* = Td: 200; MV: 187)
Pulmonary toxicity		Td: 0 MV: 5 0.45 (0.12 to 1.76)
Congestive heart failure	Td: 0 A: 3.7 0.08 (0.00 to 1.39)	
Cardiac death	Td: 0 A: 1.8 0.15 (0.01 to 2.81)	
Discontinued because of cardiac toxicity	Td: 0 A: 9.2 0.03 (0.00 to 0.55)	

Discussion

Of the four RCTs, three (303 Study, 304 Study and the Scand trial) showed docetaxel to be superior to control in terms of response. Survival curves were available for the same three trials. The median length of progression-free survival was significantly greater for docetaxel than mitomycin plus vinblastine (304 Study) and methotrexate plus fluorouracil (Scand). Patients in the docetaxel arm of the 304 Study survived for significantly longer than those in the mitomycin arm. There were no significant differences in the median length of survival for the other three trials. The Scand trial allowed cross-over on documented progression and many patients in the methotrexate plus fluorouracil arm also received docetaxel. Consequently, because the survival data were analysed on an ITT basis, the curves show survival after the sequential administration of the two regimens.

Haematological side-effects were relatively frequent and, with the exception of thrombocytopenia, more common in the docetaxel arms. Gastrointestinal adverse effects were rare. Neurological adverse events were significantly more frequent in the docetaxel group but cardiovascular adverse events were more common in anthracycline-containing regimens. Alopecia was present in the majority of patients who were treated with docetaxel. Asthenia was significantly more common in patients treated with docetaxel in two trials. A minority of the patients treated with docetaxel suffered fluid retention. Two of the trials investigated QoL; neither showed a significant difference between docetaxel and controls.

TABLE 43 *Other adverse events*

Adverse event	**303 Study (%) RR (95% CI) (*n* = Td: 159; A: 163)**	**304 Study (%) RR (95% CI) (*n* = Td: 200; MV: 187)**	**Scand (%) RR (95% CI) (*n* = Td: 134; MtF: 135)**
Alopecia	Td: 91.2 A: 90.8 1.00 (0.94 to 1.08)		Td: 74 MtF: 17 11.44 (6.04 to 21.7)
Asthenia	Td: 14.5 A: 12.3 1.18 (0.67 to 2.06)	Td: 16.0 MV: 6.4 2.49 (1.32 to 4.69)	Td: 12 MtF: 2 5.67 (1.70 to 18.91)
Skin toxicity	Td: 1.9 A: 0.6 3.08 (0.32 to 29.26)	Td: 4.0 MV: 0 15.9 (0.92 to 273.6)	Td: 2 MtF: 0 5.0 (0.24 to 103.22)
Nail disorder	Td: 2.5 A: 0 9.22 (0.5 to 169.9)	Td: 2.5 MV: 0 10.29 (0.57 to 184.8)	Td: 5 MtF: 0 15.11 (0.87 to 261.9)
Local toxicity		Td: 1.5 MV: 2.1 0.70 (0.16 to3.09)	
Conjunctivitis			Td: 0 MtF: 1 0.33 (0.01 to 8.11)
Local phlebitis			Td: 1 MtF: 0 3.00 (0.12 to 73.02)
Allergy	Td: 2.5 A: 1.2 2.05 (0.38 to 11.04)		Td: 1.4 MtF: 0 5.00 (0.24 to 103.2)
Severe fluid retention	Td: 5.0 A: 0 11.28 (0.63 to 202.2)	Td: 8.0 MV: 0 30.87 (1.86 to 510)	Td: 3 MtF: 2 1.33 (0.30 to 5.85)
Toxic death		Td: 2.0 MV: 1.6 1.24 (0.28 to 5.47)	

The 303, 304 and Scand studies were all high-quality, RCTs. The median lengths of follow-up for these trials were 23 months, 19 months and 11 months respectively. During this time, about two-thirds of the patients in the 303, 304 and Scand trials had died; consequently, the data were adequately mature to permit reliable analysis. The Scand study allowed cross-over on progression; therefore the overall survival was based not only on docetaxel and methotrexate plus fluorouracil but also on the sequential administration of the alternative treatment. The two curves were similar. Insufficient details were given in the Bonneterre abstract to assess its quality properly and accrual is ongoing. Any results are therefore tentative and should be treated with caution.

Although all the trials required participants to have undergone previous chemotherapy, two different groups of patients were investigated. Three specified that first-line chemotherapy should have included anthracyclines; the 303 Study excluded patients who were receiving first-line anthracycline but specified alkylating agent chemotherapy. The UK licensed indications for docetaxel state that patients should have previously received cytotoxic chemotherapy with either an anthracycline or an alkylating agent, so the role of docetaxel in both these situations has been evaluated.

TABLE 44 *Differences in mean changes in QoL scores from baseline*

Dimension	303 Study[a]	304 Study[a]
Global health status QoL	ns	ns
Physical functioning	ns	ns
Role functioning	ns	Greater increase in MV (p = 0.029)
Emotional functioning	Greater increase in A (p = 0.037)	ns
Cognitive functioning	ns	ns
Social functioning	ns	Greater increase in MV (p = 0.006)
Fatigue	ns	ns
Nausea/vomiting	Greater increase in A (p = 0.0001)	Greater decrease in MV (p = 0.002)
Pain	ns	ns
Dyspnoea	ns	ns
Insomnia	ns	ns
Appetite loss	ns	Greater increase in MV (p = 0.037)
Constipation	Greater increase in A (p = 0.05)	ns
Diarrhoea	Greater increase in Td (p = 0.004)	ns
Financial difficulties	ns	–

[a] *Wilcoxon rank sum test*
ns, not statistically significant

All four trials used the same dose and administration schedule for docetaxel; this was in line with the recommended dose in the UK licensed indications (i.e. 100 mg/m^2, administered as a 1-hour infusion every 3 weeks). Four different control chemotherapy regimens were used. One of these was doxorubicin, which is likely to have been given as first-line chemotherapy unless contraindicated (e.g. because of cardiac disease).

The results suggest that docetaxel increases the length of progression-free survival in patients who have been previously treated with anthracycline compared with mitomycin plus vinblastine (304 Study) and methotrexate plus fluorouracil (Scand trial). In addition, the 304 Study showed that docetaxel increased overall survival compared with mitomycin plus vinblastine. There was no advantage to docetaxel over doxorubicin in terms of progression free- or overall survival among patients who had previously received alkylating agent chemotherapy, although significant differences were found when the Wilcoxon rather than the logrank test was used. However, because such patients may not be eligible for anthracycline therapy, docetaxel appears to be an equally effective option but without the cardiac adverse events.

Summary: docetaxel as second-line treatment for advanced breast cancer

Four RCTs were included in this analysis, involving a total of 1092 patients. One trial (91 patients) was a preliminary analysis. The response to docetaxel ranged from 30% to 54% and was significantly superior to controls in three out of four studies. The time to disease progression ranged from 19 to 28 weeks among patients treated with docetaxel; this was significantly longer than controls in two studies. The overall length of survival ranged from 10.4 to 15 months; this was significantly longer than the control arm in one trial. QoL in terms of global health status was no different from controls in the two studies in which this was considered.

Economic evaluations of taxanes (paclitaxel and docetaxel) in advanced breast cancer

Description of studies

A total of 11 economic evaluations presented in seven reports of paclitaxel or docetaxel use in breast cancer were found (one of which was submitted in confidence and has been removed from this document). All of these were cost–utility analyses, although one also presented a cost-effectiveness analysis. The publication dates ranged from 1996 to 1999, representing analyses in four countries. Modelling was used to extrapolate effectiveness from the trials used to life-years gained (LYG), or to estimate resource use in a 'real world' scenario. Resource use outside of a clinical trial can vary considerably due to, for example, local practice patterns, patient compliance, and rates of hospitalisation for treating adverse effects. *Table 45* presents study descriptions;[20,55–59] included are:

- the country in which the study was undertaken
- the currency used in the analysis (and, where given, the year of currency used)
- the stage of breast cancer included
- the drug regimen and response rates used
- the sources of efficacy data
- resource use and cost data
- the type of model employed.

The body surface area assumed when calculating costs of chemotherapy and related drugs was given in only three studies.

Table 46 presents the results of these studies, including:

- which costs were included in the analysis
- total costs (typically per patient)
- benefits assumed
- synthesis of costs and benefits
- authors' conclusions.

Benefits in these studies are typically QALYs gained or quality-adjusted progression-free life-years gained (PFLYG).

Table 47 is a validity assessment based on the methods of Drummond *et al.*[29]

Six of these studies presented analyses of paclitaxel versus docetaxel in the treatment of advanced breast cancer. Three of the evaluations addi-tionally considered docetaxel versus vinorelbine.

Choice of comparator

The choice of comparator (alternative treatment) in economic analyses is important. If the comparator is inappropriate, the results may not be generalisable. Another importance of the comparator chosen is the effect it can have on the incremental benefits and costs, such as differing response rates, drug costs or treatment of adverse effects. These differences in benefits or costs can move in either a positive or a negative direction. The comparator used in these studies of advanced breast cancer was most often paclitaxel, which was marketed before docetaxel; docetaxel is therefore considered as the 'new' drug in these evaluations. Many chemotherapy regimens are available and used for treating advanced breast cancer, and no gold standard has been set. Vinorelbine is a reasonable alternative, but not necessarily the one used locally.

Resources and costs included

The identification of resources used, costs included, and the source of these cost data can also have a significant impact on the generalisability of the results. Resource use and costs in non-NHS systems may be quite different. However, if the relative costs are similar to England, then comparisons can still be made by using incremental costs and cost-effectiveness ratios. The choice of costs included can alter the incremental costs, particularly if important costs are omitted. Auxiliary drugs used, such as the premedications that are given prior to taxane use, and stem cell-stimulating drugs that are given in the event of myelo-suppression, are examples that could alter costs. More important may be hospitalisation costs for drug administration and treatment of adverse events. Docetaxel is infused over 1 hour and may not require an overnight stay. In comparison, the choice of infusion time for paclitaxel (24-hour versus 3-hour) could alter the hospitalisation costs. Assumptions regarding the need for hospitalisation to treat myelo-suppression or infections and the rate of significant side-effects may also affect costs. Sensitivity analyses or comparing similar studies that have and have not included these factors may help to define the significance of these variations.

Economic dominance is a term that is used when one treatment is both more effective (in these cases efficacy adjusted for QoL) and less costly than another. In this case, an incremental cost–utility analysis is not calculated because the choice of therapy is obvious.

TABLE 45 *Cost–utility analyses of taxanes in metastatic breast cancer: study design*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Methods
Leung, 1999[55]	Canada/ Can$ 1999	Anthracycline-resistant metastatic	Tp: paclitaxel 175 mg /m^2 or 135 mg/m^2 every 3 wk Td: docetaxel 100 mg/m^2 every 3 wk Vinorelbine 30 mg/m^2 weekly **% *Response rates assumed*** Td: 30 Tp: 21 Vinorelbine: 16	Retrospective chart review 1996–1997	Published sources 1992–1998	Decision analysis model
Aventis, 1999[20]	UK/ £ sterling 1999 (update of Hutton 1996[58])	Disease progression after chemotherapy	Td: docetaxel (100 mg/m^2), 1-h i.v. infusion every 3 wk for up to 6 cycles Tp: paclitaxel (175 mg/m^2), 3-h infusion every 3 wk for up to 6 cycles Vinorelbine i.v. (30 mg/m^2), weekly x 12 cycles Body surface area of 1.75 m^2 assumed **% *Response rates*** Td: 42 Tp: 28 Vinorelbine: 16	Td: weighted average response rate and safety data from 3 Phase III studies pooled (1999 publications) Tp: response rate from 1 Phase III study used (1995); safety data pooled from Phase II trials Expert opinion also used for probabilities in model. Vinorelbine: 1 Phase III trial (1995) **% *Overall response rate*** Td: 41.7 Tp: 28 Vinorelbine: 16	Resource use estimated by 1 oncologist for 4 stages of disease considered (early progressive, late progressive, stable disease and terminal disease), which was then reviewed by 4 oncologists Costs from national databases (not referenced) except laboratory costs, and chest radiography costs from specific hospital data (not referenced) Costs 'updated to 1997–1998 levels' using the NHS hospital and community health service inflation index Costs of Td and Tp obtained from the *Monthly Index of Medical Specialties* (MIMS), August 1999	Decision analysis model; time frame: 3 years from start of therapy Utilities derived from 30 oncology nurses

continued

TABLE 45 contd *Cost–utility analyses of taxanes in metastatic breast cancer: study design*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Methods
Brown and Hutton, 1998[56]	USA/ US$ 1997	Advanced metastatic	Tp: paclitaxel 200 mg/m^2 every 21 d for 6 cycles (body surface area of 1.66 m^2 assumed) Td: docetaxel 100 mg/m^2 every 21 d for 7 cycles (body surface area of 1.66 m^2 assumed) **% *Assumed response rates*** Td: 47.8 Tp: 25	Data for the effectiveness analysis are from two Phase III studies published in 1997	Resource use estimated from a study published in 1996 Estimation of costs was based on published prices from Medicare, private third-party payers, and the *Redbook* (drug prices) These data were collected for 1997, with some prices being reflated The specific costs that were reflated and the method used were not stated	Modified Markov model
Yee, 1997[57]	UK £/ converted to US$, year not stated (based on Hutton model[58])	Anthracycline-resistant metastatic	Td: docetaxel (100 mg/m^2) 1-h infusion Tp: paclitaxel (175 mg/m^2) 3-h infusion **% *Assumed response rates*** Td: 47 Tp: 21	Two Phase II studies, 1 each of Tp or Td and their respective package inserts (1995–1996) **% *Assumed response rates*** Tp: 21 Td: 47	Costs estimated from UK NHS Resources used based on opinions of UK oncology experts (years not stated)	Markov model Assumptions: overall duration of progressive deterioration of health
Hutton *et al.*, 1996[58]	UK/ £ sterling 1994	Anthracycline-resistant metastatic	Td: docetaxel (100 mg/m^2) 1-h i.v. infusion every 3 wk for up to 6 cycles Tp: paclitaxel (175 mg/m^2) 3-h infusion every 3 wk for up to 6 cycles Based on a body surface area of 1.7 m^2 **% *Assumed response rates*** Td: 47 Tp: 21	Published Phase II studies Td: 3 studies pooled (1995 publications) Tp: 1 study used (1995) Expert opinion also used for probabilities in model. **% *Overall response rate*** Td: 47 Tp; 21	Costs from national data-bases and pub-lished literature (not referenced) Costs 'updated to 1994 levels' using the NHS hospital and community health service inflation index (1994) Costs of Td and Tp obtained from MIMS, May 1996	Markov model 1 oncologist identified resources needed for 4 stages of disease considered (early progressive, late progressive, stable disease and terminal disease), which then reviewed by 4 oncologists

continued

TABLE 45 contd *Cost–utility analyses of taxanes in metastatic breast cancer: study design*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Methods
Launois *et al.*, 1996[59]	France/ FF 1993	Metastatic	Td: docetaxel 100 mg/m^2 every 21 d (premedication: dexamethasone 8 mg oral daily x 5 d) Tp: paclitaxel 175 mg/m^2 every 21 d (premedications: dexamethasone 20 mg p.o. b.d., diphenhydramine 50 mg i.v., ranitidine 50 mg i.v.) Vinorelbine 30 mg/m^2 every 7 d Maximum 6 cycles assumed **% *Assumed response rates*** Td: 57 Tp: 29 Vinorelbine: 16	Phase II clinical trials (1993–1995 publication) **% *Assumed response rates*** Td: 57 Tp: 29 Vinorelbine: 16	Retrospective chart review of resource uses (153 patients from 5 hospitals) Prices were assigned by DRG grouping, using 1993 prices (cost survey published in 1995)	Markov model

DRG, diagnosis-related group

Cost–utility analysis

If it assumed that resource use and the relative costs of drugs are the same across all these studies, the results can be converted to pounds sterling for comparison purposes. The years when these studies were carried out are quite similar, therefore no reflation to 1999 prices is necessary.

Paclitaxel versus mitomycin

One UK study compared paclitaxel with an older chemotherapeutic agent, mitomycin, in the treatment of metastatic breast cancer. However, this study was submitted in confidence and its results have been removed from this document.

Docetaxel versus paclitaxel

For studies comparing docetaxel with paclitaxel, the range of cost–utility ratios for QALYs gained was £1990–£5233. The low estimate was for the UK[20] and the high value was for the USA.[56] Two studies did not present an incremental analysis. One showed docetaxel to be the dominant strategy over paclitaxel, while the other found vinorelbine to be dominant over either taxane.[55,59]

Docetaxel versus vinorelbine

In the three studies comparing docetaxel to vinorelbine, the one UK study showed the cost of docetaxel per QALY gained was £14,050.[20] Although the efficacy rates used were not the result of a direct-comparison clinical study, the economic evaluation was otherwise of a relatively high quality. A Canadian study showed vinorelbine to be the dominant strategy.[55] In this study, the average cost per quality-adjusted PFLYG (converted to pounds) was £45,837 for docetaxel and £13,008 for vinorelbine. However, the third study (from France), comparing docetaxel and vinorelbine, indicated the opposite, that docetaxel was dominant to vinorelbine.[59] Although these two studies used similar assumed rates of response for vinorelbine (16%) and paclitaxel (21–29%), the rates used for docetaxel were quite different (57% in the French study and 30% in the Canadian study). In cost–utility studies it is standard practice to use the valuations (utilities) of healthy people in estimating quality-adjusted benefit, as was done in the Canadian study. However, if the utilities assigned by patients are used instead, vinorelbine is no longer dominant. The other main difference between these studies was the cost of vinorelbine used. Converted to pounds, the cost of a cycle in Canada was £67, while it was £207 in France. The price of vinorelbine per weekly cycle used in the Aventis study was £147.

Quality assessment

In examining the quality of these studies, it becomes clear that generalisability could be a problem because of a lack of specific information, source of efficacy, resource use and cost data and the assumptions that were made. *Table 47* is a critical assessment of these economic evaluations. The areas examined in each study are:

TABLE 46 *Breast cancer cost–utility studies: results*

Reference	Costs	Benefits	Synthesis	Conclusions
Leung, 1999[55]	Included: acquisition, preparation and administration costs of chemotherapy, premedications, laboratory tests, hospitalisation, clinic visits, management of adverse effects or complications, and all related physician fees ***Mean cost per cycle (Can$)*** Tp: 1680 (95% CI: 1574 to 1976) Td: 2653 (95% CI: 2363 to 3053) Vinorelbine: 503 (95% CI: 453 to 641)	***Quality-adjusted progression-free survival (d)*** Tp: 39.8 Td: 33.2 Vinorelbine: 35.0 (from patient sample, healthy volunteers)	***Cost per quality-adjusted progression-free year (Can$)*** Tp: 59,096 Td: 110,072 Vinorelbine: 31,220	Palliative chemotherapy with vinorelbine in anthracycline-resistant metastatic breast cancer patients has economic advantages over the taxanes and provides at least equivalent progression-free survival These benefits are largely related to its lower drug acquisition costs and better toxicity profile
Aventis, 1999[20]	Included: drug, hospital day, medical staff, diagnostic tests, and therapeutic procedures; costs occurring after 1 yr are discounted at 6% ***Total per patient costs for base-case (£)*** Td: 7817 Tp: 7645 Incremental cost: 172 Vinorelbine: 4268 Incremental cost of Td: 3549	***QALYs*** Td: 0.7347 Tp: 0.6485 Incremental QALY: 0.0862 Vinorelbine: 0.4822 Incremental QALY with Td: 0.2525	***Incremental cost per QALY (£)*** Td vs. Tp: 1990 Td vs. vinorelbine: 14,050	Taxotere (Td) is considered to be cost-effective compared with Tp or vinorelbine in the treatment of advanced breast cancer when compared alongside other licensed therapies
Brown and Hutton, 1998[56]	Included: physician visit, general blood chemistry, hospital day, i.v. antibiotic home treatment, ciprofloxacin (1000 mg daily), Tp and Td Resources measured: physician and nurse time, chemotherapeutic agents, antibiotic regimens, inpatient or outpatient management of infections and febrile neutropenia, progressive and terminal disease palliative medication, and monitoring tests Costs for Td $15, 683 and $13,904 for Tp over a 3-yr period of follow-up: costs of adverse effects were included	The cumulative QALYs for Td were 0.8670, and 0.6605 for Tp, over a 3-yr follow-up period; side-effects were included	The incremental cost per QALY for Td compared with Tp was $8615	The cost/QALY gained by Td was $8615 and ranged between $3943 and $9416 in sensitivity analyses These results confirm those of an earlier model using preliminary data and compare favourably with other cost–utility results in this patient group

continued

TABLE 46 contd *Breast cancer cost–utility studies: results*

Reference	Costs	Benefits	Synthesis	Conclusions
Yee, 1997[57]	Included: treatment (drug and administration costs), toxicity and progressive disease/death ***Total costs ($)*** Td: 13,584 Tp: 13, 221	Incremental QALY with Td vs. Tp: 0.0905 per patient; equivalent to 33 d of perfect health Utility scores based on decisions of 100 oncology nurses	Incremental cost per QALY associated with Td: $4022 Sensitivity analysis showed that cost and response rate changes for Td significantly changed the ratio	Although results of the model are not easily generalisable, the incremental costs per QALY fall within acceptable levels in the USA
Hutton *et al.*, 1996[58]	Included: drugs, hospital day and medical staff, diagnostic tests, therapeutic processes ***Total per patient costs for base-case (£)*** Td: 8233 Tp: 8013	Higher response rate associated with Td was 0.0905 QALYs or 33 incremental quality-adjusted days Benefits considered from commencement of treatment to death of patient Side-effects were taken into account in this analysis	Incremental analysis: when comparing Td with Tp there was an incremental cost–utility ratio of £2431 per QALY (£7 per health day): this was sensitive to the efficacy of Td; it falls to £1186 if Td response rates increase from 47% to 56%	Response rate is the key parameter that determines utility and cost–utility of treatments for metastatic breast cancer Td produced a higher response rate compared with Tp, resulting in an improvement in QoL, which clearly outweighed the side-effects Td further produced a substantially larger utility benefit than Tp at a smaller additional cost of £2431 per QALY gained, an incremental health cost that was acceptable according to available defined limits and which did not alter in terms of Td dominance for all scenarios tested by the model
Launois *et al.*, 1996[59]	Included: professional services, medicines, procedures related to treatment and follow-up, treatment-related complications and disease-related complications Full cost per DRG, direct total cost per DRG, and variable medical costs per DRG were reported for 23 DRGs ***Total costs (FF)*** Tp: 251,100 Td: 250,400 Vinorelbine: 257,200 ***Incremental costs (FF)*** Td vs. vinorelbine: –6,800 Td vs. Tp: –700	***Progression-free survival (d)*** Td: 173 Tp: 145 Vinorelbine: 99 ***Quality-adjusted progression-free survival (d)*** Td; 125 Tp: 103 Vinorelbine: 68	Td was the dominant strategy, with longer progression-free survival and lower cost	Td brings a net benefit of 57 progression- and discomfort-free days compared with vinorelbine and 22 such days compared with Tp Td is self-financing because of savings of FF6800 compared with vinorelbine and FF700 compared with Tp

TABLE 47 *Validity assessment of economic evaluations of taxanes in breast cancer (Drummond* et al.[29]*)*

Critical assessment questions[29]	**Leung, 1999**[55]	**Aventis, 1999**[20]	**Brown and Hutton, 1998**[56]	**Yee, 1997**[57]	**Hutton *et al.*, 1996**[58]	**Launois *et al.*, 1996**[59]
Well-defined question	✔	✔	✔	✔	✔	✔
Comprehensive description of alternatives	✔– Unclear if premedications included	✔	✔– Unclear if premedications included	✔– Unclear if premedications included	✔– Unclear if premedications included	✔
Effectiveness established	✔– Response rates taken from three trials – no direct comparisons; overall response rate for Tp calculated from 2 doses	✔– Response rate taken from various trials with no direct comparisons; Tp response rate from only 1 trial	✔– Comparing two different groups of patients, one mostly chemotherapy naive, the other not	✔– Phase II studies only; only 1 using Tp	✔– Phase II studies only; only 1 using Tp	✔– Phase II studies only; only 1 using Tp
All important and relevant costs and consequences for each alternative identified	✔	✔	✔– Treatment of adverse effects limited to the use of ciprofloxacin, i.v. at home	✔	✔	✔
Costs and consequences measured accurately	✔	✔	✔	– US study based on NHS resource use	✔	✔
Costs and consequences valued credibly	✔	✔	✔– Some methods not clear	– US study based on NHS resource use	✔	✔– Costs by DRG
Costs and consequences adjusted for differential timing	NA	Costs occurring after 1 yr discounted at 6%	NA	NA	NA	NA
Incremental analysis of costs and consequences	–	✔	✔	✔	✔	–
Sensitivity analyses to allow for uncertainty in estimates of cost or consequences	✔	✔	✔	✔	✔	✔
Study results/discussion include all issues of concern to users	✔	✔	✔	✔–	✔	✔

✔, yes; ✔–, maybe/partially; –, no; NA, not applicable

- the study question posed
- a comprehensive description of competing alternative therapies
- how established is the effectiveness of the interventions
- the inclusion of all important costs and consequences
- the accurate measurement of these costs and consequences
- the credibility of their valuations
- the use of discounting if appropriate
- the use of an incremental analysis
- the use of sensitivity analysis
- the breadth and depth of the discussion and conclusions.

The areas where the studies were most often deficient were those relating to descriptions and effectiveness of therapeutic alternatives. Several of the studies did not give a clear definition of the competing therapies. Most importantly, premedications to prevent hypersensitivity with taxanes and treatments for adverse effects, such as colony-stimulating factors for myelosuppression or prophylactic serotonin antagonists for nausea and vomiting, were not mentioned. The numbers of cycles assumed for given therapies were also rarely discussed. All of these factors can have a significant impact on both resource use and costs. All of the evaluations used effectiveness rates from disparate trials. Some of these trials were non-randomised Phase II trials, using more than one dose of the drug being studied. In one case, the two studies used had enrolled very different patient populations, one that was chemotherapy naive and one that was not.[56] While the lack of direct comparison data certainly weakens the strength of the evidence from these economic evaluations, these disparate data were used because there were no 'head to head' clinical comparison studies available for any of the combinations considered, with the exception of paclitaxel versus mitomycin. This is not to say that other comparators could have been used for which there are clinical data with direct comparisons.

The discounting of costs or benefits was not attempted.

Overall, the studies did well on: using an incremental analysis; using a sensitivity analysis; providing an appropriate discussion; and forming a well-defined study question.

Summary of economic evaluations of taxanes in advanced breast cancer

Two of the three UK economic evaluations of taxanes in advanced breast cancer compared docetaxel to paclitaxel and found a range of incremental cost per QALY gained of £1990–£2431. One also compared docetaxel with vinorelbine and found the incremental cost per QALY gained to be £14,050. The third study compared paclitaxel with mitomycin (results not reported here).

The acceptability of an incremental cost per QALY gained as low as £1990 for docetaxel over paclitaxel would be very high if this is indeed the desired comparison. The comparison of docetaxel versus vinorelbine, with an incremental cost per QALY gained of £14,050, may be more appropriate. This number is within the accepted range, if at the upper end.[29] However, the weakness of the estimates of efficacy must be kept in mind.

Chapter 5

Ovarian cancer

The effectiveness of paclitaxel as first-line treatment for advanced ovarian cancer

Description of included trials

Fifteen reports were identified that evaluated the effectiveness of paclitaxel as a first-line treatment for advanced ovarian cancer. These pertained to four Phase III trials: GOG111, GOG132, OV10 and ICON3 (*Table 48*). With the exception of GOG111,[60–67] these studies have not been published in journals.[68–74] The results of the GOG111 trial that were included in the full version of the review were derived from an ITT analysis given in an unpublished trial report.[66] For confidentiality reasons these results have been removed from this document and substituted with those from a published paper.[67] The following descriptions of the other studies are based on study protocols, meeting abstracts and meeting presentations.

These were all randomised, controlled Phase III trials with calculations of sample size and accurate and standard definitions of outcome variables. The ICON3 trial permitted a choice of control prior to randomisation (ICON3a: carboplatinum; ICON3b: cyclophosphamide, doxorubicin and cisplatinum (CAP)). It is important to note that the ICON3 trial completed accrual in October 1998, 6 months before the results were presented at the annual conference of the American Society of Clinical Oncologists.[73,74] Seventy per cent of the participants were still alive at this stage. The long-term results are awaited. Secondly, a large number of participants in the GOG132 trial crossed over to alternate treatment.[68,69] The rationale for such cross-over was not specified. Patients who had changed therapies were censored from the progression analyses in the OV10 trial. No details of such manipulations were given for the ICON3 or GOG132 trials.

Both the GOG111 and GOG132 trials included only patients with suboptimally debulked Stage III or Stage IV ovarian cancer; a wider range of patients were eligible for inclusion in the OV10 and ICON3 trials (*Table 49*).

Although they all included a paclitaxel/platinum combination arm, only the GOG111 and GOG132 trials used the same combination and schedule: paclitaxel (135 mg/m^2) with cisplatin (75 mg/m^2) given as a 24-hour infusion. OV10 used paclitaxel (175 mg/m^2) with cisplatin (75 mg/m^2) given as a 3-hour infusion; the ICON3 trial used paclitaxel (175 mg/m^2) with carboplatin (dosed at six times the area under the curve) given as a 3-hour infusion. Carboplatin is the platinum analogue most commonly used in the UK. The control arms all included platinum analogues, either alone or in combination, often with cyclophosphamide (*Table 50*).

The differences in the inclusion criteria influenced the characteristics of the participants in the trials. The GOG111 and GOG132 trials contained a higher proportion of participants with Stage IV cancer and all patients had suboptimal debulking compared with the OV10 and ICON3 trials (*Table 51*).

The differences between the studies made pooling inappropriate. Although the trials were all of a similar high quality, a variety of interventions and controls were used, and the study populations and resulting samples differed.

Synthesis

Overall response rates

Overall response rates (complete response plus partial response) were presented for three trials: GOG111, GOG132 and OV10 (*Figure 9*). These ranged from 46% (GOG132) to 72% (GOG111) in the paclitaxel combination arms. When comparing the paclitaxel plus platinum arm with the control arm, no significant difference in response rates were found in the GOG111 (72% versus 60%) or the OV10 trial (52% versus 44%). However, cisplatin alone had a superior response rate compared with combined cisplatin and paclitaxel in the GOG132 trial (74% versus 46%, RR = 0.62 (95% CI: 0.53 to 0.73)).

A greater proportion (over 90%) of patients in the GOG132 trial were evaluable for response compared with the GOG111 (56%) or the OV10 trial (approximately 50%).

TABLE 48 *Design of included trials*

Trial: source	Quality	Design	Accrual dates	No. randomised	ITT	No. evaluated	Rationale for cross-over (%)	No. crossing over (%)	Median length of follow-up (mo)	No. participants surviving (%)
GOG111: meeting abstracts and journal articles[60–65,67]	IA	Randomised Outcomes defined Multicentre Open label	Apr 1990 – Mar 1992	***Eligible for analysis*** TpP: 184 CP: 202	All eligible patients	***Evaluable for clinical response: measurable disease*** TpP: 100 CP: 116	No details	No details	37	TpP: (47) CP: (32)
GOG132: meeting abstract and presentation,[68] protocol[69]	IA	Randomised Power calculations Outcomes defined Multicentre Open label	Mar 1992 – May 1994	Tp: 224 P: 209 TpP: 215	Yes	***Evaluable*** Tp: 213 P: 200 TpP: 201	Not defined	Tp: 184 P: 162 TpP: 157	Not stated	Overall: (34)
OV10: protocol,[70] meeting presentation and abstracts[71,72]	IA	Randomised Power calculations Outcomes defined Multicentre Open Label	Apr 1994 – Aug 1995	TpP: 338 CP: 300	Yes	***Evaluable for response*** TpP: 149 CP: 151	Cross-over from control arm to taxanes on documented first progression	134 (52)	30	TpP: 211 (62) CP: 169 (50)
ICON3: protocol,[73] meeting abstract and presentation[74]	IA	Randomised Power calculations Outcomes defined Multicentre Open label	Feb 1995 – Oct 1998	***ICON3a*** TpP(P): 478 P: 943 ***ICON3b*** TpP(CAP): 232 CAP: 421	Yes		Treatment on progression; rationale not defined	TpP: (79)[a] Control: (83)[a]	18	TpP: 505 (71) Control: 942 (69)

a Proportion of those who had progression

Tp, paclitaxel; CP, cyclophosphamide, platinum; P, platinum; C, cyclophosphamide; CAP, cyclophosphamide, doxorubicin, cisplatin; TpP(P), paclitaxel, carboplatin (platinum control); TpP(CAP), paclitaxel, carboplatin (CAP control)

TABLE 49 *Comparison of inclusion criteria*

Trial	Cancer	Stage	PS	Previous treatment
GOG111	Pathologically verified epithelial ovarian cancer Borderline cancers excluded	Stage III: suboptimal residual disease (> 1 cm residual mass) All patients with Stage IV disease	GOG 0–2	No prior radiotherapy or chemotherapy
GOG132	Histologically confirmed ovarian epithelial cancer Borderline cancers excluded	Stage III: suboptimal (> 1 cm diameter) Stage IV	GOG 0–2	No prior radiotherapy or chemotherapy
OV10	Histologically verified epithelial ovarian carcinoma Borderline cancers excluded	FIGO Stages IIb, IIc, III and IV with or without successful debulking	WHO 0–3	No prior radiotherapy or chemotherapy
ICON3	Clinical diagnosis and histologically consistent with invasive ovarian carcinoma of epithelial origin			No prior radiotherapy or chemotherapy

TABLE 50 *Comparison of interventions*

Trial	Intervention	Control A	Control B
GOG111	TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2) Tp: 24-h infusion; followed by P, 6 x 3-wk cycles Premedication: dexamethasone 20 mg; any histamine H_2 antagonist, diphenhydramine 50 mg i.v.	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), 6 x 3-wk cycles	
GOG132	Tp: paclitaxel (200 mg/m^2) Tp: 24-h infusion 6 x 3 wk cycles Premedication: dexamethasone 20 mg, cimetidine 50 mg i.v., diphenhydramine 50 mg i.v.	P: cisplatin (100 mg/m^2), 6 x 3-wk cycles Hydration Prophylactic antiemetic	TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2) Tp: 24-h infusion followed by P, 6 x 3-wk cycles Premedication: dexamethasone 20 mg, cimetidine 50 mg i.v., diphenhydramine 50 mg i.v. Prophylactic antiemetic
OV10	TpP: paclitaxel (175 mg/m^2) + cisplatin (75 mg/m^2) Tp: 3-h infusion followed by P, up to 9 x 3-wk cycles Premedication: dexamethasone 20 mg, ranitidine 50 mg i.v., diphenhydramine 50 mg i.v. Prophylactic antiemetics and oral magnesium recommended	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), up to 9 x 3-wk cycles Prophylactic antiemetics and oral magnesium recommended	
ICON3	TpP: paclitaxel (175 mg/m^2) + carboplatin (6 AUC) T: 3-h infusion followed by P, 6 x 3-wk cycles Premedication: dexamethasone 20 mg, ranitidine 50 mg i.v., chlorpheniramine 10 mg i.v.	***ICON3a*** P: carboplatin (dosed at six times the area under the curve), 6 x 3-wk cycles Prophylactic antiemetics	***ICON3b*** CAP: cyclophosphamide (500 mg/m^2), doxorubicin (50 mg/m^2), cisplatin (50 mg/m^2), 6 x 3-wk cycles Prehydration Prophylactic antiemetics

TABLE 51 *Comparison of participants*

Trial	Median age (yr)	PS (%)	FIGO stage (%)	Measurable disease (%)	Results of surgery	Previous treatment (%)
GOG111	TpP: 60 CP: 59	***GOG 0*** TpP: 30 CP: 27 ***GOG 1*** TpP: 53 CP: 54 ***GOG 2*** TpP: 17 CP: 19	***Stage III*** TpP: 67 CP: 64 ***Stage IV*** TP: 33 CP: 36	TpP: 54 CP: 57	Suboptimal: residual mass > 2 cm	None
GOG132	Tp: 59.9 P: 60.1 TpP: 59.4	***GOG 0*** Tp: 31 P: 30 TpP: 27 ***GOG 1*** Tp: 55 P: 55 TpP: 56 ***GOG 2*** Tp: 14 P: 15 TpP:17	***Stage III*** Tp: 72 P: 65 TpP: 73 ***Stage IV*** Tp: 28 P: 35 TpP: 27	Tp: 62 P: 61 TpP: 62	Suboptimal	None
OV10	TpP: 58 CP: 58	***WHO 0*** TpP: 46 CP: 51 ***WHO 1*** TpP: 40 CP: 36 ***WHO 2*** TpP: 12 CP: 12 ***WHO 3*** TpP: 2 CP: 1	***Stage II*** TpP: 6 CP: 7 ***Stage III*** TpP: 75 CP: 71 ***Stage IV*** TpP: 19 CP: 22	TpP: 44 CP: 46	***Residual disease > 1 cm (%)*** TpP: 62 CP: 65	No previous treatment
ICON 3	P: 59.4 TpP(P): 60.7 CAP: 56.9 TpP(CAP): 56.6		***Stage III*** P: 65 TpP(P): 64 CAP: 63 TpP(CAP): 63 ***Stage IV*** P: 16 TpP(P): 17 CAP: 15 TpP(CAP): 16		***Residual bulk > 2 cm (%)*** P: 46 TpP(P): 47 CAP: 47 TpP(CAP): 44	None

Progression-free survival

Kaplan–Meier curves were presented for each of the trials.

The median progression-free survival for the paclitaxel/platinum combination ranged from 14.1 months (GOG132) to 18 months (GOG111); it was not calculated for the ICON3 trial. Both the GOG111 and OV10 trials reported a significantly greater median length of progression-free survival for the paclitaxel arm than the control: 18 months versus 13 months and 16.5 months versus 11.8 months respectively (*Table 52*).

No probability levels were given for the GOG132 trial but patients treated with single-agent platinum appeared to survive longer without progression.

Figure 10 illustrates the estimates of progression-free survival rates at 1, 2 and 3 years obtained from these analyses. These were estimated from the Kaplan–Meier graphs. These allow the generation of RR point estimates but not their CIs. For the ICON3 trial the control figures represent the two control arms combined. The authors of the ICON3 report maintained that their results are reliable

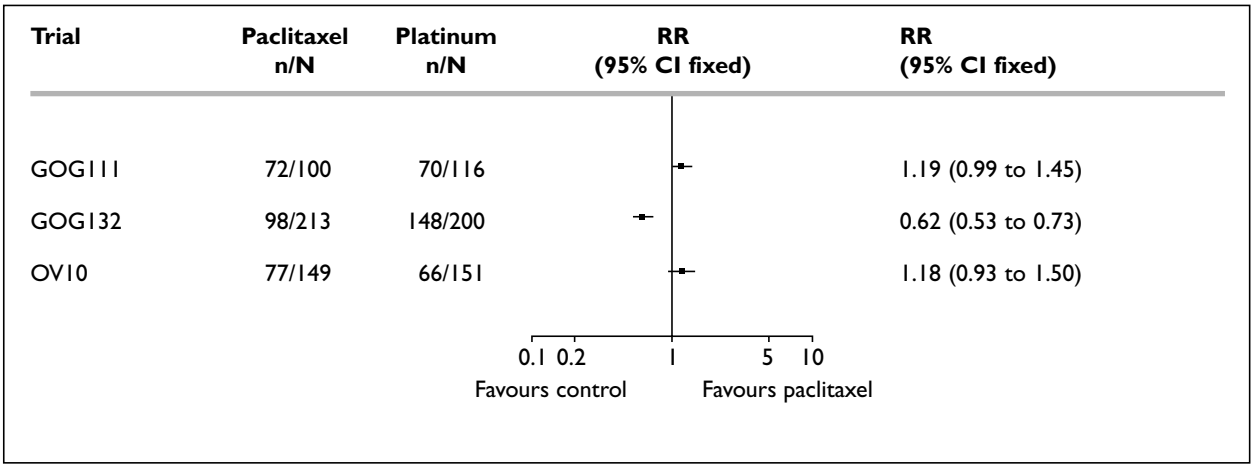

FIGURE 9 *Paclitaxel and platinum as first-line treatment for ovarian cancer: overall response rates*

to around 2 years. For the GOG132 trial the comparisons represent paclitaxel alone versus platinum alone.

At 12 months, the progression-free survival rate in the paclitaxel arm ranged from 64% (ICON3) to 72% (GOG111).

At 24 months, the progression-free survival rate in the paclitaxel arm ranged from 35% (GOG111) to 41% (ICON3).

Overall survival

Kaplan–Meier curves were presented for each of the trials.

The median length of survival for patients treated with the paclitaxel/platinum combination ranged from 26.6 months (GOG132) to 38 months (GOG111) (*Table 52*). Both the GOG111 and OV10 trials reported significantly greater median survival times for the paclitaxel arm than the control: 38 months versus 24 months and 35 months versus 25 months respectively. No probability levels were given for the GOG132 trial but patients treated with single-agent platinum appeared to survive longer (30.2 months). The median length of survival has not been calculated for the ICON3 trial.

Figure 11 illustrates the estimates of overall survival rates at 1, 2 and 3 years obtained from these

TABLE 52 *Median survival times for paclitaxel as first-line treatment for ovarian cancer*

Trial	Median progression-free survival (mo) (95% CI)	Median survival (mo) (95% CI)
GOG111	TpP: 18 (16 to 21) CP: 13 (11 to 15) RR[a] = 0.7 (0.5 to 0.8), $p < 0.001$	TpP: 38 (32 to 44) CP: 24 (21 to 30) RR[a] = 0.6 (0.5 to 0.8), $p < 0.001$
GOG132	Tp: 11.4 TpP: 14.1 P: 16.4 No analysis	Tp: 26 TpP: 26.6 P: 30.2 No analysis
OV10	TpP: 16.5 CP: 11.8 p[b] < 0.001	TpP: 35 CP: 25 p[b] < 0.001
ICON3	Not presented	Not presented

[a] *95% CIs calculated using Brookmeyer and Crowley method; 2-tailed logrank test*
[b] *2-sided logrank test*

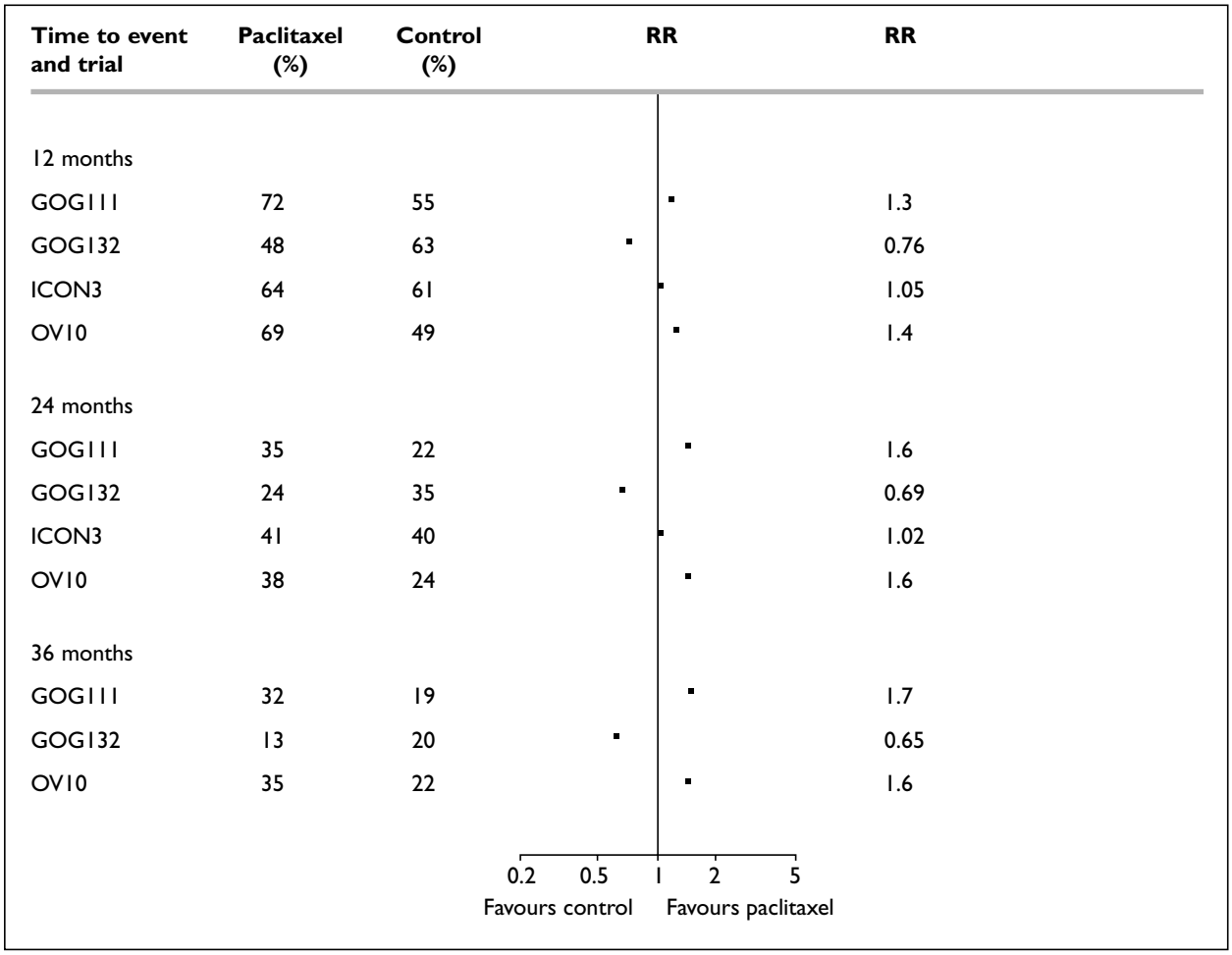

FIGURE 10 *Paclitaxel and platinum as first-line treatment for ovarian cancer: progression-free survival*

analyses. These were estimated from the Kaplan–Meier graphs. These allow the generation of RR point estimates but not their CIs. For the ICON3 the trial control figures represent the the two control arms combined. The authors of the ICON3 report maintained that their results are reliable to around 2 years. For the GOG132 trial the comparison represents paclitaxel alone and platinum alone.

At 12 months, the overall survival rate in the paclitaxel arm ranged from 82% (ICON3) to 89% (OV10).

At 24 months, the overall survival rate in the paclitaxel arm ranged from 66% (ICON3) to 78% (OV10).

At 36 months, the overall survival rate in the paclitaxel arm ranged from 34% (GOG132) to 58% (GOG111).

Compliance (*Table 53*)

Patient compliance and reasons for discontinuation of therapy may give an indication of the acceptability of treatment. However, because all these trials were open label, there may have been different pressures on or by patients either to continue treatment or to cross over, depending on the arm. Compared with the other trials, in GOG132, fewer patients in the platinum-only arm completed all cycles. Adverse events were the reason most frequently given by this group, followed by withdrawal of consent.

Adverse events

The reports were not consistent in the way that adverse events were noted; the results of the GOG132 trial were impossible to interpret. A summary of the side-effect profiles of the included drugs is given in *Table 3*.

*Haematological adverse events (*Table 54*)*

Haematological side-effects were not reported for the OV10 trial. Reductions in the numbers of white cells and neutropenia were frequently reported in both arms of the GOG111 trial (pacletaxel/platinum 92%; cyclophosphamide/

platinum 83%). Overall haematological adverse events were less common in the ICON3 trial, at about 37% in all arms. Significantly more infections and febrile episodes were reported in the paclitaxel arm than in the carboplatin-alone arm of the ICON3a trial (10% versus 1%, RR = 3.38 (95% CI: 2.15 to 5.32)). However, fewer infectious and febrile episodes were found in the paclitaxel arm than the CAP control of ICON3b (14% versus 22%; RR = 0.59 (95% CI: 0.40 to 0.86)).

Gastrointestinal adverse events

Nausea and vomiting were reported by less than a fifth of those treated with paclitaxel (range 7–18%). A greater incidence of nausea and vomiting was found in the CAP arm than in the paclitaxel arm of ICON3b (paclitaxel/platinum 10%; cyclophosphamide/doxorubicin/cisplatin 22%; RR = 0.45 (95% CI: 0.29 to 0.69) *Table 55*).

Neurological adverse events

Significantly more neurosensory adverse events were reported in the paclitaxel arms of the ICON3 and OV10 trials (ICON3a: paclitaxel/ carboplatin 18%, carboplatin 1%, RR = 21.2 (95% CI: 10.4 to 43.4); ICON3b: paclitaxel/ carboplatin 18%, cyclophosphamide/ doxorubicin/cisplatin 3%, RR = 5.86 (95% CI: 3.21 to 10.69); OV10: paclitaxel/cisplatin 20%, cyclophosphamide/cisplatin 9%, RR = 21.48 (95% CI: 6.82 to 67.64) *Table 56*). In addition, although rare, significantly more neuromotor adverse events were reported in the paclitaxel arm of the OV10 trial (paclitaxel/cisplatin 5%, cyclophosphamide/cisplatin < 1%, RR = 8.3 (95% CI: 1.93 to 35.64)).

Cardiovascular adverse events

Cardiovascular adverse events were not reported.

Time to event and trial	Paclitaxel (%)	Control (%)	RR	RR
12 months				
GOG111	86	77		1.1
GOG132	80	85		0.94
ICON3	82	82		1.0
OV10	89	81		1.1
24 months				
GOG111	67	52		1.3
GOG132	52	60		0.87
ICON3	66	62		1.1
OV10	78	54		1.4
36 months				
GOG111	58	30		1.9
GOG132	34	44		0.77
OV10	49	36		1.4

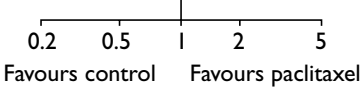

FIGURE 11 *Paclitaxel and platinum as first-line treatment for ovarian cancer: overall survival*

TABLE 53 *Treatment received*

Trial	Completing all cycles (%)	Median no. cycles (range)	Reasons for early discontinuation (%)				
			Disease progression	Adverse events	Withdrew consent	Death	Other
GOG111	TpP: 87 CP: 78						
GOG132	Tp: 71 P: 69 TpP: 83		Tp: 19 P: 7 TpP: 6	Tp: 1 P: 12 TpP: 4	Tp: 3 P: 6 TpP: 1	Tp: 4 P: 4 TpP: 5	Tp: 1 P: 2 TpP: < 1
OV10	TpP: 86 CP: 81	TpP: 6 (0–10) CP: 6 (0–10)	TpP: 5 CP: 13	TpP: 6 CP: 4	TpP: < 1 CP < 1%		
ICON3	TpP: 82 Con: 82		TpP: 4 Con: 7	TpP: 6 Con: 2	TpP: 1 Con: 1	TpP: 2 Con: 2	TpP: 2 Con: 2

Con, combined control

TABLE 54 *Haematological adverse events*

Adverse event	GOG111 (%) RR (95% CI) (*n* = TpP: 179; CP: 197)	ICON3a (%) RR (95% CI) (*n* = TpP: 478; P: 943)	ICON3b (%) RR (95% CI) (*n* = TpP: 232; CAP: 421)
Haematological		TpP: 35 P: 36 0.97 (0.8 to 1.1)	TpP: 38 CAP: 35 1.1 (0.9 to 1.3)
Reduced white cells or neutropenia	TpP: 92 CP: 83 1.12 (1.04 to 1.21)		
Infection		TpP: 10[a] P: 1 3.38 (2.15 to 5.32)	TpP: 14[a] CAP: 22 0.59 (0.40 to 0.86)
Fever	TpP: 3 CP: 0 16.38 (0.83 to 284)		
Anaemia	TpP: 8 CP: 8 1.10 (0.57 to 2.13)		

[a] *Fever requiring antibiotics*

TABLE 55 *Gastrointestinal adverse events*

Adverse event	GOG111 (%) RR (95% CI) (*n* = TpP: 184; CP: 201)	OV10 (%) RR (95% CI) (*n* = TpP: 330; CP: 338)	ICON3a (%) RR (95% CI) (*n* = TpP: 478; P: 943)	ICON3b (%) RR (95% CI) (*n* = TpP: 232; CAP: 421)
Nausea/vomiting		TpP: 18 CP: 23 0.78 (0.58 to 1.05)	TpP: 7 P: 8 0.9 (0.6 to 1.3)	TpP: 10 CAP: 22 0.45 (0.29 to 0.69)
Gastrointestinal	TpP: 15 CP: 11 1.39 (0.83 to 2.34)			

TABLE 56 *Neurological adverse events*

Adverse event	GOG111 (%) RR (95% CI) (*n* = TpP: 184; CP: 201)	OV10 (%) RR (95% CI) (*n* = TpP: 338; CP: 330)	ICON3a (%) RR (95% CI) (*n* = TpP: 478; P: 943)	ICON3b (%) RR (95% CI) (*n* = TpP: 232; CAP: 421)
Neurosensory		TpP: 20 CP: 9 21.48 (6.82 to 67.64)	TpP: 18 P: 1 21.2 (10.4 to 43.4)	TpP: 18 CAP: 3 5.86 (3.21 to 10.69)
Neuromotor		TpP: 5 CP: < 1 8.3 (1.93 to 35.64)		
Neurological	TpP: 4 CP: 4 0.98 (0.35 to 2.58)			

Other adverse events

Alopecia was a frequent adverse event in the paclitaxel arms (range 68–77%). It was more frequent in the paclitaxel than the carboplatin arm of ICON3a (paclitaxel/carboplatin 68%, carboplatin 3%, RR = 22.90 (95% CI: 15.82 to 33.15)); there was no such difference between the paclitaxel/carboplatin (77%) and cyclophosphamide/doxorubicin/cisplatin arms (71%). Although not common, significantly more arthralgia/myalgia was reported in the paclitaxel than in the control arm of the OV10 trial (paclitaxel/cisplatin 7%, cyclophosphamide/ cisplatin < 1%, RR = 11.72 (95% CI: 2.79 to 49.18) *Table 57*). For the OV10 trial a greater incidence of hypersensitivity and allergic reactions was reported in the paclitaxel than in the control arm, despite premedications (RR = 3.35 (95% CI: 1.46 to 7.66)).

Quality of life

None of the trials reported on QoL. It was assessed in the OV10 trial by using the EORTC-QLQ-C30+3 questionnaire and a trial-specific checklist for ovarian cancer. No results are available. In the ICON3 trial, QoL was assessed in terms of treatment-related toxicity, and of anxiety and depression. These results have not yet been reported.

Discussion

About half the patients in the paclitaxel plus platinum arms responded to this treatment (range 46–72%). With the exception of the GOG132 trial, there was no significant difference between the treatments in terms of response rates. Cisplatin had a superior response rate to paclitaxel in the GOG132 trial.

The median length of progression-free survival for the paclitaxel/platinum combination arms ranged from 14.1 months (GOG132) to 18 months (GOG111). Two of the four trials (GOG111 and OV10) showed the progression-free survival rate of the paclitaxel arm to be significantly superior to the control arm; differences in the other trials were not statistically significant.

TABLE 57 *Other adverse events*

Adverse event	GOG111 (%) RR (95% CI) (*n* = TpP: 184; CP: 201)	OV10 (%) RR (95% CI) (*n* = TpP: 338; CP: 330)	ICON3a (%) RR (95% CI) (*n* = TP: 478; P: 943)	ICON3b (%) RR (95% CI) (*n* = TpP: 232; CAP: 421)
Alopecia	TpP: 63 CP: 37 1.71 (1.38 to 2.12)		TpP: 68 P: 3 22.9 (15.82 to 33.15)	TpP: 77 CAP: 71 1.1 (0.99 to 1.20)
Arthralgia/myalgia		TpP: 7 CP: < 1 11.72 (2.79 to 49.18)		
Allergy	TpP: 4 CP: 0 16.38 (0.94 to 284)	TpP: 7 CP: 2 3.35 (1.46 to 7.66)		
Other			TpP: 2 P: 3 0.7 (0.35 to 1.44)	TpP: 1 CAP: 4 0.21 (0.1 to 0.9)

The median length of overall survival for the paclitaxel/platinum combination arms ranged from 26.6 months (GOG132) to 38 months (GOG111). Again, significant differences between treatment and control arms were found in two of the four trials (GOG111 and OV10), with paclitaxel superior to control.

Haematological adverse events and alopecia were reported frequently but gastrointestinal adverse events were less common. Neurosensory and neuromotor adverse events were significantly more likely to occur among patients treated with the paclitaxel combination. Allergy was also significantly more common among patients treated with paclitaxel. In the GOG132 trial, more patients in the platinum-only than the combined platinum and paclitaxel arm discontinued treatment early because of adverse events. This underlines the problems of dealing with non-blinded trials. The patients in these two arms might have been under different pressures to discontinue their treatment and try an alternative; possibly taxanes were considered to be more desirable.

Although QoL was measured in two trials the results have not been reported.

A major problem in interpreting these trials is the lack of publications. Only the GOG111 trial has been published in a peer-reviewed journal; the others have appeared only as conference presentations. This severely limits the amount of information available. Although trial protocols were made available, they do not contain results. The numbers of patients surviving in two trials were estimated from Kaplan–Meier curves and may not be accurate.

Superficially, the trials appear to be high-quality RCTs. They all allowed alternate treatment to be given on disease progression. Patients who change their treatment in such a way should be considered as treatment failures and censored from further analysis. The OV10 trial specified that progression should be documented before cross-over was allowed. In the GOG132 trial, a large number of participants in all arms crossed over to alternate treatments before progression, thus confounding results. A larger proportion of patients in the control arm of this trial discontinued that treatment because of adverse events or at their own request. The problems inherent in this trial and their implications have been discussed at length elsewhere.[75]

The ICON3 trial completed accrual only in October 1998; the results are based on a conference presentation in May 1999. These results are therefore very early, although the authors state that they are reliable for up to 2 years. This trial used a different baseline population; ICON3 included a wider range of patients than the other trials. In addition, carboplatin was used, unlike the GOG111, GOG132 and OV10 trials, which used cisplatin. Carboplatin is the platinum compound most commonly used in the UK.

Even if the ICON3 trial does eventually produce different results, this does not invalidate the GOG111 and OV10 trials, which are of high quality. The ICON3 trial included a far wider range of patients than either of these. Furthermore, it is sufficiently large to allow subgroup analyses. It is possible that the effectiveness of paclitaxel depends on the stage of ovarian cancer. The mature results of the ICON3 trial should be able to elucidate such issues.

A second reason why the ICON3 trial could produce different results is because of the use of carboplatin rather than cisplatin. Carboplatin is the platinum analogue of choice in the UK; no difference has been shown in the effectiveness of these two single-agent analogues.[13] However, this may not be the case when they are used in combination. A trial by the AGO research group is currently comparing the effectiveness of cisplatin and carboplatin combinations as first-line treatment of ovarian cancer.[76]

Summary: paclitaxel as first-line treatment for advanced ovarian cancer

Four RCTs were identified that investigated the first-line use of paclitaxel in ovarian cancer. A total of 3746 patients were included. Two of the trials found paclitaxel/platinum combinations to be superior to a control in terms of median progression-free survival and numbers of patients surviving without progression at 12 months. Both these trials suggest that, for one extra patient to survive without progression to 1 year, six patients would have to be treated with the paclitaxel/platinum combination. This difference was not found in the two other trials, one of which was confounded by cross-over; the other was reported very early. The paclitaxel/platinum combination is currently the recommended first-line treatment for ovarian cancer. There is no reliable evidence to support changing these recommendations. It will be necessary to review these findings when the ICON3 trial is suitably mature, in about mid-2000.

Economic evaluations of paclitaxel in advanced ovarian cancer

Description of studies

A total of 13 cost evaluations of paclitaxel use in ovarian cancer were found. Among these were ten cost-effectiveness analyses (although one of these was submitted in confidence and has not been included here) and three cost–utility analyses. The publication dates ranged from 1996 to 1999, representing analyses in eight countries and are largely based on the results of the GOG111 trial. Modelling was used to extrapolate effectiveness from the trial length (48 months) to LYG, or to estimate resource use in a "real world" scenario. Resource use outside of a clinical trial can vary considerably owing to factors such as local practice patterns, patient compliance and rates of hospitalisation for treating adverse effects. *Table 58* presents descriptions of cost-effectiveness studies, which included:

- country in which the study was undertaken
- currency used in the analysis (and, where given, the year of currency used)
- stage of ovarian cancer
- drug regimen and response rates
- sources of efficacy data
- resource use and cost data
- type of model employed.

The body surface area assumed when calculating the costs of chemotherapy and related drugs was given in only three studies.

Results

Table 59 presents the results of these studies in terms of the following:

- which costs are included in the analysis
- total costs (typically per patient)
- benefits assumed
- synthesis of costs and benefits
- authors' conclusions.

Benefits measured in these studies are typically LYG or PFLYG.

Quality issues

Tables 60 and *61* present descriptions and results of the three cost–utility analyses. *Table 62* is a validity assessment of 12 studies based on the methods of Drummond *et al.*[29]

In all of these studies, the intervention being studied was paclitaxel plus cisplatin.

Choice of comparator

The choice of comparator (alternative treatment) in economic analyses is important. If the comparator is inappropriate, the results may not be generalisable. In the economic analyses reviewed, the estimation of benefit was based on a direct comparison in only eight of 13 studies. The comparator used in these studies of ovarian cancer was most often cyclophosphamide and cisplatin because this was the comparator used in the GOG111 trial. It has been stated that this regimen is not the most common alternative used in the UK,[11] but rather carboplatin alone is used. Until the results of the ICON3 study are available, there is no direct comparison of paclitaxel plus carboplatin with carboplatin alone. Either the results of the GOG111 trial must be used, or assumptions about carboplatin's efficacy must be made from other trials, which can introduce bias. Another reason for the importance of the comparator chosen is because of the effect it can have on the incremental benefits and costs, such as differing response rates, drug costs or the treatment of adverse effects. These differences in benefits or costs can move in either a positive or a negative direction.

Resources and costs included

The identification of resources used, costs included and the source of these cost data can also have a significant impact on the generalisability of the results. Resource use and costs in non-NHS systems may be quite different. However, if the relative costs are similar to the UK, then comparisons can still be made by using incremental costs and cost-effectiveness ratios. The choice of costs included can alter the incremental costs, particularly if important costs are omitted. Auxiliary drugs used, such as the premedications that are given prior to paclitaxel use, and stem cell-stimulating drugs that are given in the event of myelosuppression, are examples that could alter costs. More important may be hospitalisation costs for drug administration and the treatment of adverse events. In the GOG111 study paclitaxel was infused on an inpatient basis over 24 hours, requiring a 2-day hospital stay. More recent studies have shown that a 3-hour infusion is safe and can be done on an outpatient basis. Assumptions regarding the need for hospitalisation to treat myelosuppression or infections and the rate of significant side-effects may also affect the costs. Sensitivity analyses or comparing similar studies that have and have not included these may help to define the significance of these variations.

TABLE 58 *Ovarian cancer cost-effectiveness studies: descriptions*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
Sugiyama *et al.*, 1999[77]	Japan/ Japanese ¥ (year not stated)	Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), x 6 cycles TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2), 24-h infusion, x 6 cycles ***% of 216 patients with measurable disease response*** TpP: 73 CP: 60 p = 0.01 ***Median survival (mo)*** TpP: 37.5 CP: 24.4 p = 0.0001 ***% major side-effects*** TpP: 4.6 CP: 3	GOG111 multicentre RCT, 1996	Japanese prices substituted into McGuire[78] model Source and specific costs used not stated	Used methods of McGuire economic study[78] Period modelled: 48 mo
Beard *et al.*, 1998[18]	UK/ £ sterling (year not stated)	AOC: ECOG level > 2, FIGO > 1	P: carboplatin alone 400 mg/m^2 (plus premedications) x 6 cycles (assuming body surface area 1.8 m^2) P: cisplatin 75 mg/m^2 Tp: paclitaxel 135 mg/m^2 i.v., 24-h infusion x 6 cycles (assuming body surface area 1.8 m^2) P: cisplatin 75 mg/m^2 Tp: paclitaxel 175–200 mg/m^2 i.v., 3-h infusion x 6 cycles (assuming body surface area 1.8 m^2) Effectiveness of TpP from the OV10 trial substituted for the GOG111 results used in 1997 report (% response rates: TpP: 77; CP: 6)	OV10 multicentre RCT, 1997 (abstract) and GOG111 multicentre 1996 Literature search for studies using carboplatin alone for sensitivity analysis	From Beard *et al.*, 1997 report[17]	None for base-case (median values used from 48-mo study) Survival gains estimated from time-to-event analysis Period modelled: lifetime

AOC, advanced ovarian cancer

continued

TABLE 58 contd *Ovarian cancer cost-effectiveness studies: descriptions*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
Berger *et al.*, 1998[79]	Germany, Italy, Spain, The Netherlands, UK/presented in US$ (year not stated)	Histologically confirmed Stage III epithelial ovarian cancer with residual mass > 1 cm or Stage IV No prior chemotherapy	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), x 6 cycles TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2), 24-h infusion, x 6 cycles Body surface area of 1.76 m^2 assumed ***% of 216 patients with measurable disease response:*** TpP: 73 CP: 60 p = 0.01 ***Median survival (mo)*** TpP: 37.5 CP: 24.4 p = 0.0001 ***% major side-effects*** TpP: 4.6 CP: 3	GOG111 multicentre RCT, 1996	Resource use determined by interviews with experts in 6 countries Additional interviews and literature used to validate results Prices obtained from interviews with hospital employees and official price lists (1995–1996)	DEALE (declining exponential approximation of life expectancy) approach to calculation of specific life expectancy based on actuarial methods Period modelled: lifetime
Messori *et al.*, 1998[85]	Italy/ presented in US$ (year not stated)	Newly diagnosed AOC	Paclitaxel–cisplatin regimens at "standard doses", non-paclitaxel–cisplatin regimens at "standard doses"and "high-dose" chemotherapy with autologous haematopoietic rescue Meta-analysis was used where more than one trial examined the same regimen	Systematic review and meta-analysis of published literature (1984–1997) 1 study found with paclitaxel–cisplatin at standard doses Only studies enrolling 50 or more patients and measured survival from time of diagnosis were included	3 published pharmaco-economic analyses (1996–1997) Incremental costs for BMT only were calculated, so no costs for standard cisplatin regimens given	Survival gains estimated from time-to-event analysis Survival curve fitting normalised to a population of 100 patients Period modelled: lifetime

BMT, bone marrow transplantation

continued

TABLE 58 contd *Ovarian cancer cost-effectiveness studies: descriptions*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
Beard *et al.*, 1997[17]	UK/ £ sterling (year not stated)	AOC: ECOG level > 2, FIGO > 1	P: carboplatin alone 400 mg/m^2 (plus premedications), x 6 cycles (assuming body surface area 1.8 m^2) P: cisplatin 75 mg/m^2 Tp: paclitaxel 135 mg/m^2 x 6 cycles (assuming body surface area 1.8 m^2) Efficacy of carboplatin alone is assumed to be the same as CP in the main analysis Response rates from other trials (not including a taxane) are used in the secondary analyses Efficacy of TpP taken from the GOG111 trial	GOG111 multicentre RCT, 1996 Literature search for studies using carboplatin alone for sensitivity analysis	Specific sources and years of cost data not stated, only that they are from the Trent region Costs of adverse effects above those seen with carboplatin were included for paclitaxel, but not the reverse (adverse effects seen with carboplatin but not with paclitaxel) Resource use based on 6 cycles of chemotherapy, and incidence of alopecia and fever for paclitaxel in the GOG111 trial Source of other resource use not stated	None for base-case (median values used from 48-mo study) Survival gains estimated from time-to-event analysis Period modelled: lifetime
Elit *et al.*, 1997[81]	Canada/ Can$, 1993	Stage III and IV ovarian cancer	CP: cyclophosphamide 750 mg/m^2 i.v. + cisplatin 75 mg/m^2 i.v. TpP: paclitaxel 135 mg/m^2 i.v. + cisplatin 75 mg/m^2 i.v., 24-h infusion Every 3 wk x 6 cycles ***% of 216 patients with measurable disease response*** TpP: 73 CP: 60 *p* = 0.01 ***Median survival (mo)*** TpP: 37.5 CP: 24.4 *p* = 0.0001 **% major side effects** TpP: 4.6 CP: 3	GOG111 multicentre RCT, 1996	Resource data derived from assumptions and hospital cost data for 1993 from a local model Pharmacy drug costs and insurance schedule of benefits "McMaster Cost Model" incorporated overhead costs	Survival gains estimated from time-to-event analysis Analysed survival at 3-mo intervals up to 5 years

continued

TABLE 58 contd *Ovarian cancer cost-effectiveness studies: descriptions*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
McGuire *et al.*, 1997[78]	USA/ US$, 1996	Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), x 6 cycles TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2), 24-h infusion, x 6 cycles ***% of 216 patients with measurable disease response rate*** TpP: 73; CP: 60 p = 0.01 ***Median survival (mo)*** TpP: 37.5; CP: 24.4 p = 0.0001 ***% major side-effects*** TpP: 4.6; CP: 3	GOG111 multicentre RCT, 1996	Total drug acquisition, facility, adverse effect management and follow-up costs Costing based on real world scenario of resource use as determined by expert panel of 5 clinical oncologists Activity-based costing approach utilised in valuing costs using the Resource Based Relative Value Schedule (RBRVS) Drug acquisition costs derived from the Oncology Therapeutics Network	Economic model based on recommendations of panel of clinical oncologists who compared clinical trial resource use with "real world" resource use Monte Carlo simulation used to analyse the robustness of the estimates to variation in data Survival gains estimated from time-to-event analysis
Covens *et al.*, 1996[82]	Canada/ Can$, 1993	Diagnosis of Stage IIIC or IV AOC, excluding patients with major co-morbidities at diagnosis	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), x 6 cycles (average achieved: 5.5) TpP: paclitaxel (135 mg/m^2), 3-h infusion + cisplatin (75 mg/m^2) 24-h infusion, x 6 cycles (average achieved: 5.4) ***% of 216 patients with measurable disease response rate*** TpP: 73; CP: 60 p = 0.01 ***Median survival (mo)*** TpP: 37.5; CP: 24.4 p = 0.0001 ***% major side effects*** TpP: 4.6; CP: 3	GOG111 multicentre RCT, 1996	Standard daily costs for each phase of the model calculated based on resource utilisation of a retrospective chart review of 18 AOC patients Dates of prices refered to not stated, but are reported in 1993 Canadian $ Source of cost information: pharmacy ordering catalogues, the Ontario Schedule of Benefits, and the Case Cost System of the Sunnybrook Center Dates for collection of resource utilisation 1988–1992, and 1995 guidelines	"Simple linear modelling" to estimate costs and effectiveness in typical Toronto population Assumptions: 1. 50% increase in average duration of survival time in the paclitaxel group 2. The 50% increase is seen in the first follow-up phase after initial chemotherapy and is attributable to the regimen alone 3. Frequency of resource utilisation is the same between groups (other than initial chemotherapy used) 4. 25% of all cycles administered on an inpatient basis

continued

TABLE 58 contd *Ovarian cancer cost-effectiveness studies: descriptions*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
Messori *et al.*, 1996[83]	Italy/ presented in US$ (year not stated)	Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), x 6 cycles TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2), 24-h infusion, x 6 cycles ***% of 216 patients with measurable disease response*** TpP: 73 CP: 60 p = 0.01 ***Median survival (mo)*** TpP: 37.5 CP: 24.4 p = 0.0001 ***% major side-effects*** TP: 4.6 CP: 3	GOG111 multicentre RCT, 1996	Resources estimated from the clinical trial used for efficacy data (GOG111) Costs estimated from published sources (1993 USA, 1995 The Netherlands)	Survival gains estimated from time-to-event analysis Survival curve fitting, normalised to a population of 100 patients to extrapolate study data to lifetime experience

TABLE 59 *Ovarian cancer cost-effectiveness studies: results*

Reference	Costs	Benefits	Synthesis	Conclusions
Sugiyama *et al.*, 1999[77]	***Medication costs for 6 cycles (¥)*** Cyclophosphamide group 469, 862 Paclitaxel group 1,438,710	***Survival duration (yr)*** CP: 2.03 TpP: 3.13 (means from effectiveness study)	Incremental cost per LYG was ¥2,201,927 (assuming outpatient treatment)	Values in Japan were similar to those found by McGuire[78]
Beard *et al.*, 1998[18]	***Incremental treatment costs per person (£)*** GOG111 results: 8368 OV10 results: 8368	***Median LYG*** GOG111 results: incremental 1.17 OV10 results: incremental 0.83 ***PFLYG*** GOG111 results: incremental 0.42 OV10 results: incremental 0.38	GOG111 results: cost (£) per extra LYG = 7173 OV10 results: cost (£) per extra LYG = 10,081 (175 mg/m^2 i.v. 3-h infusion = 10,827; 200 mg/m^2 i.v. 3-h infusion = 12,417) GOG111 results: cost (£) per PFLYG = 20,084 OV10 results: cost (£) per PFLYG = 22,021	Economic analysis varies little irrespective of which trial results used OV10 survival benefits show slightly less difference from those suggested by the GOG111 trial, despite the fact that patients with a wider scope of disease severity were recruited into the study; however, they remain significant
Berger, 1998[79]	Costs included: medications (chemotherapy, premedications, treatment of adverse events), hospitalisation/clinic stay for chemotherapy administration, average number of consultant and laboratory tests or investigations ***Total treatment costs per patient by country (US$)*** *Germany*: CP: 12,578; TpP 24,487 *Spain*: CP: 9290; TpP: 17,520 *France*: CP: 8502; TpP: 17,150 *Italy*: CP: 6578; TpP: 21,230 *Netherlands*: CP: 6537; TpP: 16,547 *UK*: CP: 4926; TpP: 13,038	***Median overall survival (yr)*** CP: 2 TpP: 3.2 ***Life expectancy by country*** *Germany*: CP: 2.56; TpP: 3.83 *Spain*: CP: 2.57; TpP: 3.86 *France*: CP: 2.58; TpP: 3.88 *Italy*: CP: 2.56; TpP: 3.85 *Netherlands*: CP: 2.57; TpP: 3.85 *UK*: CP: 2.56; TpP: 3.82	***Incremental costs per LYG (US$)*** *Germany*: 9362 *Spain*: 6395 *France*: 6642 *Italy*: 11,420 *Netherlands*: 7796 *UK*: 6403	Cost-effectiveness of paclitaxel + cisplatin compares favourably with other oncological interventions

continued

TABLE 59 contd *Ovarian cancer cost-effectiveness studies: results*

Reference	Costs	Benefits	Synthesis	Conclusions
Messori *et al.*, 1998[85]	Hospitalisation and drugs were the main costs included Only costs for BMT given (US$60,000 per person)	***Mean lifetime survival (yr)*** TpP: 2.95 (from McGuire study[67]) Pooled estimate for cisplatin regimens: 3.05 High-dose chemotherapy plus BMT rescue: 5.76 (from Legros study[87]) ***Incremental LYG*** High-dose chemotherapy + BMT rescue: 2.34	No survival difference found between cisplatin and TpP-based regimens, so no cost-effectiveness ratio calculated High-dose chemotherapy + BMT rescue: US$26,641 per discounted LYG	In the treatment of patients with AOC, high-dose chemotherapy with haematopoietic rescue seems to be more effective and more cost-effective than standard treatments with cisplatin-based regimens at conventional doses
Beard *et al.*, 1997[17]	***Total annual per patient cost (£)*** TpP: 10,427 P: 2059 Incremental cost per patient = £8368	***Median LYG*** TpP 3.17 P: 2.00 Incremental: 1.17 LYG ***PFLYG*** TpP 1.5 P: 1.08 Incremental: 0.42 PFLYG	Cost per extra LYG: £7173 Cost per PFLYG: £20,084 Sensitivity analyses did not change the results	Economic analysis of the treatment calculated that the introduction of a paclitaxel/cisplatin treatment programme for an average district population would cost £258,368 per year The treatment is expected to give each patient an average of 1.17 years extra survival at a cost of £7200 per LYG
Elit *et al.*, 1997[81]	Costs included: hospitalisation, drug, adverse event, physician and cancer centre (overheads) ***Costs per patient (Can$)*** TpP: 17,469 CP: 5228	Mean survival duration estimated to be prolonged from 2.06 yr with CP to 2.44 yr with TpP	Incremental analysis at 1993 prices and using 5% discount rates for both costs and benefits: additional cost of TpP per additional LYG relative to CP was estimated to be Can$32,213 Sensitivity analysis did not alter the results	Although paclitaxel prolongs survival it comes at an increased cost It may not be possible to fund paclitaxel using resources allocated to first-line therapy
McGuire *et al.*, 1997[78]	***Inpatient setting per-patient cost (US$)*** TpP: 29,824 CP: 21,086 ***Outpatient (US$)*** TpP: 27,320 CP: 17,964 Annual discount rate of 4% used	***Survival duration (yr)*** TpP: 3.13 CP: 2.03 (Means from effectiveness study)	Using 1996 prices and 4% discount, incremental cost (US$) per LYG: TpP: US$19,820 – inpatient treatments TpP: US$21,222 – outpatient treatments	Paclitaxel + cisplatin mean survival cost per LYG adds substantial benefit at an acceptable cost compared with cyclophosphamide + cisplatin Paclitaxel + cisplatin is a cost-effective alternative to the standard therapy for AOC Benefit at an acceptable cost compared with cyclophosphamide + cisplatin

continued

TABLE 59 contd *Ovarian cancer cost-effectiveness studies: results*

Reference	Costs	Benefits	Synthesis	Conclusions
Covens *et al.* 1996[82]	Costs included: inpatient and outpatient consultants and procedures, nursing care, laboratory tests and drugs Standard daily costs for each phase of the model were calculated based on resource utilisation of a retrospective chart review of 18 patients, carried out using AOC patients diagnosed between 1988 and 1992 The dates prices refer to are not stated Sources of cost information: the Ontario Schedule of Benefits and the Case Cost System of the Sunnybrook Center Incremental and average costs reported ***Total average cost per patient (Can$)*** Tp group: 50,054 Usual care group: 36, 837 Incremental cost for paclitaxel treatment: Can$13,217 Costs of adverse effects were included at the resource-use level for the usual care group, not specifically for Tp group	Overall weighted survival was 7.8 mo longer in the Tp group	Incremental costs per LYG were Can$20,355 Sensitivity analysis showed that the incremental cost-effectiveness ratio decreases as survival increases, the average cost of treatment increases moderately as survival increases, and the incremental costs per LYG drop significantly as survival increases	Even though paclitaxel combination therapy has a considerably higher drug acquisition cost, the results of the current analysis suggest that this new chemotherapy regimen provides patients with substantially quality-adjusted progression-free survival benefit at a reasonable cost to the Canadian health care system
Messori *et al.*, 1996[83]	Costs included: chemotherapeutic drugs, premedications, hospitalisation for chemotherapy administration, and hospitalisation and treatment costs for febrile neutropenia ***Total costs (US$)*** TpP: 1,302,002 per 100 patients CP: 400,279 per 100 patients Incremental cost of TpP: US$901,723 per 100 patients	Incremental undiscounted LYG: US$46 per 100 patients	Incremental cost per undiscounted LYG: US$19,603 per 100 patients	Pharmacoeconomic profile of paclitaxel compares favourably with economic data previously calculated for other types of pharmacological treatment

TABLE 60 *Ovarian cancer cost–utility analysis studies: description*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Methods
Messori *et al.*, 1997[80]	Italy/ reported in US$	Re-analysis of 1996 report[83] Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), x 6 cycles TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2), 24-h infusion, x 6 cycles ***% of 216 patients with measurable disease response*** TpP: 73; CP: 60 p = 0.01 ***Median survival (mo)*** TpP: 37.5; CP: 24.4 p = 0.0001 ***% major side-effects*** TpP: 4.6; CP: 3	GOG111 multicentre RCT, 1996	Resources estimated from the clinical trial used for efficacy data (GOG111) Costs estimated from published sources (1993 USA, 1995 The Netherlands)	Q-TWIST method combined with survival curve fitting
Ortega *et al.*, 1997[84]	Canada/ Can$, 1996	Stage IIIC and IV AOC	CP: cyclophosphamide (750 mg/m^2) + cisplatin (75 mg/m^2), x 6 cycles TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2), 24-h infusion, x 6 cycles ***% of 216 patients with measurable disease response*** TpP: 73; CP: 60 p = 0.01 ***Median survival (mo)*** TpP: 37.5; CP: 24.4 p = 0.0001 ***% major side-effects*** TpP: 4.6; CP: 3	GOG111 multicentre RCT, 1996	Resource use was estimated from a retrospective chart review of 36 patients, 12 of whom were treated with paclitaxel + cisplatin as first-line therapy Costs were obtained from pharmacy catalogues, nursing workload statistics, individual hospital departments, and the 1992 Schedule of Benefits	Decision analysis model

Q-TWIST, quality time spent without symptoms and toxicity

continued

TABLE 60 contd *Ovarian cancer cost–utility analysis studies: description*

Reference	Country/ currency	Stage of disease	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Methods
Best and Anthony, 1996[16]	UK/ £ sterling, 1996	Stage III and IV AOC	TpP: paclitaxel (135 mg/m^2) + cisplatin (75 mg/m^2), 24-h infusion, x 6 cycles P: carboplatin alone 400 mg/m^2 x 6 cycles CAP: cyclophosphamide (600 mg/m^2) + doxorubicin (45 mg/m^2) + cisplatin (50 mg/m^2), x 6 cycles **% *response*** TpP: 73 P: 54 CAP: 67 Body surface area of 1.73 m^2 assumed	TpP: GOG111 multicentre RCT, 1996 P and CAP: literature search of RCTs	Resource use taken largely from GOG111 trial Costs of hospital and clinic stays from NHS trust figures from South and West regions Sources of other costs not given	Calculated QALYs for an untreated patient and QALYS gained for each treatment regimen

Cost-effectiveness analyses

If it is assumed that resource use and the relative costs of drugs are the same across all of these studies, the results can be converted to pounds sterling for comparison purposes. The years of these studies are quite similar, so no reflation to 1999 prices is necessary. For studies comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin, the range of cost-effectiveness ratios for LYG was £3960–£13,360. The low estimate was for Spain[79] and the high rate was for Japan.[77] Two cost-effectiveness studies carried out in the UK compared carboplatin alone to paclitaxel plus cisplatin (one of these was an update of another).[17,18,86] One of the economic evaluations[86] is not discussed here because of confidentiality. The range of cost-effectiveness ratios for LYG was £7173–£12,417. These studies also calculated a PFLYG ratio; the range was £20,084–£22,021. The difference between these two measures, LYG and PFLYG, may have important QoL issues. Progression-free life-years may be preferable to overall life-years because the QoL would be generally assumed to be better during the progression-free period.

Cost–utility analyses

One cost–utility analysis was carried out in the UK.[16] This compared paclitaxel plus cisplatin, carboplatin alone, and CAP, to no treatment. Although superficially similar to the ICON3 trial, the data on response rates were obtained from a variety of disparate trials. Very few details on how QALYs gained were derived were given, except that the Index of Health-Related QoL measure was used. Cost per QALY was calculated for each regimen compared with no treatment, but an incremental analysis comparing treatments to each other was not carried out. For the purposes of this report, an analysis that is compared with no treatment is not appropriate. However, by using the costs and QoL estimates given in this analysis, the incremental cost per QALY gained can be calculated. On comparing paclitaxel/platinum with CAP, this is £5433 and, versus carboplatin alone, it is £5273.

The two non-British cost–utility analyses also addressed QALYs. The cost per QALY gained in the Messori study when using the Q-TWIST method was £11,269.[80] In Ortega *et al.*'s study, which incorporated patients' preferences, the cost per quality-adjusted PFLYG ranged from a low of £6860 to a high of £10,377.[84] In a sensitivity analysis, the maximum cost per quality-adjusted PFLYG was £18,000.

TABLE 61 *Ovarian cancer cost–utility analysis: results*

Reference	Costs	Benefits	Synthesis	Conclusions
Messori *et al.*, 1997[80]	Included costs: chemotherapeutic drugs, premedications, hospitalisation for chemotherapy administration, and hospitalisation and treatment costs for febrile neutropenia ***Total costs (US$)*** TpP: 1,302,002 per 100 patients CP: 400,279 per 100 patients Incremental cost of TpP = US$900,000 per 100 patients	Incremental undiscounted QALY: 49.4 per 100 patients	Incremental cost per QALY per 100 patients: $18,200	Limitations of this technique include: 1. The measured survival time must be much greater than the extrapolated time 2. The assumptions of utilities used in standard Q-TWIST studies were transferred without modification for this disease/treatment
Ortega *et al.*, 1997[84]	Included costs: hospitalisation, outpatient clinic visits, antiemetics, chemotherapy, laboratory tests, patient monitoring, adverse effects, management, and related physician fees during treatment phases, and physician visits and laboratory monitoring during progression-free survival ***Total median costs per cycle (Can$)*** TpP: 1911 CP: 459 ***Total median costs of second-line therapy (Can$ per cycle)*** Tp: 2443 Ifosfamide: 5190 Hexamethylamine: 670 Tamoxifen: 67	Incremental progression-free months with Tp: 3 Healthy months equivalent gained, using healthy volunteer valuations: 6.1 Healthy months equivalent gained, using patient preferences: 10–10.6	Incremental cost per quality-adjusted progression-free year ranged from Can$11,600 to $24,200, depending on which second-line treatment was chosen Sensitivity analysis showed that the maximum incremental cost per quality-adjusted progression-free year was Can$42,000	Paclitaxel, in combination with cisplatin, appears to be a cost-effective first-line treatment for AOC A moderate increase in incremental cost compares favourably with other life-saving strategies currently in use As more data become available for paclitaxel, this pilot study will provide a basis for a more extensive economic evaluation of this agent
Best and Anthony, 1996[16]	Total costs of treatment and management of adverse effects given in summary form ***Total costs per patient (£)*** TpP: 8680 C: 2880 CAP: 3790	***QALYs*** 100 untreated patients: 27 ***QALYs gained with treatment (per 100 patients)*** TpP: 200 C: 90.5 CAP: 112.3	***Cost per QALY gained (£)*** TpP: 4340 C: 3180 CAP: 3370	The use of paclitaxel + platinum was recommended, with the caveat that this recommendation be reviewed in 12–18 mo, after more clinical trial data were available

Quality assessment

On examining the quality of these studies, it becomes clear that generalisability could be a problem because of a lack of specific information, source of efficacy, resource use and cost data, and the assumptions that were made. *Table 62* is a critical assessment of these economic evaluations. The areas examined in each study are:

- study question posed
- comprehensive description of competing alternative
- how established is the effectiveness of the interventions
- inclusion of all important costs and consequences
- accurate measurement of these costs and consequences
- credibility of their valuations
- use of discounting if appropriate
- use of an incremental analysis
- use of sensitivity analysis
- breadth and depth of the discussion and conclusions.

The areas where the studies were most often deficient were those relating to costs and consequences. Several studies did not report in enough detail which costs and consequences were considered, or they had somewhat limited or vague inclusion lists. Likewise, the methods for measuring and valuing these costs and consequences were often vague or were lacking altogether. The discounting of costs or benefits was not attempted in most studies, owing to the short time-course of the chemotherapy costs and the incremental benefits. One study did discount both costs and benefits for those that did extend beyond the 1-year mark.[81] All costs were discounted by 4% in another study,[78] and a third included a 5% discount of benefits in the sensitivity analysis.[83] Overall, the studies did well on using an incremental analysis, sensitivity analysis, providing an appropriate discussion, and formulating a well-defined study question. Whether the effectiveness rates used were well established is debatable; however, at the time that many of these studies were carried out, the GOG111 trial was the only completed study comparing paclitaxel plus cisplatin with any standard regimen. The description of treatments was rather poor in that the use of premedications and the body surface area used were rarely reported.

Two UK studies assumed in their primary analysis that the effectiveness of carboplatin alone was the same as that with the use of cisplatin plus cyclophosphamide in the GOG111 trial.[17,18,86] A secondary analysis used efficacy rates for carboplatin found in the literature, in studies comparing carboplatin to a non-taxane-containing regimen. Both of these methods have drawbacks, which are acknowledged by the authors. They state that, in using the response rates of cisplatin plus cyclophosphamide for carboplatin, carboplatin's benefits may be overstated. They considered that this was acceptable because a cost-effectiveness ratio in favour of paclitaxel plus carboplatin under these conditions would be more convincing. In the 1997 report,[17] only the costs related to adverse effects associated with paclitaxel were included. It was assumed that the costs of adverse effects related to carboplatin and cisplatin would be equivalent; those of cyclophosphamide were not mentioned. Sources of cost resource-use information and methods of valuing these were not well described, which limits generalisability. However, a sensitivity analysis using national costs compared with regional costs is presented.

In the 1998 report,[18] response rates for paclitaxel plus cisplatin from the OV10 (ECOCIT) trial were substituted for those of the GOG111 trial. The OV10 trial included patients diagnosed with Stage II ovarian cancer, whereas the cost-effectiveness exercise is based on only Stage III–IV patients. The OV10 trial also used a dose range of 175–200 mg/m^2 of paclitaxel administered over 3 hours (rather than 135 mg/m^2 over 24 hours as used in the GOG111 trial). Various combinations of the resource-use and cost implications from the OV10 and GOG111 trials were presented.

However, these are the only studies originating in the UK that compared paclitaxel plus cisplatin with the standard first-line drug used in this country.

The range of incremental costs per LYG (£7173–£12,417) found in these two UK studies is within the range reported above for all studies comparing paclitaxel/platinum to cyclophosphamide/platinum (£3960 to £13,360). The incremental cost per QALY gained was between £5273 and £11,269, also within the same range. The incremental cost per progression-free life-year reported in two of the UK studies[17,18] was higher (£20,084–£22,021); however the quality-adjusted PFLYG calculated by Ortega *et al.*[84] in a more robust analysis (*Table 61*) was lower (£6860–£10,377) and within the range identified for cost per LYG.

TABLE 62 *Validity assessment of economic evaluations (Drummond* et al.[29]*)*

Critical assessment questions[29]	Sugiyama *et al.*, 1999[77]	Beard *et al.*, 1998[18]	Berger *et al.*, 1998[79]	Messori *et al.*, 1998[85]	Beard *et al.*, 1997[17]	Elit *et al.*, 1997[81]	McGuire *et al.*, 1997[78]	Messori *et al.*, 1997[80 a]	Ortega *et al.*, 1997[84 a]	Best and Anthony, 1996[16 a]	Covens *et al.*, 1996[82]	Messori *et al.*, 1996[83]
Well-defined question	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Comprehensive description of alternatives	✔	✔– Applying ECOCIT results to a different patient population	✔	– Only described as "standard doses"	✔	✔– Unclear if premedication included	✔– Unclear if premedication included	– Based on 1996 study[83]	✔– Unclear if premedication included	✔	✔– Unclear if premedication included	✔
Effectiveness established	✔	✔– Effectiveness of P (carboplatin) alone assumed to be the same as CP	✔	✔	✔ Effectiveness of P (carboplatin) alone assumed to be the same as CP	✔	✔	–	✔	✔	✔	✔
All important and relevant costs and consequences for each alternative identified	✔– Unclear if same resources as in McGuire study[78]	✔– Difficult to identify specific costs included; adverse effects of Tp considered, but not those of C	✔	✔– Only hospital and drug costs	✔– Difficult to identify specific costs included; adverse effects of Tp considered, but not those of C	✔	✔	–	✔	✔	✔	✔
Costs and consequences measured accurately	? Method of measurement not stated	? Method of measurement not stated	✔	? Not clearly stated	? Method of measurement not stated	✔	✔	–	✔	✔	✔	✔– Estimated from clinical trial
Costs and consequences valued credibly	? Method of valuation not stated	✔–	✔– Mixed sources compared	? Taken from previous cost-effectiveness analyses, but costs used for TpP/CP not stated	✔–	✔	✔	? Utility scores arbitrarily assigned at 0.5	✔	✔– Sources of some costs/ consequences not clearly stated	✔– "Standard" daily costs reported	✔– Costs from The Netherlands and USA used in same model

[a] *Cost–utility analysis, all others cost-effectiveness analysis*

✔*yes;* ✔*– maybe/partially;? unknown; – no*

continued

TABLE 62 contd *Validity assessment of economic evaluations (Drummond* et al.[29]*)*

Critical assessment questions[29]	**Sugiyama *et al.*, 1999**[77]	**Beard *et al.*, 1998**[18]	**Berger *et al.*, 1998**[79]	**Messori *et al.*, 1998**[85]	**Beard *et al.*, 1997**[17]	**Elit *et al.*, 1997**[81]	**McGuire *et al.*, 1997**[78]	**Messori *et al.*, 1997**[80 a]	**Ortega *et al.*, 1997**[84 a]	**Best and Anthony, 1996**[16 a]	**Covens *et al.*, 1996**[82]	**Messori *et al.*, 1996**[83]
Costs and consequences adjusted for differential timing	NA	NA	NA	NA	NA	Costs and benefits occurring after 1 yr discounted at 5%	Costs discounted at 4%	NA	NA	NA	NA	NA Discounted benefits at 5% in sensitivity analysis
Incremental analysis of costs and consequences	✔	✔	✔	✔– Incremental analysis for haematopoietic rescue only	✔	✔	✔	✔	✔	–	✔	✔
Sensitivity analyses to allow for uncertainty in estimates of cost or consequences	–	✔ Results not found to be sensitive to parameters tested	✔	✔	✔	✔	✔	–	✔	✔	✔	✔
Study results/ discussion include all issues of concern to users	✔	✔	✔	✔– Addressed the results with respect to BMT only	✔	✔	✔	–	✔	✔– Very little discussion	✔	✔– Not clear to what setting these results refer

[a] *Cost–utility analysis, all others cost-effectiveness analysis*

✔*yes;* ✔*– maybe/partially; ? unknown; – no*

Summary of economic evaluation of paclitaxel in advanced ovarian cancer

The acceptability of an incremental cost-effectiveness ratio of £13,000 per LYG or £20,000 per PFLYG must be considered. A cut-off of £20,000 has previously been suggested; ratios above this mark are often accepted.[29] The fact that these data rely primarily on one study for efficacy data, and that only three analyses including carboplatin alone as the alternative therapy have been carried out, should be kept in mind. However, at this point, the cost-effectiveness and cost–utility ratios of the paclitaxel/cisplatin regimen compared with either cyclophosphamide/platinum or carboplatin alone appear to fall within accepted ranges.

Chapter 6
Conclusions

Both paclitaxel and docetaxel are licensed for use as second-line treatment for breast cancer. The evidence to support the use of paclitaxel in this context is not strong: a single, small Phase II RCT. However, there are ongoing, multicentre randomised controlled Phase III trials, one comparing epirubicin and paclitaxel versus epirubicin and cyclophosphamide (ABO1), and another comparing doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide (EORTC), in the treatment of women with metastatic breast cancer. These trials should provide a clearer picture of the role of paclitaxel in breast cancer.

There is a greater body of evidence to support the use of docetaxel as a second-line treatment for advanced breast cancer, especially among women who are resistant to anthracyclines. In one trial there was an advantage in overall survival of 2.5 months compared with control. There were no differences in QoL. In addition, docetaxel was found show similar effectiveness to doxorubicin, so it may be useful in the treatment of women for whom anthracyclines are contraindicated.

In terms of cost-effectiveness in the second-line treatment of breast cancer there is some evidence of mixed quality, which suggests that docetaxel versus vinorelbine or paclitaxel versus mitomycin are cost-effective in the UK setting. These studies are weakened by the lack of direct comparison data. Docetaxel and paclitaxel have been compared, despite the lack of a direct clinical comparison. Docetaxel was found to be highly cost-effective when compared with paclitaxel.

The best available evidence supports the use of paclitaxel, in combination with platinum, in the first-line treatment of ovarian cancer. Two trials showed paclitaxel to be superior to control in terms of overall survival. This treatment combination was also found to be cost-effective. The mature results of the ICON3 trial will also add to our understanding of the comparative costs and benefits of cisplatin and carboplatin. As the results of the ICON3 trial mature, they may be able to demonstrate for which subgroups of women this treatment is more or less appropriate. In addition, when complete and mature, the SCOTROC Phase III comparison of paclitaxel/carboplatin versus docetaxel/carboplatin as first-line chemotherapy in ovarian cancer should provide information on the comparative merits of these two taxanes.

The range of median progression-free and overall survivals found in the RCTs are given in *Table 63*.

This review is based on currently available evidence. There are several relevant trials in progress, which will need to be taken into consideration once they are suitably mature. Further recommendations for primary research are premature before the final results of ongoing research are published in full. Updating this systematic review is therefore the most pertinent research recommendation at this stage.

TABLE 63 *Summary of effectiveness evidence*

Review question			Range (mo) of median progression-free survival or median time to treatment failure (control)	Range (mo) of median overall survival (control)
Cancer	**Level of treatment**	**Chemotherapy**		
Breast	First-line	Tp	4.0–5.9[a] (6.0 – 7.5)	17.3–22.2 (13.9–18.9)
		Tp + A	8.0–8.3[b] (6.0–6.2)	22.0–22.7[c] (18.3–18.9)
	Second-line	Tp	3.5[d] (1.6)	12.7[e] (8.4)
		Td	4.7–7.0[f] (2.7–5.0)	10.4–15[g] (8.7–14)
Ovary	First-line	Tp	14.1–18[h] (11.8–16.4)	26.6–38[h] (25–30.2)

[a] *Control significantly better than Tp in 1/3 trials*
[b] *Tp + A significantly better than control in 2/2 trials*
[c] *Tp + A significantly better than control in 1/2 trials*
[d] *Tp significantly better than control in 1/1 trial*
[e] *Tp significantly better than control in 1/1 trial*
[f] *Td significantly better than control in 2/4 trials*
[g] *Td significantly better than control in 1/4 trials*
[h] *Tp + P significantly better than control in 2/4 trials*

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Appendix 1

Staging of ovarian and breast cancer

FIGO staging for epithelial cancer of the ovary (adapted from Williams, 1990[4])

Stage Ia–b may be referred to as early ovarian cancer; later stages may be referred to as advanced.

Stage I: growth limited to the ovaries:

Ia one ovary involved
Ib both ovaries involved
Ic ascites (an accumulation of fluid in the abdominal (peritoneal) cavity) present or peritoneal washings positive for malignant cells.

Stage II: growth limited to pelvis:

IIa extension to gynaecological adnexae (on or in a structure associated with the uterus such as an ovary, fallopian tube or uterine ligament)
IIb extension to other pelvic tissues
IIc ascites or positive washings.

Stage III: growth extending to abdominal cavity

Tumour involves one or both ovaries, with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastases; tumour limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.

IIIa tumour grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel or mesentery
IIb tumour of one or both ovaries with histologically confirmed implants; peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
IIIc Peritoneal metastasis beyond the pelvis > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV: metastases to distant sites (including hepatic parenchymal disease)

Simplified UICC staging of breast cancer (adapted from Williams, 1990[4]):

T	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	N0	no palpable axillary lymph nodes
	N1	mobile ipsilateral nodes
	N2	fixed ipsilateral nodes
	N3	supraclavicular or infraclavicular nodes
M	M0	no distant metastases
	M1	distant metastases.

Clinical staging

Combinations of the above two staging classifications are used to define clinical staging. Early breast cancer comprises Stages I and II; advanced Stages III and IV.

Stage I

Small tumour (< 2 cm).

Stage II

Tumour > 2 cm but < 5 cm, lymph nodes negative
or
Tumour < 5 cm, lymph nodes positive, no detectable distant metastases.

Stage 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 no detectable distant metastases.

Stage IV:
- tumour of any size
- lymph nodes either positive or negative
- distant metastases.

Appendix 2

Search strategy

MEDLINE

No.	Records	Request
001	43,556	explode "Breast-Neoplasms"/ all subheadings
002	10,216	ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
003	3,858	ovar* near4 ((oncolog* or carcinoma*) in ti ab)
004	8,158	breast* near4 ((oncolog* or carcinoma*) in ti ab)
005	33,236	breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
006	12,781	explode "Ovarian-Neoplasms"/ all subheadings
007	413	(adnexa* near mass*)
008	62,631	#1 or #2 or #3 or #4 or #5 or #6 or #7
009	3,225	"Paclitaxel"/ all subheadings
010	3,698	paclitaxel*
011	645	docetaxel*
012	2,226	taxol*
013	306	taxotere*
014	245	taxanes
015	4,222	#9 or #10 or #11 or #12 or #13 or #14
016	1,484	#8 and #15
017	155,093	trial in pt
018	34,593	explode "Clinical-Trials"/ all subheadings
019	33,955	(clin* near trial*) in ti ab
020	29,834	((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
021	5,087	Placebos
022	34,045	placebo* in ti ab
023	30,200	random in ti ab
024	9,745	research-design
025	238,118	#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
026	782	#16 and #25
027	32,870	exact{199801} in UD
028	29,902	exact{199802} in UD
029	37,979	exact{199803} in UD
030	35,221	exact{199804} in UD
031	32,443	exact{199805} in UD
032	31,625	exact{199806} in UD
033	39,481	exact{199807} in UD
034	34,067	exact{199808} in UD
035	31,128	exact{199809} in UD
036	38,577	exact{199810} in UD
037	32,157	exact{199811} in UD
038	33,456	exact{199812} in UD
039	39,266	exact{199901} in UD
040	31,845	exact{199902} in UD
041	39,104	exact{199903} in UD
042	35,845	exact{199904} in UD
043	35,417	exact{199905} in UD
044	32,628	exact{199906} in UD
045	42,976	exact{199907} in UD
046	34,225	exact{199908} in UD
047	43,309	exact{199909} in UD
048	30,766	exact{199910} in UD
049	774,287	#27 or #28 or #29 ... or #46 or #47 or #48
050	303	#26 and #49

EMBASE

No.	Records	Request
1	47,788	explode "Breast-Neoplasms"/ all subheadings
2	10,866	ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
3	4,342	ovar* near4 ((oncolog* or carcinoma*) in ti ab)
4	8,509	breast* near4 ((oncolog* or carcinoma*) in ti ab)
5	34,398	breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
6	14,633	explode "Ovarian-Neoplasms"/ all subheadings
7	451	(adnexa* near mass*)
8	66,698	#1 or #2 or #3 or #4 or #5 or #6 or #7
9	6,026	"Paclitaxel"/ all subheadings
10	2,488	paclitaxel*
11	679	docetaxel*
12	6,423	taxol*
13	1,474	taxotere*
14	365	taxanes
15	7,041	#9 or #10 or #11 or #12 or #13 or #14
16	2,416	#8 and #15
17	159,624	explode "Clinical-Trials"/ all subheadings

18	34,896	((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
19	345	Placebos
20	39,237	placebo* in ti ab
21	39,328	"randomized-controlled-trial"/ all subheadings
22	32,589	(clinical trial*) in ti ab
23	122,001	random* in ti ab
24	272,599	#17 or #18 or #19 or #20 or #21 or #22 or #23
25	1,213	#24 and #16
26	6,026	"taxol"/ all subheadings
27	1,455	"Taxotere"/ all subheadings

CancerLIT

Set	Items	Description
1	1,876	BREAST NEOPLASMS!/DE
2	120,403	(OVARIAN OR BREAST)/TI,AB
3	21,453	OVARIAN NEOPLASMS!/DE
4	388	ADNEXA?(W)MASS?
5	142,808	S1:S4
6	2,803	PACLITAXEL/DE
7	5,402	PACLITAXEL? OR DOCETAXEL? OR TAXOL? OR TAXOTERE? OR TAXANES
8	5,402	S6:S7
9	0	COST BENEFIT ANALYSIS/DE
10	2,943	COST(W)EFFECT?/TI,AB
11	569	COST(W)BENEFIT?/TI,AB
12	52	COST(W)UTIL?/TI,AB
13	119	ECONOMIC(W) EVALUATION?/TI,AB
14	82	TECHNOLOGY (W) ASSESSMENT?/TI,AB
15	66	PHARMACOECONOMIC?/TI,AB
16	3,642	S9:S15
17	0	DT=TRIAL
18	17,354	CLINICAL TRIALS!/DE
19	19,353	(CLIN? (4W) TRIAL?)/TI,AB
20	3,575	((SINGL? OR DOUBL? OR TREBL? OR TRIPL?) (4W)(BLIND? OR MASK?))/TI,AB
21	459	PLACEBOS/DE
22	4,459	PLACEBO?/TI,AB
23	36,673	RANDOM?/TI,AB
24	2,202	RESEARCH DESIGN/DE
25	65,621	S17:S24
26	1,177,668	SF=MEDL
27	30	S8 AND S5 AND S16
28	671	S8 AND S5 AND S25
29	2,158	COST-BENEFIT ANALYSIS/DE
30	49,542	DT="CLINICAL TRIAL": DT="CLINICAL TRIAL, PHASE IV"
31	4,033	DT="CONTROLLED CLINICAL TRIAL"
32	42,462	DT="MULTICENTER STUDY" OR S23
33	22,455	DT="MULTICENTER STUDY" OR DT="RANDOMIZED CONTROLLED TRIAL"
34	33	S8 AND S5 AND (S16 OR S29)
35	1,261	S8 AND S5 AND (S25 OR S30 OR S31 OR S33)
36	11	S34 NOT S26
37	11	S36/1990:1999

Appendix 3

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Appendix 4

Prescreen for titles and abstracts

The following codes were used to classify the titles and abstracts:

Prescreen codes

Type of study	REVIEW PRIMARY	BACKGROUND	ECONOMIC OTHER		
Type of cancer	OVARIAN	BREAST	OTHER		
Stage	EARLY	ADVANCED	RECURRENT	REFRACTORY	
Chemo. used	PACLITAXEL	DOCETAXEL	OTHER		
Level of treatment	FIRSTLINE	SECONDLINE	THIRDLINE		
Type of trial	RCT	PHASE1	PHASE2	PHASE3	OTHER
Get paper decision	dlsGET	msmGET	dlsREJECT	msmREJECT	
Final decision	AGREEGET	AGREEREJECT			

Status codes

Request	PAPER REQUESTED	AUTHOR CONTACTED
	OBTAINED	
	FINALINCLDE	
	FINALREJECT	
	DATEXTRACTED	

Appendix 5

Data extraction

The following data were extracted from the included trials and entered into six linked Access files:

A. Study details

Trial_name
Cancer_sitetype
Endnote_reference
primary_source
Author
Date
Type_of_report
phasetype_of_study
Intervention_A
number_of_cycles_A
length_cycle_A
administration_A
Intervention_B
number_of_cycles_B
length_cycle_B
administration__B
Intervention_C
number_of_cycles_C
length_cycle_C
administration_C
Intervention_D
number_of_cycles_D
length_cycle_D
administration_D
Comments_on_intervention

B. Participants

Disease_focus
Stage
Early_stage
Advanced_stage
Results_of_surgery
Previous_treatment
Residual_disease
Refractory_disease
Secondary_spread
sex
age
other
comments

C. Numbers in conditions

power_calculations
Final_number_needed
Accrual_dates
number_recruited_or_accrued
length_of_followup
number_and_time_of_followup
number_evaluated
attrition
Intention_to_treat_analysis
Type_of_analysis
Comments

D. Quality

Prospective_study
Retrospective_study
Cross_sectional
comparison_group
random_allocation
sample_size_calculation
outcomes_defined
adjustment_for_confounds
Methodological_quality

E. Outcomes

Survival_outcomes
Response
symptom_relief
other_outcomes
Adverse_effects
Quality_of_Life
other_qualitative_outcomes
validity_of_qual_outcomes
Cost

F. Results

Overall_survival
Progression_free_survival_PFS
Mortality
Median_survival
Response
recurrance_free_survival_RFS
Symptom_relief
other_outcomes
haematological_toxicity
neutropenia
febrile_neutropenia
fever_requiring_antibiotics
leucopenia
thrombocytopenia
metabolic_toxicity
nonhaematological_toxicity
emesis_nausea
gastrointestinal
pain
peripheral_neuropathy
sensory_neuropathy
Other_adverse_effects
Long_term_results
Quality_of_Life
other_qualitative_outcomes
cost (see table G)
Comments

G. Costs

Economic study type
Study population
Setting
Dates to which data relate
Source of effectiveness data
Modelling
Measures of benefits used in economic analysis
Direct costs
Indirect costs
Currency
Statistical analysis of costs
Sensitivity analysis
Estimated benefits used in the economic analysis
Cost results
Synthesis of costs and benefits
Comments

Appendix 6

Rejected studies

Awada A, Paridaens R, Bruning P, 1997. Doxorubicin or Taxol as firstline chemotherapy for metastatic breast cancer (MBC): results of EORTC-IDBBC/ECSG randomised trial with crossover [abstract]. *Breast Cancer Res Treat*;**46**:23.
(Superseded.)

Bauknecht T, Luck HJ, du Bois A, Meier W, Mobus V, Costa S, *et al.*, 1997. Interim analysis of a randomized trial comparing cisplatin/paclitaxel vs carboplatin/paclitaxel as first-line chemotherapy in advanced ovarian cancer [abstract]. *Proc AACR*;**38**:A715.
(Compares carboplatin and cisplatin.)

Bennett C, Stinson T, Yang T, Lurain J, 1999. The effect of reimbursement policies on the management of Medicare patients with refractory ovarian cancer. *Semin Oncol*;**26**(1 Suppl 1):40–5.
(Second-line ovarian.)

Bishop J, Dewar J, Tattersal I, Smith J, Olver I, Ackland S, *et al.*, 1996. A randomized Phase III study of Taxol (paclitaxel) vs CMFP in untreated patients with metastatic breast cancer [abstract]. *Proc ASCO*;**15**:A107.
(Superseded.)

Bishop J, Dewar J, Toner G, Tattersall M, Olver I, Ackland S, *et al.*, 1997. A randomized study of paclitaxel versus cyclophosphamide/methotrexate/5-fluorouracil/prednisone in previously untreated patients with advanced breast cancer: preliminary results. Taxol Investigational Trials Group, Australia/New Zealand. *Semin Oncol*;**24**(5 Suppl 17):S17–19.
(Superseded.)

Bolis G, Parazzini F, Scarfone G, Villa A, Amoroso M, Rabaiotti E, *et al.*, 1999. Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer. *Gynecol Oncol*;**72**:60–4.
(Second-line ovarian.)

Bomalaski J, 1999. The treatment of recurrent ovarian carcinoma. Balancing patient desires, therapeutic benefit, cost containment and quality of life. *Curr Opin Obstet Gynecol*;**11**(1):11–15.
(Second-line ovarian.)

Botto H, Botto M, Otegui M, 1998. Taxotere vs vinorelbine and taxol in patients with metastatic breast cancer anthracycline resistance. *Proc ASCO*;**17**:130.
(Not RCT.)

Buzdar AU, Hortobagyi G, Asmar L, Theriault R, Rahman Z, McNeese M, *et al.*, 1997. Prospective randomized trial of paclitaxel alone versus 5-fluorouracil/doxorubicin/cyclophosphamide as induction therapy in patients with operable breast cancer. *Semin Oncol*;**24**(5 Suppl 17):S17–S34.
(Neoadjuvant.)

Carmichael J, Gordon A, Malfetano J, Gore M, Spaczynski M, Davidson N, *et al.*, 1996. Topotecan, a new active drug, vs paclitaxel in advanced epithelial ovarian carcinoma: International Topotecan Study Group Trial [abstract]. *Proc ASCO*;**15**:A765.
(Second line.)

Chan S, 1997. Docetaxel (Taxotere) vs doxorubicin in patients with metastic breast cancer (MBC) who have failed alkylating chemotherapy. Randomized multicenter Phase III trial [abstract]. *Proc ASCO*;**16**:154A.
(Superseded.)

Chan S, 1997. Docetaxel vs doxorubicin in metastatic breast cancer resistant to alkylating chemotherapy. *Oncology*;**11**(8 Suppl 8):19–24.
(Superseded.)

Chan S, Friedrichs K, Noel D, Duarte R, Vorobiof D, Pinter D, *et al.*, 1997. A randomized Phase III study of Taxotere (T) versus doxorubicin (D) in patients (pts) with metastatic breast cancer (MBC) who have failed an alkylating containing regimen: preliminary results [abstract]. *Proc ASCO*;**16**:A540.
(Superseded.)

Colombo N, Marzola M, Parma G, Cantu MG, Tarantino G, Fornara G, *et al.*, 1996. Paclitaxel vs CAP (cyclophosphamide, adriamycin, cisplatin) in recurrent platinum sensitive ovarian cancer: a randomized Phase II study [abstract]. *Proc ASCO*;**15**:A751.
(Second line.)

Dieras V, Marty M, Tubiana M, Corette L, Morvan F, Serin D, *et al.*, 1995. Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. *Semin Oncol*;**22**(4 Suppl 8):33–9.
(Superseded.)

du Bois H, Lueck W, Meier V, Moebus S, Costa T, Bauknecht B, *et al.*, 1999. Cisplatin/paclitaxel vs carboplatin/paclitaxel in ovarian cancer: update of an AGO Study Group trial [abstract]. *Proc ASCO*;**18**:A1374.
(Compares one taxane combination with another (carboplatin vs cisplatin).)

Gamucci T, Piccart M, Bruning P, 1998. Single agent Taxol versus doxorubicin as first-line chemotherapy in advanced breast cancer. Final results of an EORTC randomised study with crossover. *Proc ASCO*;**17**:111.
(Superseded.)

Gianni L, Munzone E, Capri G, Villani F, Spreafico C, Tarenzi E, *et al.*, 1995. Paclitaxel in metastatic breast cancer: a trial of two doses by a 3-hour infusion in patients with disease recurrence after prior therapy with anthracyclines. *J Natl Cancer Inst*;**87**:1169–75.
(Not RCT.)

Hainsworth J, 1997. Mitoxantrone, 5-fluorouracil and high-dose leucovorin (NFL) in the treatment of metastatic breast cancer: randomized comparison to cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and attempts to improve efficacy by adding paclitaxel. *Eur J Cancer Care Engl*;**6**(4 Suppl):4–9.
(Not RCT.)

Hamilton A, 1999. Taxanes as neoadjuvant therapy for locally advanced breast cancer. In: Proceedings of the 10th European Cancer Conference ECCO 10; Sep 12–16. Vienna, Austria.
(Review.)

Harper P, 1997. ICON 2 and ICON 3 data in previously untreated ovarian cancer: results to date. *Semin Oncol*;**24**(5 Suppl 15):S15–S25.
(Brief sketch of trial.)

Harvey J, Cantrell J, Campbell M, Cartmell A, Urba W, Rubin A, *et al.*, 1997. Mitoxantrone + paclitaxel (NT) versus paclitaxel (T) alone for metastatic breast cancer (MBC) [abstract]. *Proc ASCO*;**16**:A601.
(Paclitaxel in both arms.)

Hortobagyi GN, Willey J, Rahman Z, Holmes FA, Theriault RA, Buzdar AU, 1997. Prospective assessment of cardiac toxicity during a randomized Phase II trial of doxorubicin and paclitaxel in metastatic breast cancer. *Semin Oncol*;**24**(5 Suppl 17):S65–68.
(Compares 1- and 3-hour infusions.)

Hoskins W, McGuire W, Brady M, Kucera P, Partridge E, Look K, *et al.*, 1997. Combination paclitaxel (Taxol registered)–cisplatin vs cyclophosphamide–cisplatin as primary therapy in patients with suboptimally debulked advanced ovarian cancer. *Int J Gynecol Cancer*;**1**:9–13.
(Superseded.)

Kavanagh J, Kudelka AP, Edwards CL, Freedman RS, Gibbs H, Gonzalez de Leon C, *et al.*, 1993. A randomized cross-over trial of parenteral hydroxyurea vs high-dose Taxol in cisplatin/carboplatin-resistant epithelial ovarian cancer [abstract]. *Proc ASCO*;**12**:A822.
(Second line.)

Kern D, 1998. Heterogeneity of drug resistance in human breast and ovarian cancers. *Cancer J Sci Am*;**4**(1):41–5.
(Background.)

Mamounas E, 1997. Preoperative doxorubicin plus cyclophosphamide followed by preoperative or postoperative docetaxel. *Oncology*;**11**(6):37–40.
(Preliminary report: no results.)

Markman M, Bundy B, Benda J, Alberts D, Wadler S, Fowler J, *et al.*, 1998. Randomised Phase III study of intravenous cisplatin/paclitaxel versus moderately high dose intravenous carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in optimum residual ovarian cancer. *Proc ASCO*;**17**:A1392.
(Intraperitoneal cisplatin.)

McGuire W, Hoskins WJ, Brady MF, Kucera PR, Look KY, Partridge EE, *et al.*, 1993. A Phase III trial comparing cisplatin/cytoxan (PC) and cisplatin/Taxol (PT) in advanced ovarian cancer (AOC) [abstract]. *Proc ASCO*;12:A808.
(Superseded.)

McGuire W, Hoskins W, Brady M, Kucera P, Partridge E, Look K, *et al.*, 1995. Taxol and cisplatin (TP) improves outcome in advanced ovarian cancer (AOC) as compared to cytoxan and cisplatin (CP) [abstract]. *Proc ASCO*;14:A771.
(Superseded.)

McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, *et al.*, 1995. Taxol/ cisplatin (TP) versus cyclophosphamide/cisplatin (CP) in Stage IV or suboptimally debulked Stage III ovarian cancer [abstract]. *Proc ASCO*;**14**:A771.
(Superseded.)

McGuire W, Hoskins W, Brady M, Kucera P, Partridge E, Look K, *et al.*, 1996. Comparison of combination therapy with paclitaxel Taxol registered and cisplatin versus cyclophosphamide and cisplatin in patients with suboptimal Stage III and Stage IV ovarian cancer. A Gynecologic Oncology Group study. *Int J Gynecol Cancer*;**6**(5):2–8.
(Superseded.)

McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, *et al.*, 1996. Cyclophosphamide and cisplatin versus paclitaxel and cisplatin: a Phase III randomized trial in patients with suboptimal Stage III/IV ovarian cancer (from the Gynecologic Oncology Group). *Semin Oncol*;**23**:40–7.
(Superseded.)

McGuire W, Hoskins W, Brady M, Kucera P, Partridge E, Look K, *et al.*, 1997. Comparison of combination therapy with paclitaxel and cisplatin versus cyclophosphamide and cisplatin in patients with suboptimal Stage III and Stage IV ovarian cancer: a Gynecologic Oncology Group study. *Semin Oncol*;**24**(1 Suppl 2):13–16.
(Superseded.)

Nabholtz JM, 1997. Docetaxel (Taxotere) vs mitomycin C + vinblastine in patients with metastatic breast cancer (MBC) who have failed an anthracycline-containing regimen. Preliminary evaluation of a randomized Phase III study [abstract]. *Proc ASCO*;**16**:148A.
(Superseded.)

Nabholtz J, Gelmon K, Bontenbal M, Spielmann M, Catimel G, Conte P, *et al.*, 1996. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. *J Clin Oncol*;**14**:1858–67.
(Comparing doses.)

Nabholtz J, Thuerlimann B, Bezwoda W, 1997. Taxotere vs mitomycin C–vinblastine in patients with metastatic breast cancer who have failed an anthracycline containing regimen [abstract]. *Breast Cancer Res Treat*;**46**:93.
(Superseded.)

Nabholtz J, Thuerlimann B, Bezwoda W, Melnychuk D, Deschenes L, Douma J, *et al.,* 1997. Docetaxel vs mitomycin plus vinblastine in anthracycline-resistant metastatic breast cancer. *Oncol*;**11**(8 Suppl 8):25–30.
(Superseded.)

Neijt J, Hansen M, Hansen S, Sorenson P, Sessa C, Witteeven P, *et al.,* 1997. Randomized Phase III study in previously untreated epithelial ovarian cancer FIGO Stage IIB, IIC, IV comparing paclitaxel–cisplatin and paclitaxel–carboplatin [abstract]. *Proc ASCO*;**16**:A1259.
(Compares carboplatin and cisplatin.)

Neuberg D, Sledge GJ, Fetting J, Cella D, Wood W, 1997. Changes in quality of life (QOL) during induction therapy in patients enrolled in a randomized trial of Adriamycin, Taxol, and Adriamycin plus Taxol in metastatic breast cancer [abstract]. *Proc ASCO*;**16**:A185.
(Neoadjuvant.)

Ozols R, Bundy B, Fowler J, Clarke-Pearson J, Mannel R, Hartenbach E, *et al*, 1999. Randomized Phase III study of cisplatin (CIS)/paclitaxel (PAC) versus carboplatin (CARBO)/PAC in optimal Stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial (GOG 158) [abstract]. *Proc ASCO*;**18**:A1373.
(Compares carboplatin and cisplatin.)

Paridaens R, Bruning P, Klijn J, Gamucci T, Biganzoli L, Van Vreckem A, *et al.*, 1997. An EORTC crossover trial comparing single-agent Taxol (T) and doxorubicin (D) as first- and second-line chemotherapy (CT) in advanced breast cancer (ABC) [abstract]. *Proc ASCO*;**16**:A539.
(Superseded.)

Piccart M, Klijn J, Paridaens R, Nooij M, Mauriac L, Coleman R, *et al.*, 1997. Corticosteroids significantly delay the onset of docetaxel-induced fluid retention: final results of a randomized study of the European Organization for Research and Treatment of Cancer Investigational Drug Branch for Breast Cancer. *J Clin Oncol*;**15**:3149–55.
(Comparison of prophylactic medication.)

Piver M, El Tabbakh G, Hempling R, Recio F, 1997. Prospective sequential trials comparing induction weekly cisplatin (P) followed by (1) monthly cisplatin, adriamycin, cyclophosphamide (PAC) (trial 1) versus (2) paclitaxel and cisplatin (TP) (trial 2) in optimal (1 cm or smaller) Stage III and IV ovarian cancer [abstract]. *Proc ASCO*;**16**:A1277.
(Not RCT.)

Schroder W, du Bois A, Kuhn W, 1999. Treatment of patients with advanced ovarian cancer (FIGO IIb–IV) with cisplatin/paclitaxel or carboplatin/paclitaxel – an interim analysis of the AGO study protocol OVAR-3. In: Proceedings of the 10th European Cancer Conference ECCO 10; Sep 12–16; Vienna, Austria. Abst 908.
(Compares cisplatin and carboplatin.)

Sjostrom J, Mouridsen H, Pluzanska A, 1998. Taxotere versus methotrexate–5-fluorouracil in patients with advanced anthracycline resistant breast cancer: preliminary results of a randomised Phase III study by Scandinavian Breast Cancer Group. *Proc ASCO*;**17**:111.
(Superseded.)

ten Bokkel Huinink W, Gore M, Carmichael J, Gordon A, Malfetano J, Hudson I, *et al.*, 1997. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*;**15**:2183–93.
(Second-line ovarian.)

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We look forward to hearing from you.

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