

A Systematic Review of the Effectiveness and Cost Effectiveness of the Taxanes used in the Treatment of Advanced Breast and Ovarian Cancer

VERSION WITH CONFIDENTIAL INFORMATION REMOVED

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 annotated. 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.

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This review will need revising late 2000.

EXECUTIVE SUMMARY

1 RESEARCH QUESTION

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

2 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 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.

3 THE BODY OF EVIDENCE

The searches identified 2,250 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 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 randomised controlled trials. Many of these were duplicate publications. On examination of the obtained papers and reports, the following were selected for review.

Review question			Number of randomised controlled trials [number of patients]	Number of economic evaluations
Cancer	Level of treatment	Chemotherapy		
Breast	First-line	Paclitaxel	4† [1545]	0
		Docetaxel	1(?) [429]	
	Second-line	Paclitaxel	1 [81]	7*
		Docetaxel	4 [1092]	6
Ovary	First-line	Paclitaxel	4† [3746]	13*

† = Data from published papers substituted for original data from confidential manufacturers submission (1 study)

* = One study not presented in this report at request of manufacturers.

(?) Phase III trial which does not specifically mention randomisation

4 RESULTS

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

4.1 BREAST CANCER

4.1.1 First-line treatment

a) *Paclitaxel*

Four randomised, controlled phase III trials were identified: EORTC, TITGANZ, E1193 and CA139-278. A total of 1425 patients were included. Of these, EORTC, E1193 and TITGANZ evaluated single agent paclitaxel and E1193 and CA139-278 evaluated combination paclitaxel/anthracycline. There are no economic evaluations of first-line breast cancer. Information about the EORTC trial has been removed from this document, since 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 studies

TITGANZ was analysed on an intention-to-treat basis and gave details of length of follow-up: 26 months. EORTC and E1193 allowed cross-over to alternate treatment and TITGANZ recommended treatment with epirubicin on progression. Patients crossing over in this way are violating the randomisation; however, no details were given as to whether such patients were censored.

i) Single agent paclitaxel

Median progression free survival

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 EORTC, the anthracycline group had significantly longer progression free survival (7.3 months versus 4.0 months, $p = 0.001$)

Median overall survival

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.

ii) Combination paclitaxel/anthracycline

Median progression free survival

The median progression free survival in the paclitaxel plus anthracycline arm 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, stratified logrank $p = 0.034$).

Median overall survival

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, stratified logrank $p = 0.02$) in one trial but not in the other (22 versus 18.9 months, $p = 0.24$) although the difference was comparable.

In the E1193 trial, the survival in the single agent paclitaxel arm and combined paclitaxel/anthracycline arms was similar (22 versus 22.2 months).

Quality of life

Quality of life was evaluated in 3 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 sub-scales. These did not appear to follow a consistent pattern across the trials.

b) 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 greater overall response than doxorubicin and cyclophosphamide combined, there were no long term results such as progression free or over-all survival.

4.1.2 Second-line treatment

a) 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 studies

It is not clear whether this trial was analysed on an intention to treat basis and no details were given of length of follow-up. However, the authors stated that most of the patients were alive at the time of analysis. Only two patients in the mitomycin control arm responded. 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 as to 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 was 3.5 months. This was significantly longer than the mitomycin control arm (1.6 month, logrank $p = 0.026$).

Median overall survival

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

Quality of life

There was no statistically significant difference in the delay of disease progression adjusted for important adverse events.

Economic evaluation

The only economic evaluation that compared paclitaxel to 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.

b) 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 study before completion of accrual (Bonneterre). Patients in the 303 study had previously received chemotherapy involving alkylating agents; those in the other three studies had received anthracycline agents. There were six economic evaluations on docetaxel.

Quality of studies

The 303 and 304 studies were analysed on an intention to treat basis; Scand excluded a single patient. Length of follow-up ranged from 11 months (Scand) to 23 months (303 Study). At least two thirds of the participants of these studies had died. The Scand study recommended crossover to alternate treatment on objective signs of disease progression. Patients crossing over in this way are violating the randomisation; however, no details were given as to whether 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, logrank $p = 0.001$; 6.3 months versus 3 months, logrank $p = 0.001$).

Median overall survival

The median over-all 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 only, survived for significantly longer than the mitomycin plus vinblastine arm (11.4 months versus 8.7 months, logrank $p = 0.03$).

Quality of life

Quality of life was evaluated in 2 of the studies: 303 and 304 studies. There were no significant differences between docetaxel and control in either of the trials in terms of global health status, although differences were apparent on some sub-scales. These did not appear to follow a consistent pattern across the trials

Economic evaluation

All six of these involved comparisons of paclitaxel and docetaxel where the range of cost utility ratios for quality adjusted life years gained was £1990 to £2431. In addition three analyses compared docetaxel and vinorelbine. The cost utility ratio in the only one of these done in the UK for quality adjusted life years gained was £14,050.

4.2 OVARIAN CANCER

4.2.1 First-line treatment.

a) Paclitaxel

Four randomised, controlled phase III trials were identified: GOG 111, GOG 132, OV10 and ICON 3. A total of 3770 patients were included. ICON 3 evaluated the effectiveness of paclitaxel combined with carboplatin; the others evaluated a paclitaxel/cisplatin combination. There were thirteen economic analyses, one of which was submitted in confidence and has been removed from this document.

Quality of studies

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 (GOG 111). The ICON 3 trial was reported only six months after accrual was completed, while over two thirds of the patients survived. All the studies allowed cross-over to alternate treatment. In the economic analyses, estimation of benefits was based on a direct clinical comparison in only eight out of thirteen studies.

Median progression free survival

The median progression free survival in the paclitaxel/platinum arm ranged from 14.1 months (GOG 132) to 16.5 months (OV10). Patients in the GOG 111 and OV 10 trial had significantly greater median progression free survivals than controls (18 months versus 13 months $p < 0.001$; 16.5 months versus 11.8 months, logrank $p = 0.001$).

Median overall survival

The median length of overall survival in the paclitaxel/platinum arm ranged from 26.6 months (GOG 132) to 38 months (GOG 111). Patients in the GOG 111 and OV 10 trial had significantly greater median overall survivals than controls (38 months versus 24 months, $p < 0.001$; 35 months versus 25 months, logrank $p = 0.001$).

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 (£7,173 to £12,417) found in two UK studies is within the range reported for all studies comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin (£3,960 to £13,360). The two UK studies used carboplatin rather than cisplatin in their analyses. In the cost utility analyses the range of cost per quality adjusted life years gained was £5273 to £11,269.

4.3 Summary of evidence on effectiveness

The range of median progression free and overall survivals found in the randomised controlled trials are given below:

Review question			Range of median progression free survival in months (control)	Range of median overall survival in months (control)
Cancer	Level of treatment	Chemotherapy		
Breast	First-line	Paclitaxel	4.0 - 5.9* (6.0 - 7.5)	17.3- 22.2 (13.9 - 18.9)
		Paclitaxel + anthracycline	8.0 - 8.3 ¹ (6.0 - 6.2)	22.0 - 22.7 ² (18.3 - 18.9)
	Second-line	Paclitaxel	3.5 ³ (1.6)	12.7 ⁴ (8.4)
		Docetaxel	4.7 - 7.0 ⁵ (2.7 - 5.0)	10.4 - 15 ⁶ (8.7 - 14)
Ovary	First-line	Paclitaxel	14.1 - 18 ⁷ (11.8 - 16.4)	26.6 - 38 ⁷ (25-30.2)

*Control significantly better than paclitaxel in 1/3 studies

1 Paclitaxel plus anthracycline significantly better than control in 2/2 trials

2 Paclitaxel plus anthracycline significantly better than control in 1/2 trials

3 Paclitaxel significantly better than control in 1/1 trial

4 Paclitaxel significantly better than control in 1/1 trial

5 Docetaxel significantly better than control in 2/4 trials

6 Docetaxel significantly better than control in 1/4 trials

7 Paclitaxel plus platinum significantly better than control in 2/4 trials

5 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, multi-centre randomised controlled phase III trials, one comparing epirubicin and paclitaxel versus epirubicin and cyclophosphamide (ABO1), and another one comparing doxorubicin and taxol 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.

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 is only one small trial and the cost-effectiveness of paclitaxel compared to mitomycin has not been proven.

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 may be useful in the treatment of women for whom anthracyclines are contraindicated. In terms of cost effectiveness in second line treatment of breast cancer there is some evidence, of mixed quality, which suggests that docetaxel costs £14,050 per quality adjusted life year gained versus vinorelbine. Docetaxel was found to have highly favourable cost effectiveness ratios in comparison with paclitaxel (cost per quality adjusted life year gained £1990 to 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 the use of paclitaxel in combination with platinum in the first-line treatment of ovarian cancer, two trials showing significant

improvement in overall survival. This treatment combination was also found to have potentially acceptable cost effectiveness ratios (cost per quality adjusted life year gained £5273 to £11,269). As the results of ICON 3 mature, they may be able to demonstrate for which subgroups of women this treatment is more or less appropriate. The mature results of ICON 3 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.

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GLOSSARY

Absolute risk reduction

The increased chance of having a response from the treatment compared to the comparator. In oncology, this can be considered as analogous to the reduction of the risk of not responding to treatment.

Adjuvant treatment

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

Advanced disease

Locally advanced and metastatic disease.

Anthracycline refractory

Never responded to anthracycline therapy.

Anthracycline resistant

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

AOC

Advanced Ovarian Cancer.

Arthralgia

Pain in the joints or in a single joint.

Ascites

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

BNF

British National Formulary.

Carcinoma

A cancerous growth.

CE Ratio

Cost-effectiveness Ratio.

Chemotherapy

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

Clinical Oncologist

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

CMF

The combination of cyclophosphamide, methotrexate and 5-fluorouracil.

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.

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.

Cytology

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

Cytotoxic

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

Debulking

Removal by surgery of a substantial proportion of cancer tissue. Optimal debulking refers to the removal of the largest possible amount of cancer while limiting damage to normal tissue; interval debulking refers to 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.

DRG

Diagnosis Related Group.

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).

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 systematic therapy.

Gynaecology

The branch of medicine which deals with the female reproductive organs.

Heterogeneous

Of differing origins, or different types.

Histological grade

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

Histological type

The type of tissue found in a tumour.

Histology

An examination of the cellular characteristics of a tissue.

HRG

Health Related Group.

Incremental cost effectiveness analysis

Estimates of the additional cost per year of life saved or gained.

Locally advanced disease (breast)

Disease which has infiltrated the skin or chest wall or disease which has matted involved axillary nodes.

Localised disease

Tumour confined to a small part of an organ.

LYG

Life Years Gained.

Lymph nodes

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

Marginal or minor response

Less than 50% but greater than 25% tumour regression for all measurable for at least 4 weeks with no new lesions appearing.

Measurable lesion

Lesion which could be unidimensionally or bidimensionally measured by physical examination, echography, x-rays or CT scan (GOG 111).

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 which 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 could be obtained eg 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 which are not.

Palliative

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

Partial response

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

PFLYG

Progression-free Life Years Gained.

Primary anthracycline resistance

Failure to respond to a first or secondline anthracycline (disease progression) or relapse.

Progressive disease

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

Prophylaxis

An intervention used to prevent an unwanted outcome.

Protocol

A policy or strategy which defines appropriate action.

Quality of life/QOL

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

QALY

Quality Adjusted Life Years. Index of survival that is weighted or adjusted by the patients 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 breast cancer to the first evidence of cancer recurrence.

Remission

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

Secondary anthracycline resistance

Disease progression after initial objective response to first or secondline 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) following 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 25% change in measurable lesions for at least 4 to 8 weeks with no new lesions appearing.

Staging

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

Time to progression

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

UKCCCR

United Kingdom Co-ordinating Committee on Cancer Research. The national committee responsible for co-ordinating clinical trials for cancer treatment in the UK.

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

Preference with risk.

Values

Preferences without risk or uncertainty.

AIM OF ASSESSMENT

Research questions

The following questions will be addressed:

1. 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?
2. How effective is **docetaxel** (Docetaxel®), 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?
3. 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?
4. 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?
5. 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?
6. What are the cost implications of the use of taxanes as above?

1. BACKGROUND

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

Table 1 Incidence and deaths from Breast and Ovarian Cancers in the UK
(3)

	Number of registrations, 1993	Incidence rate 1995	Deaths, 1996
Breast cancer	30,495	27%	13,760
Ovarian Cancer	5,337	5%	4,580

1.1. 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 first 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 the brain. Staging is based on tumour size (T), presence of axillary nodes (N) and presence of metastases (M) (see Appendix 1)

The prognosis for women developing metastatic disease is poor and metastatic disease is often considered incurable (5). For most patients with metastatic disease, 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 (eg doxorubicin, epirubicin), cyclophosphamide, methotrexate, fluorouracil, mitomycin and mitoxantrone and the taxanes. (7)

1.2. Ovarian Cancer

The natural history of ovarian cancer is inconsistent. (8) Again, hormonal factors may play a part in the aetiology of this cancer, with reduced ovulation, pregnancy and early menopause associated with reduced risk. (2). There appears to be an inherited pre-disposition to develop ovarian cancer in about 5 to 10% of cases (8) and 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 ovarian cancer: persistent abdominal distension, pain, pressure in the pelvis can be attributed to a number of

causes. In the majority of cases, 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 stage II to IV at time of diagnosis. (2) Five year survival in European countries which report to FIGO has increased from 27% in 1958-62 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 following expert surgery. (2)

The recent consensus statement on standard practice recommended that standard chemotherapy for patients with ovarian cancer should include a platinum compound, and 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 survival.

1.3. 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 semisynthetic 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 following initial treatment by surgery or radiotherapy, to destroy any cancer cells that have spread.

1.3.1. 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 (> 1cm) 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

1.3.2. *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

1.4. Current Recommendations

1.4.1. *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 revealed no clearly superior regimen. (1). The recent meta-analysis of polychemotherapy in breast cancer (15) concentrated on early disease, 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**"

1.4.2. *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 (DEC) 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 to 18 months.

Additionally, the Trent DEC 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 DEC report investigated second and third-line use of paclitaxel in advanced ovarian cancer. The report 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 were mature.

1.5. Projected Unit Cost

1.5.1. Paclitaxel

NHS List Price excluding VAT: 30 mg vial: 124.79 100 mg vial: 374.00

Recommended dosage: First-line ovarian: 135mg/m²
 Second-line breast cancer: 175mg/m²

Assuming average body surface area of 1.75m², required dose for
Ovarian = 236.25 can be given from 2 x 100mg vials and 2 x 30 mg vials
Breast = 306.25 can be given from 3 x 100mg vials and 1 x 30 mg vials

Total cost per cycle:
Ovarian = £997.58
Breast = £1246.79

This costing does NOT include any premedication or other medication required to manage adverse events e.g. G-CSF for neutropenia.

1.5.2. 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

SPC Recommended dosage: 100 mg/m²

The dose can be given from 2 x 80 mg vials.

Total cost per cycle = 2 x £575 = £1,150

The average number of cycles of docetaxel received by a breast cancer patient is four.

Total cost of treatment per patient = £1,150 x 4 = £4,600.

This costing does NOT include any premedication or other medication required to manage adverse events eg G-CSF for neutropenia.

1.6. Licensed Indications, Contraindications and Warnings

1.6.1. Paclitaxel

1.6.1.1. Therapeutic indications

Ovarian carcinoma

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.

Breast carcinoma

The treatment of 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 is recommended consisting of paclitaxel 135mg/m² administered over 24 hours followed by cisplatin 75 mg/m², with a three week interval between courses.

Recommended dosage: Secondary treatment of ovarian and breast carcinoma

The recommended dose of paclitaxel is 175mg/m² 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.

Paclitaxel should not be readministered until the neutrophil count is $\geq 1.5 \times 10^9/L$ and the platelet count is $\geq 100 \times 10^9/L$. Patients who experience severe neutropenia (neutrophil count $< 0.5 \times 10^9/L$ 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 H₂ antagonists prior to paclitaxel.

1.6.1.2. Contra-indications

Paclitaxel is contra-indicated in patients with severe hypersensitivity reactions to paclitaxel or any other component of the formulation, especially polyethoxylated castor oil.

Paclitaxel is contra-indicated during pregnancy and lactation.

Paclitaxel should not be used in patients with baseline neutrophils $< 1.5 \times 10^9/L$.

1.6.1.3. Special warnings and special precautions for use

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

Patients must be pretreated with corticosteroids, antihistamines and H₂ 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 reactions, paclitaxel should be discontinued immediately,

symptomatic therapy should be initiated and the patient should not be rechallenged 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 $\geq 1.5 \times 10^9/L$ and the platelet recover to a level $\geq 100 \times 10^9/L$.

Cardiovascular: Severe cardiac conduction abnormalities have been reported rarely. 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 paclitaxel. 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 paclitaxel infusion is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

Nervous system: 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.

Patients with 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 hepatic impairment.

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

Other: Since paclitaxel contains dehydrated alcohol (396 mg/mL), consideration should be given to possible CNS and other effects.

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

1.6.2. Docetaxel

1.6.2.1. 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 only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

Recommended dosage: The recommended dosage of docetaxel monotherapy is 100 mg/m² administered as a one-hour infusion every three weeks. A premedication consisting of an oral corticosteroid, such as dexamethasone, 16 mg per day for three 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.

1.6.2.2. Contra-indications

Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to the drug or polysorbate 80. Docetaxel should not be used in patients with a baseline neutrophil count of < 1,500 cells/mm³. Docetaxel must not be used in pregnant or breast-feeding women. Docetaxel should not be used in patients with severe liver impairment since there is no data available.

1.6.2.3. Special warnings and special precautions for use

A premedication consisting of an oral corticosteroid such as dexamethasone 16 mg per day (eg 8 mg BID) for 3 days starting one 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.

Haematology: Neutropenia is the most frequent adverse reaction of docetaxel. Neutrophil nadirs occurred 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 $\geq 1,500$ cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of docetaxel therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended.

Hypersensitivity reactions: Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. As hypersensitivity reactions may occur within a few minutes following the initiation of infusion of docetaxel, facilities for 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 appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with docetaxel.

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

Fluid retention: A premedication consisting of an oral corticosteroid such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting one day prior to

docetaxel administration, unless contra-indicated, 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 and ascites should be monitored closely.

Patients with liver impairment: In patients treated with docetaxel that have serum transaminase levels (ALT and/or AST) greater than 1.5 times the 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 deaths including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of docetaxel in patients with elevated liver function test (LFTs) is 75 mg/m² and LFTs should be conducted at baseline and before each cycle. For patients with serum bilirubin levels > ULN and/or ALT and AST > 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.

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

Others: Contraceptive measures must be taken during and for at least three months after cessation of therapy.

Table 1.6 provides a summary of the comparative toxicities of paclitaxel and docetaxel.

Table 1.6 Toxicity of taxoids in recommended dosages (21)

Adverse effect	Paclitaxel		Docetaxel
	3 hour	24 hour	1 hour
Neutropenia	+	++	++
Hypersensitivity reaction	+	+	+
Hair loss	++	++	++
Mucositis	-	+	+
Cardiac arrhythmia	+	+	-
Arthralgia/myalgia	+	+	-
Neurosensory	+*	+*	+/-
Cumulative oedema	-	-	+
Skin/nail	-	-	+

* Dose related and also more prominent when paclitaxel is given over 3 hours
 - = absent; +/- = mild; + = moderate; ++ = severe

1.7. Chemotherapy Used In Breast And Ovarian Cancer

Table 1.7 provides a summary of some of the chemotherapeutic agents used in the treatment of breast and ovarian cancers, their toxicities and mode of administration

Table 1.7 Summary of chemotherapeutic agents

Drug	Mode of action	Toxicity/side effects	Administration
5-fluorouracil	Anti-metabolites - prevent normal cell division	Toxicity unusual but may include myelosuppression, mucositis Nausea and vomiting Diarrhoea Dermatological toxicity Cerebellar syndrome	IV over 4 hours
Carboplatin	Binds to DNA, forms interstrand cross-links and intrastrand adducts	Myelosuppressive, especially thrombocytopenia. Nausea and vomiting. Side effects less severe than with cisplatin	Intravenous over 15 to 60 minutes
Cisplatin	Binds to DNA, forms interstrand cross-links and intrastrand adducts	Severe nausea and vomiting Nephrotoxicity Myelotoxicity Ototoxicity Peripheral neuropathy Hypomagnemia Visual disturbances	Pre-treatment hydration mandatory Intravenous over 6 to 8 hours
Cyclophosphamide	Metabolite alkylates to DNA	Myelosuppression Haemorrhagic cystitis Nausea and vomiting Alopecia Cardiomyopathy (rare) "allergic" interstitial pneumonitis	By mouth or intravenous over 5 to 15 minutes. Increased fluid intake advised
Docetaxel	Promotes microtubule assembly and arrests cell cycle in G ₂ and M phases	Hypersensitivity Fluid retention	Premedication with dexamethasone by mouth for 5 days Intravenous over 1 hour
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	Intravenous over 2 to 3 minutes
Methotrexate	Anti-metabolite - inhibits the enzyme dihydrofolate reductase.	Myelosuppression Mucositis Pneumonitis	By mouth, intravenous, intramuscular, intrathecally. Folinic acid following administration helps to prevent mucositis or 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 hour or 24 hour 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	Intravenous over 1 minute
Vinorelbine	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	Injection

2. METHODS

2.1. Search Strategy and Bibliographic Database used

The following databases were searched for relevant literature (See Appendix 2 for Strategy)

- MEDLINE
- EMBASE
- CCTR
- 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 authors of trials identified by the NRR were contacted for further information of their studies (Appendix 3).

Other contacts included the Cochrane Breast Cancer Group and the Cochrane Gynaecological Cancer Group (Appendix 3)

2.2. Inclusion And Exclusion Criteria

2.2.1. Interventions

- a) Taxanes
 - I. paclitaxel (Taxol ® Bristol-Myers Squibb) used either alone or in combination with other drugs as part of a chemotherapy regimen
 - II. docetaxel (Taxotere ® Aventis) used either alone or in combination with other drugs as part of a chemotherapy regimen.
- b) Other standard chemotherapy regimens.
 - I. For ovarian cancer these include non-platinum drugs such as cyclophosphamide, doxorubicin (Adriamycin), and platinum (cisplatin and carboplatin) either alone or in combination. (10)
 - II. Standard chemotherapy used in advanced breast cancer includes CMF (cyclophosphamide, methotrexate and 5-Fluoroucil) (5), anthracyclines (epirubicin, doxorubicin), mitozantrone and mitomycin C.

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

2.2.2. Participants

(See Appendix 1 for definition of stages)

- a) Women with ovarian cancer
 - i) early (FIGO stage I)
 - ii) advanced (FIGO stages II to IV)

- b) People with breast cancer
 - i) Locally advanced (stages II to III)
 - ii) Metastatic (stage IV)
 - iii) recurrent (second-line treatment)

2.2.3. Outcomes

- a) Overall response (complete response + partial response)
- b) progression free survival
- c) overall survival
- d) symptom relief
- e) quality of life
- f) adverse effects
- g) cost per quality adjusted life year (QALY)
- h) cost per progression free life year
- i) incremental cost per QALY
- j) incremental cost per progression free life year

2.2.4. Design

- a) Randomised, controlled trials comparing a taxane to a standard chemotherapy regimen
- b) Economic *evaluations*

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

Phase II trials where randomisation was employed were considered for inclusion.

All obtained titles and abstracts were independently assessed for inclusion by two reviewers (dls, msm and kk) using a prescreen form (Appendix 4). Any discrepancies were resolved by discussion and full papers obtained where possible.

2.3. Data Extraction Strategy

The data was extracted into an Access database (See Appendix 5). A second reviewer checked this.

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

2.4. Quality Assessment Strategy

One reviewer assessed the quality of the studies using the rating system used in the NHS Cancer Guidance Reports (1, 2, 22, 23) as follows

Grade I (Strong evidence)

Randomised controlled trial or review of randomised controlled trials

- 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-randomised controlled trial 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.

2.5. Analysis

Response rates, progression free survival and overall survival rates were analysed using the Cochrane Collaboration's Metaview 4.0.3 software. Relative risks 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-analysis using individual patient data (25). Such analyses require a long time frame so have not been undertaken here.

The crossover 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, crossover trials are ideally suited for chronic benign conditions where the outcomes are reversible (28). Under these circumstances the various periods of a crossover trial can be completed. In this overview, when patients are 'crossed over' to the other arm of the study, this represents allocated treatment's failure, not a planned crossover at the end of a defined treatment as is the case in crossover 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 according to treatments allocated at randomisation.

Where the authors discussed differences in e.g median time to progression, the statistics presented in the primary study are given in the tables.

2.6. 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 forest plots (without pooling). Both beneficial and adverse effects have been discussed in the light of study quality. Heterogeneity of studies has been assessed by clinical judgements of differences regarding (i) patients, (ii) interventions, (iii) outcomes, (iv) costs and (v) quality. Because of heterogeneity of included studies, quantitative syntheses were not under taken.

All economic analyses in first line ovarian cancer and in advanced breast cancer were reviewed. Their quality was assessed 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*

using these grades

- + = Item properly addressed*
- = Item not properly addressed*
- +/- = Item partially addressed*
- ? = Unknown*

The main focus was on studies originating in the UK.

2.7 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 annotated. Where possible this information has been replaced by trial details 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.

3. RESULTS

The searches identified 2,250 articles related to the taxanes. After independent assessment against the inclusion criteria by 2 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, 11 were reviews and background information, 32 were economic evaluations and the remaining 68 appeared to be reports of relevant randomised controlled trials.

On closer examination, 27 studies were rejected (see Appendix 6).

	Number of publications	Number of trials	Number of economic evaluations
Paclitaxel in first line treatment of ovarian cancer	8	4 [†]	13*
Docetaxel as adjuvant treatment for breast cancer	0	0	0
Docetaxel as first line treatment for breast cancer	1(?)	1(?)	0
Paclitaxel for first line treatment of breast cancer	6	4 [†]	0
Docetaxel as second line treatment of breast cancer	13	4	6
Paclitaxel as second line treatment of breast cancer	2	1	7*

[†] = Data from published papers substituted for original data from confidential manufacturers submission (1 study)

*= One study not presented in this report at request of manufacturers

(?) Phase III trial which does not specifically mention randomisation

The number of studies includes duplicate publications. No randomised controlled trials evaluating the effectiveness of docetaxel as adjuvant or first line treatments of breast cancer were found.

4. BREAST CANCER

4.1. The Effectiveness of Paclitaxel as First-Line Treatment for Advanced Breast Cancer

4.1.1. Description of included trials

Ten publications were identified which evaluated the effectiveness of paclitaxel as a first-line treatment for advanced breast cancer. These pertained to four Phase III trials: EORTC-IDBBC/ECSG (30-33); TITGANZ (34-37); Intergroup E1193 (38) and CA139-278 (39). The results of the TITGANZ trial only, have been published in journals. A paper detailing the EORTC trial is awaiting publication. However the results from this paper are not reported 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 Trial and CA139-278 have been taken from meeting abstracts and overheads.

Table 4.1.1.a: Design of included trials

Trial	Accrual dates	Number evaluated	Number crossing over	Median length of follow up
Quality	Number randomised			Number of patients surviving (%)
EORTC-IDBBC/ECSG interim report, meeting abstract (30, 32, 33)	Randomised Multi-centre Non-blinded 1	Aug 1993 - May 1996 T: 166 A: 165	ITT: not defined Evaluable for toxicity = 327 Evaluable for response to first-line CT = 299	Cross-over on demonstrated disease progression. If cross-over without documented progression then counted as treatment failure. Not stated
TITGANZ Published reports (34-37)	Randomised Power calculations Outcomes defined Multi-centre Open label 1A	Sept 1993 - T: 107 CMFP: 102	ITT: all randomised patients T: 107 CMFP: 102	No crossover but patients whose disease progressed were recommended to receive epirubicin Number not stated T: 30% CMFP: 20%
Intergroup E1193 Meeting abstract and overheads (38)	Randomised Multi-centre Non-blinded 1C	July 1994 – Feb 1997 T: 245 A: 248 AT: 245	Analysable T: 229 A: 224 AT: 230	Not stated Not stated
CA139-278 Meeting abstract and overheads (39)	Randomised Power calculations Multi-centre Open Label 1B	Nov 96 - April 97 AT: 134 FAC: 133	Evaluable for response A: 128 FAC: 131	Not stated AT: 56% FAC: 42%

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone

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 or CA139-278 abstracts and overheads to properly assess the quality of these trials. Only EORTC and TITGANZ was said to have been analysed on an intention to treat basis; and the TITGANZ trial defined

what was meant by this. Both the EORTC and the Intergroup trial allowed crossover to alternate treatment on progression; TITGANZ recommended treatment with epirubicin (an anthracycline) on progression; the number, if any, so treated was not mentioned. Patients crossing over to alternate treatment are violating 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 a randomised trial of second line treatment. Consequently, the cross-over part of EORTC and CA139-278 have not been considered.

The TITGANZ trial only, stated the median length of follow-up. More than half the participants in CA139-278 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 4.1.1.b). Consequently, these trials are looking 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 months delay. All but the TITGANZ trial specifically excluded previous treatment with anthracyclines.

Table 4.1.1.b Comparison of inclusion criteria

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

Three of the trials included a paclitaxel only arm (EORTC, E1193 and CA139-278). Both the EORTC and CA139-278 trials used 200 mg/m² of paclitaxel given as a three hour infusion (See Table 4.1.1.c); The E1193 trial used 175 mg/m² given as a 24 hour infusion. Two trials included a paclitaxel plus 50 mg/m² doxorubicin arm. The TITGANZ trial used 220 mg/m² given as a three hour infusion; Intergroup used 150 mg/m² of paclitaxel with G-CSF support. No information was given about length of infusion. Both the EORTC and the Intergroup trials allowed crossover to alternate treatment on discovery of progressive disease. With the exception of CA139-278, all the trials included an anthracycline in the control groups - usually doxorubicin. Only

TITGANZ give details of premedication and prophylactic medication. It is unclear whether prophylactic G-CSF was permitted in all arms of E1193

Table 4.1.1.c: Comparison of interventions

	Intervention	Control A	Control B	Control C
EORTC-IDBBC/ECSG	T: paclitaxel (200 mg/m ²) 3 hour infusion 7 x 3 week cycles Standard antihypersensitivity premedication.	A: doxorubicin (75 mg/m ²) 7 x 3 week cycle Premedication of dexamethasone and 5HT antagonist		Crossover on progression or within 4 weeks of receiving 7 th cycle
TITGANZ	T: paclitaxel (200 mg/m ²) 3 hour infusion 8 x 3 week cycles Premedication with dexamethasone 2 x 20mg; diphenhydramine 50mg; cimetidine 300mg Anti-emetics permitted	CMFP: cyclophosphamide (100 mg/m ²), + methotrexate (40 mg/m ²), + 5 fluorouracil (600 mg/m ²), + prednisone 6 x 4 week cycles Anti-emetics permitted		Patients whose disease progressed while receiving front-line therapy were recommended to receive epirubicin 90mg/m IV every 3 weeks
Intergroup E1193	T: paclitaxel (175 mg/m ²) 24 hour infusion 3 week cycles	A: doxorubicin (60 mg/m ²) 8 x 3 week cycles	AT: doxorubicin (50 mg/m ²) + paclitaxel (150 mg/m ²) 8 x 3 week cycles Prophylactic G-CSF	Crossover on progression
CA139-278	AT: doxorubicin (50 mg/m ²) + paclitaxel (220 mg/m ²) 3 hour infusion 8 x day1 day2 3week cycles	FAC: fluorouracil (500 mg/m ²), anthracycline (50 mg/m ²), cyclophosphamide (500 mg/m ²) 8 x 3 week cycles		

There was variation between the trials in terms of included patients. The details for the EORTC trial are taken from the interim report (30) which included only 235 participants. The proportions of women who were oestrogen receptor positive were: TITGANZ (around 38%) and E1193 (about 45%). Women who are not oestrogen receptor positive have a worse prognosis. A greater proportion of women in CA139-278 were fully active (ECOG 0) than in the other studies (see Appendix 7). More than half the women in E1193 had three or more metastatic sites, compared with about a third in EORTC. There were also variations in previous treatments (See Table 4.1.1.d). Less than half the women in CA139-278 or TITGANZ had received radiotherapy, compared with three-quarters of those in EORTC. Previous adjuvant chemotherapy ranged from 21% in one of TITGANZ to 46% in an arm of CA139-278 and prior hormone therapy ranged from 34% in CA139-278 to 77% in TITGANZ.

Table 4.1.1.d Comparison of participants

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

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone

It was not possible to assess the quality of E1193 or CA139-279 study. 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 differences between the studies make pooling inappropriate.

4.1.2. Results

4.1.2.1. Single agent paclitaxel versus control

4.1.2.1.1. Overall response rates

Overall response rates (complete response + partial response) were presented for the 2 relevant trials: E1193 and TITGANZ (See Figure 4.1.2.1a: Insufficient data was 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 people 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%, $p = 0.004$).

Figure 4.1.2.1a Single agent paclitaxel as first-line treatment of breast cancer.
Overall Response Rates

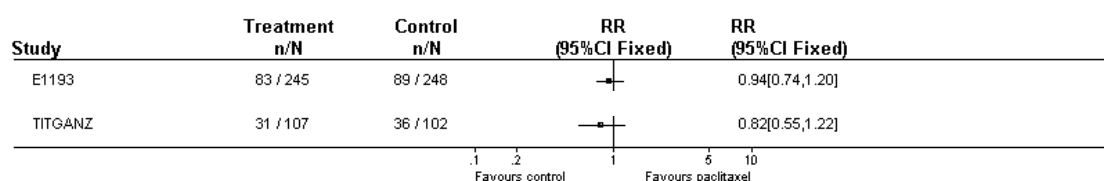


Table 4.1.2.1.1 Median times

Study	Median duration of response (months)	Median progression free survival (months)	Median time to treatment failure	Median length of survival
EORTC- IDBBC/ECSCG		T: 4.0 A: 7.5 P=0.0001		
Intergroup E1193			T: 5.9 A: 6 p = 0.35 ³	T: 22.2 A: 18.9 p = 0.24 ³
TITGANZ		T: 5.3 (95% CI: 4.1, 6.4) ⁴ CMFP: 6.4 (95% CI: 5.2, 7.8) ⁴ P ⁵ = 0.25		T: 17.3 (95% CI: 12.5, 21.4) ⁴ CMFP: 13.9 (95% CI: 11.4, 16.5) ⁴ P ⁵ = 0.068

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone
1: 2 sided log-rank test

2: Cox's Proportional hazards regression analysis

3: No details of tests used

4: Confidence intervals estimated using Brookmeyer Crowley method

5: Mantel-Cox log-rank test

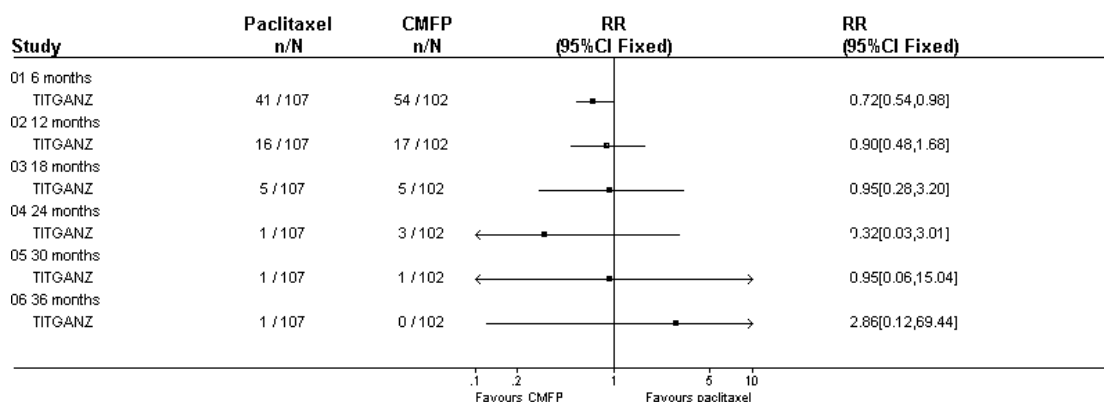
4.1.2.1.2. *Progression Free Survival*

Kaplan Meier curves were presented only the TITGANZ trial.

The median time to progression was similar for paclitaxel and CMFP in the TITGANZ trial (5.3 months (95% CI: 4.1, 6.4) versus 6.4 months (95% CI: 5.2, 7.8) P = 0.25). The median time to treatment failure was similar for paclitaxel and doxorubicin in the E1193 trial (5.9 months versus 6 months respectively, p = 0.35).

Figure 4.1.2.1b illustrates the estimates of progression free survival rates at 6, 12, 18, 24, 30 and 36 months for the TITGANZ trial.

Figure 4.1.2.1b Single agent paclitaxel as first-line treatment for breast cancer. Progression free survival.



The progression free survival rates were generally similar. However, at 6 months, significantly more patients treated with CMFP than paclitaxel survived progression free (53% versus 38%: RR: 0.72 (95% CI: 0.54, 0.98); number needed to treat = 7). The survival rates were similar at 12 and 18 months, by which time only 5 women in each arm survived without progression. By 36 months there was only one progression free survivor - in the paclitaxel group.

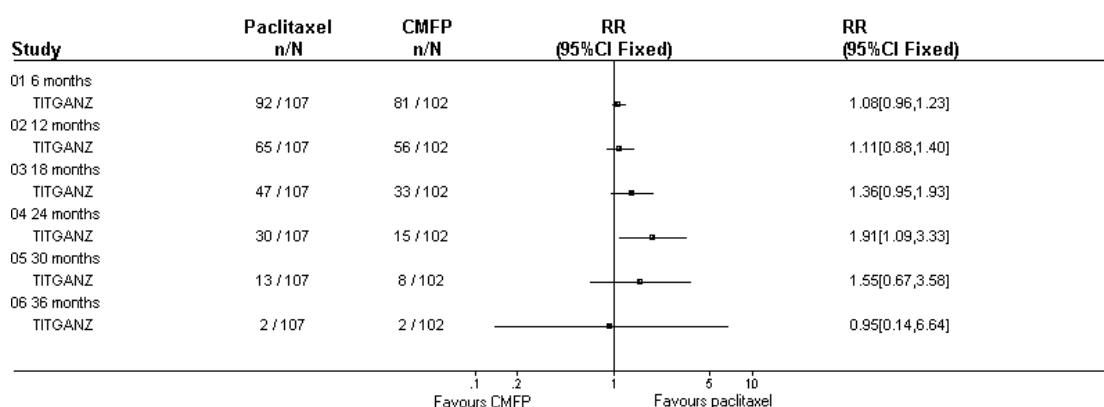
4.1.2.1.3. Overall survival

Kaplan Meier curves were presented only the TITGANZ trial.

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 intention to treat basis (Table 4.1.2.1c). There were no significant differences between the arms of the trials in median length of overall survival.

Figure 4.1.2.1c illustrates the estimates of overall survival rates at 6, 12, 18, 24, 20 and 36 months for the TITGANZ trial.

Figure 4.1.2.1c Single agent paclitaxel as first-line treatment for breast cancer. Overall survival



There was no significant difference between paclitaxel and doxorubicin in the number of patients surviving up to 18 months (Figure 3). However, by 24 months, significantly more women in the paclitaxel arm than the doxorubicin arm survived (28% versus 15%, RR: 1.91 (95% CI: 1.09, 3.33); number needed to treat = 8). Although still favouring paclitaxel, the difference in survival rate was not significant at 30 and by 36 months, only 2 patients in each arm survived.

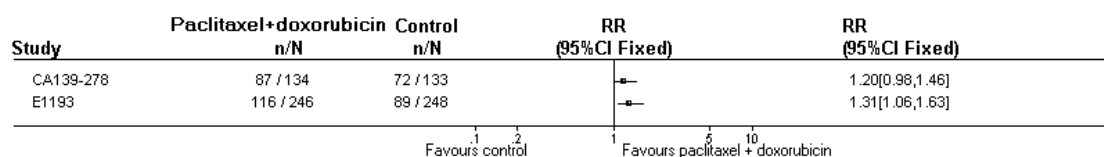
4.1.2.2. Paclitaxel plus anthracycline versus control

4.1.2.2.1. Overall response rates

Overall response rates (complete response + partial response) were presented for both trials comparing paclitaxel plus doxorubicin with control: CA139-278 (65%) and E1193 (47%) (See Figure 4.1.2.2.d). In both trials, more women in the paclitaxel plus doxorubicin arm responded - this difference was statistically significant in E1193, which compared paclitaxel plus doxorubicin with doxorubicin alone (47% versus 36% RR: 1.31 (95% CI: 1.06, 1.63); number needed to treat = 9).

Neither trial reported time to, nor duration of, response.

Figure 4.1.2.2a Combined paclitaxel/anthracycline as first-line treatment for breast cancer. Overall response rates



4.1.2.2.2. 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 the FAC arm (Table 4.1.2b 8.3 months (95% CI: 7.2, 9.0) versus 6.2 months (95% CI: 5.8,7.6) p = 0.035)). The

median time to treatment failure was also significantly longer for the paclitaxel plus doxorubicin arm than doxorubicin alone (8 months versus 6 months, $p = 0.003$).

Table 4.1.2b Median times

Study	Median progression free survival (months)	Median time to treatment failure (months)	Median length of survival (months)
Intergroup E1193		AT: 8 A: 6 $p = 0.003^1$	AT: 22 A: 18.9 $p = 0.24)^1$ Unclear if ITT
CA139-278 (39)	AT: 8.3 (95% CI: 7.2, 9.0) FAC: 6.2 (95% CI: 5.8, 7.6) $P^2 = 0.034$		AT: 22.7 (95% CI: 20.2, ?) FAC: 18.3 (95% CI: 16.1, 21.8) $P^2 = 0.02$

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone
1: No details of tests used

2: Stratified log-rank p

4.1.2.2.3. 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 (AT: 22.7 months (95% CI: 20.2, ?), FAC: 18.3 months (95% CI: 16.1, 21.8) $p = 0.02$).

4.1.2.3. Comparing paclitaxel alone to paclitaxel plus other

The E1193 trial allowed single agent paclitaxel to be compared to paclitaxel in combination with docetaxel. The median time to treatment failure was significantly longer with the 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).

4.1.3. Compliance

Details about numbers completing all cycles and reasons for early discontinuation were patchy. In CA139-278, patients in the FAC arm were more likely to discontinue because of disease progression.

Table 4.1.2.4 Treatment received

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

4.1.4. Adverse effects

The 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.

4.1.4.1. Haematological side effects

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

4.14a). More patients in the doxorubicin than the paclitaxel arm of EORTC suffered neutropenia (85% versus 40%) and febrile neutropenia (20% versus 7%). In CA139-278 more patients treated with paclitaxel plus anthracycline than FAC suffered neutropenia (47% versus 20%. RR 2.33 (95% CI: 1.59, 3.42) and febrile neutropenia (29% versus 16%. RR: 1.84 (95% CI: 1.14, 2.95)).

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

Table 4.1.4a Haematological adverse events - Percentage of participants in each trial

Trial	EORTC	TITGANZ	E1193	CA139-278
Numbers in arms	N = 327 (32) % RR (95% CI)	T: 107 CMFP: 102 % RR (95% CI)	T: 241 AT: 242 A: 241 % RR (95% CI)	AT: 131 FAC: 133 % RR (95% CI)
Neutropenia	T: 40 A: 85	T: 68 CMFP: 74 0.93 (0.78,1.10)		AT: 47 FAC: 20 2.33 (1.59,3.42)
Febrile Neutropenia	T:7 A: 20			AT: 29 FAC: 16 1.84 (1.14, 2.95)
Infections		T: 1 CMFP: 7 0.14 (0.02,1.09)	T: 9 AT: 12 A: 4 T versus A: 2.2 (1.06, 4.55) AT versus T: 1.36 (0.57, 2.43) AT versus A: 2.89 (1.44, 5.79)	AT: 2 FAC: 0 5.08 (0.25, 104.7)
Thrombocytopenia		T: 1 CMFP: 12 0.08 (0.01,0.60)	T: 2 AT: 16 A: 5 T versus A: 0.42 (0.15, 1.16) AT versus T: 9.07 (3.53, 23.44) AT versus A: 3.24 (1.74, 6.03)	
leucopenia		T: 29 CMFP: 66 0.44 (0.32, 0.61)		
granulocytopenia			T: 79 AT: 57 A: 66 T versus A: 1.19 (1.07, 1.34) AT versus T: 0.36 (0.24, 0.53) AT versus A: 0.86 (0.75, 1.00)	

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone

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 paclitaxel experienced thrombocytopenia (12% versus 1% RR: 0.08 (95% CI: 0.01, 0.60)) and leucopenia (66% versus 29% . RR: 0.44 (95% CI: 0.32, 0.61). Significantly more women treated with paclitaxel plus doxorubicin suffered thrombocytopenia than treated with paclitaxel or doxorubicin alone (RR: 9.07 (95% CI: 3.53, 23.44) and 3.24 (95% CI: 1.74, 6.03) respectively).

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

4.1.4.2. Gastrointestinal adverse events

Gastrointestinal events reported in the TITGANZ and CA139-278 trials were rare in the paclitaxel arms of the trials (See Table 4.1.4b). Nausea and or vomiting were more frequent in the control arms of the TITGANZ trial (RR: 0.12 (95% CI: 0.02, 0.94)). Stomatitis was also more common among patients treated with doxorubicin rather than paclitaxel in the EORTC trial (15% vs 1%).

Table 4.1.4b Gastrointestinal adverse events

Trial	EORTC	TITGANZ	CA139-278
Numbers in arms	N = 327 (32)	T: 107	AT: 131
	%	CMFP: 102	FAC: 133
	RR (95% CI)	%	%
		RR (95% CI)	RR (95% CI)
vomiting		T: 1* CMFP: 8 0.12 (0.02,0.94)	AT: 6 FAC: 14 0.45 (0.20,1.00)
stomatitis	T: 1 A: 15		AT: <1 FAC: <1 1.02 (0.06,16.06)
diarrhoea			AT: 2 FAC: 0 5.11 (0.25, 105.51)

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone
* nausea and vomiting

4.1.4.3. Neurological adverse events

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

Table 4.1.4c Neurological adverse events

Trial	EORTC	TITGANZ	E1193
Numbers in arms	N = 327 (32)	T: 107	T: 241
	%	CMFP: 102	AT: 242
	RR (95% CI)	%	A: 241
		RR (95% CI)	%
			RR (95% CI)
Neurosensory	T: 9 A: 0		T: 3* AT: 10 A: 2 T versus A: 1.4 (0.45, 4.35) AT versus T: 3.68 (1.55, 8.71) AT versus A: 4.78 (1.85, 12.32)
Peripheral neuropathy		T: 10 CMFP: 0 21.94 (1.31,367.48)	

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone
* includes neuromotor

4.1.4.4. Cardiovascular adverse events

Cardiovascular adverse events were reported only in EORTC and E1193. These were more frequent in patients treated with anthracyclines than paclitaxel (Table 4.1.4d). 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 (0.22, 0.94) and 9% versus 4% RR: 2.31 (1.07, 4.99) respectively).

Table 4.1.4d Cardiovascular adverse events

Trial	EORTC	E1193
Numbers in arms	N = 327 (32) % RR (95% CI)	AT: 242 A: 241 % RR (95% CI)
Myocardial infarction		
Congestive heart failure	T: 0 A: 4	
Cardiac deaths		T: <1 A: 3 AT: <1 AT versus A 0.33 (0.03, 3.17)
Cardiac		T: 4 AT: 9 A: 9 T versus A: 0.45 (0.22, 0.94) AT versus T: 2.31 (1.07, 4.99) AT versus A: 1.00 (0.57, 1.75)

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone

4.1.4.5. Other adverse events

Most other adverse effects were rare (Table 4.1.4e). However, the majority of patients treated with paclitaxel in the TITGANZ trial suffered alopecia (76% compared to 25% in the CMFP arm RR: 3.09 (95% CI: 2.16, 4.41)). Arthralgia and myalgia occurred significantly more frequently in the paclitaxel arm than control of both TITGANZ and CA139-278 (20% versus 1% RR: 20.02 (2.74, 146.11) and 8% versus 0% RR: 21.32 (95% CI: 1.26, 360.12))

Table 4.1.4e Other adverse events

Trial	EORTC	TITGANZ	E1193	CA139-278
Numbers in arms	N = 327 (32) % RR (95% CI)	T: 107 CMFP: 102 % RR (95% CI)	T: 241 AT: 242 A: 241 % RR (95% CI)	AT: 131 FAC: 133 % RR (95% CI)
Alopecia		T: 76 CMFP: 25 3.09 (2.16, 4.41)		
mucositis		T: 3 CMFP: 6 0.48 (0.12, 1.86)		
Hospitalisation (any cause)				
Toxic death			T: 1 A: 2 AT: 1 AT versus A: 0.5 (0.13, 1.97)	
Arthralgia/myalgia	T: 4 A: 0	T: 20 CMFP: 1 20.02 (2.74, 146.11)		AT: 8 FAC: 0 21.32 (1.26, 360.12)

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone

4.1.5. Quality of Life

Quality of life was evaluated in 3 studies TITGANZ, E1193 and CA139-278. There were no significant differences between paclitaxel and control in any of the 3 trials in terms of overall quality of life, although differences were apparent on some subscales. These did not reach significance in TITGANZ.

	TITGANZ ³	E1193 ¹	CA139-278
Overall QoL	T: 2.2 CMFP: -3.7 P = 0.07	Global FACT B T: -2.9 A: -1.8 AT: -2.8	AT = FAC
Physical well being	T: 1.9 CMFP: -4.3 P = 0.08		FAC greater
Mood	T: 4.2 CMFP: 1.1 P = 0.49		
Pain	T: -0.4 CMFP: 3.5 P = 0.35		FAC greater
Nausea/vomiting	T: -2.5 CMFP: -5.3 P = 0.07		AT greater
Appetite	T: 1.8 CMFP: -3.6 P = 0.24		
QoL by physician	T: 1 CMFP: -2.5 P = 0.25		
Sexual functioning			FAC greater
Fatigue			FAC greater
Insomnia			FAC greater
Diarrhoea			FAC greater
Role			AT = FAC
Emotional			AT = FAC
Cognitive			AT = FAC
Social			AT = FAC

T: paclitaxel; A: anthracycline (doxorubicin); FAC: fluorouracil, anthracycline, cyclophosphamide; CMFP: cyclophosphamide, methotrexate, 5 fluorouracil, prednisone

1: 16 week paired Global FACT-B QoL - Baseline (paired) Global FACT B QoL

3: Average changes in quality of life relative to baseline

4.1.6. Discussion

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

4.1.6.1. Single agent paclitaxel

Of the three randomised controlled trials, none found single agent paclitaxel superior to control in terms of response; in one trial (EORTC) significantly more women responded to doxorubicin than paclitaxel. The median length of progression free survival was significantly longer in the doxorubicin control than 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 six months; whereas more women in the paclitaxel arm survived at 2 years. There were no significant differences in 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. Arthralgia/myalgia were significantly more common in patients treated with paclitaxel. Three of the trials investigated quality of life - none found a significant difference between paclitaxel and control.

The TITGANZ study was a high quality, randomised controlled trial. However, insufficient details were given in the EORTC and E1193 abstracts and overheads to properly assess its quality. E1193 and EORTC allowed crossover on progression and TITGANZ recommended that patients who progressed received epirubicin. It was not clear from the available information whether E1193 distinguished between early and late crossovers and patients who did not crossover in survival analysis and was analysed on an intention to treat basis. No mention was made in TITGANZ 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/m² given as a three hour infusion compared to 175 mg/m² given over 24 hours respectively) and in the dose of doxorubicin (75 mg/m² compared to 60 mg/m²). TITGANZ used a dose of 220 mg/m². These differ from the recommended dose of 175 mg/m² given over 3 hours for paclitaxel in advanced breast cancer. This, however, is specified for second - line treatment

Of the two trials, one included anthracyclines in the control arm; one (TITGANZ) did not, consequently the survival curves of TITGANZ should not be generalised to E1193. 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.

4.1.6.2. Paclitaxel plus anthracycline

Two randomised controlled trials evaluated the effectiveness of paclitaxel combined with an anthracycline (E1193 and CA139-278). The response rate of paclitaxel plus doxorubicin was statistically superior to doxorubicin alone in E1193. No survival curves were presented; however, in both trials, patients in paclitaxel/anthracycline combination than control arms survived significantly longer without progression and in CA139-278, overall. In a comparison of single agent and combined paclitaxel (E1193), patients treated with the latter had longer, median progression free survivals.

Although both Phase III randomised controlled trials, insufficient details were given in the E1193 or CA139-278 abstracts and overheads to properly assess their quality. The combination used in CA139-278 involved a higher dose of paclitaxel than E1193 (220 mg/m² compared to 150 mg/m²). The control used in E1193 was single agent doxorubicin (60 mg/m²); CA139-278 used FAC - a combination of fluorouracil, anthracycline (50 mg/m²; specific type not specified) and cyclophosphamide. A larger proportion of participants in E1193 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.

4.1.7. Summary: Paclitaxel as first line treatment for advanced breast cancer

Four randomised controlled were identified which investigated the first line use of paclitaxel in breast cancer. A total of 1425 patients were included. None of the trials found single agent paclitaxel 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 doxorubicin arm was 8.3 months compared with 6.2 months in the FAC control ($p = 0.035$). The median time to treatment failure was also greater for paclitaxel plus doxorubicin than single agent doxorubicin (8 months versus 6 months, $p = 0.003$). There were no significant differences between paclitaxel and control in terms of over-all quality of life.

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

4.2.1 Description of included trial

Only one phase III study was identified which evaluated the effectiveness of docetaxel as a first -line treatment for advanced breast cancer. (40) This was the subject of a conference abstract - no further details have been located.

Table 4.2.1a Design of included trials

Trial	Accrual dates	Number evaluated	Number crossing over	Median length of follow up
Quality	Number entered			Number of participants surviving (%)
TAX 306 (40)	No details	June 1996 to March 1998	ITT	1 year
		AT: 215 AC: 214	Number treated AT: 213 AC: 210	

A: doxorubicin; T: docetaxel; C: cyclophosphamide

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 4.2.1b).

Table 4.2.1b Inclusion criteria

Trial	Disease	Previous treatment
TAX306	Metastatic breast cancer	Anthracycline naive

The trial compared doxorubicin (50mg/m²) plus docetaxel (75mg/m²) to doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) both given in three week cycles. Prophylactic colony stimulating factors or anti-biotics were not given unless after a prior neutropenic complication.

Table 4.2.1c Intervention

Trial	Intervention	Control
Tax306	AT: doxorubicin (50mg/m ²) plus docetaxel (75mg/m ²) 3 week cycle	AC: doxorubicin (60 mg/m ²) plus cyclophosphamide (600 mg/m ²) 3 week cycle

Details of the included participants are given in Table 4.2.1d. These were not broken down by intervention in the abstract; the authors state there was no imbalance.

Table 4.2.1d Participants

Trial	Median Age (years)	Secondary spread	Median disease free interval
n	Oestrogen receptor status	Number of metastatic sites	Previous treatment
	Performance status		
TAX306	Overall: 53 years Overall median Karnofsky Performance: 90	Extent of disease: 3 organs: 41% visceral: 63% bone: 52%	Median disease free interval 25 months Previous adjuvant chemotherapy Overall: 42%

4.2.2 Results

4.2.2.1 Overall response rates

Participants treated with docetaxel plus doxorubicin had significantly greater overall response rates than those treated with doxorubicin plus cyclophosphamide (60% vs 47%, $p = 0.008$ {from abstract}). Complete responses were found 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.

4.2.2.2 Progression Free Survival

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

4.2.2.3 Overall survival

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

4.2.2.4 Compliance

Fifteen percent 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 8 and 7 respectively.

4.2.3 Adverse effects.

Only Grade 3 to 4 toxicity are reported here.

4.2.3.1 Haematological side effects

Neutropenia was common in both arms of the trial.

Table 4.2.3.1 Haematological adverse events

Trial	TAX306
Numbers in arms	AT: 215 AC: 214 %
Neutropenia	AT: 82 AC: 69
Febrile Neutropenia	AT: 6 AC: 2
Infections	AT: 1 AC: <1

A: doxorubicin; T: docetaxel; C: cyclophosphamide

4.2.3.2 Gastrointestinal adverse events

Gastrointestinal events were rare.

Table 4.2.3.2 Gastrointestinal adverse events

Trial	TAX306
Numbers in arms	AT: 215 AC: 214
	%
diarrhoea	AT: 2 AC: <1

A: doxorubicin; T: docetaxel; C: cyclophosphamide

4.2.3.3 Neurological adverse events

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

4.2.3.4 Cardiovascular adverse events

Clinical coronary heart failure was found in 2% of the docetaxel plus doxorubicin group and 4% of the doxorubicin plus cyclophosphamide group. LVEF decrease of 30 points from baseline in 2% of the docetaxel plus doxorubicin group and 5% of the doxorubicin plus cyclophosphamide group.

4.2.3.5 Other adverse events

Severe oedema was reported in 1% of participants in the docetaxel plus doxorubicin; overall oedema was reported in 31% of this group. There was 1 toxic death in the docetaxel plus doxorubicin group compared with 3 in the doxorubicin plus cyclophosphamide group.

4.2.4 Quality of Life

Quality of life was not assessed.

4.2.5 Discussion

Only one Phase III trial was found which 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 a randomised controlled trial. Consequently, the findings should be treated with extreme caution. In addition, it appears to be an early report (median follow-up of one 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.

4.2.6 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.

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

4.3.3 Description of included trial

Only two randomised, controlled studies were identified which evaluated the effectiveness of paclitaxel as a second -line treatment for advanced breast cancer. These both relate to the same trial, CA139-047 (41, 42). One is a report submitted by the manufacturer, the second a journal article.

Table 4.3.1a Design of included trials

Trial	Accrual dates	Number evaluated	Number crossing over	Median length of follow up	
Quality	Number randomised			Number of participants surviving (%)	
CA139-047	Randomised	April 1992 to	Not clear if IIT	T→M: 0	Not stated
Trial report (41)	Open label	December 1993		M→T: 22	
Journal article (42)	Nonblinded	T: 41 M: 40	72 evaluable efficacy		55 (68%)
	1A				

T: paclitaxel M: mitomycin

This was a randomised, controlled Phase II trial. Power calculations and accurate and standard definitions of outcome variables were provided. Patients were permitted to crossover to the alternate arm on disease progression - more than half the patients in the mitomycin arm crossed over compared to 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, where one was adjuvant chemotherapy (Table 4.3.1b). The permissible cytotoxic drugs were not specified.

Table 4.3.1b Inclusion criteria

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

The trial compared paclitaxel (175 mg/m²) given as a three hour infusion in a three week cycle to mitomycin (12 mg/m²) given as a slow bolus injection in a six week cycle.

Table 4.3.1c Intervention

Trial	Intervention	Control
CA139-047	T: paclitaxel (175 mg/m ²) 3 hour infusion 3 week cycle	M: mitomycin (12 mg/m ²) Slow bolus injection 6 week cycle

Details of the included participants are given in Table 4.3.1d.

Table 4.3.1d Participants

Trial	Median Age (years)	Secondary spread	Median disease free interval
n	Oestrogen receptor status	Number of metastatic sites	Previous treatment
Performance status			
CA139-047	Age T: 52 M: 52.5 ER positive: T: 54% M: 48% ECOG PS 0: T: 39% M: 45% ECOG PS 1: T: 51% M: 40% ECOG PS 2: T: 10% M: 15%	Extent of disease: Soft tissue: T: 51% M: 48% Bone: T: 56% M: 43% Liver: T: 59% M: 60% Lung T: 34% M: 45% Dominant site of disease: Soft tissue only: T: 7% M: 0% Bone +/- soft tissue T: 12% M: 5% Visceral +/- bone +/- soft tissue T: 80% M: 95%	Median time from diagnosis: T: 48.2 months M: 53.5 months Previous chemotherapy Metastatic only: T: 49% M: 48% Metastatic + adjuvant: T: 51% M: 53%. Anthracycline: T: 98% M: 98% Vinca alkaloid: T: 24% M: 38%

T: paclitaxel M: mitomycin

4.3.4 Overall response rates

None of the patients in CA139-047 showed a complete response; consequently, overall response was based on partial response only (Figure 4.3.2a). Although more patients in the paclitaxel arm responded, the difference between arms was not statistically significant (RR: 2.93 (95% CI: 0.63, 13.65)).

Figure 4.3.2a Paclitaxel as second-line treatment for breast cancer. Overall response rate

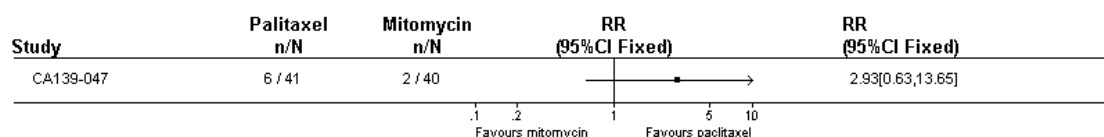


Table 4.3.2 Median times

Study	Time to response in weeks (range)	Duration of response in months (range)	Median duration of disease control (months)	Median length of survival (months)
CA139-047			T: 3.5 (95% CI: 1.8, 5.0) ¹ M: 1.6 (95% CI: 1.5, 2.8) P ² = 0.026	T: 12.7 months M: 8.4 months P ² = 0.15
CA139-047 crossover			M→T: 2.2 (95% CI: 1.7, 3.5)	

T: paclitaxel M: mitomycin

¹ Confidence intervals calculated using Brook Meyer and Crowley method

² Log rank test

4.3.4.2 Progression Free Survival

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 mitomycin, had significantly longer duration of disease control (3.5 months (95% CI: 1.8, 5.0) vs 1.6 months (95% CI: 1.5, 2.8) P² = 0.026). The duration of disease control in patients crossing over from mitomycin to paclitaxel was 2.2 months (95% CI: 1.7, 3.5).

4.3.4.3 Overall survival

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

4.3.5 Compliance

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

4.3.6 Adverse effects.

Adverse events are only reported for about half the participants. Only Grade 3 to 4 toxicity are reported here.

4.3.6.2 Haematological side effects

More than 60% of the patients in the paclitaxel arm suffered neutropenia, compared with 3% of the mitomycin arm (RR: 23.61 (95%CI: 3.35,166.19). Anaemia and leucopenia occurred in 27 and 21% of patients in the paclitaxel arm respectively. There was no significant difference between the arms in either case.

Table 4.3.4a Haematological adverse events

Trial	CA139-047
Numbers in arms	T: 38 M: 39 % RR (95% CI)
Neutropenia	T: 61 M: 3 23.61(3.35, 166.19)
Febrile Neutropenia	T: 3 M: 0 3.08 (0.13,73.26)
Infections	T: 3 M: 0 3.08 (0.13,73.26)
Thrombocytopenia	T: 3 M: 20 RR: 0.13 (0.02, 0.98)
leucopenia	T: 21 M: 5 RR: 4.11 (0.93, 18.10)
anaemia	T: 27 M: 8 2.05 (0.55,7.62)

T: paclitaxel M: mitomycin

4.3.6.3 Gastrointestinal adverse events

Gastrointestinal events were rare - nausea and vomiting occurred in only 3% of the paclitaxel group.

Table 4.3.4b Gastrointestinal adverse events

Trial	CA139-047
Numbers in arms	T: 38 M: 39 % RR (95% CI)
Nausea/vomiting	T: 3 M: -

T: paclitaxel M: mitomycin

4.3.6.4 Neurological adverse events

Peripheral neuropathy was reported in 4% of the paclitaxel arm (Table 4.3.4c).

Table 4.3.4c *Neurological adverse events*

Trial	CA139-047
Numbers in arms	T: 38 M: 39
	% RR (95% CI)
Peripheral neuropathy	T: 4 M: -

T: paclitaxel M: mitomycin

4.3.6.5 Cardiovascular adverse events

No cardiovascular adverse events were reported.

4.3.6.6 Other adverse events

Arthralgia/myalgia occurred in 11% of patients treated with paclitaxel; this was not significantly different from the incidence among patients receiving mitomycin (Table 4.3.4e)

Table 4.3.4e *Other adverse events*

Trial	CA139-047
Numbers in arms	T: 38 M: 39
	% RR (95% CI)
mucositis	T: 1 M: - 3.08 (0.13, 73.26)
Arthralgia/myalgia	T: 11 M: 5 1.54 (0.27, 8.71)
anorexia	T: 0 M: 5 0.21 (0.01, 4.14)
hospitalisations	T: 16 M: 23 0.68 (0.27, 1.74)

T: paclitaxel M: mitomycin

4.3.7 Quality of Life

Quality of life was not assessed.

4.3.8 Discussion

Only one randomised controlled trial was found which 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 is an open label trial, a variety of factors may have influenced the patients' decision to cross from mitomycin to paclitaxel treatment. Patients 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.

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

4.3.9 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 single trial provides very weak evidence that paclitaxel is an effective second-line treatment for metastatic breast cancer.

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

4.4.3 Description of included trials

Thirteen publications were identified which 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) (see Table 4.4.1a). With the exception of Bonneterre, for which only a meeting abstract is available, these studies have been published in journals.

Table 4.4.1a Design of included trials

Trial Source	Quality	Accrual dates	Intention to Treat (ITT)	Criteria for cross-over	Median length of follow up
		Number randomised	Number evaluated	Number crossing over	Number of participants surviving (%)
303 Study Group Journal article (43-47)	Randomised Power calculations Outcomes defined Multi-centre Non-blinded 1A	July 1994 - Jan 1997 D: 161 A: 165	ITT: 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: 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 months D: 59 (37) A: 27 (16)
304 Study Group Journal article (48-52)	Randomised Power calculations Outcomes defined Multi-centre Non-blinded 1A	July 1994 - Feb 1997 D: 203 MV: 189	ITT: 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 months D: 66 (33) MV: 51 (27)
Scand Journal article (54)	Randomised Power calculations Outcomes defined Multi-centre Open label 1A	Dec 1994 - Oct 1997 D: 143 MF: 140	ITT: all randomised patients <i>except one</i> Eligible: met all inclusion criteria receiving ≥ 1 cycle D: 136 MF: 131	Crossover recommended if objective signs of disease progression D→MF: 48 MF→D: 74	11 months 99 patients surviving (35%)
Bonneterre Meeting abstract (53)	Randomised Multi-centre Open Label 1	On-going? D: 46 FUN: 45	D: 46 FUN: 45		No details

D: docetaxel; A: anthracycline (doxorubicin); MV: mitomycin + vinblastine; FUN: 5 fluorouracil + navelbine; MF: methotrexate + 5 fluorouracil

All four were randomised, controlled Phase III trials. The 303 study, 304 study and Scand 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, the 304 studies and Scand 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 searches did not

identify any further papers dealing with this trial. The Scand study allowed crossover to alternate treatment on progression. Both the 303 and 304 studies analysed response rate, time to progression, time to treatment failure and survival on an intention to treat principle, including all randomised patients. The Scand study excluded one randomised patient from the "intention to treat" analyses of response, time to progression and overall survival. No such details were given in Bonneterre.

All the included trials required participants to have undergone previous chemotherapy (Table 4.4.1b). 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.

Table 4.4.1b Comparison of inclusion criteria

Trial	Disease	Previous treatment
303 Study Group	Histologically or cytologically confirmed metastatic breast cancer	Previous alkylating agent chemotherapy (eg CMF); either adjuvant or for advanced disease
	Measurable or evaluable disease	No more than 1 previous line of chemotherapy for metastatic disease
	Karnofsky PS > 60	No previous treatment with anthracyclines, anthracenes or taxoids
304 Study Group	Histologically or cytologically confirmed metastatic breast cancer	Previous anthracycline chemotherapy for advanced disease or relapse within last 12 months of anthracycline adjuvant therapy
	Measurable or evaluable disease	No more than 1 previous line of chemotherapy for metastatic disease
	Karnofsky PS > 60	No previous treatment with mitomycin, vinca alkaloids or taxoids
Scand	Histologically proven primary breast cancer	Previous anthracycline chemotherapy for advanced disease or relapse within last 12 months of anthracycline adjuvant therapy
	Measurable or evaluable lesions	No more than 1 previous line of chemotherapy for metastatic disease
	PS 0 to 2	No previous treatment with taxanes
Bonneterre	Metastatic breast cancer	Prior anthracycline chemotherapy

All of the trials contained docetaxel (100 mg/m²) given as a one hour infusion as the experimental condition; the control conditions were all different (see Table 4.4.1c). The 303, 304 and Scand studies included premedication of the docetaxel group; this was not mentioned in Bonneterre. The 303 and 304 studies allowed prophylactic anti-emetic premedication; this was not given in Scand. Neither the 303 study, 304 study nor Scand allowed prophylactic administration of colony stimulating factors. No details were given in the Bonneterre abstract.

Table 4.4.1c Comparison of interventions

Trial	Intervention	Comparison	Crossover
303 Study Group	D: docetaxel (100 mg/m ²) 1 hour infusion Up to 7 x 3 week cycles Premedication: oral dexamethasone 2 x 8 mg for 5 days Usual anti-emetic premedication No prophylactic G-CSF	A: doxorubicin (75 mg/m ²) Up to 7 x 3 week cycles Usual anti-emetic premedication No prophylactic G-CSF	None
304 Study Group	D: docetaxel (100 mg/m ²) 1 hour infusion Up to 10 x 3 week cycles Premedication: oral dexamethasone 2 x 8 mg for 5 days Usual antiemetic premedication No prophylactic G-CSF	MV: mitomycin C (12 mg/m ²) + vinblastine (6 mg/m ²) Bolus injection M: 42 day cycle V:21 day cycle Up to 10 cycles Usual antiemetic premedication No prophylactic G-CSF	None
Scand	D: docetaxel (100 mg/m ²) 1 hour infusion At least 6 x 3 week cycles Premedication: oral dexamethasone or betamethasone 2 x 8mg for 5 days No prophylactic anti-emetics No prophylactic G-CSF	MF: methotrexate (200 mg/m ²) + 5 fluorouracil (600 mg/m ²) At least 6 cycles. Day 1 & 8 of 3 week cycle Urinary alkalisation (NaHCO ₃) Leucovorin 4 x 15mg for 2 days No prophylactic anti-emetics No prophylactic G-CSF	Crossover on progression if appropriate
Bonneterre	D: docetaxel (100 mg/m ²) 3 week cycles	FUN: 5 fluorouracil (750 mg/m ²) + navelbine (25 mg/m ²)	

The differences in the inclusion criteria influence the patient mix of the 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.

Table 4.4.1d Comparison of participants

Trial	Median Age (years)	Secondary spread	Median disease free interval
n	Oestrogen receptor status (ER)	Number of metastatic sites	Previous treatment
Performance status			
303 Study Group	Age D: 52 A: 52 Median Karnofsky PS: D: 90 A: 90	Soft tissue only: D: 9% A: 12% Bone: D: 55% A: 63% Viscera: D: 75% A: 76% Liver D: 43% A: 40% Number of metastatic sites 1 site : D: 22% A: 19% 2 sites: D: 34% A: 38% ≥ 3 organs: D: 44% A: 43%	Time from first diagnosis to first relapse (months) D: 27 A: 25 Adjuvant only: D: 51% A: 42% Advanced only: D: 43% A: 49%. Resistance to last chemotherapy. Primary: D: 10% A: 14% Secondary: D: 37% A: 36% Not resistant: D: 53% A: 50%
304 Study Group	Age D: 51 A: 52 Median Karnofsky PS: D: 90 MV: 90	Soft tissue only: D: 8% MV: 10% Bone: D: 57% MV: 65% Viscera: D: 75% MV: 73% Liver D: 50% MV: 47% Number of metastatic sites 1 site : D: 23% MV: 21% 2 sites: D: 37% MV: 27% ≥ 3 sites: D: 39% MV: 52%	Time from first diagnosis to first relapse (months) D: 18 MV: 18 Adjuvant only D: 17% MV: 21% Advanced only D: 49% MV: 50% Resistance to last chemotherapy. Primary: D: 23% MV: 21% Secondary: D: 34% MV: 34% Not resistant: D: 43% MV: 44%
SCAND	Age: D: 50 MF: 51 ER positive: D: 35 MF: 31 WHO PS 0: D: 32% MF: 27% WHO PS 1: D: 57% MF: 57% WHO PS 2: D: 12% MF: 16%	Visceral: D: 73% MF: 69% Liver: D: 51% MF: 41% Bone: D: 46% MF: 39% Soft tissue: D: 48% MF: 50% Number of organs involved 1: D: 35% MF: 38% 2+: D: 40% MF: 33%	Median disease free interval D: 18.7 months, MF: 16.9 months Adjuvant only: D: 17% MF: 12% Advanced only: D: 82% MF: 86% Both D: 1% MF: 1% None MF: 1%
Bonneterre	Age: 54.3 Median PS: 1	sites of disease: liver: 70% bone: 45% lung: 25% skin and soft-tissue: 20% Number of involved sites: 1 site: 30% 2 sites: 31% ≥3 sites: 37%	Median time from diagnosis: 35 months

D: docetaxel; A: anthracycline (doxorubicin); MV: mitomycin + vinblastine; FUN: 5 fluorouracil + navelbine; MF: methotrexate + 5 fluorouracil

The differences between the studies made pooling inappropriate. It was not possible to assess the quality of the Bonneterre study and preliminary results only were presented. Although the trials all investigated the same experimental intervention, different controls have been used. The 303 study included patients who had not been previously treated with anthracyclines; patients in the other studies had deteriorated since anthracycline treatment.

4.4.4 Synthesis

4.4.4.2 Overall response

Median time to response was only presented for the 303 study (Table 4.4.2a). Patients in the docetaxel arm responded significantly more quickly than patients in the doxorubicin arm ($p = 0.007$). There was no statistical analysis of the duration of response for the Bonneterre trial.

Table 4.4.2a Median times

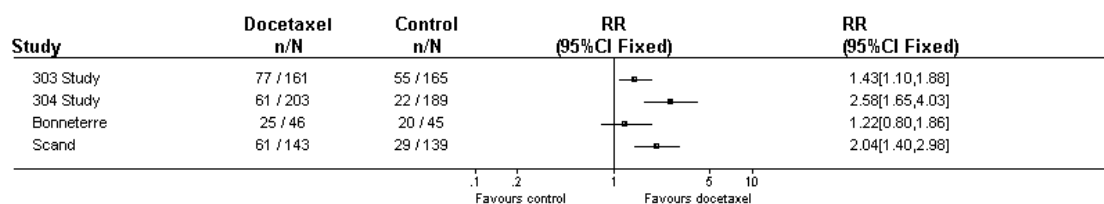
Study	Median time to response	Median duration of response	Median time to treatment failure	Median time to progression	Median length of survival
303 Study Group	D: 12 weeks A: 23 weeks P ¹ = 0.007		D: 22 weeks A: 18 weeks P ² = 0.10 P ³ = 0.01	D: 26 weeks A: 21 weeks P ² = 0.45 P ³ = 0.09	D: 15 months A: 14 months P ² = 0.39 P ³ = 0.41
304 Study Group			D: 16 weeks MV: 10 weeks P ² = 0.0003 P ³ = 0.0002	D: 19 weeks MV: 11 weeks P ² = 0.001 P ³ = 0.0001	D: 11.4 months MV: 8.7 months P ² = 0.01 P ³ = 0.03
Scand				D: 6.3 months MF: 3 months P ² = 0.001	D: 10.4 months MF: 11 months
Bonneterre		D: 8 months FUN: 6 months		D: 7 months FUN: 5 months	

D: docetaxel; A: anthracycline (doxorubicin); MV: mitomycin + vinblastine; FUN: 5 fluorouracil + navelbine; MF: methotrexate + 5 fluorouracil

1 = Chi Square; 2 = Log rank test; 3 = Wilcoxon Test

Overall response rates (complete response + partial response) were presented for all 4 trials: 303 Study, 304 Study, Bonneterre and Scand (See Figure 4.4.2a). 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, 1.88); number need to treat = 7); to mitomycin C plus vinblastine (30% versus 12%; RR: 2.58 (95% CI: 1.65, 4.03); number needed to treat = 5) and methotrexate plus 5 fluorouracil (43% versus 21%; RR: 2.04 (95% CI: 1.40, 2.98); number needed to treat = 5). The preliminary results of the Bonneterre study showed no significant difference between the conditions.

Figure 4.4.2a Docetaxel as second-line treatment for breast cancer: Overall response rates.



4.4.4.3 Progression Free Survival

Kaplan Meier curves were presented for three of the trials: 303 Study, 304 Study and Scand. 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 5 fluorouracil 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 time to disease progression of 28 weeks for docetaxel and 20 weeks for 5 fluorouracil and navelbine - no statistics were given.

Figure 4.4.2b illustrates the estimates of progression free survival rates at 8 weekly intervals until 80 weeks obtained from these analyses. The 1 year estimate for Scand has been entered at 48 weeks.

At 8 weeks there was no significant difference between the treatment arms in either trial.

At 16 weeks, in both trials, significantly more patients survived progression free in the docetaxel arm than the control arm (303 Study: 68% versus 56%; RR: 1.21 (95% CI: 1.02, 1.44); 304 Study: 51% versus 33% RR: 1.54 (95% CI: 1.21, 1.96). Numbers needed to treat: 8 and 6 respectively).

At 24 weeks, statistically significantly more patients in the docetaxel arm of the 304 had survived without disease progression than in the mitomycin plus vinblastine arm (33% versus 16%; RR: 2.08 (1.42, 3.05), number need to treat: 6). Although, overall a greater number of patients survived progression free in the 303 study (47% versus 37%), there was no significant difference between the docetaxel and doxorubicin arms.

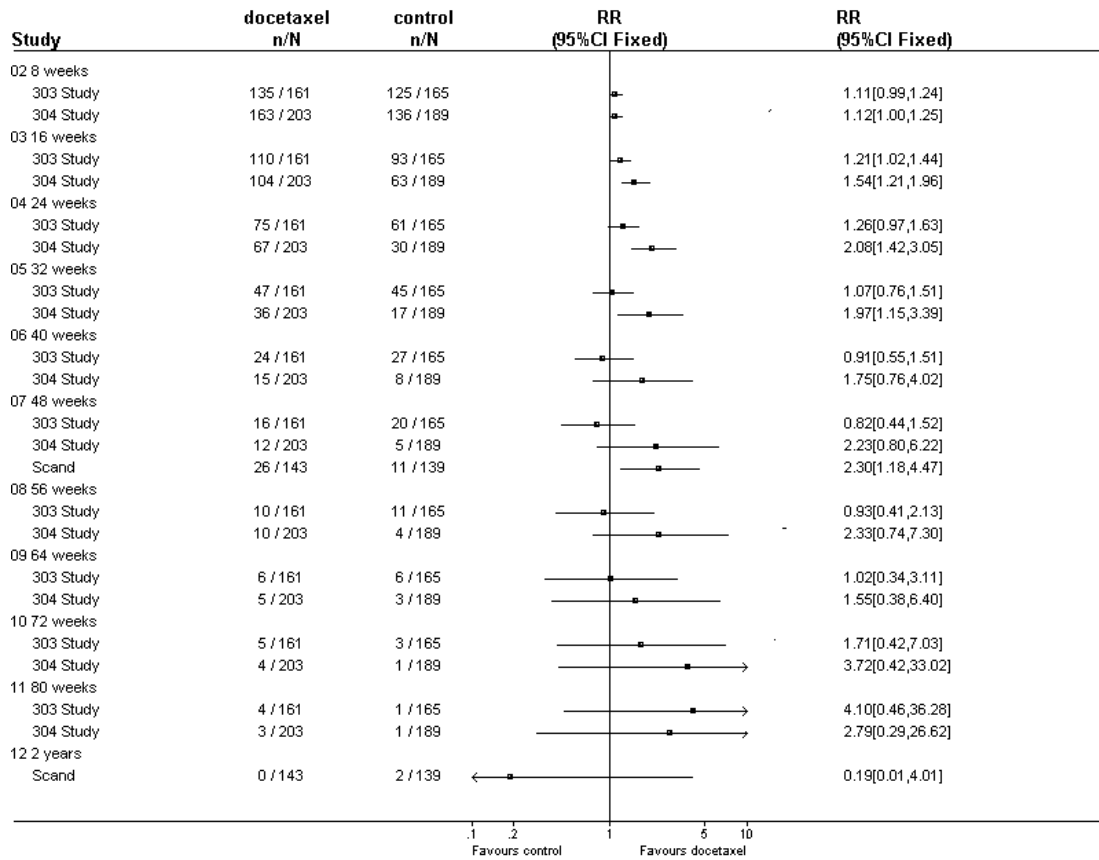
At 32 weeks, statistically significantly more patients in the docetaxel arm of the 304 had survived without disease progression than in the mitomycin plus vinblastine arm (18% versus 9%; RR: 1.97 (95% CI: 1.15, 3.39) number needed to treat: 11). There was no significant difference between the docetaxel and doxorubicin arms in the 303 study (29% versus 27%).

From 40 to 80 weeks, there were no significant differences between the arms of either the 303 or 304 trial, although patients in the doxorubicin arm of the 303 study appeared to fare marginally better than those treated with docetaxel at 40, 48 and 56 weeks. However, at 1 year (entered as 48 weeks), in the Scand study, significantly more patients in the docetaxel than methotrexate plus fluorouracil survived progression free (18% versus 8% RR: 2.3 (95% CI: 1.18, 4.47); number need to treat = 10).

By 80 weeks, only 9 patients out of 718, overall were surviving without disease. These were more likely to have been treated with docetaxel but there were no statistically significant differences between the arms of the trials.

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

Figure 4.4.2b Docetaxel as second-line treatment for breast cancer. Progression free survival



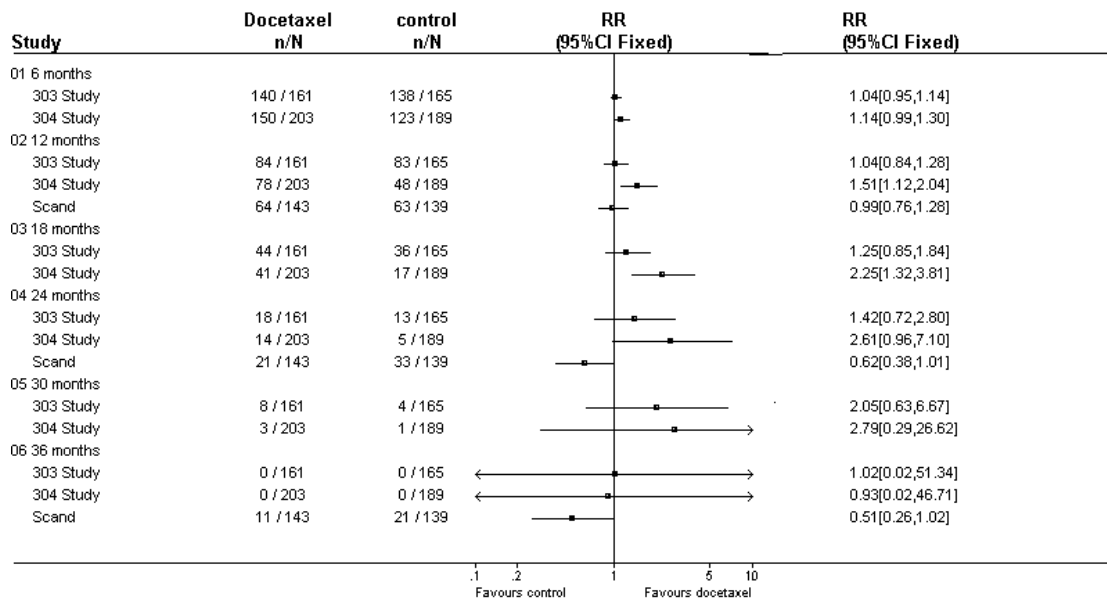
4.4.4.4 Overall survival

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

The median length of 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 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 progression.

The numbers of patients surviving at 6, 12, 18, 24, 30 and 36 months in each of the arms were compared. It is important to note that many of the patients in Scand had crossed over to alternate treatment.

Figure 4.4.2c Docetaxel as second-line treatment for breast cancer. Overall survival



At six months there was no significant difference between the arms of either trial in the number of patients surviving.

At one year, significantly more patients in the docetaxel arm of the 304 study than the mitomycin plus vinblastine arm had survived (38% versus 25%; RR: 1.51 (95% CI: 1.12, 2.04). There was no significant difference between the docetaxel and control arms in the 303 study (52% versus 50%) or Scand study (45% in both groups).

At eighteen months, significantly more patients in the docetaxel arm of the 304 study than the mitomycin plus vinblastine arm had survived (20% versus 9%; RR: 2.25 (95% CI: 1.32, 3.81). There was no significant difference between the docetaxel and doxorubicin arms (27% versus 22%) in the 303 study.

At 24 months, less than ten per cent of patients in the 303 and 304 studies survived. There was no statistically significant difference between the arms of either trial, although more patients in the docetaxel tended to survive. In the Scand study, however, more patients in the methotrexate plus fluorouracil tended to survive (24% versus 15%) although this was not significant.

Only 16 patients survived at 30 months. No patients survived to 3 years in 303 or 304 studies. In the Scand study, however, more patients in the methotrexate plus fluorouracil tended to survive (15% versus 8%) although this was not significant.

4.4.5 Compliance

The numbers completing all cycles specified by the protocol were given for the 303 and 304 studies. Few patients completed all cycles - the median number of cycles of docetaxel completed across all trials was 6. This was generally slightly more than the

control group. In the Scand trial 14 patients continued with treatment but there are no details of which group they belong to or whether they had crossed over. None of the studies were blinded so there may have been different pressures to continue with treatment or crossover depending on the treatment arm.

Table 4.4.2.4 Compliance

Trial	Completing all cycles	Median number of cycles (range)	Reasons for early discontinuation (%)					
			Disease progression	Adverse events	Withdraw consent	Death	Protocol violation	Other
303 study	D: 46% A: 34% P = 0.027	D: 7 (1 to 11) A: 6 (1 to 7)	D: 30 A: 36	D: 12 A: 16	D: 3 A: 7	D: 3 A: 2	D: 1 A: 1	D: 5 A: 4
304 study	D: 12% MV: 7%	D: 6 (1 to 12) MV: 4 (1 to 12)	D: 51 MV: 65	D: 14 MV: 10	D: 9 MV: 6	D: 5 MV: 4	D: 1 MV < 1	D: 7 MV: 6
Scand		D: 6 (1 to 20) MF: 4 (1 to 19)	D: 49 MF: 80	D: 21 MF: 3	D: 9 MF: 3	D: 6 MF: 4	D: 1 MF < 1	D: 7 MF: 4
Bonneterre		D: 6 (1 to 11) FUN: 4 (1 to 9)						

4.4.6 Adverse effects

The 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. .

4.4.6.2 Haematological side effects

The proportion of participants experiencing neutropenia in the docetaxel arms of the trials ranged from 78% to 94% (Table 4.4.2a). The 303, 304 and Scand studies did not allow the prophylactic administration of colony stimulating factors.

Table 4.4.2a Haematological adverse events – Percentage of participants in each trial

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

Significantly more patients in the docetaxel arm than the mitomycin plus vinblastine arm of the 304 study suffered from neutropenia (RR: 1.49 (95% CI: 1.32, 1.67)). Less than ten percent of patients in the docetaxel arms experienced febrile neutropenia (range 6% to 9%). This was significantly more prevalent in the doxorubicin arm of the 303 study (RR: 0.46 (95% CI: 0.22, 0.98)); but significantly less so in the mitomycin plus vinblastine arm of the 304 study (RR: 16.8 (95% CI: 1.3, 124.8)). A greater proportion of patients suffered serious infections in the docetaxel arms of 304

and Scand compared to controls (RR: 10.3 (95% CI: 2.5, 43.1) and RR: 4.5 (95%CI: 2.2, 9.3) respectively. Thrombocytopenia was rare in the docetaxel group (range 1 to 4 percent) and significantly less frequent than control in 303 and 304 studies (RR: 0.17 (95% CI: 0.04, 0.6) and RR: 0.34 (95% CI: 0.2, 0.7) 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 methotrexate plus fluorouracil (RR: 2.73 (95% CI: 1.8, 4.2)).

4.4.6.3 Gastrointestinal adverse events

Gastrointestinal events were relatively rare in the docetaxel arm: nausea (range 3 to 6%), vomiting (range 2.5 to 3%); stomatitis (range 5 to 9%); diarrhoea (range 7.5 to 11%); constipation (0.5). With the exception of diarrhoea, these were more frequent in the doxorubicin arm of 303 study (See Table 4.4.4b). Prophylactic anti-emetics were allowed in the 303 and 304 studies but not in the Scand study.

Table 4.4.4b Gastrointestinal adverse events

Trial	303 Study	304 Study	Scand
Numbers in arms	D: 159 A: 163 %	D: 200 MV: 187 %	D: 134 MF: 135 %
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Nausea	D: 3.1 A: 14.1 0.22 (0.09, 0.57)	D: 4.5 MV: 2.1 2.1 (0.66, 6.72)	D: 6.0 MF: 11 0.51 (0.23, 1.17)
vomiting	D: 3.1 A: 12.3 0.26 (0.10, 0.67)	D: 2.5 MV: 2.7 0.94 (0.28, 3.18)	
stomatitis	D: 5 A: 12.3 0.41 (0.19, 0.90)	D: 9.0 MV: 0.5 16.8 (2.27, 124.8)	D: 9 MF: 5 1.71 (0.70, 4.23)
diarrhoea	D: 10.7 A: 1.2 8.71 (2.05, 37.1)	D: 7.5 MV: 0 29.0 (1.7, 481.2)	D: 10 MF: 10 1.0 (0.5, 2.02)
constipation		D: 0.5 MV: 3.2 0.16 (0.02, 1.28)	

4.4.6.4 Neurological adverse events

Five per cent of patients in the docetaxel arms of the 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 confidence intervals are very wide (Table 4.4.4c).

Table 4.4.4c Neurological adverse events

Trial	303 Study	304 Study	Scand
Numbers in arms	D: 159 A: 163 %	D: 200 MV: 187 %	D: 134 MF: 135 %
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Neurosensory	D: 5.0 A: 0 17.43 (1.01, 299.4)	D: 5.0 MV: 0.5 9.53 (1.21, 72.34)	
neuromotor	D: 5.0 A: 0 17.43 (1.01, 299.4)		
Peripheral neuropathy			D: 5 MF: 1 7.0 (0.87, 56.15)

4.4.6.5 Cardiovascular adverse events

None of the patients in the docetaxel arms reported cardiological adverse events (Table 4.4.4d). More patients in the doxorubicin arm of the 303 study discontinued because of cardiac toxicity than the docetaxel arm (RR: 0.03 (95% CI: 0.00, 0.55)).

Table 4.4.4d Cardiovascular adverse events

Trial	303 Study	304 Study
Numbers in arms	D: 159 A: 163 % RR (95% CI)	D: 200 MV: 187 % RR (95% CI)
Pulmonary toxicity		D: 0 MV: 5 0.45 (0.12, 1.76)
Congestive heart failure	D: 0 A: 3.7 0.08 (0.00, 1.39)	
Cardiac deaths	D: 0 A: 1.8 0.15 (0.01, 2.81)	
Discontinue because of cardiac toxicity	D: 0 A: 9.2 0.03 (0.00, 0.55)	

4.4.6.6 Other adverse events

Most other adverse effects were rare. However, the majority of patients suffered alopecia (74 to 91 per cent of patients in the docetaxel arms) and the incidence of asthenia ranged from 12 to 16 per cent. Significantly more asthenia was found among patients treated with docetaxel than mitomycin plus vinblastine or methotrexate plus fluorouracil (RR: 2.5 (95% CI: 1.32, 4.69) and RR: 5.6 (95% CI: 1.7, 18.9) respectively).

There was a higher incidence of severe fluid retention in the docetaxel than mitomycin plus vinblastine arm of the 304 study but the confidence intervals are very wide.

Table 4.4.4e Other adverse events

Trial	303 Study	304 Study	Scand
Numbers in arms	D: 159 A: 163 % RR (95% CI)	D: 200 MV: 187 % RR (95% CI)	D: 134 MF: 135 % RR (95% CI)
Alopecia	D: 91.2 A: 90.8 1.00 (0.94, 1.08)		D: 74 MF: 17 11.44 (6.04, 21.7)
Asthenia	D: 14.5 A: 12.3 1.18(0.67, 2.06)	D: 16.0 MV: 6.4 2.49 (1.32, 4.69)	D: 12 MF: 2 5.67 (1.70, 18.91)
Skin toxicity	D: 1.9 A: 0.6 3.08 (0.32, 29.26)	D: 4.0 MV: 0 15.9 (0.92, 273.6)	D: 2 MF: 0 5.0 (0.24, 103.22)
Nail disorder	D: 2.5 A: 0 9.22 (0.5, 169.9)	D: 2.5 MV: 0 10.29 (0.57, 184.8)	D: 5 MF: 0 15.11(0.87, 261.9)
Local toxicity		D: 1.5 MV: 2.1 0.70 (0.16,3.09)	
Conjunctivitis			D: 0 MF: 1 0.33 (0.01, 8.11)
Local phlebitis			D: 1 MF: 0 3.00 (0.12, 73.02)
Allergy	D: 2.5 A: 1.2 2.05 (0.38, 11.04)		D: 1.4 MF: 0 5.00 (0.24, 103.2)
Severe fluid retention	D: 5.0 A: 0 11.28(0.63, 202.2)	D: 8.0 MV: 0 30.87 (1.86, 510)	D: 3 MF: 2 1.33 (0.30, 5.85)
Toxic death		D: 2.0 MV: 1.6 1.24 (0.28, 5.47)	

4.4.7 Quality of Life

Quality of life was only reported in the 303 and 304 studies. Mean changes in quality of life scores from baseline were calculated (Table 4.4.5) but the data were only presented graphically. The global health status was not different between the arms in either study.

Table 4.4.5 Differences in mean changes in Quality of Life scores from baseline

Dimension: EORTC-C30	303 Study ¹	304 study ¹
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
Dyspnea	Ns	Ns
Insomnia	Ns	Ns
Appetite loss	Ns	Greater increase in MV (p = 0.037)
Constipation	Greater increase in A (p = 0.05)	Ns
Diarrhea	Greater increase in T (p = 0.004)	ns
Financial difficulties	Ns	

1: Wilcoxon Rank Sum Test

ns: no statistically significant difference

4.4.8 Discussion

Of the four randomised controlled trials, three (303 Study, 304 Study and Scand) found docetaxel superior to control in terms of response. Survival curves were available for three of the trials: 303 Study, 304 Study and Scand. The median length of progression free survival was significantly greater for docetaxel than mitomycin C plus vinblastine (304 study) and methotrexate plus fluorouracil (Scand). Patients in the docetaxel arm of the 304 study survived for significantly longer than in the mitomycin arm. There were no significant differences in median length of survival for the other three trials. The Scand trial allowed crossover on documented progression and many patients in the methotrexate plus fluorouracil also received docetaxel. Consequently, because the survival data were analysed on an intention to treat basis, the curves show survival after 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 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 quality of life - neither found a significant difference between docetaxel and control.

The 303, 304 and Scand studies were all high quality, randomised controlled trials. 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 crossover on progression; consequently, the overall survival was based not only on docetaxel and methotrexate plus fluorouracil but also included sequential administration of the alternate treatment. The two curves were similar. Insufficient details were given in the Bonnetterre abstract to properly assess its quality and accrual is on-going. Consequently, any results are tentative and should be treated with caution.

Although all the trials required participants to have undergone previous chemotherapy, two different groups of patients have been investigated. Three specified that first-line chemotherapy should have included anthracyclines; the 303 study excluded patients 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 alkylating agent, so the role of docetaxel in both these situations has been evaluated.

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 - ie 100 mg/m², administered as a one hour infusion every three 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 contra-indicated, 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 to mitomycin C plus vinblastine (304 study) and methotrexate plus fluorouracil (Scand). In addition, the 304 study found docetaxel increased overall survival compared to mitomycin C 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 log-rank 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.

The manufacturer's of docetaxel, Aventis provided a review of the effectiveness of docetaxel as second-line therapy in advanced breast cancer. This was abstracted using the NHS CRD DARE process. The review was based on a reasonable search and included the 303, 304 and Scand studies. In addition, non-randomised phase II trials were considered. The results of the Aventis review are similar to those presented here, although the conclusions seem based on response rather than progression free or overall survival - indicators which may be more important to the patients.

4.4.9 Summary: Docetaxel as second-line treatment for advanced breast cancer

Four randomised controlled trials 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 control in three out of 4 studies. The time to disease progression ranged from 19 to 28 weeks among patients treated with docetaxel; this was significantly longer than control in 2 studies. The over-all length of survival ranged from 10.4 to 15 months; this was significantly longer than control in 1 trial. Quality of life in terms of global health status was no different from control in the two studies where this was considered.

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

4.5.3 Description of Studies

A total of seven economic evaluations 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, or to estimate resource use in a 'real world' scenario. Resource use outside of a clinical trial can vary considerably due to local practice patterns, patient compliance, rates of hospitalisation for treating adverse effects, etc. Table 4.5.1 presents study descriptions. 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 only given in three studies.

Table 4.5.1 Cost-Utility Analyses of Taxanes in Metastatic Breast Cancer

	Country/ Currency	Stage	Drugs/doses	Source of efficacy data	Source of cost data	Methods
Leung, 1999 (55)	Canada 1999 Canadian dollars,	Anthracycline resistant metastatic	Paclitaxel 175mg/m ² or 135mg/m ² every three weeks Docetaxel 100mg/m ² every 3 weeks Vinorelbine 30mg/m ² weekly Response rates assumed: Docetaxel 30% Paclitaxel 21% Vinorelbine 16%	Retrospective chart review 1996/97	Published sources 1992-98	Decision analysis model
<u>Aventis, 1999 (20)</u>	UK, 1999 British pounds (update of Hutton, 1996)	Disease progression following chemotherapy	Docetaxel (100mg/m ²) 1 hour IV infusion every 3 weeks for up to 6 cycles Paclitaxel (175mg/m ²) 3 hour infusion every 3 weeks for up to 6 cycles Vinorelbine iv (30mg/m ²), every week x 12 cycles Body surface area of 1.75m ² assumed. Response rates: docetaxel: 42% paclitaxel 28% vinorelbine 16%	Docetaxel: weighted average response rate and safety data from 3 phase III studies pooled (1999 publications) Paclitaxel: 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 Docetaxel 41.7% , Paclitaxel 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 then reviewed by 4 oncologists. Costs from national databases (not referenced) except laboratory costs, and chest x-ray costs from specific hospital data (not reference). Costs 'updated to 1997-8 levels' using the NHS hospital and community health service inflation index. Costs of Docetaxel and Paclitaxel obtained from the Monthly Index for Medical specialties (MIMS), August 1999.	Decision analysis model, timeframe: 3 years from start of therapy. Utilities derived from 30 oncology nurses
Brown, 1998 (56)	USA, 1997 US dollars	Advanced metastatic	Paclitaxel 200mg/m ² every 21 days for six cycles (body mass of 1.66 m ² assumed) Docetaxel 100mg/m ² every 21 days for seven cycles (body mass of 1.66 m ² assumed) Assumed response rates: Docetaxel 47.8% Paclitaxel 25%	Data for the effectiveness analysis are from two Phase III studies published in 1997.	Resource use is 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). This data was collected for 1997, with some prices being reflated. The specific costs that were reflated	Modified Markov model

	Country/ Currency	Stage	Drugs/doses	Source of efficacy data	Source of cost data	Methods
					and the method used were not stated.	
Yee, 1997 (57)	UK, converted to US dollars, year not stated (based on Hutton model)	Anthracycline resistant metastatic	Docetaxel (100) 1 hour infusion Paclitaxel (175) 3 hour infusion Response rates assumed: Docetaxel 47% Paclitaxel 21%	Two Phase II studies, 1 each of Paclitaxel or Docetaxel and their respective package inserts. (95-96) Assumed response rates: Paclitaxel: 21% Docetaxel 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, 1996 (58)	UK, 1994 pounds sterling,	Anthracycline resistant metastatic	Docetaxel (100mg/m2) 1 hour IV infusion every 3 weeks for up to 6 cycles Paclitaxel (175mg/m2) 3 hour infusion every 3 weeks for up to 6 cycles based on a body surface area of 1.7m2 Response rates assumed: Docetaxel 47% Paclitaxel 21%	Published Phase II studies. Docetaxel: 3 studies pooled (1995 publications) Paclitaxel: 1 study used (1995). Expert opinion also used for probabilities in model. Overall response rate Docetaxel 47% Paclitaxel 21%	Costs from national databases and published literature (not referenced). Costs 'updated to 1994 levels' using the NHS hospital and community health service inflation index (1994). Costs of Docetaxel and Paclitaxel obtained from the Monthly Index for Medical specialties (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.
Launois, 1996 (59)	France 1993 French Francs	Metastatic	Docetaxel 100mg/m2 every 21 days (pre-medication dexamethasone 8mg oral daily x 5 days) Paclitaxel 175 mg/m2 every 21 days (pre-medications: dexamethasone 20mg oral twice daily, diphenhydramine 50mg iv, ranitidine 50mg iv) Vinorelbine 30mg/m2 every 7 days Maximum 6 cycles assumed Response rates assumed: Docetaxel 57% Paclitaxel 29% Vinorelbine 16%	Phase II clinical trials (1993-5 publication) Assumed response rates: Docetaxel 57% Paclitaxel 29% Vinorelbine 16%	Retrospective chart review of resource uses (153 subjects from 5 hospitals). Prices were assigned by DRG grouping, using 1993 prices (cost survey published in 1995).	Markov model

Table 4.5.2 presents the results of these studies. Included are:

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

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

Table 4.5.2 Breast Cancer Cost-Utility Studies Results

	Costs	Benefits	Synthesis	Conclusions
Leung, 1999 (55)	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 : Paclitaxel \$1,680 (95%CI 1574 to 1976) Docetaxel \$2,653 (95%CI 2363 to 3053) Vinorelbine \$503 (95%CI 453 to 641)	Quality adjusted progression free survival 39.8 days with Paclitaxel, 33.2 days with docetaxel, 35.0 days with Vinorelbine (from patient sample, healthy volunteers)	Cost per Quality adjusted progression free year: Paclitaxel \$59,096 Docetaxel \$110,072 Vinorelbine \$31220	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.
<u>Aventis, 1999 (20)</u>	Includes drug, hospital day, medical staff, diagnostic tests, and therapeutic procedures. Costs occurring after 1 year are discounted at 6%. Total per patients costs for base-case Docetaxel £7,817 Paclitaxel£7,645 Incremental cost = £172 per patient Vinorelbine £4268, Incremental cost of docetaxel: £3,549	QALYs: Docetaxel: 0.7347 Paclitaxel: 0.6485 Incremental QALY = 0.0862 Vinorelbine: 0.4822 Incremental QALY with docetaxel: 0.2525	Incremental Cost per QALY Docetaxel vs Paclitaxel: £1990 Docetaxel vs Vinorelbine: £14,050	Taxotere (docetaxel) is considered to be cost-effective compared to paclitaxel or vinorelbine in the treatment of advanced breast cancer when compared alongside other licensed therapies.
Brown, 1998 (56)	Costs included were physician visit, general blood chemistry, hospital day, iv. Antibiotic home treatment, ciprofloxacin (1000mg daily), Paclitaxel and docetaxel. Resources measured were physician and nurse time, chemotherapeutic agents, antibiotic regimens, inpatient or outpatient management of infections and febrile neutropenia, progressive and terminal disease palliative medication, monitoring tests and hospital days. Costs for Docetaxel are \$15, 683 and \$13,904 for Paclitaxel over a three-year period of follow-up. Costs of adverse effects were included.	The cumulative qalys for Docetaxel is 0.8670 and 0.6605 for Paclitaxel, over a three year follow up period. Side effects are included.	The incremental cost per QALY for Docetaxel compared to Paclitaxel was \$8615.	The cost/QALY gained by Docetaxel is \$8615 and ranges 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.
Yee, 1997 (57)	Costs included those of treatment (drug and administration costs), toxicity, and progressive disease/death. Total costs: Docetaxel \$13,584 Paclitaxel \$13, 221	Incremental QALY with Docetaxel vs. Paclitaxel: 0.0905 per patient. Equivalent to 33 days of perfect health. Utility scores based on decisions of 100 oncology nurses	Incremental cost per QALY associated with Docetaxel \$4022. Sensitivity analysis showed cost and response rate changes for Docetaxel significantly changed the ratio.	Although results of the model are not easily within acceptable level in USA

	Costs	Benefits	Synthesis	Conclusions
Hutton, 1996 (58)	<p>Includes drug, hospital day and medical staff, diagnostic tests, therapeutic processes.</p> <p>Total per patients costs for base-case Docetaxel £8,233 Paclitaxel£8,013</p>	<p>Higher response rate associated with Docetaxel was 0.0905. QALYs or 33 incremental quality adjusted days (qads). Benefits considered from commencement of treatment to death of patient. Side effects</p>	<p>Using incremental analysis When comparing Docetaxel with Paclitaxel there was an incremental cost-utility ratio of £2431 per QLAY (£7 per health day). This was sensitive to efficacy of Docetaxel - it falls to £1,186 if Docetaxel response rates increase from 47% to 56%</p>	<p>Response rate is the key parameter determining utility and cost utility of treatments for metastatic breast cancer. Docetaxal produced a higher response rate compared with Paclitaxel, resulting in an improvement in QOL, which clearly outweighed the side effects. Docetaxel further produced a substantially larger utility benefit than Paclitaxel at a smaller additional cost of £2431 per QLAY gained, an incremental health cost that was acceptable according to available defined limits and which did not alter in terms of Docetaxel dominance for all</p>
Launois, 1996 (59)	<p>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 DRG's.</p> <p>Total costs were Paclitaxel 251,100 FF Docetaxel 250,400FF Vinorelbine 257,200 FF.</p> <p>Incremental costs: Docetaxel vs. Vinorelbine : -6,800FF Docetaxel vs. Paclitaxel: -700FF</p>	<p>Progression-free survival Docetaxel: 173 days Paclitaxel 145 days Vinorelbine 99 days</p> <p>Quality adjusted PFS days: Docetaxel 125 Paclitaxel 103 Vinorelbine 68</p>	<p>Docetaxel was the dominant strategy, with longer progression free survival and lower cost.</p>	<p>Docetaxel brings net benefit of 57 progression- and discomfort free days compared to Vinorelbine and 22 such days compared to Paclitaxel. Docetaxel is self-financing because of savings of FF6,800 compared with Vinorelbine and FF700 with Paclitaxel.</p>

Table 4.5.3 is a validity assessment based on the methods of Drummond. (29)

Table 4.5.3 Validity assessment of economic evaluations of taxanes in breast cancer (29)

Critical Assessment Questions (29)	Leung, 1999 (55)		Aventis(20)	Brown, 1998 (56)	Yee, 1997 (57)	Hutton, 1996 (58)	Launois, 1996 (59)
Well defined question	•		•	•	•	•	•
Comprehensive description of alternatives	•- (unclear if pre-mediations included)		•	•- (unclear if pre-mediations included)	•- (unclear if pre-mediations included)	•- (unclear if pre-mediations included)	•
Effectiveness established	•- (response rates taken from three trials - no direct comparisons, rate for TP calculated from 2 doses of paclitaxel)		•- (response rate taken from various trials with no direct comparisons. paclitaxel response rate from only 1 trial)	•- (comparing two different groups of patients, one mostly chemotherapy naïve, the other not).	•- (Phase II studies only, only 1 using paclitaxel)	•- (Phase II studies only, only 1 using paclitaxel)	•- (Phase II studies only, only 1 using paclitaxel)
All important and relevant costs and consequences for each alternative identified	•		•	•- (treatment of adverse effects limited to the use of ciprofloxacin, iv at home)	•	•	•
Costs and consequences measured accurately	•		•	•	- (USA study based on NHS resource use)	•	•
Costs and consequences valued credibly	•		•	•- (some methods not clear)	- (USA study based on NHS resource use)	•	•- (costs by DRG)
Costs and consequences adjusted for differential timing	NA		Costs occurring after 1 year 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	•		•	•	•-	•	•

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

4.5.3.2 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 reason that the comparator chosen is important is because of the effect it can have on the incremental benefits and costs, such as differing response rates, cost of drug or treating adverse effects. These differences in benefits or costs can go in either the positive or negative direction. The comparator used in these studies of advanced breast cancer was most often paclitaxel. As paclitaxel was marketed before docetaxel, docetaxel is being considered 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.

4.5.3.3 Resources and Cost Included

The identification of resources used, costs included, and 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 pre-medications that are given prior to taxane use, and stem-cell stimulating drugs that are given in the event of myelosuppression, are examples which could alter costs. More important may be hospitalisation costs for drug administration and treatment of adverse events. Docetaxel is infused over 1 hour, may not require an overnight stay. In comparison, the choice of infusion time for paclitaxel (24 hour vs 3 hour) could alter the hospitalisation costs. Assumptions regarding the need for hospitalisation to treat myelosuppression or infections and the rate of significant side effects may also alter the costs. Sensitivity analyses or comparing similar studies that have and have not included these may help define the significance of these variations.

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

4.5.4 Cost Effectiveness 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. Since the years of these studies are quite similar, no reflation to 1999 prices is necessary.

4.5.4.2 Paclitaxel versus Mitomycin C

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

4.5.4.3 Docetaxel versus Paclitaxel

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

4.5.4.4 Docetaxel versus Vinorelbine

In the three studies comparing docetaxel to vinorelbine, the one UK study found the cost per QALY gained of docetaxel 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 relatively high quality. A Canadian study found vinorelbine to be the dominant strategy. (55) In this study the average cost per quality adjusted progression free life year gained (converted to pounds) was £45,837 for docetaxel and £13,008 for vinorelbine. However, the third study comparing docetaxel and vinorelbine (from France) found the opposite; that docetaxel was dominant to vinorelbine. Although these two studies used similar 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 were 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.

4.5.5 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 4.5.3 is a critical assessment of these economic evaluations. The areas examined in each study are the

- study question posed,
- comprehensive description of competing alternative,
- 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,
- and finally the breadth and depth of the discussion and conclusions.

The areas where the studies most often were 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 number of cycles assumed for given therapies were also rarely discussed. All of these 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 naïve 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 studied, with the exception of paclitaxel versus mitomycin C. This is not to say that other comparators could have been used for which there are clinical data with direct comparisons.

Discounting of costs or benefits was not attempted.

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

4.5.6 Summary of economic evaluations of taxanes in advanced breast cancer

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

The acceptability of an incremental cost per quality adjusted life years gained ratio 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 incremental cost per quality adjusted life years gained of £14,000, 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.

5 OVARIAN CANCER

5.2 The Effectiveness of Paclitaxel as First-Line Treatment for Advanced Ovarian Cancer

5.2.3 Description of included trials

Fifteen reports were identified which evaluated the effectiveness of paclitaxel as a first-line treatment for advanced ovarian cancer. These pertained to four Phase III trials: GOG 111, GOG 132, OV10 and ICON 3 (see Table 5.1.1a). With the exception of GOG 111 (60-67), these studies have not been published in journals. The results of the GOG 111 trial that were included in the full version of the review derive from an intention-to-treat analysis given in an unpublished trial report. For confidentiality these results have been removed from this current 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 overheads.

Table 5.1.1a Design of included trials

Trial Source	Quality Quality level	Accrual dates Number randomised	Intention to treat (ITT) Number evaluated	Rationale for cross-over Number crossing over	Median length of follow up Number of participants surviving (%)
GOG 111 Journal article (60-65, 67),	Randomised Outcomes defined Multi-centre Open label 1A	April 1990 - March 1992 Eligible for analysis TP: 184 CP: 202	ITT: all eligible cases Evaluable for clinical response: measurable disease TP: 100 CP: 116	No details	37 months TP: 47% CP: 32%
GOG 132 Meeting abstract and overheads (68) Protocol (69)	Randomised Power calculations Outcomes defined Multi-centre Open label 1A	March 1992 - May 1994 T: 224 P: 209 TP: 215	ITT Evaluable T: 213 P: 200 TP: 201	Rationale for crossover not defined T: 184 P: 162 TP: 157	Not stated Overall: 34%
OV 10 Protocol (70) Meeting overheads and abstracts (71, 72)	Randomised Power calculations Outcomes defined Multi-centre Open Label 1A	April 1994 - Aug 1995 TP: 338 CP: 300	ITT Evaluable for response TP: 149 CP: 151	Crossover from control arm to taxoids on documented first progression 134 (52%)	30 months TP: 211 (62) CP: 169 (50)
ICON 3 Protocol (73) Meeting abstract and overheads (74)	Randomised Power calculations Outcomes defined Multi-centre Open label 1A	Feb 1995 - October 1998 TP(P): 478 P: 943 TP (CAP): 232 CAP: 421	ITT	Treatment on progression. Rationale not defined. TP: 79% Control: 83%	18 months TP: 505 (71) Control: 942 (69)

T: paclitaxel; P: platinum; C: cyclophosphamide; CAP: cyclophosphamide, doxorubicin and cisplatin; TP(P): paclitaxel\carboplatin (platinum control); TP (CAP): paclitaxel\carboplatin (CAP control)

These were all randomised, controlled Phase III trials with calculations of sample size and accurate and standard definitions of outcome variables. The ICON 3 trial permitted choice of control prior to randomisation. It is important to note that the ICON 3 trial completed accrual in October, 1998, six months before the results were

presented at the Annual Conference of the American Society of Clinical Oncologists. (73, 74) Seventy percent of the participants were still alive at this stage. Consequently, any long term results are likely to be unreliable. Secondly, a large number of participants in the GOG 132 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 OV10. No details of such manipulations are given for ICON 3 or GOG 132.

Both GOG 111 and GOG 132 included only patients with sub-optimally debulked Stage III or Stage IV ovarian cancers; a wider range of patients were eligible for OV10 and ICON 3 (Table 5.1.1b).

Table 5.1.1b Comparison of inclusion criteria

Trial	Cancer	Performance status
	Stage	Previous treatment
GOG 111	Pathologically verified epithelial ovarian cancer. Borderline cancers excluded Stage III: suboptimal residual disease (> 1cm residual mass); All patients with stage IV disease	GOG PS 0 to 2 No prior radiotherapy or chemotherapy
GOG 132	Histologically confirmed ovarian epithelial cancer. Borderline cancers excluded Stage III: suboptimal (> 1 cm diameter); Stage IV	GOG PS 0 to 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 status 0 to 3 No prior radiotherapy or chemotherapy
ICON 3	Clinical diagnosis and histologically consistent with invasive ovarian carcinoma of epithelial origin	No prior radiotherapy or chemotherapy

Although each of the trials included a paclitaxel\platinum combination arm, only GOG 111 and GOG 132 used the same combination and schedule: paclitaxel (135mg/m²) with cisplatin (75mg/m²) given as a 24-hour infusion. OV10 used paclitaxel (175mg/m²) with cisplatin (75mg/m²) given as a three hour infusion; ICON 3 used paclitaxel (175 mg/m²) with carboplatin (6AUC) given as a three-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 (See Table 5.1.1c).

Table 5.1.1c Comparison of interventions

Trial	Intervention	Control	
GOG 111	TP: paclitaxel (135mg/m ²) + cisplatin (75mg/m ²) T: 24 hour infusion; followed by P. 6 x 3 week cycle Premedication: dexamethasone 20mg; any histamine H ₂ antagonist, diphenhydramine 50 mg iv	CP: cyclophosphamide (750mg/m ²) + cisplatin (75 mg/m ²) 6 x 3 week cycles	
GOG 132	T: paclitaxel (200mg/m ²) T: 24 hour infusion 6 x 3 week cycles Premedication: dexamethasone 20mg; cimetidine 50 mg iv; diphenhydramine 50 mg iv	P: cisplatin (100mg/m ²) 6 x 3 week cycles Hydration Prophylactic anti-emetic	TP: paclitaxel (135mg/m ²) + cisplatin (75mg/m ²) T: 24 hour infusion followed by P. 6 x 3 week cycles Premedication: dexamethasone 20mg; cimetidine 50 mg iv; diphenhydramine 50 mg iv Prophylactic anti-emetic
OV 10	TP: paclitaxel (175mg/m ²) + cisplatin (75mg/m ²) T: 3 hour infusion followed by P; up to 9 x 3 week cycle Premedication: dexamethasone 20mg; ranitidine 50 mg iv; diphenhydramine 50 mg iv Prophylactic anti-emetics and oral magnesium recommended	CP: cyclophosphamide (750mg/m ²) + cisplatin (75 mg/m ²) up to 9 x 3 week cycles Prophylactic anti-emetics and oral magnesium recommended	
ICON 3	TP: paclitaxel (175 mg/m ²) + carboplatin (6AUC) T: 3 hour infusion followed by P; 6 x 3 week cycles Premedication: dexamethasone 20mg; ranitidine 50 mg iv; chlorpheniramine 10 mg iv	P: carboplatin (6AUC) 6 x 3 week cycles Prophylactic anti-emetics	CAP: cyclophosphamide (500 mg/m ²), doxorubicin (50 mg/m ²) and cisplatin (50 mg/m ²) 6 x 3 week cycles Prehydration Prophylactic anti-emetics

The differences in the inclusion criteria influenced the participants of the trials. GOG III and GOG 132 contained a higher proportion of participants with Stage IV cancers and all patients had sub-optimal debulking compared with OV10 and ICON 3. (Table 5.1.1d). In addition, about 20% of participants in ICON 3 had previously undergone chemotherapy.

Table 5.1.1d Comparison of participants

Trial Name	Median Age (years)	FIGO Stage	Results of surgery
	GOG Performance Status	Measurable disease	Previous treatment
GOG 111	Age: TP: 60 CP: 59 GOG 0: TP: 30% CP: 27% GOG 1: TP: 53% CP: 54% GOG 2: TP: 17% CP: 19%	Stage III: TP: 67% CP: 64% Stage IV: TP: 33 % CP: 36% Measurable disease: TP: 54% CP: 57%	Sub-optimal: residual mass > 2cm None
GOG 132	Age: T:59.9 P:60.1 TP: 59.4 GOG 0: T: 31% P: 30% TP: 27% GOG 1: T: 55% P:55% TP: 56%; GOG 2: T: 14% P: 15% TP:17%	Stage III: T: 72% P: 65% TP: 73%; Stage IV: T: 28% P: 35% TP: 27% Measurable disease: T: 62% P: 61% TP: 62%	Sub-optimal None
OV10	Age: TP: 58 CP: 58 WHO PS 0: TP: 46% CP: 51% WHO PS 1: TP: 40% CP: 36% WHO PS 2: TP: 12% CP: 12% WHO PS 3: TP: 2% CP: 1%	Stage II: TP: 6% CP: 7%; Stage III: TP: 75% CP: 71%; Stage IV: TP: 19% CP: 22% Measurable disease: TP: 44% CP: 46%	Residual disease > 1cm: TP: 62% CP: 65% No previous treatment
ICON 3	Age: P:59.4TP(P): 60.7 CAP: 56.6	Stage III: P: 65% TP (P): 64% CAP: 63% TP(CAP): 63%. Stage IV: P:16% TP(P): 17% CAP: 15% TP(CAP): 16%	Residual bulk > 2cm P: 46% TP(P): 47% CAP: 47% TP(CAP): 44% Previous treatment None: P+CAP: 81% TP: 78%. Taxane: P+CAP:3% TP: 4% Platinum: P+CAP: 11% TP: 13%. Other chemotherapy P+CAP: 1% TP: 2%. Non-chemotherapy: T+CAP:3% TP:2%

T: paclitaxel; P: platinum; C: cyclophosphamide; CAP: cyclophosphamide, doxorubicin and cisplatin;
TP(P): paclitaxel\carboplatin (platinum control); TP (CAP): paclitaxel\carboplatin (CAP control)

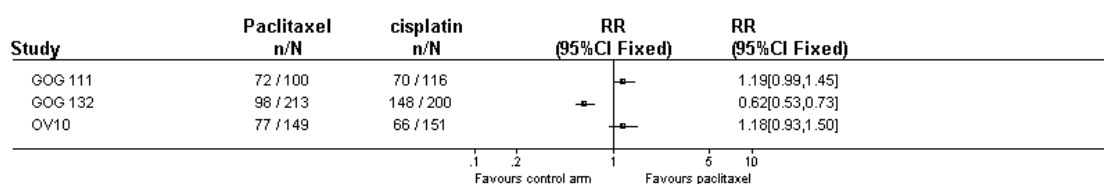
The differences between the studies made pooling inappropriate. Although the trials were all of similar high quality, a variety of interventions and controls were used and the study populations and resulting samples differed.

5.2.4 Synthesis

5.2.4.2 Overall response rates

Overall response rates (complete response + partial response) were presented for 3 trials: GOG 111, GOG 132 and OV 10 (See Figure 1). These ranged from 46% (GOG 132) to 73% (GOG 111) 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 GOG 111 (73% versus 60%) or OV10 (52% versus 44%). However, cisplatin alone had a superior response rate compared to combined cisplatin and paclitaxel in GOG 132 (74% versus 46%; RR: 0.62 (95% CI: 0.53, 0.73)).

Figure 5.1.2a Paclitaxel and platinum as first-line treatment for ovarian cancer. Overall response rates.



A greater proportion (over 90%) of patients in GOG 132 were evaluable for response compared with GOG 111 (56%) or OV10 (approximately 50%) (see Table 5.1.2a).

Table 5.1.2a Median times

Study	Median progression free survival in months	Median length of survival in months
GOG 111	TP: 18 (95% CI: 16 to 21) CP: 13 (95% CI: 11 to 15) RR ² : 0.7 (95% CI: 0.5, 0.8) p <0.001	TP: 38 (95% CI: 32, 44) CP: 24 (95% CI: 21, 30) RR: 0.6 (95% CI: 0.5, 0.8) p <0.001
GOG 132	T: 11.4 TP: 14.1 P: 16.4 No analysis	T: 26 TP: 26.6 P: 30.2 No analysis
OV10	TP: 16.5 CP: 11.8 P ³ <0.001	TP: 35 CP: 25 P ³ <0.001
ICON 3	Not presented	Not presented

T: paclitaxel P: platinum C: cyclophosphamide

1: Kruskal Wallis test

2: 95% confidence intervals calculated using Brookmeyer and Crowley method. Two tailed log rank test.

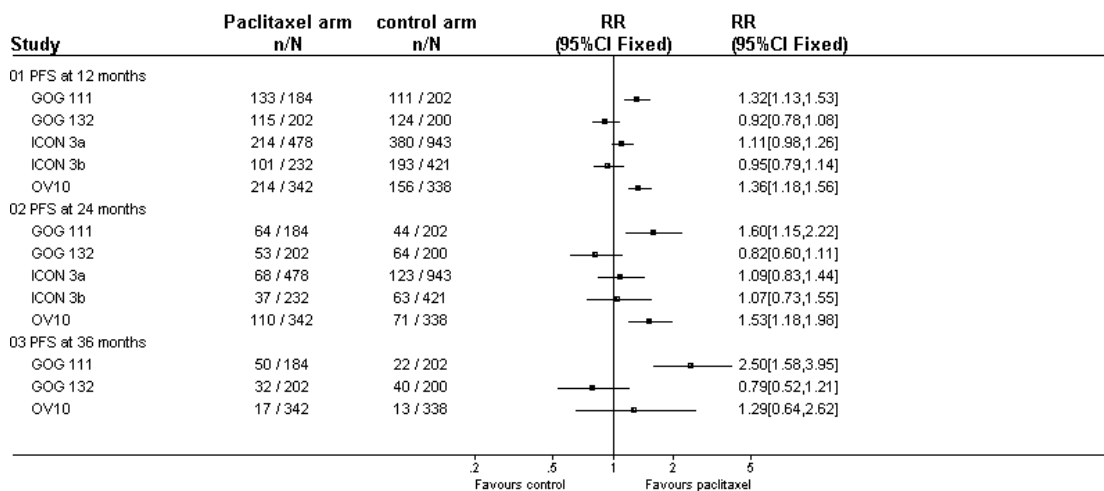
3: 2 sided log rank test

5.2.4.3 Progression Free Survival

Kaplan Meier curves were presented for each of the trials. Median progression free survival for the paclitaxel/platinum combination ranged from 14.1 months (GOG 132) to 18 months (GOG 111) - it was not calculated for ICON 3. Both the GOG 111 and OV10 trials reported 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 5.1.2a). No probability levels were given for GOG 132 but patients treated with single agent platinum appeared to survive longer without progression.

Figure 5.1.2b illustrates the estimates of progression free survival rates at one, two and three years obtained from these analyses. These were estimated from the graph for GOG 111 and GOG 132. The design of ICON 3 allowed the two control arms to be presented separately. The authors of ICON 3 maintained their results are reliable to around 2 years.

Figure 5.1.2b Paclitaxel and platinum as first-line treatment for ovarian cancer. Progression free survival



At 12 months, the progression free survival rate in the paclitaxel arm ranged from 44% (ICON 3) to 72% (GOG 111). In GOG 111 and OV 10 a statistically significant, greater number of patients in the paclitaxel than control arm, survived without disease progression (GOG 111: 72% versus 55%; RR: 1.31 (95% CI: 1.13 1.53) number needed to treat = 6; OV10: 63% versus 46% RR: 1.36 (95% CI: 1.18, 1.56) number needed to treat = 6). Although not statistically significant, patients treated with paclitaxel tended to fare worse than comparisons in the CAP control arm of ICON 3 (44% versus 46%) and in GOG 132 (57% versus 62%).

At 24 months, the progression free survival rate in the paclitaxel arm ranged from 14% (ICON 3) to 35% (GOG 111). In OV 10, a statistically significant, greater number of patients in the paclitaxel arm than the control arm, survived without disease progression (OV10: 32% versus 21%, RR: 1.53 (95% CI: 1.18, 1.98) number needed to treat = 9). Although not statistically significant, patients treated with paclitaxel tended to fare worse than control in GOG 132 (26% versus 32%).

At 36 months, the progression free survival rate in the paclitaxel arm ranged from 5% (OV 10) to 27% (GOG 111). In GOG 111 only, a statistically significant, greater number of patients in the paclitaxel arm than the control arm, survived without disease progression (GOG 111: 27% versus 11% RR: 2.50 (95% CI: 1.58, 3.95) number needed to treat = 6). Although not statistically significant, patients treated with paclitaxel tended to fare worse than comparisons in GOG 132 (16% versus 20%). The ICON 3 data are not reliable to 3 years.

5.2.4.4 Overall survival

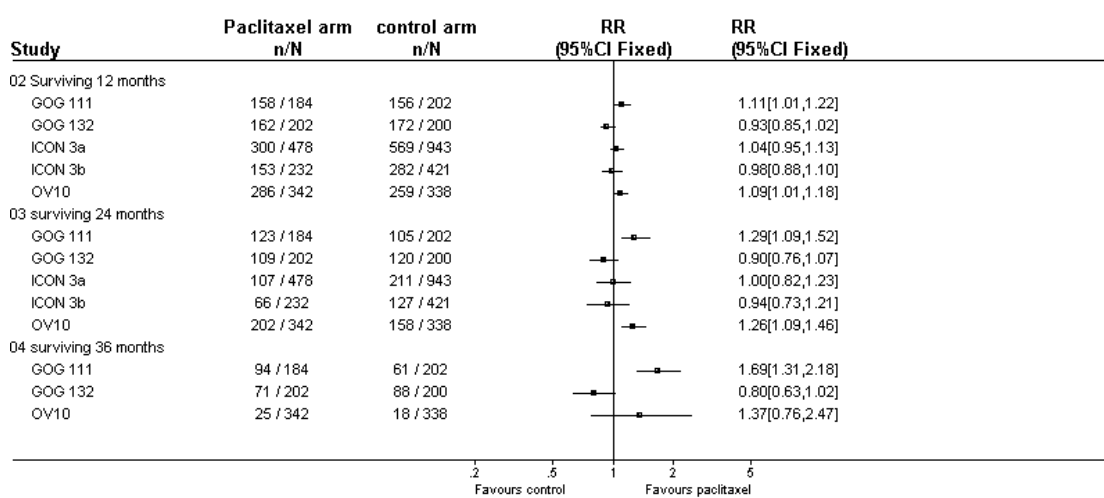
Kaplan Meier curves were presented for each of the trials.

Median length of survival for patients treated with the paclitaxel/platinum combination ranged from 26.6 months (GOG 132) to 38 months (GOG 111) (Table 5.1.2a). Both the GOG 111 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 are given for

GOG 132 but patients treated with single agent platinum appeared to survive longer (30.2 months). Median length of survival has not been calculated for ICON 3.

Figure 5.1.2c illustrates the estimates of overall survival rates at one, two and free years obtained from these analyses. These were estimated from the graph for GOG 111 and GOG 132. The design of ICON 3 allowed the two control arms to be presented separately. The authors of ICON 3 maintained their results are reliable to around 2 years.

Figure 5.1.2c Paclitaxel and platinum as first-line treatment for ovarian cancer. Overall survival



At 12 months, the overall survival rate in the paclitaxel arm ranged from 62% (ICON 3) to 86% (GOG 111). In two trials (GOG 111 and OV 10), a statistically significant, greater number of patients in the paclitaxel arm than the control arm, survived for 12 months (GOG 111: 86% versus 77%; RR: 1.11 (95% CI: 1.01, 1.22) number needed to treat = 11; OV10: 84% versus 77%; RR: 1.09 (95% CI: 1.01, 1.18) number needed to treat = 14). Although not statistically significant, patients treated with paclitaxel tended to fare worse than comparisons in the CAP control arm of ICON 3 (66% versus 67%) and in GOG 132 (80% versus 86%).

At 24 months, the overall survival rate in the paclitaxel arm ranged from 22% (ICON 3) to 67% (GOG 111). In the same two trials (GOG 111 and OV 10) a statistically significant, greater number of patients in the paclitaxel arm than the control arm, survived for 2 years (GOG 111: 67% versus 52%; RR: 1.29 (95% CI: 1.09, 1.52) number needed to treat = 7; OV10: 59% versus 47%; RR: 1.26 (95% CI: 1.09, 1.46) number needed to treat = 8). Although not statistically significant, patients treated with paclitaxel tended to fare marginally worse than control in GOG 132 (54% versus 60%) and the CAP control arm of ICON 3 (28% versus 30%).

At 36 months, the overall survival rate in the paclitaxel arm ranged from 7% (OV10) to 54% (GOG 111). In GOG 111 only, a statistically significant, greater number of patients in the paclitaxel arm than the control arm, survived for 3 years (GOG 111: 54% versus 30%; RR: 1.69 (95% CI: 1.31, 2.18) number needed to treat = 5). Although not statistically significant, patients treated with paclitaxel tended to fare

worse than comparisons in GOG 132 (35% versus 44%). The ICON 3 data are not reliable to 3 years.

5.2.5 Compliance

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 to either continue treatment or cross-over depending on the arm. Compared with the other trials, in GOG 132, 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.

Table 5.2.1.4 Treatment received

Trial	Completing all cycles	Median number of cycles (range)	Reasons for early discontinuation					
			Disease progression	Adverse events	Withdraw consent	Death	Other	
GOG 111	TP: 87% CP: 78%							
GOG 132	T: 71% P: 69% TP: 83%		T: 19% P: 7% TP: 6%	T: 1% P: 12% TP: 4%	T: 3% P: 6% TP: 1%	T: 4% P: 4% TP: 5%	T: 1% P: 2% TP: <1%	
OV10	TP: 86% CP: 81%	TP: 6 (0-10) CP: 6 (0-10)	TP: 5% CP: 13%	TP: 6% CP: 4%	TP: <1% CP: <1%			
ICON 3	TP: 82% Con: 82%		TP: 4% Con: 7%	TP: 6% Con: 2%	TP: 1% Con: 1%	TP: 2% Con: 2%	TP: 2% Con: 2%	

5.2.6 Adverse effects

The reports were not consistent in the way adverse events were reported - the results of GOG 132 were impossible to interpret. A summary of the side effect profiles of the included drugs are given in Table 1.7.1.

5.2.6.2 Haematological side effects

Haematological side effects were not reported in OV10. Reductions in white cells and neutropenia were frequently reported in both arms of GOG111 (TP: 92% CP: 83%). Overall haematological adverse events were less common in ICON 3: about 37% in all arms. Significantly more infectious and febrile episodes were reported in the paclitaxel arm than the carboplatin alone arm of ICON 3 (10% versus 1%; RR: 3.38 (95% CI: 2.15, 5.32)). However, fewer infectious and febrile episodes were found in the paclitaxel arm than the CAP control of ICON 3 (14 versus 22%; RR: 0.59 (95% CI: 0.40, 0.86)).

Table 5.1.4a Haematological adverse events -

Trial	GOG 111	ICON 3	ICON 3
Numbers in arms	TP: 179 CP: 197	TP: 478 P: 943	TP: 232 CAP: 421
	% RR (95% CI)	% RR (95% CI)	% RR (95% CI)
Haematological		TP: 35 P: 36 0.97 (0.8,1.1)	TP: 38 CAP: 35 1.1: (0.9, 1.3)
Reduction in white cells or neutropenia	TP: 92 CP: 83 1.12 (1.04, 1.21)		
Infections		TP: 10* P: 1 3.4 (2.2,5.3)	TP: 14* CAP: 22 0.6 (0.4,0.9)
Fever	TP: 3 CP: 0 16.38 (0.83, 284)		
Anaemia	TP: 8 CP: 8 1.10 (0.57, 2.13)		

* fever requiring antibiotics

5.2.6.3 Gastrointestinal adverse events

Nausea and vomiting were reported by less than a fifth those treated with paclitaxel (range 7 to 18%) A greater incidence of nausea and vomiting was found in the CAP than paclitaxel arm of ICON 3 (TP: 10% CAP: 22%; RR: 0.45 (95% CI: 0.29, 0.69). Table 5.1.4b)

Table 5.1.4b Gastrointestinal adverse events

Trial	GOG 111	OV 10	ICON 3a	ICON 3b
Numbers in arms	TP: 184 CP: 201	CP: 338 TP: 330	TP: 478 P: 943	TP: 232 CAP: 421
	% RR (95% CI)	% RR (95% CI)	% RR (95% CI)	% RR (95% CI)
Nausea/vomiting		TP: 18 CP: 23 0.78 (0.58, 1.05)	TP: 7 P: 8 0.9 (0.6,1.3)	TP: 10 CAP: 22 0.45 (0.3, 0.7)
Gastro-intestinal	TP: 15 CP: 11 1.39 (0.83, 2.34)			

5.2.6.4 Neurological

Significantly more neurosensory adverse events were reported in the paclitaxel arms of ICON 3 and OV 10 (ICON 3a (carboplatin) TP: 18% P: 1%: RR: 21.2 (95% CI: 10.4, 43.4); ICON 3b (CAP): TP: 18% CAP: 3%: RR 5.86 (95% CI: 3.21, 10.69); OV10 TP: 20% CP: 9% RR: 21.48 (95% CI: 6.82, 67.64) Table 5.1.4c). In addition, although rare, significantly more neuromotor adverse events were reported in the paclitaxel arm of OV 10 (TP: 5% CP <1%: RR: 8.3 (95% CI: 1.93, 35.64).

Table 5.1.4c Neurological adverse events

Trial	GOG 111	OV 10	ICON 3a	ICON 3b
Numbers in arms	TP: 184 CP: 201 %	TP: 338 CP: 330 %	TP: 478 P: 943 %	TP: 232 CAP: 421 %
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Neurosensory		TP: 20 CP: 9 21.48 (6.82, 67.6)	TP: 18 P: 1 21.2 (10.4, 43.4)	TP: 18 CAP: 3 5.9 (3.2, 10.7)
Neuromotor		TP: 5 CP: <1 8.3 (1.93, 35.6)		
Neurological	TP: 4 CP: 4 0.98 (0.35,2.58)			

5.2.6.5 Cardiovascular

Cardiovascular adverse events were not reported.

5.2.6.6 Other adverse events

Alopecia was a frequent adverse event in the paclitaxel arms (range 68 to 77%). It was more frequent in the paclitaxel than carboplatin arm of ICON 3 (TP: 68 P: 3 RR: 22.90 (95% CI: 15.82, 33.15)); there was no such difference between the paclitaxel and CAP arms (TP: 77% CAP: 71%). Although not common, significantly more arthralgia/myalgia was reported in the paclitaxel than control arm of OV 10 (TP: 7% CP: <1%; RR: 11.72 (95% CI: 11.72 (95% CI: 2.79, 49.18) see Table 5.1.4e). OV10 reported a greater incidence of hypersensitivity and allergic reactions in the paclitaxel than control arms despite premedications (RR: 3.35 (95% CI: 1.46, 7.66)).

Table 5.1.4e Other adverse events

Trial	GOG 111	OV 10	ICON 3a	ICON 3b
Numbers in arms	TP: 184 CP: 201 %	TP: 338 CP: 330 %	TP: 478 P: 943 %	TP: 232 CAP: 421 %
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Alopecia	TP: 63 CP: 37 1.71 (1.38, 2.12)		TP: 68 P: 3 22.9 (15.8, 33.2)	TP: 77 CAP: 71 1.1 (0.99, 1.2)
Anorexia				
Arthralgia/myalgia		TP: 7 CP: <1 11.72 (2.79, 49)		
Allergy	TP: 4 CP: 0 16.38 (0.94, 284)	TP: 7 CP: 2 3.35 (1.46, 7.66)		
Other			TP: 2 P: 3 0.7 (0.35, 1.44)	TP: 1 CAP: 4 0.21 (0.1, 0.9)

5.2.7 Quality of Life

None of the trials reported quality of life. Quality of life was assessed in OV10 using the EORTC-QLQ-C30+3 and a trial specific checklist for ovarian cancer. No results are available. In ICON 3, quality of life was assessed in terms of treatment related toxicity and anxiety and depression. The results have not yet been reported.

5.2.8 Discussion

About half the patients in the paclitaxel plus platinum arms responded to this treatment (range 46% to 52%). With the exception of the GOG 132 trial, there was no

significant difference between the treatments in terms of response rates. Cisplatin had a superior response rate to paclitaxel in GOG 132.

The median length of progression free survival for the paclitaxel/platinum combination arms ranged from 14.1 months (GOG 132) to 16.5 months (OV10). Two of the four trials (GOG 111 and OV 10) found the progression free survival rate of the paclitaxel arm significantly superior to control; differences in the other trials were not statistically significant.

The median length of overall survival for the paclitaxel/platinum combination arms ranged from 26.6 months (GOG 132) to 35 months (OV10). Again, significant differences between treatment and control were found in two of the four trials (GOG 111 and OV10), with paclitaxel superior to control.

Haematological adverse events were frequently reported but gastro-intestinal adverse events were rare. Neurosensory and neuromotor adverse events were significantly more likely to occur among patients treated with the paclitaxel combination. Cardiovascular adverse events were also significantly more frequent. Allergy was also more significantly common among patients treated with paclitaxel. In the GOG 132 trial, more patients in the platinum only than combined platinum and paclitaxel arm discontinued treatment early because of adverse events. This underlines the problems of dealing with non-blinded trials. Patients in these two arms may have been under different pressures to discontinue their treatment and try an alternative - possibly taxanes were considered more desirable.

Although quality of life was measured in all three trials the results havenot been reported.

A major problem in interpreting these trials is the lack of publications. Only GOG111 has been published in a peer reviewed journals; 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. In some instances, the number surviving in two trials were estimated from Kaplan-Meier curves and may not be accurate.

Superficially, all three trials appear to be high quality randomised controlled trials. All the trials allowed alternate treatment to be given on disease progression. Unless progression is properly validated by blinded, external sources, then cross-over under such circumstances is a violation of randomisation, which introduces bias and non-comparability in various ways. 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 GOG 132, 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 patient request. The problems inherent in this trial and their implications have been discussed at length elsewhere. (75)

The ICON 3 trial only completed accrual in October 1998, and the results are based on a conference presentation from May 1999. These results are therefore very early,

although the authors state that they are reliable for up to two years. This trial used a different baseline population - stage of cancer was not specified. In addition, carboplatin was used, unlike GOG 111, GOG 132 and OV 10, which used cisplatin. Carboplatin is the platinum compound most commonly used in the UK.

Even if the ICON 3 trial does eventually produce different results, this does not invalidate GOG 111 and OV 10, which are high quality trials. ICON 3 included a far wider range of patients than either of these. However, 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 ICON 3 should be able to elucidate such issues.

A second reason why ICON 3 could produce different results is because it uses carboplatin rather than cisplatin. Carboplatin is the platinum analogue of choice in the UK, and no difference has been shown in the effectiveness of these two single agent analogues. (13) However, this may not be the case 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)

5.2.9 Summary: Paclitaxel as first-line treatment for advanced ovarian cancer

Four randomised controlled trials were identified which investigated the first-line use of paclitaxel in ovarian cancer. A total of 3770 patients were included. Two of the trials found paclitaxel/platinum combinations superior to control in terms of median progression free survival and numbers of patients surviving without progression at 12 months. Both these trials suggests that for 1 extra patient to survive without progression to 1 year, 6 patients would have to be treated with paclitaxel/platinum combination. This difference was not found in two other trials, one of which was confounded by crossover, the other which 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 ICON 3 is suitably mature in about mid 2000.

5.3 Economic evaluations of paclitaxel in advanced ovarian cancer

5.3.3 Description of Studies

A total of thirteen 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 publications dates ranged from 1996 to 1999, representing analyses in eight countries and are largely based on the results of the GOG-111 trial. Modelling was used to extrapolate effectiveness from the trial length (48 months) to life years gained, or to estimate resource use in a 'real world' scenario. Resource use outside of a clinical trial can vary considerably due to local practice patterns, patient compliance, rates of hospitalisation for treating adverse effects, etc. Table 5.2.1 presents study descriptions of cost-effectiveness studies. 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 ovarian 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 only given in four studies.

5.3.4 Results

Table 5.2.2 presents the results of these studies. Included are:

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

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

5.3.5 Quality Issues

Table 5.2.3 presents the descriptions and results of the two cost-utility analyses. Table 5.2.4 is a validity assessment based on the methods of Drummond. (29)

Table 5.2.1 Ovarian Cancer Cost-Effectiveness Study Descriptions

	Country/ Currency	Stage of Cancer	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
Sugiyama, 1999 (77)	Japan, Japanese Yen (year not stated)	Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750) + cisplatin (75). 6 cycles TP: paclitaxel (135) + cisplatin (75). 24 hour infusion. 6 cycles Of the 216 with measurable disease response rate: TP: 73% CP: 60% (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: Multicentre RCT. (1996)	Japanese prices substituted into McGuire model. Source and specific costs used not stated.	Used methods of McGuire economic study (78). Time period modelled: 48 months
Beard, 1998 (18)	UK, Pounds sterling (year not stated)	Advanced ovarian cancer) ECOG level >2, FIGO >1	Carboplatin alone 400mg/m2 (plus pre-medications) x 6 cycles (assuming 1.8m2) Cisplatin 75mg/m2 Paclitaxel 135mg/m2 iv 24 hour infusion x 6 cycles (assuming 1.8mg/m2) Cisplatin 75mg/m2 Paclitaxel 175-200mg/m2 iv 3 hour infusion x 6 cycles (assuming 1.8mg/m2) Effectiveness of TP from the OV 10 trial substituted for the GOG-111 results used in 1997 report (response rates TP 77%, CP 66%).	OV 10 Multicentre RCT (abstract 1997) and GOG-111 Multicentre RCT (1996) Literature search for studies using carboplatin alone for sensitivity analysis	Cost data from 1997 report used. (17)	None for based-case (median values used from 48 month study). Survival gains estimated from time-to-event analysis. Time period modelled lifetime.
Berger, 1998 (79)	Germany, Italy, Spain, the Netherlands, UK Presented in US dollars, year not stated	Histologically confirmed stage III epithelial ovarian cancer with residual mass > 1cm or stage IV. No prior chemotherapy	CP: cyclophosphamide (750) + cisplatin (75). 6 cycles TP: paclitaxel (135) + cisplatin (75). 24 hour infusion. 6 cycles Body surface area of 1.76m2 assumed. Of the 216 with measurable disease response rate: TP: 73% CP: 60% (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: 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 (1995-96).	DEALE (declining exponential approximation of life expectancy) approach to calculate specific life expectancy based on actuarial methods. Time period modelled lifetime.
Messori, 1997 (80)	Italy, Presented in US dollars, year not stated.	Newly diagnosed advanced ovarian cancer	Paclitaxel-cisplatin regimens at 'standard doses', Non-paclitaxel cisplatin regimens at 'standard doses' and 'high dose' chemotherapy with autologous hematopoietic rescue. Meta-analysis was used where more than one trial examined the same regimen.	Systematic review and meta-analysis of published literature. (1984-19970 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.	The source of cost data was from three published pharmaco-economic analyses (1996-97) Only incremental costs for BMT 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. Time period modelled lifetime.

	Country/ Currency	Stage of Cancer	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
Beard, 1997 (17)	UK, Pounds sterling (year not stated)	Advanced ovarian cancer) ECOG level >2, FIGO >1	Carboplatin alone 400mg/m2 (plus pre-medications) x 6 cycles (assuming 1.8m2) Cisplatin 75mg/m2 Paclitaxel 135mg/m2) x 6 cycles (assuming 1.8mg/m2) 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 TP taken from the GOG 111 trial.	GOG 111: Multicentre RCT. (1996) Literature search for studies using carboplatin alone for sensitivity analysis	The specific sources and years of cost data are 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 GOG 111 trial. Source of other resource use not stated.	None for based-case (median values used from 48 month study). Survival gains estimated from time-to-event analysis. Time period modelled lifetime.
Elit, 1997 (81)	Canada Canadian dollars, 1993	Stage III and IV ovarian cancer	CP: cisplatin 75mg/m2/ iv cyclophosphamide 750mg/m2 iv TP: cisplatin/ 75mg/m2 iv/ paclitaxel 135mg/m2 iv 24 hour infusion Every three weeks x 6 cycles Of the 216 with measurable disease response rate: TP: 73% CP: 60% (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: 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 month intervals out to 5 years.
Mcguire, 1997 (78)	USA US dollars, 1996	Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750) + cisplatin (75). 6 cycles TP: paclitaxel (135) + cisplatin (75). 24 hour infusion. 6 cycles Of the 216 with measurable disease response rate: TP: 73% CP: 60% (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: 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. An activity based costing approach was used in valuing costs using the Resource Based Relative Value Schedule (RBRVS) and 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. A Monte Carlo simulation was used to analyse the robustness of the estimates to variation in data. Survival gains estimated from time-to-event analysis.

	Country/ Currency	Stage of Cancer	Drugs/doses/response rates	Source of efficacy data	Source of cost data	Modelling
Covens, 1996 (82)	Canada 1993 Canadian dollars	Diagnosis of stage IIIC or IV advanced ovarian cancer, excluding patients with major co- morbidities at diagnosis	CP: cyclophosphamide (750) + cisplatin (75). 6 cycles (average achieved = 5.5) TP: paclitaxel (135) (3 hour infusion) + cisplatin (75). (24 hour infusion) 6 cycles (average achieved = 5.4). Of the 216 with measurable disease response rate: TP: 73% CP: 60% (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: Multicentre RCT. (1996)	Standard daily costs for each phase of the model were calculated based on resource utilisation of a retrospective chart review of 18 AOC patients. The dates prices refer to are not stated but are reported in 1993 Canadian dollars. The source of cost information was pharmacy ordering catalogs, 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); and 4) 25% of all cycles are administered on an inpatient basis.
Messori, 1996 (83)	Italy, Presented in US dollars, year not stated.	Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750) + cisplatin (75). 6 cycles TP: paclitaxel (135) + cisplatin (75). 24 hour infusion. 6 cycles Of the 216 with measurable disease response rate: TP: 73% CP: 60% (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: Multicentre RCT. (1996)	Resources estimated from the clinical trial used for efficacy data (GOG 111). 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

TP = Taxol/Platinum CP = Cyclophosphamide/Platinum

Table 5.2.2 Ovarian Cancer Cost-Effectiveness Studies - Results

	Costs	Benefits	Synthesis	Conclusions
Sugiyama, 1999 (77)	Medication costs for 6 cycles were yen 469, 862 in the cyclophosphamide group and yen 1, 438, 710 in the paclitaxel group	Survival duration: CP: 2.03 TP: 3.13 (means from Effectiveness study)	The incremental cost per life year gained was yen 2,201,927 (assuming outpatient treatment)	The values in Japan were similar to those found by mcguire.
Beard, 1998 (18)	Incremental treatment costs per person: GOG-111 results: £8,368 OV 10 results: : £8,368	Median Life years gained GOG-111 results: Incremental 1.17 OV 10 results: :Incremental 0.83 Progression Free Years gained GOG-111 results: Incremental 0.42 OV 10 results: : Incremental 0.38	GOG-111 results: Cost per extra LYG 7173 OV 10 results: Cost per extra LYG 10,081 (175mg/m2 iv 3 hours infusion = 10,827; 200mg/m2 iv 3 hours infusion = 12,417) GOG-111 results: Cost per PFYG 20,084 OV 10 results: : Cost per PFYG 22,021	The economic analysis varies little irrespective of which trial results are used. The OV 10 survival benefits show slightly less difference from those suggested the the GOG-111 trial, despite the fact that patient 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 in US\$: Germany CP: 12,578 TP 24,487; Spain CP: 9,290 TP: 17,520; France CP: 8,502 TP: 17,150; Italy CP: 6,578: TP: 21,230; Netherlands CP: 6,537 TP: 16,547 UK: CP 4926, TP: 13038	Median overall survival (years) CP: 2 TP: 3.2. Life expectancy by country: Germany CP: 2.56 TP 3.83; Spain CP: 2.57 TP: 3.86; France CP: 2.58 TP: 3.88; Italy CP: 2.56: TP: 3.85; Netherlands CP: 2.57 TP: 3.85 UK: CP: 2.56 TP: 3.82	Incremental costs per life year saved: Germany \$9,362; Spain \$ 6,395; France \$6,642; Italy \$11,420; Netherlands: \$7,796; UK: \$6,403	Cost effectiveness of TP compares favourably with other oncological interventions
Messori, 1997 (80)	Hospitalisation and drugs were the main costs included. Only costs for BMT given (\$60,000 per person)	Mean lifetime survival (years): TP: 2.95 (from McGuire study) Pooled estimate for C-regimens: 3.05 High dose chemotherapy plus BMT rescue: 5.76 (from Legros study) Incremental years of life gained with High dose chemotherapy plus BMT rescue:2.34	No survival difference found between CP and C-based regimens, so no CE ratio calculated. High dose chemotherapy plus BMT rescue: \$26,641 per discounted year of life gained.	In the treatment of patients with advanced ovarian cancer, high-dose chemotherapy with hematopoietic rescue seems to be more effective and ore cost-effective than standard treatments with cisplatin-based regimens at conventional doses
Beard, 1997 (17)	Total annual per patient cost for the TP group 10,427, and 2059 in the Carboplatin group. Incremental cost = £8368 per patient.	Median Life years gained TP 3.17 C 2.00 Incremental =1.17 LYG Progression Free Years gained TP 1.5 C 1.08 Incremental =0.42 PFYG	Cost per extra LYG £7173 Cost per PFYG £20,084 Sensitivity analyses did not change the results.	An economic analysis of the treatment calculated that the introduction of 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 life year gained.
Elit, 1997 (81)	Hospitalisation, drug, adverse-event, physician and cancer centre (overhead) costs. TP: Can\$17,469; CP: Can\$5,228 per patient	Mean survival duration estimated to be prolonged From 2.06 years with CP to 2.44 with TP	Incremental analysis at 1993 prices and using 5% discount rates for both costs and benefits, the additional cost of TP per additional life year gained relative to CP was estimated to be Can\$32,213. The 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 1st line

	Costs	Benefits	Synthesis	Conclusions
Mcguire, 1997 (78)	Inpatient setting per patient cost TP: \$29,824 CP \$21,086. Outpatient: TP: \$27,320 CP: \$17,964. An annual discount rate of 4% used	Survival duration: CP: 2.03 TP: 3.13 (means from Effectiveness study)	Using 1996 prices and 4% discount incremental cost per life year gained (LYG) TP: 19,820 and \$21,222 for inpatient and outpatient treatments respectively	TP mean survival cost per LYG adds substantial benefit at an acceptable cost compared with CP. TP is a cost effective alternative. Benefit at an acceptable cost compared with CP. TP
Covens, 1996 (82)	Included costs were 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. The chart review was done using AOC patients diagnosed between 1988 and 1992. The dates prices refer to is not stated. The source of cost information was the Ontario Schedule of Benefits, and the Case Cost System of the Sunnybrook Center. Incremental and average costs are reported. The total average cost per patient was \$50,054 for paclitaxel group and \$36,837 for the usual care group. The incremental cost for paclitaxel treatment is \$13,217. Costs of adverse effects were included at the resource use level for the usual care group, not specifically for paclitaxel.	Overall weighted survival was 7.8 months longer in the paclitaxel group.	The incremental costs per life year gained were \$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 life year gained significantly drops 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, 1996 (83)	Included costs were chemotherapeutic drugs, pre-medications, hospitalisation for chemotherapy administration, and hospitalisation and treatment costs for febrile neutropenia. Total costs: TP \$1,302,002 per 100 patients CP: \$400,279 per 100 patients Incremental cost of TP: \$901,723 per 100 patients.	Incremental undiscounted years of life gained = 46 per 100 patients.	Incremental cost per undiscounted year of life gained per 100 patients = \$19,603.	The pharmacoeconomic profile of paclitaxel compares favourably with economic data previously calculated for other types of pharmacologic treatment.

TP = Taxol/Platinum (TPc = Taxol/Carboplatin)

LYG = life years gained

PFYG = progression free life years gained

CP = Cyclophosphamide/Platinum C = Carboplatin

Table 5.2.3 Ovarian Cost Utility Analysis

Study Descriptions

	Country/ Currency	Stage of disease	Drugs/doses and response rates	Source of efficacy data	Source of cost data	Methods
Messori 1997* (80)	Italy, reported in US dollars	Reanalysis of 1996 report Stage III and IV epithelial ovarian cancer	CP: cyclophosphamide (750) + cisplatin (75). 6 cycles TP: paclitaxel (135) + cisplatin (75). 24 hour infusion. 6 cycles Of the 216 with measurable disease response % TP: 73 CP: 60 (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: Multicentre RCT. (1996)	Resources estimated from the clinical trial used for efficacy data (GOG 111). Costs estimated from published sources (1993 USA, 1995 the Netherlands)	Q-TWIST method (quality-time spent without symptoms and toxicity) combined with survival curve fitting.
Ortega, 1997 (84)	Canada, 1996 Canadian dollars	Stage IIIC and IV advanced ovarian cancer	CP: cyclophosphamide (750) + cisplatin (75). 6 cycles TP: paclitaxel (135) + cisplatin (75). 24 hour infusion. 6 cycles Of the 216 with measurable disease response % TP: 73 CP: 60 (p = 0.01). Median survival (months) TP: 37.5 CP: 24.4 (p =0.0001). Rate of major side effects TP: 4.6% CP: 3%	GOG 111: Multicentre RCT. (1996)	Resource use was estimated from a retrospective chart review of 36 patients, 12 of which were treated with TP as first line therapy. Costs were obtained from pharmacy catalogues, nursing workload statistics, individual hospital departments, and the 1992 Schedule of Benefits.	A decision analysis model was used.
Best, 1996 (16)	UK, 1996 British pounds	Stage III and IV advanced ovarian cancer	TP: paclitaxel (135) + cisplatin (75). 24 hour infusion x 6 cycles (response rate 73%) C: Carboplatin alone 400mg/m ² x 6 cycles (response rate 54%) CAP: cyclophosphamide (600) +doxorubicin (45) + cisplatin (50).x 6 cycles (response rate 67%) Body surface area of 1.73m ² assumed.	GOG 111: Multicentre RCT. (1996) for TP Literature search of RCTs for C and CAP	Resource use taken largely from GOG-111 trial. Costs of hospital and clinic stays from NHS Trust figures from S&W Region. Sources of other costs not given.	Calculated quality adjusted life years (QALYs) for an untreated patient, and QALYS gained for each treatment regimen.

TP = Taxol/Platinum CP = Cyclophosphamide/Platinum C = Carboplatin CAP = Cyclophosphamide/Doxorubicin/Platinum

QALY = Quality Adjusted Life Years

Ovarian Cancer Cost Utility Analysis

Study Results

	Costs	Benefits	Synthesis	Conclusions
Messori 1997* (80)	Included costs were chemotherapeutic drugs, pre-medications, hospitalisation for chemotherapy administration, and hospitalisation and treatment costs for febrile neutropenia. Total costs: TP \$1,302,002 per 100 patients CP: \$400,279 per 100 patients Incremental cost of TP: \$900,00 per 100 patients.	Incremental undiscounted QALYs = 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, and 2) the assumptions of utilities used in standard Q-TWIST studies were transferred without modification for this disease/treatment.
Ortega, 1997 (84)	Included costs were 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: TP: \$1911 CP: \$459 Total Median costs of second-line therapy (per cycle) Paclitaxel: \$2443 Ifosfamide: \$5190 Hexamethylamine: \$670 Tamoxifen: \$67	Incremental progression-free months with paclitaxel were 3 months. Healthy months equivalent gained was 6.1 (using healthy volunteers valuations) Healthy months equivalent using patient preferences was 10-10.6.	Incremental cost per quality adjusted progression-free year ranged from \$11,600 to \$24,200 depending on which second line treatment is chosen. Sensitivity analysis showed that the maximum Incremental cost per quality adjusted progression-free year was \$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 the use of paclitaxel, this pilot study will provide a basis for more extensive economic evaluation of paclitaxel
Best, 1996 (16)	Total costs of treatment and management of adverse effects given in summary form. Total costs: TP: £8680 per patient C: £2880 per patient CAP: £3790 per patient	QALYs 100 untreated patients: 27 QALYs QALYs gained with treatment: 100 TP treated patients: 200 QALYs 100 C treated patients: 90.5 QALYs 100 CAP treated patients: 112.3 QALYs	Cost per QALY gained: TP: £4340 C: £3180 CAP: £3370	The use of TP was recommended, with the caveat that the recommendation be reviewed in 12-18 months, after more clinical trial data was available.

TP = Taxol/Platinum CP = Cyclophosphamide/Platinum C = Carboplatin CAP = Cyclophosphamide/Doxorubicin/Platinum

QALY = Quality Adjusted Life Years

Table 5.2.4 Validity assessment of economic evaluations {Drummond}

Critical Assessment Questions (29)	Sugiyama, 1999 (77)	Beard, 1998 (18)	Berger, 1998 (79)	Messori, 1998 (85)	Beard, 1997 (17)	Elit, 1997 (81)	McGuire, 1997 (78)	Messori, 1997 (80)*	Ortega, 1997 (84)*	Best, 1996 (16)*	Covens, 1996 (82)	Messori, 1996 (83)
Well defined question	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Comprehensive description of alternatives	✓	✓- (applying ECOGIT results to a different patient population)	✓	- (only described as 'standard doses')	✓	✓- (unclear if pre-medication included)	✓- (unclear if pre-medication included)	- (based on 1996 study)	✓- (unclear if pre-medication included)	✓	✓- (unclear if pre-medication included)	✓
Effectiveness established	✓	✓- (effectiveness of carboplatin alone assumed to be the same as CP)	✓	✓	✓	✓- (effectiveness of 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)	✓- (difficult to identify specific costs included, adverse effects of paclitaxel considered, but not those of cyclophosphamide)	✓	✓- (only hospital and drug costs)	✓- (difficult to identify specific costs included, adverse effects of paclitaxel considered, but not those of cyclophosphamide)	✓	✓	-	✓	✓	✓	✓
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)	✓- (method of valuation not stated)	✓- (mixed sources compared)	? (taken from previous CE analyses, but costs used for TP/CP not stated.)	✓- (method of measurement not stated)	✓	✓	? (utility scores arbitrarily assigned at 0.5)	✓	✓- (sources of some cost/ consequences not clearly stated)	✓- (('Standard' daily costs reported)	✓- (costs from the Netherlands and USA used in same model)-
Costs and	NA	NA	NA	NA	NA	Costs and	Costs	NA	NA	NA	NA	NA

Critical Assessment Questions (29)	Sugiyama, 1999 (77)	Beard, 1998 (18)	Berger, 1998 (79)	Messori, 1998 (85)	Beard, 1997 (17)	Elit, 1997 (81)	McGuire, 1997 (78)	Messori, 1997 (80)*	Ortega, 1997 (84)*	Best, 1996 (16)*	Covens, 1996 (82)	Messori, 1996 (83)
consequences adjusted for differential timing						benefits occurring after 1 year discounted at 5%	discounted at 4%					(discounted benefits at 5% in sensitivity analysis)
Incremental analysis of costs and consequences	✓	✓	✓	✓- (incremental analysis only for hematopoietic rescue)	✓	✓	✓	✓	✓	-	✓	✓
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	✓	✓	✓	✓- (only addressed the results with respect to BMT)	✓	✓	✓	-	✓	✓- (very little discussion)	✓	✓- (not clear what setting these results refer to)

* = Cost utility analysis, all other cost-effectiveness analyses.

✓ = Yes ✓- = Maybe/Partially

? = Unknown

- = No

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

5.3.5.2 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. The comparator used in these studies of ovarian cancer was most often cyclophosphamide and cisplatin (CP) because this was the comparator used in the GOG-111 trial. It has been stated that this regimen is not the most common alternative used in England (11), but rather carboplatin alone is used. Until results of the ICON-3 study are available, there is no direct comparison of paclitaxel plus carboplatin with carboplatin alone. Either the results of the GOG-111 trial must be used, or assumptions about carboplatin's efficacy must be made from other trials, which can introduce bias. Another reason that the comparator chosen is important is because of the effect it can have on the incremental benefits and costs, such as differing response rates, cost of drug or treating adverse effects. These differences in benefits or costs can go in either the positive or negative direction.

5.3.5.3 Resources and Costs Included

The identification of resources used, costs included, and 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 pre-medications that are given prior to paclitaxel use, and stem-cell stimulating drugs that are given in the event of myelosuppression, are examples which could alter costs. More important may be hospitalisation costs for drug administration and treatment of adverse events. In the GOG-111 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 could 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 alter the costs. Sensitivity analyses or comparing similar studies that have and have not included these may help define the significance of these variations.

5.3.6 Cost-effectiveness Analyses

If it is 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. Since the years of these studies are quite similar, no reflation to 1999 prices is necessary. For studies comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin, the range of cost-effectiveness ratios for life years gained was £3,960 to £13,360. The low estimate was for Spain (79) and the high was for Japan. (77) Two cost-effectiveness studies done in England compared carboplatin alone to paclitaxel plus cisplatin (one of these was an update of another). (17, 18, 86) The range of cost-effectiveness ratios for life years gained was £7173 to £12,417. These studies also calculated a progression-free life years-gained ratio, the range was £20,084 to £22,021. The difference between these two measures, life-years gained and progression free life-years gained may have important quality of life issues.

Progression free life years may be preferable to overall life years, since the quality of life would be generally assumed to be better during the progression free period.

5.3.7 Cost-utility Analyses

One cost-utility analysis has been done in England. (16) This analysis compared paclitaxel plus cisplatin, carboplatin alone and also with cyclophosphamide plus doxorubicin plus cisplatin (CAP) to no treatment. Although superficially similar to the ICON 3 trial, data on response rates was obtained from a variety of disparate trials. Very few details on how QALYS gained were derived were given, except that the IHQL measure was used. Cost per quality adjusted life years were calculated for each regimen compared to no treatment, but an incremental analysis comparing treatments to each other was not done. For the purposes of this report, an analysis compared to no treatment is not appropriate. However, using the costs and quality of life estimates given in this analysis incremental cost per QALY gained can be calculated. The incremental cost per QALY gained comparing paclitaxel/platinum to CAP is £5433, and versus carboplatin alone is £5273.

The two non-British cost-utility analyses also address quality adjusted life years. The cost per QALY gained in the Messori study using the Q-TWIST method was £11,269. (80) In the Ortega study, incorporating patient preferences, the cost per quality adjusted progression free life year gained ranged from a low of £6860 to a high of £10,377. (84) In sensitivity analysis, the maximum cost per quality adjusted progression free life year gained was £18,000.

5.3.8 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 5.1.4d is a critical assessment of these economic evaluations. The areas examined in each study are the

- study question posed,
- comprehensive description of competing alternative,
- 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,
- and finally the breadth and depth of the discussion and conclusions.

The areas where the studies most often were deficient were those relating to costs and consequences. Several of the studies did not report details of which costs and consequences were considered in enough detail, or had somewhat limited or vague inclusion lists. Likewise, the methods for measuring and valuing these costs and consequences were often vague or lacking altogether. Discounting of costs or benefits was not attempted in most studies, due 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 one-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, a sensitivity analysis, providing an appropriate discussion, and forming a well-defined study question. Whether the effectiveness rates used were well established, is debatable, however at the time many of these studies were done GOG-111 was the only completed study comparing paclitaxel plus cisplatin to any standard regimen. The description of treatments was rather poor, in that the use of pre-medications and the body surface area used were rarely reported.

Two UK studies assumed that the effectiveness of carboplatin alone was the same as that of cisplatin plus cyclophosphamide, in the GOG-111 trial in their primary analysis. (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 felt 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, and 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 to regional costs is presented.

In the 1998 report, response rates for paclitaxel plus cisplatin from the OV 10 (ECOCIT) trial were substituted for those of the GOG-111 trial. The OV10 trial included patients diagnosed with stage II ovarian cancer, whereas the cost effectiveness exercise is based on only grade III-IV patients. The OV10 trial also used a dose range of 170-200 mg/m² of paclitaxel given over 3 hours (rather than 135mg/m² given over 24 hours used in GOG 111). Various combinations of the resource use and cost implications from OV10 and GOG 111 were presented. The third UK study compared paclitaxel/carboplatin to carboplatin alone in the primary analysis. The response rates used to calculate benefits in this analysis were taken from the GOG 111 trial, using paclitaxel/cisplatin response rates for paclitaxel/carboplatin and cyclophosphamide/cisplatin response rates for carboplatin alone. It is unclear if the cost difference between adverse effects associated with cisplatin and those associated with carboplatin are taken into account.

However, these are the only studies originating in the UK and comparing paclitaxel plus cisplatin to the standard first-line drug in this country.

The range of incremental costs per life year gained (£7,173 to £12,417) found in these two UK studies is within the range reported above for all studies comparing Taxol/Platinum to Cyclophosphamide/Platinum (£3,960 to £13,360). The range of incremental cost per quality adjusted life year gained ranged from £5273 to £11,269 and are also within the same range. The incremental cost per progression free life year found in two of the English studies was higher (£20,084 to £22,021); however the quality adjusted progression free life year gained calculated by Ortega (84) in a more robust analysis (Table 5.2.3) was lower (£6,860 to £10,377) and within the range found for cost per life years gained.

5.3.9 Summary of economic evaluation of paclitaxel in advanced ovarian cancer

The acceptability of an incremental cost-effectiveness ratio of £13,000 per life year gained or £20,000 per progression free life year gained must be considered. The cut-off of £20,000 has previously been suggested, and ratios above this mark are often accepted. (29) The fact that these data are based primarily on one study for efficacy data, and only three analysis including carboplatin alone as the alternative therapy have been done should be kept in mind. However, at this point, the cost-effectiveness and cost-utility ratios of the Paclitaxel/Cisplatin regimen compared to either Cyclophosphamide/Platinum or carboplatin alone appears to fall within accepted ranges.

6 CONCLUSIONS

Both paclitaxel and docetaxel are licensed for use as secondline treatment for breast cancer. The evidence to support the use of paclitaxel in this context is not strong - a single, small phase II randomised controlled trial. However, there are ongoing, multi-centre randomised controlled phase III trials, one comparing epirubicin and paclitaxel versus epirubicin and cyclophosphamide (ABO1), and another one comparing doxorubicin and taxol 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 secondline treatment of advanced breast cancer, especially among women who are resistant to anthracyclines. In one trial only, there was an advantage in overall survival of 2.5 months compared with control. There were no differences in quality of life. In addition, docetaxel was found to be of similar effectiveness to doxorubicin, so may be useful in the treatment of women for whom anthracyclines are contraindicated.

In terms of cost effectiveness in 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 lack of a direct clinical comparison. Docetaxel was found to be highly cost effective in comparison 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. As the results of ICON 3 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 randomised controlled trials are given below:

Review question			Range of median progression free survival in months (control)	Range of median overall survival in months (control)
Cancer	Level of treatment	Chemotherapy		
Breast	First-line	Paclitaxel	4.0 - 5.9* (6.0 - 7.5)	17.3- 22.2 (13.9 - 18.9)
		Paclitaxel + anthracycline	8.0 - 8.3 ¹ (6.0 - 6.2)	22.0 - 22.7 ² (18.3 - 18.9)
	Second-line	Paclitaxel	3.5 ³ (1.6)	12.7 ⁴ (8.4)
		Docetaxel	4.7 - 7.0 ⁵ (2.7 - 5.0)	10.4 - 15 ⁶ (8.7 - 14)
Ovary	First-line	Paclitaxel	14.1 - 18 ⁷ (11.8 - 16.4)	26.6 - 38 ⁷ (25-30.2)

*Control significantly better than paclitaxel in 1/3 studies

1 Paclitaxel plus anthracycline significantly better than control in 2/2 trials

2 Paclitaxel plus anthracycline significantly better than control in 1/2 trials

3 Paclitaxel significantly better than control in 1/1 trial

4 Paclitaxel significantly better than control in 1/1 trial

5 Docetaxel significantly better than control in 2/4 trials

6 Docetaxel significantly better than control in 1/4 trials

7 Paclitaxel plus platinum significantly better than control in 2/4 trials

This treatment combination was also found to be cost effective. The mature results of ICON 3 will also add to our understanding of the comparative costs and benefits of cisplatin and carboplatin.

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.

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CONFLICTS OF INTEREST

None

EXPIRY DATE

July 2000 - when the results of ICON 3 are mature.

REFERENCES

1. NHS Executive. Guidance for purchasers. Improving outcomes in breast cancer. The research evidence; 1996.
2. NHS Executive. Guidance on Commissioning Cancer Services. Improving outcomes in gynaecological cancer. The research evidence; 1999.
3. Cancer Research Campaign. www.crc.org.uk/cancer. In:; 2000.
4. Williams C. Cancer Biology and Management: An Introduction. Chichester: John Wiley and Sons Ltd; 1990.
5. Scottish Health Purchasing Information Centre. Breast cancer. Aberdeen: Scottish Health Purchasing Information Centre; 1997.
6. Fornier MM, P; Seidman, AD. Update on the management of advanced breast cancer. *Oncology* 1999;13(5):647-58.
7. Wiseman LS, CM. Paclitaxel. An update of its use in the treatment of metastatic breast cancer and ovarian and other gynaecological cancers. *Drugs Aging* 1998;12(4):305-34.
8. Kitchener H. Gynaecological cancer. *POSTGRAD MED J*. Postgraduate Medical Journal 1999;75(884):332-338.
9. Gore M. The evidence base for medical intervention in ovarian cancer. In: Maclean A, Gore M, Miles A, editors. *The Effective management of Ovarian cancer: AESCULAPIUS Medical Press*; 1999.
10. NHS Centre for Reviews and Dissemination. Management of Gynaecological Cancers. *Effective Health Care* 1999;5(3).
11. Adams MC, AH; Carmichael, J; Clark, PI; Coleman, RE; Earl, HM; Gallagher, CJ; Ganesan, TS; Gore, ME; Graham, JD; Harper, PG; Jayson, GC; Kaye, SB; Ledermann, JA; Osborne, RJ; Perren, TJ; Poole, CJ; Radford, JA; Rustin, GJ; Slevin, ML; Smyth, JF; Thomas, H; Wilkinso. Chemotherapy for ovarian cancer--a consensus statement on standard practice [editorial] [see comments]. *Br J Cancer* 1998;78(11):1404-6.
12. Joint Council for Clinical Oncology. The current role of paclitaxel in the first-line chemotherapy of Ovarian cancer: Royal College of Physicians; 1998 September, 1998.
13. Advanced Ovarian Cancer Trialists' Group. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. *British Journal of Cancer* 1998;78:1479-1487.
14. Miller KS, GW, Jr. Taxanes in the treatment of breast cancer a prodigy comes of age. *Cancer Invest* 1999;17(2):121-36.
15. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998;352:930-942.
16. Best L, Anthony D. Paclitaxel as a first line chemotherapy agent in the treatment of ovarian cancer. DEC Report. Southampton: Wessex Institute for Health Research and Development; 1996. Report No.: 56.
17. Beard S, Coleman R, Radford J, al e. The use of cisplatin and paclitaxel as a first line treatment in ovarian cancer. Guidance note for Purchasers: Trent Institution for Health Services Research; 1997. Report No.: 97/05.
18. Beard S, Coleman R, Radford J, al e. Supplementary document: The use of paclitaxel in the first line treatment of ovarian cancer. Guidance note for Purchasers: Trent Institute for Health Services Research; 1998 1998. Report No.: 98/10 (Supplement to 97/05).
19. Anthony D, Stevens A. Paclitaxel in the treatment of advanced stage ovarian cancer. DEC (Development and Evaluation Committee). Bristol: R and D Directorate, South and West Regional Health Authority; 1995 September 1995. Report No.: 42.
20. Rhone-Poulenc Rorer (Aventis). Sponsor Submission to the National Institute For Clinical Excellence - Taxotere (docetaxel); 1999.COMMERCIAL IN CONFIDENCE
21. Eisenhauer EV, JB. The taxoids. Comparative clinical pharmacology and therapeutic potential. *Drugs* 1998;55(1):5-30.
22. NHS Executive. Guidance on Commissioning Cancer Services. Improving outcomes in colorectal cancer. The research evidence.; 1997.
23. NHS Executive. Guidance on Commissioning Cancer Services. Improving outcomes in lung cancer. The research evidence.; 1998.
24. Katz M, Hauck W. Proportional Hazards (Cox) Regression. *J Gen Intern Med* 1993;8:702 - 711.
25. Stewart L, Clarke M. Practical methodology of meta-analyses (overviews) using updates individual patient data. *Stat Med* 1995;14:2057 - 2079.
26. Petrie A. The crossover design. In: Tygstrup N, Lachin J, Juhl E, editors. *The randomized clinical trial and therapeutic decisions*. New York: Marcel Dekker inc.; 1982. p. 199 - 204.
27. Woods J, Williams J, Tavel M. The two-period crossover design in medical research. *Ann Intern Med* 1989;110:560 - 566.
28. Hills M, Armitage P. Two periodcross-over clinical trial. *B. J. Pharmac* 1979;8:7 - 20.
29. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the economic evaluation of health care programmes*. Second ed. Oxford: Oxford University Press; 1997.
30. Piccart-Gebhart MB, P; Gamucci, T; Klijn, J; Roy, J, A; Awada, A; Kusenda, Z; Van, Vreckem, A; Paridaens, R. An ongoing European Organization for Research and Treatment of Cancer crossover trial comparing single-agent paclitaxel and doxorubicin

- as first- and second-line treatment of advanced breast cancer. SEMIN ONCOL. Seminars in Oncology 1996;23(5):11-15.
31. Paridaens R. Taxol versus doxorubicin as first-line single agent chemotherapy for metastatic breast cancer - an EORTC randomised study with cross-over. Forthcoming. NOT FOR COMMENT.
 32. Awada A, Paridaens R, Bruning P. Doxorubicin or Taxol as firstline chemotherapy for metastatic breast cancer (MBC): results of EORTC-IDBBC/ECSG randomised trial with crossover. Breast Cancer Res Treat 1997;46:23.
 33. Paridaens R, Bruning P, Klijn J, Gamucci T, Biganzoli L, Van Vreckem A, et al. An EORTC crossover trial comparing single-agent Taxol (T) and doxorubicin (D) as first- and second-line chemotherapy (CT) in advanced breast cancer (ABC) (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol 1997;16:A539.
 34. Bishop J, Dewar J, Tattersall LMH, Smith J, Olver I, Ackland S, et al. A randomized phase III study of Taxol (paclitaxel) vs CMFP in untreated patients with metastatic breast cancer (Meeting abstract). Proc-Annu-Meet-Am-Soc-Clin-Oncol 1996;15:A107.
 35. Bishop JF, Dewar J, Toner GC, Tattersall MH, Olver IN, Ackland S, et al. Paclitaxel as first-line treatment for metastatic breast cancer. The Taxol Investigational Trials Group, Australia and New Zealand. Oncology-Huntingt 1997;11(4 Suppl 3):19-23.
 36. Bishop JD, J; Toner, G; Tattersall, MH; Olver, I; Ackland, S; Kennedy, I; Goldstein, D; Gurney, H; Walpole, E; Levi, J; Stephenson, J. 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 1997;24(5 Suppl 17):S17-9.
 37. Bishop JD, J; Toner, GC; Smith, J; Tattersall, MHN; Olver, IN; Ackland, S; Kennedy, I; Goldstein, D; Gurney, H; Walpole, E; Levi, J; Stephenson, J; Canetta, R. Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. J CLIN ONCOL. Journal of Clinical Oncology 1999;17(8):2355-2364.
 38. Sledge GW, Jr., Neuberg D, Ingle J, Martino S, Wood W. Phase III trial of doxorubicin (A) vs paclitaxel (T) vs doxorubicin + paclitaxel (A + T) as first-line therapy for metastatic breast cancer (MBC): an intergroup trial (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol 1997;16:A2.
 39. Pluzanska A, Jassem J. Randomised open-label phase III multicenter trial comparing Taxol/doxorubicin vs 5-fluorouracil and cyclophosphamide as firstline treatment for patients with metastatic breast cancer. European Journal of Cancer 1999;Suppl 4(S314):A1260.
 40. Nabholz J, Falkson G, Campos D, Szanto J, Martin M, Chan S, et al. A Phase III Trial Comparing Doxorubicin (A) and Docetaxel (T) (AT) to Doxorubicin and Cyclophosphamide (AC) as First Line Chemotherapy for MBC. Proc An Meeting Am Soc Clin Oncol 1999.
 41. CA139-047 Trial report. CA139-047 trial report. A phase II randomised study of taxol versus mitomycin C in patients with advanced breast cancer. COMMERCIAL IN CONFIDENCE
 42. Dieras V, Marty M, Tubiana N, Corette L, Morvan F, Serin D, et al. Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. Semin-Oncol 1995;22(4 Suppl 8):33-9.
 43. Chan SF, K; Noel, D; Pinter, T; Van, Belle, S; Vorobiof, D; Duarte, R; Gil, MG; Bodrogi, I; Murray, E; Yelle, L; Von, Minckwitz, G; Korec, S; Simmonds, P; Buzzi, F; Mancha, RG; Richardson, G; Walpole, E; Ronzoni, M; Murawsky, M; Alakl, M; Riva, A; Crown, J. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J CLIN ONCOL. Journal of Clinical Oncology 1999;17(8):2341-2354.
 44. Chan S. Docetaxel (Taxotere) vs doxorubicin in patients with metastatic breast cancer (MBC) who have failed alkylating chemotherapy. Randomized multicenter phase III trial. Proceedings of American Society of Clinical Oncology 1997;16:154A.
 45. Chan S. Docetaxel vs doxorubicin in metastatic breast cancer resistant to alkylating chemotherapy. Oncology Huntingt 1997;11(8 Suppl 8):19-24.
 46. Chan S, Friedrichs K, Noel D, Duarte R, Vorobiof D, Pinter T, et al. 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 (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol; 1997;16:A540.
 47. Aapro M. Docetaxel versus doxorubicin in patients with metastatic breast cancer who have failed alkylating chemotherapy a preliminary report of the randomized phase III trial. 303 Study Group. Semin Oncol 1998;25(5 Suppl 12):7-11.
 48. Nabholz JT, B; Bezwoda, WR; Melnychuk, D; Deschenes, L; Douma, J; Vandenberg, TA; Rapoport, B; Rosso, R; Trillet, Lenoir, V; Drbal, J; Aapro, MS; Alaki, M; Murawsky, M; Riva, A. Docetaxel vs mitomycin plus vinblastine in anthracycline-resistant metastatic breast cancer. Oncology Huntingt 1997;11(8 Suppl 8):25-30.
 49. Nabholz JS, HJ; Bezwoda, WR; Melnychuk, D; Deschenes, L; Douma, J; Vandenberg, TA; Rapoport, B; Rosso, R; Trillet, Lenoir, V; Drbal, J; Molino, A; Nortier, JW; Richel, DJ; Nagykalnai, T; Siedlecki, P; Wilking, N; Genot, JY; Hupperets, PS; Pannuti, F; Skarlos, D; Tomi, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing

- despite previous anthracycline-containing chemotherapy. 304 Study Group. *J Clin Oncol* 1999;17(5):1413-24.
50. Nabholz JM. 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. *Proceedings of American Society of Clinical Oncology* 1997;16:148A.
 51. Nabholz J, Thuerlimann B, Bezwoda W. Taxotere vs mitomycin C-vinblastine in patients with metastatic breast cancer who have failed an anthracycline containing regimen. *Breast Cancer Res Treat* 1997;46:93.
 52. Nabholz JM, Thuerlimann B, Bezwoda WR, Melnychuk D, Alak M, Murawsky M, et al. Taxotere (T) versus mitomycin C + vinblastine (MV) in patients (pts) with metastatic breast cancer (MBC) who have failed an anthracycline containing regimen: preliminary results of a randomized phase III study (Meeting abstract). *Proc Annu Meet Am Soc Clin Oncol*; 1997;16:A519.
 53. Bonneterre J, Roche H, Monnier A, Serin D, Fargeot P, Guastalla JP, et al. Taxotere (TXT) versus 5-fluorouracil + navelbine (FUN) as second-line chemotherapy (CT) in patients (pts) with metastatic breast cancer (MBC) (preliminary results) (Meeting abstract). *Proc Annu Meet Am Soc Clin Oncol* 1997;16:A564.
 54. Sjostrom J, Mouridsen H, Pluzanska A. Taxotere versus mEhtotrexare-5-fluorouracil in patients with advanced anthracycline resistant breast cancer: preliminary results of a randomised phase III study by Scandinavian Breast Cancer Group. *Proc Am Soc Clin Oncol* 1998;17:111.
 55. Leung P. Cost-utility analysis of chemotherapy using paclitaxel, docetaxel, or vinorelbine for patients with anthracycline-resistant breast cancer. *J Clin Oncology* 1999;17:3082-3090.
 56. Brown RH, J. Cost-utility model comparing docetaxel and paclitaxel in advanced breast cancer patients. *Anticancer Drugs* 1998;9(10):899-907.
 57. Yee G. Cost-utility analysis of taxane therapy. *Am J Health Syst Pharm* 1997;54(24 Suppl 2):S11-5.
 58. Hutton JB, RE; Borowitz, M; Abrams, K; Rothman, M; Shakespeare, A. A new decision model for cost-utility comparisons of chemotherapy in recurrent metastatic breast cancer. *PHARMACOECONOMICS. Pharmacoeconomics*. 1996;2:8-22.
 59. Launois RR, Marty, J; Henry, B; Bonneterre, J. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine. *PHARMACOECONOMICS. Pharmacoeconomics*. 1996;10(5):504-521.
 60. McGuire W, Hoskins, W. J. Brady, M. F. Kucera, P. R. Look, K. Y. Partridge, E. E., Davidson M. A Phase III trial comparing cisplatin/cytoxan (PC) and cisplatin/Taxol (PT) in advanced ovarian cancer (AOC) (Meeting abstract). *Proc-Annu-Meet-Am-Soc-Clin-Oncol* 1993;12:A808.
 61. McGuire WH, W. J. Brady, M. F. Kucera, P. R. Partridge, E. E. Look, K. Y., Davidson M. Taxol and cisplatin (TP) improves outcome in advanced ovarian cancer (AOC) as compared to cytoxan and cisplatin (CP) (Meeting abstract). *Proc-Annu-Meet-Am-Soc-Clin-Oncol* 1995;14:ABS. A771.
 62. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. 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* 1996;23:40-47.
 63. McGuire WH, WJ; Brady, MF; Kucera, PR; Partridge, EE; Look, KY; Clarke, Pearson, DL; Davidson, M. 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. International Journal of Gynecological Cancer* 1996;6(5):2-8.
 64. McGuire, et al. Taxol/cisplatin (TP) versus cyclophosphamide/cisplatin (CP) in stage IV or suboptimally debulked stage III ovarian cancer. *Annual-American-Society-of-Clinical-Oncology-(ASCO)-Meeting-1995* 1995.
 65. Hoskins WM, WP; Brady, MF; Kucera, PR; Partridge, EE; Look, KY; Clarke, Pearson, DL; Davidson, M. Combination paclitaxel (Taxol registered)-cisplatin vs cyclophosphamide-cisplatin as primary therapy in patients with suboptimally debulked advanced ovarian cancer. *INT J GYNECOL CANCER. International Journal of Gynecological Cancer* 1997;1:9-13.
 66. Bristol-Myers Squibb. GOG-111a: Study CA139-022. Study Report. Phase III randomised study of Cyclophosphamide (NSC 26271) and Cisplatin (NSC 119875) versus TAXOL (NSC 125973) in patients with suboptimal stage III and stage IV epithelial ovarian carcinoma. *COMMERCIAL IN CONFIDENCE*
 67. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer [see comments]. *N-Engl-J-Med* 1996;334(1):1-6.
 68. Muggia F, Brady P, Brady M, al e. Phase III study of cisplatin and or paclitaxel versus the combination in suboptimal stage III and IV epithelial ovarian cancer: Gynecological Oncology Group (GOG) study. *Proc Annu Meet Am Soc Clin Oncol* 1997;16:A1257.
 69. GOG. GOG-132a: Study protocol. Phase III of cisplatin (p) or paclitaxel(T), versus their combination in suboptimal stage III and IV epithelial ovarian cancer (EOC): Gynecologic Oncology Group (GOG) study # 132; 1992. *COMMERCIAL IN CONFIDENCE*
 70. Intergroup. Intergroup Phase III comparison of a combination of taxol-platinum and a combination of cyclophosphamide-platinum chemotherapy in the treatment of

- advanced epithelial ovarian cancer. Protocol No. CA 139-209; 1994. COMMERCIAL IN CONFIDENCE
71. Piccart M, Bertelson K, Stuart G, et al. Is cisplatin-paclitaxel the standard first-line treatment in advanced ovarian cancer? The EORTC-COCCG, NOCOVA, NCIC CTG and Scottish Intergroup experience. *Proc Annu Meet Am Soc Clin Oncol* 1997;16:A1394.
72. Stuart G, Bertelsen K, Mangioni C, et al. Updated analysis shows a highly significant overall improved survival for cisplatin-paclitaxel as first-line treatment of advanced ovarian cancer: mature results of the EORTC-COCCG, NOCOVA, NCIC CTG and Scottish Intergroup trial. *Proc Annu Meet Am Soc Clin Oncol* 1999;17:A1394.
73. MRC, Gynaecological Cancer Working Party. A randomised trial of paclitaxel (Taxol) with Carboplatin vs Carboplatin or CAP in the treatment of women with advanced ovarian cancer: MRC ICON-3; 1995 April 1995. COMMERCIAL IN CONFIDENCE
74. Harper P. A randomised comparison of paclitaxel (T) and carboplatin (J) versus a control arm of single agent carboplatin (J) or CAP (cyclophosphamide, doxorubicin, cisplatin): 2075 patients randomised into the 3rd International Collaborative Ovarian Neoplasm Study. *Proc Am Soc Clin Oncol* 1999;18:A1375.
75. Sandercock J, Parmar M, Torri V. First-line chemotherapy for advanced ovarian cancer paclitaxel, cisplatin and the evidence [see comments]. *Br J Cancer* 1998;78(11):1471-8.
76. du Bois H, Lueck W, Meier V, Moebus S, Costa T, Bauknecht B, et al. Cisplatin/paclitaxel vs carboplatin/paclitaxel in ovarian cancer: Update of an AGO study Group Trial. *Proc Am Soc Clin Oncol* 1999;18:A1374.
77. Sugiyama TK, K; Kumagai, S; Imaishi, K; Ushijima, K; Okura, N; Nishida, T; Yakushiji, M. Analysis of the cost-effectiveness of paclitaxel as first-line chemotherapy for advanced ovarian cancer. *ACTA OBSTET GYNAECOL JPN. Acta Obstetrica et Gynaecologica Japonica* 1999;51(5):287-292.
78. McGuire WN, AI; Arikian, S; Doyle, J; Dezii, CM. Analysis of the cost-effectiveness of paclitaxel as alternative combination therapy for advanced ovarian cancer. *J Clin Oncol* 1997;15(2):640-5.
79. Berger KF, T; Szucs, TD. Cost-effectiveness analysis of paclitaxel and cisplatin versus cyclophosphamide and cisplatin as first-line therapy in advanced ovarian cancer. A European perspective. *Eur J Cancer* 1998;34(12):1894-901.
80. Messori AC, M; Becagli, P; Trippoli, S. Pharmacoeconomic profile of paclitaxel as a first-line treatment for patients with advanced ovarian carcinoma. A lifetime cost-effectiveness analysis [letter]. *Cancer* 1997;79(11):2264-6.
81. Elit LG, A; Levine, MN. Economic and policy implications of adopting paclitaxel as first-line therapy for advanced ovarian cancer an Ontario perspective. *J Clin Oncol* 1997;15(2):632-9.
82. Covens AB, S; Roche, K; Macdonald, M; Pettitt, D; Jolain, B; Souetre, E; Riviere, M. Is paclitaxel and cisplatin a cost-effective first-line therapy for advanced ovarian carcinoma? *Cancer* 1996;77(10):2086-91.
83. Messori AT, S; Becagli, P; Tendi, E. Pharmacoeconomic profile of paclitaxel as a first-line treatment for patients with advanced ovarian carcinoma. A lifetime cost-effectiveness analysis. *Cancer* 1996;78(11):2366-73.
84. Ortega AD, G; Sturgeon, J; Sutherland, H; Oza, A. Cost-utility analysis of paclitaxel in combination with cisplatin for patients with advanced ovarian cancer. *Gynecol Oncol* 1997;66(3):454-63.
85. Messori AT, S; Becagli, P; Tendi, E. Treatments for newly diagnosed advanced ovarian cancer analysis of survival data and cost-effectiveness evaluation. *Anticancer Drugs* 1998;9(6):491-502.
86. Bristol-Myers Squibb. Taxol (paclitaxel). Submission to the National Institute for Clinical Evidence (sic) (NICE). "For the treatment of carcinoma of the ovary, in combination with cisplatin, in patients with advanced disease or residual disease (>1cm) after initial laparotomy". Hounslow, Middlesex: Bristol Myers Squibb; 1999. COMMERCIAL IN CONFIDENCE
87. National Institute of Clinical Effectiveness. Health Technology Assessment: Commissioning Assessment Reports (Draft). Draft: National Institute of Clinical Effectiveness; 1999 October, 1999.

APPENDIX 1

Staging of ovarian and breast cancers

FIGO Staging for Epithelial Cancer of the Ovary (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
- Ib Both ovaries involved
- Ic, Ascites (an accumulation of fluid in the abdominal (peritoneal) cavity) present or positive peritoneal washings

Stage II: Growth limited to pelvis

- Iia Extension to gynaecological adnexae (on or in a structure associated with the uterus such as on 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 involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals Stage III. Tumour is 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 histologic-proven extension to small bowel or mesentery
- IIIb 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 (4)

T	T1	tumour less than 2cm
	T2	tumour 2-5 cm
	T3	tumour more than 5cm
	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

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

Stage I Small tumour (<2 cm)

Stage II Tumour >2cm but < 5cm, lymph nodes negative
Or
Tumour < 5cm, lymph nodes positive, no detectable distant metastases

Stage III Large tumour (> 5cm)
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
		The searches below are from: A:\MEDTAX.HIS.
1	43556	explode "Breast-Neoplasms"/ all subheadings
2	10216	ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
3	3858	ovar* near4 ((oncolog* or carcinoma*) in ti ab)
4	8158	breast* near4 ((oncolog* or carcinoma*) in ti ab)
5	33236	breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
6	12781	explode "Ovarian-Neoplasms"/ all subheadings
7	413	(adnexa* near mass*)
8	62631	#1 or #2 or #3 or #4 or #5 or #6 or #7
9	3225	"Paclitaxel"/ all subheadings
10	3698	paclitaxel*
11	645	docetaxel*
12	2226	taxol*
13	306	taxotere*
14	245	taxanes
15	4222	#9 or #10 or #11 or #12 or #13 or #14
16	1484	#8 and #15
		The searches above are from: A:\MEDTAX.HIS.
17	155093	trial in pt
18	34593	explode "Clinical-Trials"/ all subheadings
19	33955	(clin* near trial*) in ti ab
20	29834	((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
21	5087	Placebos
22	34045	placebo* in ti ab
23	30200	random in ti ab
24	9745	research-design
25	238118	#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	782	#16 and #25
27	32870	exact{199801} in UD
28	29902	exact{199802} in UD
29	37979	exact{199803} in UD
30	35221	exact{199804} in UD
31	32443	exact{199805} in UD
32	31625	exact{199806} in UD
33	39481	exact{199807} in UD
34	34067	exact{199808} in UD
35	31128	exact{199809} in UD
36	38577	exact{199810} in UD
37	32157	exact{199811} in UD
38	33456	exact{199812} in UD
39	39266	exact{199901} in UD
40	31845	exact{199902} in UD
41	39104	exact{199903} in UD
42	35845	exact{199904} in UD
43	35417	exact{199905} in UD
44	32628	exact{199906} in UD
45	42976	exact{199907} in UD
46	34225	exact{199908} in UD
47	43309	exact{199909} in UD
48	30766	exact{199910} in UD
49	774287	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
or #37 or #38 or		#39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48
* 50	303	#26 and #49

EMBASE

No.	Records	Request
		The searches below are from: A:\EMTAX1.HIS.
1	47788	explode "Breast-Neoplasms"/ all subheadings
2	10866	ovar* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
3	4342	ovar* near4 ((oncolog* or carcinoma*) in ti ab)
4	8509	breast* near4 ((oncolog* or carcinoma*) in ti ab)
5	34398	breast* near4 ((cancer* or tumo?r* or malignant*) in ti, ab)
6	14633	explode "Ovarian-Neoplasms"/ all subheadings
7	451	(adnexa* near mass*)
8	66698	#1 or #2 or #3 or #4 or #5 or #6 or #7
9	6026	"Paclitaxel"/ all subheadings
10	2488	paclitaxel*

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11      679      docetaxel*
12      6423      taxol*
13      1474      taxotere*
14      365       taxanes
15      7041      #9 or #10 or #11 or #12 or #13 or #14
16      2416      #8 and #15
17      159624     explode "Clinical-Trials"/ all subheadings
18      34896      ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in
ti ab
19      345       Placebos
20      39237      placebo* in ti ab
21      39328      "randomized-controlled-trial"/ all subheadings
                The searches above are from: A:\EMTAX1.HIS.
22      32589      (clinical trial*) in ti ab
23      122001     random* in ti ab
24      272599     #17 or #18 or #19 or #20 or #21 or #22 or #23
* 25      1213      #24 and #16
26      6026      "taxol"/ all subheadings
27      1455      "taxotere"/all subheadings

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Cancerlit

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Set      Items Description
1        1876  BREAST NEOPLASMS!/DE
2        120403 (OVARIAN OR BREAST)/TI,AB
3        21453  OVARIAN NEOPLASMS!/DE
4         388   ADNEXA?(W)MASS?
5        142808 S1:S4
6         2803  PACLITAXEL/DE
7         5402  PACLITAXEL? OR DOCETAXEL? OR TAXOL? OR TAXOTERE?
OR
8         5402  TAXANES
9         0     S6:S7
10        2943  COST BENEFIT ANALYSIS/DE
11        569  COST(W)EFFECT?/TI,AB
12        52   COST(W)BENEFIT?/TI,AB
13        119  COST(W)UTIL?/TI,AB
14        82   ECONOMIC(W)EVALUATION?/TI,AB
15        66   TECHNOLOGY (W) ASSESSMENT?/TI,AB
16        3642 PHARMACOECONOMIC?/TI,AB
17        0     S9:S15
18        17354 DT=TRIAL
19        19353 CLINICAL TRIALS!/DE
20        3575 ((CLIN? (4W) TRIAL?)/TI,AB
                ((SINGL? OR DOUBL? OR TREBL? OR TRIPL?) (4W)(BLIND? OR
                MASK?))/TI,AB
21        459  PLACEBOS/DE
22        4459 PLACEBO?/TI,AB
23        36673 RANDOM?/TI,AB
24        2202 RESEARCH DESIGN/DE
25        65621 S17:S24
26        1177668 SF=MEDL
27         30   S8 AND S5 AND S16
28         671  S8 AND S5 AND S25
29        2158  COST-BENEFIT ANALYSIS/DE
30        49542 DT="CLINICAL TRIAL":DT="CLINICAL TRIAL, PHASE IV"
31        4033  DT="CONTROLLED CLINICAL TRIAL"
32        42462 DT="MULTICENTER STUDY" OR S23
33        22455 DT="MULTICENTER STUDY" OR DT="RANDOMIZED CONTROLLED
                TRIAL"
34         33   S8 AND S5 AND (S16 OR S29)
35        1261  S8 AND S5 AND (S25 OR S30 OR S31 OR S33)
36         11   S34 NOT S26
37         11   S36/1990:1999

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Prints requested : ('*' indicates user print cancellation)

25oct 05:15:40 P079: PR S37/7/1-11 TAG ADDR ADYORK (VIA EMAIL)

APPENDIX 3

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APPENDIX 4

Prescreen for titles and abstracts

The following codes will be 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			
	DATEEXTRACTED				

APPENDIX 5

Data extraction

The following data will be extracted from the included trials and entered into 6 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
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
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
recurrence_free_survival_RFS
Symptom_relief
other_outcomes
haematological_toxicity
neutropenia
febrile_neutropenia
fever_requiring_antibiotics
leukopenia
thrombocytopenia
metabolic_toxicity
nonhaematological_toxicity
emesisnausea
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

Report Format

NICE Assessment Report Format (87)

1. Front cover
 - Title of assessment report
 - Authors and Institution
 - Report date
 - Statement: "Report commissioned by the NHS HTA Programme on behalf of the national Institute of Clinical Excellence"
2. Contents Page
3. Executive Summary
4. Abbreviations and Definitions
5. Aim of Assessment
 - Brief clear statement of specific questions being addressed by the assessment
6. Background
 - Description of health problem (to include epidemiology, aetiology, pathology prognosis, significance in terms of burden of disease).
 - Current service provision (to include service cost, current variation in service)
 - Description of technology (brief account of technology itself; current indications or uses or uses for which it is (or will be) promoted; summary of information provided to health professionals; projected unit cost)
 - Licensed indications, contraindications and warnings.
7. Methodology
 - Search strategy and bibliographic database used
 - Inclusion and exclusion criteria for studies used (key characteristics of included studies should be included as appendix)
 - Data extraction strategy
 - Quality assessment strategy
 - If appropriate, method(s) of quantitative data pooling
 - Identification of other unpublished sources of evidence (in addition to the contact point nominated by NICE)
 - If appropriate, explanation of modelling/simulation approach
 - If appropriate, explanation of methodological assumptions (e.g. rationale for sensitivity analyses)
 - Any other methodological issues specific to a technology assessment not detailed above.
 - In addition to above, a detailed description of methods by which industry submission (where provided) has been handled within the assessment
8. Results
 - Quantity and quality of overall studies identified
 - Studies excluded, with reasons for specific exclusions
 - Studies included, including characteristics and quality
 - Tabulation of results of included studies
 - Assessment of clinical effectiveness of technology - identify benefit(s) and adverse effect(s).
 - Assessment of cost effectiveness of technology - estimates net benefit(s), estimation of net cost and estimation of cost effectiveness/cost utility/cost benefit.
 - The previous two points should include any important sub-group analyses
9. Discussion
 - Summary statement of evidence of effectiveness and cost effectiveness of technology
 - Potential methodological shortcomings of the technology assessment
 - Implications of the assessment findings to the NHS, patients and carers, likely public health and economic impact of the technology
 - Implications for future research
 - Conclusions
10. Acknowledgements
11. Conflicts of Interest
12. Expiry Date
 - Statement of time period after which the report is likely to be out of date e.g. relevant trials currently in progress whose findings might alter conclusions
13. References and Bibliography
 - In Vancouver style
14. Appendices

APPENDIX 6

Rejected studies

- Ozols R, Bundy B, Fowler J, et al. 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). Proc Ann Meet Am Soc Clin Oncol 1999;18:A1373. **compares carboplatin and cisplatin**
- Gianni, L., et al., 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 [see comments]. J Natl Cancer Inst, 1995. **87**(15): p. 1169-75.
Not RCT
- Neijt, J., et al., Randomized phase III study in previously untreated epithelial ovarian cancer FIGO stage IIB, IIC, IV comparing paclitaxel-cisplatin and paclitaxel-carboplatin. Proc Annu Meet Am Soc Clin Oncol, 1997. **16**: p. A1259.
compares carboplatin and cisplatin
- Dieras, V., et al., Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. Semin-Oncol, 1995. **22**(4 Suppl 8): p. 33-9. **superceded**
- Bauknecht, T., et al., Interim analysis of a randomized trial comparing cisplatin/paclitaxel vs carboplatin/paclitaxel as first-line chemotherapy in advanced ovarian cancer (Meeting abstract). Proc Annu Meet Am Assoc Cancer Res, 1997. **38**: p. A715. **compares carboplatin and cisplatin**
- Harvey, J., et al., Mitoxantrone + paclitaxel (NT) versus paclitaxel (T) alone for metastatic breast cancer (MBC) (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol, 1997. **16**: p. A601. **paclitaxel in both arms**
- Chan, S., et al., 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 (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol; 1997. **16**: p. A540. **superceded**
- Buzdar, A.U., et al., Prospective randomized trial of Taxol (Tax) alone versus fluorouracil, doxorubicin, cyclophosphamide (FAC) as an induction therapy in patients with operable breast cancer (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol, 1997. **16**: p. A498. **neoadjuvant**
- Neuberg, D., et al., 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 (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol, 1997. **16**: p. A185. **neoadjuvant**
- Carmichael, J., et al., Topotecan, a new active drug, vs paclitaxel in advanced epithelial ovarian carcinoma: International Topotecan Study Group Trial (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol, 1996. **15**: p. A765.
secondline
- Paridaens, R., et al., An EORTC crossover trial comparing single-agent Taxol (T) and doxorubicin (D) as first- and second-line chemotherapy (CT) in advanced breast cancer (ABC) (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol, 1997. **16**: p. A539. **superceded**
- Nabholtz, J., et al., Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. Journal of Clinical Oncology, 1996. **14**: p. 1858-1867. **comparing doses**
- Markman, M., et al., 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 Am Soc Clin Oncol, 1998. **17**: p. A1392. **looking at intraperitoneal cisplatin**
- Awada, A., R. Paridaens, and P. Bruning, Doxorubicin or Taxol as firstline chemotherapy for metastatic breast cancer (MBC): results of EORTC-IDBBC/ECSG randomised trial with crossover. Breast Cancer Res Treat, 1997. **46**: p. 23.
superceded
- Bennett, C.S., TJ; Yang, T; Lurain, JR, The effect of reimbursement policies on the management of Medicare patients with refractory ovarian cancer. Semin Oncol, 1999. **26**(1 Suppl 1): p. 40-5. **secondline ovarian**

- Bishop, J.D., J; Toner, G; Tattersall, MH; Olver, I; Ackland, S; Kennedy, I; Goldstein, D; Gurney, H; Walpole, E; Levi, J; Stephenson, J, 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*, 1997. **24**(5 Suppl 17): p. S17-9. **superceded**
- ten Bokkel Huinink, W., et al., Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer [see comments]. *J-Clin-Oncol*, 1997. **15**(6): p. 2183-93. **secondline ovarian**
- Bolis, G.P., F; Scarfone, G; Villa, A; Amoroso, M; Rabaiotti, E; Polatti, A; Reina, S; Pirlletti, E, Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer. *Gynecol Oncol*, 1999. **72**(1): p. 60-4. **secondline ovarian**
- Bomalaski, J., The treatment of recurrent ovarian carcinoma Balancing patient desires, therapeutic benefit, cost containment and quality of life. *CURR OPIN OBSTET GYNECOL*. Current Opinion in Obstetrics and Gynecology, 1999. **11**(1): p. 11-15. **secondline ovarian**
- Chan, S., Docetaxel vs doxorubicin in metastatic breast cancer resistant to alkylating chemotherapy. *Oncology Huntingt*, 1997. **11**(8 Suppl 8): p. 19-24. **superceded**
- Chan, S., Docetaxel (Taxotere) vs doxorubicin in patients with metastatic breast cancer (MBC) who have failed alkylating chemotherapy. Randomized multicenter phase III trial. Proceedings of American Society of Clinical Oncology, 1997. **16**: p. 154A. **superceded**
- Colombo, N., Marzola, M. Parma, G. Cantu, M. G. Tarantino, G. Fornara, G. and D. Guelli Alletti, Paclitaxel vs CAP (cyclophosphamide, Adriamycin, cisplatin) in recurrent platinum sensitive ovarian cancer: a randomized phase II study (Meeting abstract). *Proc-Annu-Meet-Am-Soc-Clin-Oncol*, 1996. **15**: p. A751. **secondline**
- du Bois H, Lueck W, Meier V, Moebus S, Costa T, Bauknecht B, et al. Cisplatin/paclitaxel vs carboplatin/paclitaxel in ovarian cancer: Update of an AGO study Group Trial. *Proc Am Soc Clin Oncol* 1999;18:A1374. **Compares one taxane combination with another (carboplatin vs cisplatin)**
- Hainsworth, J., 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*, 1997. **6**(4 Suppl): p. 4-9. **Not RCT**
- Harper, P., ICON 2 and ICON 3 data in previously untreated ovarian cancer results to date. *Semin Oncol*, 1997. **24**(5 Suppl 15): p. S15-25. **brief sketch of trial**
- Hoskins, W.M., WP; Brady, MF; Kucera, PR; Partridge, EE; Look, KY; Clarke, Pearson, DL; Davidson, M, Combination paclitaxel (Taxol registered)-cisplatin vs cyclophosphamide-cisplatin as primary therapy in patients with suboptimally debulked advanced ovarian cancer. *INT J GYNECOL CANCER*. International Journal of Gynecological Cancer, 1997. **1**: p. 9-13. **superceded.**
- Hortobagyi, G.N., Willey, J., Rahman, Z; Holmes, F.A., Theriault, R.A., Buzdar, A.U. Prospective assessment of cardiac toxicity during a randomized phase II trial of doxorubicin and paclitaxel in metastatic breast cancer. *Semin Oncol* (1997) **24** (5) Suppl 17 p. S17-65- S17-68. **Compares 1 and 3 hour infusion.**
- Kavanagh, J., Kudelka, A. P. Edwards, C. L. Freedman, R. S. Gibbs, H. Gonzalez de Leon, C. Canetta, R. Harper, K. J. Kopplin, S. Mante, R. and et al., A randomized cross-over trial of parenteral hydroxyurea vs high-dose Taxol in cisplatin/carboplatin-resistant epithelial ovarian cancer (Meeting abstract). *Proc-Annu-Meet-Am-Soc-Clin-Oncol*, 1993. **12**: p. A822. **secondline**
- Mamounas, E., Preoperative doxorubicin plus cyclophosphamide followed by preoperative or postoperative docetaxel. *Oncology Usa. Oncology.*, 1997. **11**(6): p. 37-40. **preliminary report - no results**
- McGuire and et al., Taxol/cisplatin (TP) versus cyclophosphamide/cisplatin (CP) in stage IV or suboptimally debulked stage III ovarian cancer. Annual-American-Society-of-Clinical-Oncology-(ASCO)-Meeting-1995, 1995. **superceded**
- McGuire, W., Hoskins, W. J. Brady, M. F. Kucera, P. R. Look, K. Y. Partridge, E. E. and M. Davidson, A Phase III trial comparing cisplatin/cytosine (PC) and

- cisplatin/Taxol (PT) in advanced ovarian cancer (AOC) (Meeting abstract)*. Proc-Annun-Meet-Am-Soc-Clin-Oncol, 1993. **12**: p. A808. **superceded**
- McGuire, W.H., WJ; Brady, MF; Kucera, PR; Partridge, EE; Look, KY; Clarke, Pearson, DL; Davidson, M, *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. International Journal of Gynecological Cancer, 1996. **6**(5): p. 2-8. **superceded**
- McGuire, W.H., W. J. Brady, M. F. Kucera, P. R. Partridge, E. E. Look, K. Y. and M. Davidson, *Taxol and cisplatin (TP) improves outcome in advanced ovarian cancer (AOC) as compared to cytoxan and cisplatin (CP) (Meeting abstract)*. Proc-Annun-Meet-Am-Soc-Clin-Oncol, 1995. **14**: p. ABS. A771. **superceded**
- McGuire, W.P., et al., *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, 1996. **23**: p. 40-47. **superceded**
- McGuire, W.P., et al., *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, 1997. **24**(1 Suppl 2): p. S2-13-S2-16. **superceded**
- Nabholtz, J., B. Thuerlimann, and W. Bezwoda, *Taxotere vs mitomycin C-vinblastine in patients with metastatic breast cancer who have failed an anthracycline containing regimen*. Breast Cancer Res Treat, 1997. **46**: p. 93. **superceded**
- Nabholtz, J.M., *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*. Proceedings of American Society of Clinical Oncology, 1997. **16**: p. 148A. **superceded**
- Nabholtz, J.T., B; Bezwoda, WR; Melnychuk, D; Deschenes, L; Douma, J; Vandenberg, TA; Rapoport, B; Rosso, R; Trillet, Lenoir, V; Drbal, J; Aapro, MS; Alaki, M; Murawsky, M; Riva, A, *Docetaxel vs mitomycin plus vinblastine in anthracycline-resistant metastatic breast cancer*. Oncology Huntingt, 1997. **11**(8 Suppl 8): p. 25-30. **superceded**
- Piccart, M, et al. *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*. Journal of Clinical Oncology, 1997. **15**: p. 3149-3155. **comparison of prophylactic medication**
- Schroder, W., A. du Bois, and W. Kuhn. *Treatment of patients with advanced ovarian cancer (FIGI IIB-IV) with cisplatin/paclitaxel or carboplatin/paclitaxel - an interim analysis of the AGO study protocol OVAR -3*. in 10th European Cancer Conference. 1999. Vienna, Austria. **compares cisplatin and carboplatin**
- Bishop, J., et al., *A randomized phase III study of Taxol (paclitaxel) vs CMFP in untreated patients with metastatic breast cancer (Meeting abstract)*. Proc-Annun-Meet-Am-Soc-Clin-Oncol, 1996. **15**: p. A107. **superceded**
- Botto, H., M. Botto, and M. Otegui, *Taxotere vs vinorelbine and taxol in patients with metastatic breast cancer anthracycline resistance*. Proc Am Soc Clin Oncol, 1998. **17**: p. 130. **Not RCT**
- Gamucci, T., M. Piccart, and P. Bruning, *Single agent taxol versus doxorubicin as first-line chemotherapy in advanced breast cancer. Final results of as EORTC randomised study with crossover*. Proc Am Soc Clin Oncol, 1998. **17**: p. 111. **superceded**
- Hamilton, A. *Taxanes as neoadjuvant therapy for locally advanced breast cancer*. in 10th European Cancer Conference ECCO 10. 1999. Vienna, Austria. **review**
- Kern, D., *Heterogeneity of drug resistance in human breast and ovarian cancers*. CANCER J SCI AM. Cancer Journal from Scientific American, 1998. **4**(1): p. 41-45. **background**
- Piver, M.S., et al., *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 (Meeting abstract)*. Proc Annu Meet Am Soc Clin Oncol; 16:A1277 1997, 1997. **16**: p. A1277. **not RCT**

- Poole, C. A randomised comparison of paclitaxel/carboplatin versus a control arm single agent carboplatin or CAP: 2074 patients randomised into a 3rd International Collaborative Neoplasm Study. in *American Society for Clinical Oncology*. 1999. **superceded**
- Sjostrom, J., H. Mouridsen, and A. Pluzanska, Taxotere versus mEthotrexare-5-fluorourocil in patients with advanced anthracycline resistant breast cancer: preliminary results of a randomised phase III study by Scandinavian Breast Cancer Group. *Proc Am Soc Clin Oncol*, 1998. **17**: p. 111. **superceded**

APPENDIX 7
Performance Status

GOG PERFORMANCE SCALE

GRADE	KARNOFSKY SCALE	PERFORMANCE
0	90 & 100	Fully active
1	70 & 80	Restricted in physically strenuous activities but ambulatory
2	50 & 60	Ambulatory, capable of self care, unable to work; up to 50% of waking hours
3	30 & 40	Limited self care; confined to bed or chair 50% of waking hours
4	10 & 20	Completely disabled. No self care

APPENDIX 8

NHS Centre for Reviews and Dissemination DARE type abstracts of manufacturers' submissions

Paclitaxel in breast cancer

Bristol Myers Squibb Submission: Paclitaxel in metastatic breast cancer

COMMERCIAL IN CONFIDENCE

The information from this appendix has been removed as it was submitted as commercial in confidence.

Docetaxel in breast cancer

Aventis submission
COMMERCIAL IN CONFIDENCE

<<AUTHOR'S OBJECTIVE>>

To detail the available evidence to support a positive recommendation to the National Institute of Clinical Excellence for the use of Taxotere in the treatment of locally advanced and metastatic breast cancer following anthracycline or alkylating agent failure.

<<TYPE OF INTERVENTION>>

Treatment

<<SPECIFIC INTERVENTIONS INCLUDED IN THE REVIEW>>

Taxotere, paclitaxel or vinorelbine used within their UK licensed indications.

<<PARTICIPANTS INCLUDED IN THE REVIEW>>

Patients with advanced breast cancer that are refractory to, or have relapsed following anthracycline or alkylating based chemotherapy.

<<OUTCOMES ASSESSED IN THE REVIEW>>

Overall response (complete and partial response), time to disease progression, survival.

<<STUDY DESIGNS OF EVALUATIONS INCLUDED IN THE REVIEW>>

The clinical data presented in this review are ordered according to quality of evidence. Data from Phase III studies are presented first, followed by data from other clinical trials, including Phase II studies.

<<WHAT SOURCES WERE SEARCHED TO IDENTIFY PRIMARY STUDIES?>>

EMBASE Alert, EMBASE, HealthStar, Cancer Lit MEDLINE, RPR Database. The cut off date was August 18th 1999. The search terms used are outlined in a table.

<<ON WHAT CRITERIA WAS THE VALIDITY OF PRIMARY STUDIES...?>>

The studies were graded according to a standard hierarchy of evidence. Category I contains "Strong evidence obtained from at least one properly designed, randomised controlled trial of appropriate size" Category IV contains "Inadequate evidence, owing to problems of methodology (eg sample size, length or comprehensiveness of follow-up) or conflicts of interest.

<<HOW WERE DECISIONS ON THE RELEVANCE OF PRIMARY STUDIES...?>>

Not stated.

<<HOW WERE JUDGEMENTS OF VALIDITY MADE?>>

Not stated.

<<HOW WAS THE DATA EXTRACTED FROM PRIMARY STUDIES?>>

Not stated.

<<NUMBER OF STUDIES INCLUDED>>

Three randomised, controlled trials (Phase III); six Phase II studies (no design details)

<<HOW WERE THE STUDIES COMBINED?>>

Each of the Phase III studies was separately summarised. A summary table indicated the comparative efficacy of docetaxel in Phase III trials in terms of overall response, time to progression and survival. The data from Phase II trials were included in the appendices.

<<HOW WERE DIFFERENCES BETWEEN STUDIES INVESTIGATED?>>

Not stated.

<<RESULTS OF THE REVIEW>>

All three randomised controlled trials found docetaxel significantly superior to competitors in terms of overall response; two found it significantly superior in terms of time to progression and one found it superior in terms of survival.

<<WAS ANY COST INFORMATION REPORTED?>>

A cost effectiveness analysis was undertaken. (See later)

<<AUTHOR'S CONCLUSIONS>>

Docetaxel has been shown to be the most active chemotherapy agent for the treatment of advanced breast cancer, after failure of previous anthracycline or alkylating agent treatment. The majority of patients benefit from treatment, leading to relief of symptoms without compromising quality of life. Docetaxel has been shown to significantly improve time to disease progression and survival when compared with other effective chemotherapy regimens. Docetaxel improves the number of months patients with advanced breast cancer spend in perfect health.

<<CRD COMMENTARY>>

This review is based on a reasonable search and the quality of included trials has been taken into consideration. However, there are no details about the mechanics of the review process, such as number of reviewers involved, so the rigour of the review process cannot be commented upon. The conclusions seem primarily based on response rates and appear overly favourable.

Paclitaxel in Ovarian cancer

Bristol Myers Squibb Submission: Paclitaxel in ovarian cancer

COMMERCIAL IN CONFIDENCE

The information from this appendix has been removed as it was submitted as commercial in confidence.