



**NATIONAL BREAST  
AND OVARIAN  
CANCER CENTRE**

**TAXANES FOR  
NEOADJUVANT TREATMENT OF  
EARLY BREAST CANCER:  
A SYSTEMATIC REVIEW**

**MAY 2007**

Prepared by National Breast and Ovarian Cancer Centre

Funded by the Australian Government  
Department of Health and Ageing

Taxanes for neoadjuvant treatment of early breast cancer: a systematic review was prepared and produced by:

National Breast and Ovarian Cancer Centre (NBOCC)  
Locked Bag 3 Strawberry Hills NSW 2012 Australia  
Suite 103, 355 Crown Street, Surry Hills, NSW, 2010  
Telephone: +61 2 9357 9400 Fax: +61 2 9357 9477  
Website: [www.nbocc.org.au](http://www.nbocc.org.au)  
Email: [director@nbocc.org.au](mailto:director@nbocc.org.au)

**ISBN Online: 978-1-74127-125-6**

© National Breast and Ovarian Cancer Centre 2008

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from National Breast and Ovarian Cancer Centre. Requests and enquiries concerning reproduction and rights should be addressed to the Public Affairs Manager, National Breast and Ovarian Cancer Centre, Locked Bag 3 Strawberry Hills NSW 2012 Australia.

#### **Recommended citation**

National Breast and Ovarian Cancer Centre. Taxanes for neoadjuvant treatment of early breast cancer: a systematic review. National Breast and Ovarian Cancer Centre, Surry Hills, NSW, 2008.

Copies of this report can be downloaded from the National Breast and Ovarian Cancer Centre website: [www.nbocc.org.au](http://www.nbocc.org.au)

#### **Disclaimer**

National Breast and Ovarian Cancer Centre does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information. National Breast and Ovarian Cancer Centre develops material based on the best available evidence, however it cannot guarantee and assumes no legal liability or responsibility for the currency or completeness of the information.

National Breast and Ovarian Cancer Centre is funded by the Australian Government Department of Health and Ageing.

# ACKNOWLEDGEMENTS

National Breast and Ovarian Cancer Centre\* gratefully acknowledge the support of all the individuals and groups who contributed to the development of this review.

## **Working Group – Taxanes Subgroup**

This review was developed with input from a multidisciplinary Working Group:

Dr Craig Lewis (Chair)

Dr Alison Davis

Dr Tom Ferguson

Dr James French

Ms Judy Iasiello

Ms Elisabeth Kochman

Dr Anna Nowak

## **National Breast and Ovarian Cancer Centre Staff**

The following people were involved in the development of this review:

Ms Rosemary Vagg (Senior Project Officer - Research)

Ms Katrina Anderson

Dr Karen Luxford

Ms Alison Pearce

Ms Jess Singleton

Ms Heidi Wilcoxon

---

\* In February 2008, National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

# CONTENTS

List of tables	5
List of abbreviations	6
<b>Executive Summary</b>	<b>8</b>
<b>Background</b>	<b>11</b>
<b>Methods</b>	<b>12</b>
Inclusion criteria	12
Literature search	13
Quality assessment	14
Data extraction	14
<b>Results</b>	<b>16</b>
International guidelines	16
Included systematic reviews	16
Included studies	19
- Description of included studies	20
- Outcomes	23
Ongoing studies	28
<b>Conclusions</b>	<b>30</b>
<b>References</b>	<b>31</b>
<b>Appendices</b>	<b>33</b>

# LIST OF TABLES

Table 1. Characteristics of included systematic reviews

Table 2. Characteristics of included studies

Table 3. Relapses and deaths at most recent report

Table 4. Overview of response rates (clinical and pathological)

Table 5. Breakdown of clinical response rates

Table 6. Rates of breast conserving therapy

Table 7. Reported toxicity data

Table 8. Ongoing studies investigating taxane-containing neoadjuvant regimens

# LIST OF ABBREVIATIONS

AC	Doxorubicin and Cyclophosphamide
ACCOG	Anglo-Celtic Cooperative Oncology Group
ASCO	American Society of Clinical Oncology
BCT	Breast Conserving Therapy
CCO	Cancer Care Ontario
cCR	Clinical Complete Response
CI	Confidence Interval
CVAPr	Cyclophosphamide, Vincristine, Doxorubicin and Prednisolone
cPOS	Positive Clinical Response
DFS	Disease Free Survival
EBC	Early Breast Cancer
FAC	Fluorouracil, Doxorubicin, and Cyclophosphamide
FEC	Fluorouracil, Epirubicin and Cyclophosphamide
HR	Hazard Ratio
LABC	Locally Advanced Breast Cancer
MDACC	MD Anderson Cancer Centre
MERGE	Method for Evaluating Research Guideline Evidence
NBCC	National Breast Cancer Centre
NBOCC	National Breast and Ovarian Cancer Centre
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	Overall Survival
pCR	Pathological Complete Response
PE	Paclitaxel and Epirubicin
RCT	Randomized Controlled Trial
RR	Risk Ratio
SABCS	San Antonio Breast Cancer Symposium
Tmx	Tamoxifen

TX

Docetaxel and Capecitabine

# EXECUTIVE SUMMARY

Taxanes are a class of chemotherapy compounds that includes paclitaxel, docetaxel and abraxane. As antimicrotuble agents, taxanes inhibit the normal process of reorganisation of the microtubule network essential for cellular function, which leads to a disruption of mitosis (cell division). Taxanes can be used as part of adjuvant or neoadjuvant chemotherapy regimens to treat early (operable) breast cancer.

The aim of this systematic review was to determine the effectiveness of taxane-containing chemotherapy regimens, compared to non-taxane-containing chemotherapy regimens. This review assessed taxanes in a neoadjuvant chemotherapy setting, while a second review (conducted by Cochrane<sup>1</sup>) examined taxanes in an adjuvant chemotherapy setting. This review examined three types of regimens:

- regimen A plus taxane vs. regimen A
- regimen A plus taxane vs. regimen B
- regimen A with taxane substituted for one or more drugs vs. regimen A.

The review included randomised controlled trials (RCTs) published up to March 2007 in women with early (operable) breast cancer. The search retrieved a total of 427 references from electronic databases, conference sites and clinical trial and guideline sites. After rigorous methods of inclusion and exclusion of articles, 20 articles were eligible for the review covering three systematic reviews and eight RCTs.

## RESULTS

Three studies examined paclitaxel,<sup>2-4</sup> while the remaining five trials examined the use of docetaxel.<sup>5-9</sup> Six of the studies included an anthracycline (doxorubicin or epirubicin) in the taxane and non-taxane arm. One study investigated the single use of paclitaxel compared to combination chemotherapy.<sup>2</sup> Another study compared the use of docetaxel and capecitabine with doxorubicin and cyclophosphamide.<sup>8</sup>

All trials included were randomised controlled trials. However, the method of allocation and/or allocation concealment to study arms was often not reported. The baseline patient characteristics were well balanced between study arms for all trials. Many trials stratified study

arms by age, size of tumour and nodal status. It is unlikely that the trials included are influenced by bias or confounding factors.

### **Overall Survival**

Overall survival (OS) was reported in four of the trials.<sup>3, 5, 6, 10</sup> Three of the four trials reported that OS did not differ significantly between the two treatment groups.<sup>3, 5, 6</sup> The remaining trial reported that OS for the taxane group was 93% while the control group was 78% ( $p=0.04$ ).<sup>10</sup> However, while this trial reported an overall survival benefit for the taxane group the trial was quite small.

### **Disease-free survival**

Disease-free survival (DFS) was reported in three of the trials.<sup>2, 3, 5</sup> The overall differences in the trials between the taxane group and control group were not statistically significant.

### **Relapse-free survival**

Four of the trials reported on relapse-free survival.<sup>2, 3, 5, 6</sup> Trends have suggested that taxanes may be associated with improved relapse-free survival. However, in each trial this was not statistically significant.

### **Response rates**

#### **Clinical response**

Taxane-containing regimens achieved higher clinical complete response rates. However, these differences between the taxane and control groups were not always significant.<sup>2-4, 8-10</sup>

#### **Pathological response**

Pathological complete response rates were higher in the taxane-containing arms in comparison to the control arms; however, only one trial<sup>11</sup> reported that the higher pathological complete response rates in the taxane arm were statistically significant.

### **Breast Conserving Therapy**

Five of the trials reported on the rates of breast conserving therapy (BCT).<sup>2, 3, 6, 8, 11</sup> Three of the trials<sup>2, 6, 11</sup> reported similar rates of BCT among the taxanes and control groups. The other

two trials<sup>3, 8</sup> reported higher rates of BCT in the taxane arms; however, statistical significance was not reported.

### **Toxicity/Adverse events**

Toxicity data was reported in six of the trials;<sup>2, 3, 5, 6, 8, 9, 11</sup> however, many reported small numbers of toxic events, so it is difficult to clearly identify differences in the toxicity profiles of taxane containing regimens compared to control regimens.

The most commonly, and consistently, reported outcome was febrile neutropenia, with four trials reporting higher rates in the taxane-containing arms compared to the control arms.<sup>2, 3, 5, 6, 11</sup>

## **CONCLUSION**

Overall at this time there is no overall or disease-free survival benefit of taxane-containing regimens compared with standard neoadjuvant chemotherapy for early breast cancer. While there appears to be a trend towards a benefit on relapse-free survival among taxane-containing regimens; however, further data is needed to determine if this is statistically significant. Taxane regimens also seem to achieve higher clinical and pathological response rates in comparison to non-taxane regimens; however, the reported differences were only statistically significant in one trial.

# BACKGROUND

In 2003, the National Breast Cancer Centre (NBCC) commissioned a systematic review on the role of taxanes in early and locally advanced breast cancer (LABC).<sup>12</sup>

The review concluded that while there was evidence to suggest that taxane-containing regimens were a reasonable option for use in both the neoadjuvant and adjuvant setting, this information was limited and longer follow-up was needed to clarify the role of taxanes in the treatment of early and locally advanced breast cancer.

Taxanes continue to be used as part of adjuvant or neoadjuvant chemotherapy regimens to treat early (operable) breast cancer. The aim of this new review is to summarise the current literature and assess the effectiveness of neoadjuvant use of taxanes (docetaxel or paclitaxel) for the management of early (operable) breast cancer. The question of adjuvant use of taxanes for the management of early (operable) breast cancer is reported elsewhere.<sup>1</sup>

# METHODS

The objective of this review is to compare taxane-containing neoadjuvant chemotherapy regimens with non-taxane-containing neoadjuvant regimens for the management of women with early (operable) breast cancer. Regimens include:

- Regimen A plus taxane vs. Regimen A
- Regimen A plus taxane vs. Regimen B
- Regimen A with taxane substituted for one or more drugs vs. Regimen A.

## INCLUSION CRITERIA

### Participants

Women with early (operable) breast cancer, including stage I, II, IIIA or TNM classification T1-3, N0-2, M0, receiving neoadjuvant chemotherapy. Studies including patients with locally advanced or inflammatory disease were also included if the majority of patients were considered operable or if results were reported separately by stage of disease.

### Intervention

Any neoadjuvant chemotherapy regimen containing a taxane. Taxanes include paclitaxel and docetaxel.

### Comparison

Any neoadjuvant chemotherapy regimen not containing a taxane.

- Endocrine therapy may be used if the same treatment has been given to all groups.

### Outcomes

- Overall survival (OS)
- Disease-free survival (DFS)
- Relapse-free survival
- Response rates (clinical and pathological)
- Breast conserving therapy (BCT)
- Toxicity/adverse events
- Quality of life.

## LITERATURE SEARCH

A systematic literature search was conducted to identify phase III RCTs which addressed the inclusion criteria. The search was conducted over several databases/sources (see Appendix 1), including:

- Medline
- EMBASE
- PubMed
- EBM reviews
- CINAHL
- Cochrane Library, Issue 1 Jan 2007.

The search strategy used combined key terms which described breast cancer, neoadjuvant chemotherapy, taxanes and randomised trials (see Appendix 2). The literature search covered the period up to March 2007. Publication date limitations were not imposed. The search was limited to trials conducted in humans and published in English.

In addition to the above databases/sources, conference sites for the San Antonio Breast Cancer Symposium (SABCS) and the American Society of Clinical Oncology (ASCO) were also searched for relevant abstracts.

Reference lists of included papers were also searched and additional relevant papers identified were sourced. A list of the guidelines, clinical trials and health technology assessment websites searched can be found in Appendix 4. Additional papers identified from personal files and the reference lists of included papers were also sourced.

After removal of duplicate citations and the addition of further citations sourced, a total of 427 citations remained. The titles and abstracts of these citations were assessed by two independent reviewers to determine eligibility for the current review based on the criteria detailed above. Ineligible studies were classified using the exclusion criteria below. For citations where insufficient detail for inclusion/exclusion was provided in the abstract, the full paper was retrieved and assessed. After application of inclusion/exclusion criteria, 54 citations remained for full text assessment (see Appendix 3).

### Exclusion criteria

- Not an original clinical study – publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters.

- Wrong population – studies conducted in a population other than women with operable breast cancer.
- Wrong intervention – studies not investigating the effect of taxanes as neoadjuvant therapy.
- Wrong design – not a RCT.
- Not a phase III trial.
- Not published in the English language.

The full text of the remaining 54 citations were retrieved and assessed to identify which met the inclusion criteria for the review. After full text assessment 20 citations were identified as eligible for the current review and the remaining 34 citations were classified as ineligible. Of the included citations, three systematic reviews and eight trials were identified (some trials were reported by multiple citations).

## **QUALITY ASSESSMENT**

The three systematic reviews and eight trials included in the review were assessed for quality. This involved assessment of specific aspects of the studies according to the NSW Health Method for Evaluating Research Guideline Evidence (MERGE) tool. Aspects of systematic reviews which were assessed included the adequacy of the search strategy used, whether study quality assessment was performed and whether a point estimate was calculated. Aspects of the studies which were assessed included randomisation and allocation concealment methods, consideration of benefits and harms, and how well potential bias was minimised.

Two of the three systematic reviews provided enough information to determine that the methods used were of sound methodological quality. One systematic review was reported only in abstract form so there was not enough information to perform quality assessment.

All trials included were randomised controlled trials; however, the method of allocation and/or allocation concealment to study arms was often not reported. The baseline patient characteristics were well balanced between study arms for all trials. Many trials stratified study arms by age, size of tumour and nodal status. It is unlikely that the trials included are influenced by bias or confounding factors.

## **DATA EXTRACTION**

Data extraction was performed independently by two reviewers and then checked by a third reviewer to ensure accuracy/consistency. Any discrepancies were discussed by all three reviewers until a consensus decision was made. Where multiple citations existed for one trial, data was extracted from the latest available publication. However, if additional information of

interest was reported in a previous publication this was also included. Descriptive data extracted from the studies included characteristics such as patient population, taxane used, chemotherapy regimen and primary end points. Outcome data extracted from the studies included OS, DFS, relapse-free survival, response rates (including both clinical and pathological), and BCT. Toxicity data was extracted including aspects such as neutropenia, vomiting, nausea, stomatitis and diarrhoea.

# RESULTS

## INTERNATIONAL GUIDELINES

In addition to the literature search, various international guidelines websites were searched to identify existing guidelines on the topic of neoadjuvant taxanes in early breast cancer and one guideline was identified.

### **Cancer Care Ontario<sup>13</sup>**

The program in evidence-based care for Cancer Care Ontario (CCO) in Canada released a practice guideline report in December 2004: *The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer*<sup>13</sup>

Recommendations from this guideline include that a neoadjuvant taxane should be offered when neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or doxorubicin and cyclophosphamide (AC) chemotherapy regimens are being considered for treatment of non-metastatic breast cancer. The following regimens are recommended:

- Paclitaxel (80mg/m<sup>2</sup>), administered weekly for 12 weeks prior to the anthracycline-based regimen.
- Docetaxel (100mg/m<sup>2</sup>), administered every three weeks for four cycles following the anthracycline-based regimen.

The guidelines state that, at the time of publication, there was no evidence to suggest that one taxane is superior to the other in the neoadjuvant setting.

## SYSTEMATIC REVIEWS

Three systematic reviews were identified as eligible for this review. Two reviews were reported as full papers and one was reported only as an abstract. One of the systematic reviews is a publication based on the original NBCC review on taxanes.<sup>12</sup> The paper by Trudeau *et al*<sup>14</sup> resulted from the systematic review conducted by the Cancer Care Ontario Program (Canada) to support their guidelines<sup>13</sup> on the neoadjuvant use of taxanes in early breast cancer. The third review by Felici *et al*<sup>15</sup> was presented at the 2005 ASCO meeting and is available as an abstract only.

Characteristics of these reviews are shown in Table 1. Each review will be considered in turn.

**Table 1. Characteristics of included systematic reviews**

Review Citation	Population	Research Question	Outcomes	Included Studies
Nowak et al., 2004 <sup>12</sup>	<ul style="list-style-type: none"> <li>• Early breast cancer, locally advanced</li> <li>• Stage I-II, I-III A, or III A-III B</li> <li>• T1-3 N0-1 M0 or T3-4 TxN2 M0</li> </ul>	Neoadjuvant treatment with taxane vs. neoadjuvant treatment without taxane	pCR, cCR, RFS, OS	5 trials 3 full papers 2 abstracts
Trudeau et al., 2005 <sup>14</sup>	<ul style="list-style-type: none"> <li>• Non-metastatic breast cancer</li> </ul>	<ul style="list-style-type: none"> <li>• Neoadjuvant taxane vs. other neoadjuvant regimen</li> <li>• Neoadjuvant taxane vs. adjuvant taxane</li> <li>• Taxane dose/scheduling comparisons</li> </ul>	Efficacy, toxicity, response rates	18 trials
Felici et al., 2005 <sup>15</sup>	Not reported	Neoadjuvant treatment with taxane vs. neoadjuvant treatment without taxane	Response rates, toxicity	10 trials

Note: cCR=clinical complete response, OS=overall survival, pCR=pathologically complete response rate, RFS=relapse free survival

### **NBCC Review<sup>12</sup>**

The paper by Nowak and colleagues was based on a NBCC review on the adjuvant and neoadjuvant use of taxanes for early and locally advanced breast cancer.<sup>13</sup> The literature search was conducted in 2003 on the Cochrane specialised breast cancer register. Abstracts from the ASCO and SABCS 2003 conference proceedings were also included. Only the neoadjuvant analyses will be discussed here.

Five neoadjuvant trials were included in this review, three reported as full papers, two reported as abstracts only. The review reports on information of the included trials separately.

Pathological and clinical response rates for included trials were discussed. At the time of publication of this review, none of the trials had reported on survival.

The authors concluded that if neoadjuvant therapy is to be used that combination regimens including a taxane are active and are a reasonable option. It was noted that the results presented in the review were “immature and do not yet warrant the adoption of taxanes as best standard practice”.

### **Cancer Care Ontario review<sup>14</sup>**

The paper by Trudeau *et al*<sup>14</sup> resulted from an evidence-based review conducted to support the Cancer Care Ontario guidelines on the neoadjuvant use of taxanes for early breast cancer

published in 2004. The literature search for this review was conducted in December 2004. Electronic databases Medline and EMBASE were searched for meta-analyses, RCTs and practice guidelines linking key terms for breast cancer, neoadjuvant chemotherapy and taxanes. ASCO and SABCS conference proceedings were also searched. Eighteen RCTs were considered eligible; however, this evidence review included phase II studies which were excluded from our current review. Trials investigating paclitaxel or docetaxel were reported separately. The eligible trials were categorised into three groups:

- neoadjuvant taxane regimens vs. other neoadjuvant regimens
- neoadjuvant taxane regimens vs. adjuvant taxane regimens
- taxane dose and/or schedule comparisons.

Ten trials were considered in the first group, four of which were phase II trials.

Reported outcomes included rates of clinical response, pathologic response, breast conservation, DFS and OS. The review concluded that some women with non-metastatic breast cancer could benefit from the use of neoadjuvant taxane therapy, in sequence with an anthracycline regimen, due to maximising local response rates.

One trial was identified regarding the question of neoadjuvant vs. adjuvant use of taxanes: the ECTO trial. As only preliminary information was available for this trial, the authors concluded that there was insufficient evidence to suggest the use of taxanes in the neoadjuvant setting is superior to taxanes in the adjuvant setting.

Seven trials were reported which investigated various taxane doses or schedule comparisons. Trials addressing sequential vs. combination therapy/longer vs. shorter chemotherapy, and weekly vs. three-weekly schedules were reported. The authors reported that:

- no conclusion could be made regarding the superiority of sequential vs. combination anthracycline-taxane regimens
- that there is evidence to suggest that six cycles of taxane therapy (in sequence with an anthracycline) are superior to combination therapy for fewer cycles
- while data regarding weekly vs. three-weekly regimens are immature, paclitaxel may be administered weekly; however, weekly docetaxel has not been shown to be superior to the three-weekly regimen.

### **Italian review<sup>15</sup>**

A pooled analysis by Felici *et al* on taxanes as neoadjuvant chemotherapy for breast cancer was presented at the ASCO meeting in 2005, and information for this review was available as an abstract only. Although there is no indication on the patient population (other than breast cancer), it is likely that RCTs included data from patients with locally advanced and/or inflammatory breast cancer. The review includes 10 RCTs which were published or presented between 1998 and

2004, including a total of 3120 patients. The review concluded that neoadjuvant taxanes increase pathological complete response (RR: 1.60; 95% CI: 1.35, 1.90;  $p < 0.001$ ) and the clinical complete response (RR: 1.48; 95% CI: 1.34, 1.62;  $p < 0.001$ ) based on information from nine trials. Based on the results from six trials, no difference was found for the rate of conservative surgery (RR: 1.05; 95% CI: 0.96, 1.14;  $p = 0.24$ ). No difference was seen regarding the axilla nodal complete response (RR: 1.06; 95% CI: 0.98, 1.15;  $p = 0.13$ ), based on the results from five trials. Three trials reported on grade III or IV febrile neutropenia which was increased in patients given taxanes (RR: 2.86; 95% CI: 2.25, 3.64;  $p < 0.001$ ).

## **INCLUDED STUDIES**

Eight RCTs were identified as eligible for this review. Six of the trials are available as full text publications;<sup>2, 3, 5-7, 9, 11, 16</sup> however, two of the trials have only been published in abstract form.<sup>4, 8</sup>

Many of the papers identified have been included in the previous systematic reviews. The current review provides additional information as the latest publication from the NSABP B-27 trial<sup>5</sup> and information from two additional trials, Dieras 2004<sup>3</sup> and Learn 2004,<sup>7</sup> have been included.

Two studies which included locally advanced and/or inflammatory breast cancer patients were included in the review as the majority of patients enrolled in the trial were considered operable (Aberdeen<sup>9, 10</sup> and ACCOG<sup>6</sup> trials).

Three studies investigated paclitaxel<sup>2-4</sup> the other five investigated docetaxel.<sup>5-9</sup> Six studies used an anthracycline (doxorubicin or epirubicin) in both the taxane and non-taxane arms. One study investigated the single use of paclitaxel compared to combination chemotherapy.<sup>2</sup> One study compared the use of docetaxel and capecitabine with doxorubicin and cyclophosphamide.<sup>8</sup> Characteristics of the included studies are summarised in Table 2.

**Table 2. Characteristics of included studies**

Study Citation	Country	Population	Taxane arm	Control arm	Outcomes
NSABP B-27, Bear 2006 <sup>5</sup> , 2003 <sup>11</sup>	US	<ul style="list-style-type: none"> <li>•N=1605</li> <li>•clinical stage T1C-3 N0-1 M0 or T1-3 N1 M0</li> </ul>	AC + D	AC	DFS, OS
MDACC, Buzdar 1999 <sup>2</sup> , 1997 <sup>16</sup>	US	<ul style="list-style-type: none"> <li>•N=174</li> <li>•age: 22-68 yrs</li> <li>•T1-3 N0-1 M0, invasive but non-inflammatory</li> </ul>	P	FAC	DFS
Dieras 2004 <sup>3</sup>	Europe	<ul style="list-style-type: none"> <li>•N=200</li> <li>•age: 28-66 yrs</li> <li>•65% hormone receptor positive</li> <li>•nodal status: T2: 63%, T3: 38%, N0: 42%, N1: 58%, M0: 100%</li> <li>•SBR grade: I: 9.5%, II: 43%, III: 7.5%</li> </ul>	AP	AC	pCR, cCR
Learn 2005 <sup>7</sup>	US	<ul style="list-style-type: none"> <li>•N=144</li> <li>•age: 27-73 yrs</li> <li>•nodal status: 38.7% positive, 61.3% negative</li> <li>•pre-treatment AJCC stages: I = 23.6%, IIA: 39.6%, IIB: 30.6%, IIIA: 6.3%</li> </ul>	AC/Tmx + D	AC/Tmx	cPOS, clinical responses
Malamos 1998 <sup>4</sup>	Greece	<ul style="list-style-type: none"> <li>•N=35</li> <li>•age: 35-70 yrs</li> <li>•operable breast cancer</li> </ul>	PE	FEC	pCR and cCR
Lee 2004 <sup>8</sup>	Korea	<ul style="list-style-type: none"> <li>•N=78</li> <li>•age: 21-66 yrs</li> <li>•stage II/III breast cancer</li> </ul>	DX	AC	Efficacy and toxicity
ACCOG, Evans 2005 <sup>6</sup>	UK	<ul style="list-style-type: none"> <li>•N=363</li> <li>•age: 25-74yrs</li> <li>•large primary (≥3cm) tumours, inflammatory or LABC. 77% considered operable by mastectomy, 15% inflammatory, 8% inoperable LABC</li> </ul>	AD	AC	pCR
Aberdeen <sup>9, 10</sup>	UK	<ul style="list-style-type: none"> <li>•N=162</li> <li>•age: 28-75yrs</li> <li>•large (≥3cm) or locally advanced (T3-4 or N2)</li> </ul>	CVAPr (4 cycles) → D (4 cycles)	CVAPr (8 cycles)	pCR

Notes:  
A=doxorubicin,  
C=cyclophosphamide,  
D=docetaxel,  
E=epirubicin,  
F=flourouracil,  
P=paclitaxel,  
Pr=prednisone,  
Tmx=taxane,  
ifn, interferon

V=vincristine, X=capecitabine

## Description of included studies

### NSABP B-27 trial<sup>5, 11</sup>

This US study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) is the largest trial on the neoadjuvant use of taxanes in women with operable breast cancer

reported in this review. The study recruited 2411 women with information available for 2404 patients at the median follow-up of 77.9 months.

This study contained three arms:

- i) four cycles of preoperative anthracycline (60mg/m<sup>2</sup>) and cyclophosphamide (600mg/m<sup>2</sup>) every three weeks (n=802)
- ii) preoperative AC as in group i) followed by four cycles of docetaxel (100mg/m<sup>2</sup>) every three weeks followed by surgery (n=803)
- iii) preoperative AC as in group i) followed by surgery then four cycles of postoperative docetaxel (100mg/m<sup>2</sup>) (n=799).

Tamoxifen (20mg/d for 5 years) was initiated on the first day of chemotherapy regardless of hormone receptor status. For this review the comparison of arms i) and ii) are of interest, however toxicity data is reported with combined results from both taxane arms (arms ii) + iii)) compared to the control group (arm i)). This study investigated overall and disease-free survival as well as response rates.

### **MD Anderson Cancer Centre (MDACC)<sup>2, 16</sup>**

This study reported by Buzdar *et al.*<sup>16</sup> investigated the single agent use of a taxane (paclitaxel, 250mg/m<sup>2</sup>) compared with combination chemotherapy (flurouracil 500mg/m<sup>2</sup>, doxorubicin 50mg/m<sup>2</sup>, cyclophosphamide 500mg/m<sup>2</sup> (FAC)). One hundred and seventy four patients, enrolled between May 1994 and June 1998, were randomised to either paclitaxel (n=87) or to FAC (n=87) at three-weekly intervals. Each patient was given four cycles of neoadjuvant chemotherapy. Response rates, local therapy and toxicity were reported.

### **Dieras 2004<sup>3</sup>**

Two hundred patients with T2-3, N0-1, M0 disease were randomly assigned in a 2:1 ratio to neoadjuvant doxorubicin (60mg/m<sup>2</sup>) plus paclitaxel (200mg/m<sup>2</sup>) (n=133) or neoadjuvant doxorubicin (60mg/m<sup>2</sup>) plus cyclophosphamide (600mg/m<sup>2</sup>) (n=67). The primary outcome of interest was pathological complete response (pCR), DFS and toxicity were also reported. The investigators planned to assess whether pCR was an independent predictor of DFS and OS.

### **Learn 2005<sup>7</sup>**

While the primary study question being investigated in this paper was not relevant for this review (to evaluate the association of HER2/neu expression and response to neoadjuvant chemotherapy), this paper has been included for assessment as some information regarding response rates is provided. One hundred and forty-four patients were enrolled, ninety-seven patients were given four cycles of neoadjuvant doxorubicin (60mg/m<sup>2</sup>), cyclophosphamide (600mg/m<sup>2</sup>) and tamoxifen (60mg/m<sup>2</sup>) (AC/Tmx), and 47 were given the same neoadjuvant AC/Tmx regimen plus docetaxel (100mg/m<sup>2</sup>). Clinical positive responses (complete + partial

response) were reported as well as complete pathologic response. Rates of a positive clinical response (cPOS) were reported by cancer stage (differences in rates were accounted for mainly by patients with stage IIB and IIIA disease).

#### **Malamos 1998<sup>4</sup>**

This Greek study reported by Malamos *et al*<sup>4</sup> has been published as an abstract only. It is a small trial of only 35 patients who were randomised to either paclitaxel (200mg/m<sup>2</sup>) and epirubicin (75mg/m<sup>2</sup>) (PE) or fluorouracil (600mg/m<sup>2</sup>) and epirubicin (75mg/m<sup>2</sup>) and cyclophosphamide (600mg/m<sup>2</sup>) (FEC). The chemotherapy regimens were given every three weeks.

#### **Lee 2004<sup>8</sup>**

An interim analysis for a Korean study has been reported by Lee *et al* in an abstract, presented at ASCO in 2004. Seventy-eight patients with stage II or III breast cancer were enrolled between August 2002 and November 2003. Patients were randomised to either four cycles of neoadjuvant doxorubicin (60mg/m<sup>2</sup>) and cyclophosphamide (600mg/m<sup>2</sup>) (AC) or four cycles of docetaxel (75mg/m<sup>2</sup>) and capecitabine (1000mg/m<sup>2</sup>) (TX). The chemotherapy regimens were administered every three weeks. Results for clinical and pathological response rates are reported as well as severe adverse events.

#### **ACCOG trial<sup>6</sup>**

The Anglo-Celtic Cooperative Oncology Group (ACCOG)<sup>6</sup> study enrolled 363 patients from 25 centres in the UK, Ireland and Belgium. Patients with large (≥3cm), locally advanced or inflammatory breast cancer were included: 77% were considered operable, 8% had LABC and 15% had inflammatory breast cancer. Patients were randomised to either doxorubicin (60mg/m<sup>2</sup>) and cyclophosphamide (600mg/m<sup>2</sup>) or doxorubicin (50mg/m<sup>2</sup>) and docetaxel (75mg/m<sup>2</sup>). The chemotherapy regimens were given every three weeks. Response rates, relapse and survival were reported, as well as grade III/IV toxicity.

#### **Aberdeen trial<sup>9, 10</sup>**

Patients presenting to the Aberdeen Breast Centre,<sup>9, 10</sup> UK, with newly diagnosed large (≥ 3cm) or LABC (T3-4, N2) were enrolled in this study from July 1996 to March 1999. This trial had a unique study design. All patients were first given four cycles of cyclophosphamide (1000mg/m<sup>2</sup>), vincristine (1.5mg/m<sup>2</sup>), doxorubicin (50mg/m<sup>2</sup>) and prednisolone (40mg) (CVAPr) and those with a positive response (n=104) were then randomised to either a further four cycles of CVAPr (n=52) or four cycles of docetaxel (100mg/m<sup>2</sup>) (n=52). Those who did not respond to the initial treatment were automatically allocated to further treatment with docetaxel. Only results from the randomised arms are reported here. Fifty patients from the CVAPr arm, and 47 from the docetaxel arm completed the further four cycles of chemotherapy and underwent surgery. Study

arms were relatively well matched by TNM classification, with over 80% patients classified with either T2-3 or N0-1 disease. Response rates and toxicity were reported.

## **Outcomes**

Outcomes have been summarised and tabulated according to how they have been reported in the trials.

### **Overall survival**

OS has been reported in four trials (see Table 3). Three trials reported that overall survival did not differ significantly between treatment groups.<sup>3, 5, 6, 10</sup> The Aberdeen trial<sup>10</sup> reports that overall survival for the taxane group was 93% compared to 78% for the control group (p=0.04). However, as this trial contains relatively small numbers of participants, caution should be used when interpreting these results. The largest trial, NSABP B-27, reported 156 and 157 deaths in the taxane and control arms respectively (HR: 0.97; p=0.82).<sup>5</sup>

### **Disease-free survival**

DFS was reported in three trials.<sup>2, 3, 5</sup> The overall differences between the taxane and control arms were not considered statistically significant. Median follow-up ranged from 18 to 78 months.

For the NSABP trial,<sup>5</sup> events included in calculating the DFS include all recurrences (local, regional or distant), all clinically inoperable and residual disease at surgery, all second cancers and contralateral breast cancer and all deaths. The NSABP B-27 trial reported that there was no statistically significant difference in DFS overall between the neoadjuvant taxane and control arms (HR: 0.90; 95% CI: 0.76, 1.06; p=0.22).<sup>5</sup> However, this trial reported that in the subset of patients who had a partial clinical response to AC, a statistically significant increase in DFS was observed in patients given the additional neoadjuvant docetaxel compared to AC alone (HR: 0.71; 95% CI: 0.55, 0.91; p=0.007).<sup>5</sup>

The Dieras trial<sup>3</sup> calculated DFS from the day of random assignment until the date of first relapse or death (regardless of cause). At 18 months, DFS was 87% in the taxane group and 79% in the control group. It was noted at a median follow-up of 31 months that DFS was higher for patients with a complete pathological response, compared to those who did not have pCR (92% vs 69%).

DFS for the MDACC trial was estimated by the Kaplan-Meier method. At 2 years the DFS rates were 94% in the taxane arm compared to 89% for the control arm (p=0.44).<sup>2</sup>

### Relapse-free survival

Relapse-free survival was reported in four trials (see Table 3). Trends suggest that taxanes may be associated with improved relapse-free survival. However, in each trial this was not statistically significant. NSABP B-27 reported 231 events in the taxane arm compared to 258 events in the control arm (HR: 0.85; 95% CI: 0.71, 1.02;  $p=0.08$ ).<sup>5</sup> The ACCOG trial reported 45 events (24.6%) in the taxane arm compared to 55 events (30.6%) in the control arm and this difference was not statistically significant ( $p=0.20$ ).<sup>6</sup>

**Table 3. Relapses and deaths at most recent report**

Trial	N	Median follow-up (months)	Relapses			Deaths		
			Control n(%)	Taxane n(%)	p-value	Control n(%)	Taxane n(%)	p-value
NSABP B-27 <sup>5</sup>	2353	77.9	258	231	0.08	157	156	0.82
MDACC <sup>2</sup>	174	23	10	7	NR	NR	NR	NR
Dieras <sup>3</sup>	200	29.7 ctrl 31.3 txne	14 (21)	28 (21)	NR	6 (9)	12 (9)	NR
ACCOG <sup>6</sup>	363	32	55 (30.6)	45 (24.6)	0.20	28 (16)	25 (14)	0.57
Aberdeen <sup>10</sup>	97	65	NR	NR	NR	12	4	0.04

Notes: ctrl=control, NR=not reported, txne=taxane

### Response rates

Response rates were classified differently by each trial, especially clinical response. Clinical complete response was often classified as the clinical absence of primary tumour (and node involvement). A clinical partial response was often defined as  $\geq 50\%$  reduction of primary tumour.

Some trials reported on all levels of response (complete, partial, minor, stable, progression), whereas others reported clinical positive response rates (combined, complete and partial response rates). Complete response rates (pathological and clinical) and clinical positive response rates are reported in Table 4.

### Clinical response

Taxane-containing regimens obtained higher clinical complete response rates (cCR); however, differences between arms were not always statistically significant. cCR ranged from 3% to 64% in the taxane containing arms and 0% to 40% in the control arms.

Rates of overall clinical positive response (complete + partial) was higher in taxane-containing arms (range: 70% to 85%) than in control arms (range: 55% to 64%).

Some trials provided more detail on clinical response, reporting complete response, partial response, minor response, stable disease, and progressive disease (see Table 5).

**Table 4. Overview of response rates (clinical and pathological)**

Trial	Response Rates								
	Clinical Response Rates						Pathologic Response Rates		
	Complete			cPOS			Complete		
	Control n(%)	Taxane n(%)	p-value	Control n(%)	Taxane n(%)	p-value	Control n(%)	Taxane n(%)	p-value
<b>NSABP 27<sup>b,11</sup></b>	(40.1)	(63.6)	<0.001				(13.7)	(26.1)	<0.001
<b>MDACC<sup>2</sup></b>	(24)	(27)							
<b>Dieras<sup>3</sup></b>	5 (7)	20 (15)					4 (6)	11 (8)	
<b>Learn<sup>7</sup></b>				53 (55)	37 (82)		20 (21)	11 (24)	
<b>Malamos<sup>4</sup></b>	0	5 (31)					0	4 (25)	
<b>Lee<sup>8</sup></b>	1	1					(6.3)	(15.2)	0.43
<b>ACCOG<sup>6</sup></b>	30 (17)	37 (20)	0.42	110 (61)	129 (70)	0.06			
<b>Aberdeen<sup>9,10</sup></b>	17 (33)	29 (56)		33 (64)	44 (85)	0.03	8 (15)	16 (31)	0.06

Notes: cPOS=clinical positive response (complete + partial)

**Table 5. Breakdown of clinical response rates**

Trial	Clinical Response Rate n(%)									
	Complete		Partial		Minor		Stable disease		Progressive disease	
	Ctrl	Taxane	Ctrl	Taxane	Ctrl	Taxane	Ctrl	Taxane	Ctrl	Taxane
<b>MDACC<sup>2</sup></b>	(24)	(27)	(55)	(53)	(13)	(14)	(5)	(5)	(3)	(1)
<b>Dieras<sup>3</sup></b>	5 (7)	20 (15)	42 (63)	98 (74)	NR	NR	20 (30)	14 (11)	0	0
<b>Malamos<sup>4</sup></b>	0	5 (31)	7 (50)	9 (56)	NR	NR	5	2	1	0
<b>Lee<sup>8</sup></b>	1	1	23	28	1	3	4	1	3	0
<b>Aberdeen<sup>9</sup></b>	17 (33)	29 (56)	16 (31)	15 (29)	NR	NR	15 (29)	3 (6)	2 (3.5)	0

Notes: Ctrl=control, NR=not reported

Learn *et al*<sup>7</sup> report the cPOS rates for both HER-2/neu positive and negative tumours were similar for docetaxel containing regimens (78% and 81% respectively, p=0.99), however HER2/neu negative tumours did not respond as well to the doxorubicin and cyclophosphamide regimen compared to HER2/neu positive tumours (51% and 75% respectively, p=0.06).<sup>7</sup>

### Pathological response

Pathological complete response (pCR) rates were higher in taxane-containing arms (range: 8% to 31%) compared to control arms (range: 0% to 21%) (see Table 4). However, the NSABP B-27 trial was the only trial to report that the higher pCR rates observed in the taxane arm were statistically significant (26% vs 14%, p<0.001).<sup>11</sup> Rates in the Aberdeen trial approached statistical significance (31% vs 15%, p=0.06).<sup>10</sup>

### Breast conserving therapy

Rates of BCT were reported in five trials (see Table 6). Rates of BCT were higher in trials including only operable patients (range: 35% to 64%) compared to rates reported in the ACCOG trial<sup>6</sup> (20%) which included inflammatory and LABC patients. Three trials reported similar rates between taxane arms and control arms.<sup>2, 6, 11</sup> Two trials reported higher rates of BCT in taxane arms, however statistical significance was not reported.<sup>3, 8</sup>

**Table 6. Rates of breast conserving therapy**

Trial	Study arms		p-value
	Control n(%)	Taxane n(%)	
NSABP B-27 <sup>11</sup>	(61.6)	(63.7)	0.33
MDACC <sup>2</sup>	(35)	(46)	0.30
Dieras <sup>3</sup>	30 (45)	77 (58)	
Lee <sup>8</sup>	(56.2)	(63.6)	
ACCOG <sup>6</sup>	36 (20)	37 (20)	

### Toxicity/adverse events

Toxicity data were reported in six of the eight trials. Each trial provided varying amounts of information regarding the toxic effects of the neoadjuvant chemotherapy regimens used. Here we describe the most commonly reported toxic events (Table 7). The NSABP B-27 trial reported combined toxicity data from the neoadjuvant and adjuvant taxane arms of the study which could not be separated.<sup>11</sup> This data has still been included as it is unlikely that the toxicity profile of taxanes differs significantly when given in the neoadjuvant or adjuvant setting. The Aberdeen trial reported limited toxicity results and is not listed in the table.<sup>9</sup> Malamos *et al*<sup>4</sup> reported no major toxicities had been observed; however, two patients in the PE arm developed liver metastases and one patient in the FEC arm had developed bone metastases. The trials did not perform tests for statistical significance in relation to toxic events. Many of the trials reported small numbers of toxic events, so it is difficult to clearly identify differences in the toxicity profiles of taxane-containing regimens compared to the control regimens.

### Toxicities reported more often in taxane-containing regimens

Taxane arms were associated with higher rates of febrile neutropenia, with approximately three times as many occurrences compared to the control arm. Severe infection appeared to be higher in taxane arms. Neurotoxicity was defined differently between trials, often neurosensory and neuromotor effects reported separately. Overall neurotoxicity appeared to be reported more often in taxane-containing arms than in control arms; however, these events were reported in small numbers. Grade III/IV stomatitis, myalgia and arthralgia also appeared to be higher in the taxane arms.

## Toxicities reported more often in non-taxane containing regimens

Rates of nausea and vomiting were consistently at least two times higher in the control arms than the taxane arms.<sup>2, 3, 6, 11</sup>

The Aberdeen trial reported that fewer grade III or IV leukopenic (p=0.001) and granulocytopenic (p<0.001) events were experienced by patients given docetaxel compared to CVAPr in the latter four cycles.<sup>9</sup> The NSABP B-27 trial also reported more grade III or IV granulocytopenia in the control arm than the taxane arm (6.3% vs. 2.3%).<sup>11</sup>

**Table 7. Reported toxicity data**

Toxicities	Study arm n(%)	Trials				
		NSABP B-27 <sup>11*</sup>	MDACC <sup>2</sup>	Dieras <sup>3</sup>	Lee <sup>8</sup>	ACCOG <sup>6**</sup>
Febrile neutropenia	<i>Control</i>	176 (7.3)	(21)	0		23 (2)
	<i>Taxane</i>	336 (21.2)	(53)	15 (11)		63 (6)
Neutropenia – grade III or IV	<i>Control</i>			51 (76)	(94)	
	<i>Taxane</i>			127 (96)	(77)	
Nausea – grade III or IV	<i>Control</i>	(4.2)	(21)	7 (10)		20
	<i>Taxane</i>	(1)	(10)	4 (3)		8
Vomiting – grade III or IV	<i>Control</i>	(4.2)	(7)	8 (11)	(3)	23
	<i>Taxane</i>	(0.9)	(2)	4 (3)	NR	7
Infection – severe or grade III or IV	<i>Control</i>	(2.2)	(5)	0		
	<i>Taxane</i>	(6.9)	(9)	3 (2)		
Stomatitis – grade III or IV	<i>Control</i>	(1.3)	(16)	0		14
	<i>Taxane</i>	(2.6)	(13)	5 (4)		32
Myalgia – grade III	<i>Control</i>		(5)	1 (1)		
	<i>Taxane</i>		(25)	7 (5)		
Arthralgia – grade III	<i>Control</i>			0		0
	<i>Taxane</i>			5 (4)		3
Diarrhoea – grade III or IV	<i>Control</i>	10 (0.4)	(16)			1
	<i>Taxane</i>	10 (0.6)	(3)		(3)	5
Cardiotoxicity	<i>Control</i>		(6)	3		
	<i>Taxane</i>		(2)	3		
Neurotoxicity	<i>Control</i>		(1)	0		
	<i>Taxane</i>		(5)	2 (2)		

Notes: \*Toxicity data from NSABP trial combined results from neoadjuvant and adjuvant taxane study arms.

\*\* Toxicity data from ACCOG trial results based on number of cycles of chemotherapy (control arm n=991 cycles, taxane arm n=1001 cycles)

## Other toxicities

Cardiotoxicity was not reported consistently between trials. However, it appears that neither the taxane-containing regimens nor the standard chemotherapy caused many significant cardiovascular events.

The NSABP trial reported slightly more second cancers in the neoadjuvant taxane group compared to the control group (3.7% vs 2.1%).<sup>5</sup>

Many studies reported that there were no deaths caused by treatment in either treatment arm. The NSABP trial reported 7 deaths (0.4%) on the taxane arm which may have been caused by treatment compared to 3 (0.1%) in the control arm.<sup>11</sup>

### **Quality of life**

Quality of life data has not been reported in any of the trials.

## **ONGOING STUDIES**

The following clinical trials websites were searched to identify any additional studies which have not yet reported.

- Australian Clinical Trials Registry (ACTR) <http://www.actr.org.au/>
- Clinical Trials.gov <http://www.clinicaltrials.gov/>
- Current Controlled Trials <http://www.controlled-trials.com/>
- National Research Register <http://www.nrr.nhs.uk/>
- National Cancer Institute <http://www.cancer.gov/clinicaltrials>

Two studies<sup>17, 18</sup> were identified, both of which are currently recruiting study participants (see Table 8). The first trial plans to investigate the use of docetaxel compared to FEC (administered differently in each participating centre). The second trial is investigating the question of docetaxel given in sequence to AC or in combination.

**Table 8. Ongoing studies investigating taxane-containing neoadjuvant regimens**

Title	Location/s	Objectives	Treatment	Participants
<b>Combination chemotherapy followed by radiation therapy with or without surgery in treating women with locally advanced or inflammatory breast cancer</b>				
NCT00017095/ EORTC-10994/ BIG 00-01 <sup>17</sup>	International - Europe	To compare treatment arms and measure progression free survival  To measure distant metastasis-free survival, overall survival, clinical response, pathological response, toxicity	Arm I: • FEC 100: FEC received IV on day 1, then every three weeks for 6 courses • Canadian FEC: C received orally, E and F via IV, days 1 and 8, every 4 weeks for 6 courses • Tailored FEC: FEC IV day 1, G-CSF days 2-15, every 3 weeks for 6 courses  Arm II: D on days 1, 22, 43. E and D on days 64, 85, 106	<ul style="list-style-type: none"> <li>• N=1850</li> <li>• Females &lt;70 years</li> <li>• Locally advanced/inflammatory or large operable breast cancer</li> <li>• No prior chemotherapy or radiotherapy</li> </ul>
<b>Sequential vs upfront intensified neoadjuvant chemotherapy in patients with large resectable or locally advanced breast cancer</b>				
NCT00314977/ INTENS/IKO 2005-01/BOOG 2007-02 <sup>18</sup>	Netherlands	To assess whether AC → T or upfront TAC results in better pathological complete response rate  To explore dose-intensity, tolerability, the value of MRI in assessing response to treatment  To compare disease free survival and overall survival rates	Arm I: AC → D Arm II: DAC	<ul style="list-style-type: none"> <li>• N=200</li> <li>• Females 18–60 years</li> <li>• Large resectable or locally advanced breast cancer</li> <li>• No prior surgery, radiotherapy or chemotherapy</li> <li>• No history of breast cancer or other malignancy</li> </ul>

Notes: A=doxorubicin, C=cyclophosphamide, D=docetaxel, E=epirubicin, F=fluorouracil, G-CSF=filgrastim

# CONCLUSIONS

There does not appear to be an overall survival or disease free survival benefit of taxane-containing regimens compared to standard neoadjuvant chemotherapy for early breast cancer. There is a trend towards a benefit of taxane-containing regimens on relapse-free survival; however, further data is needed to determine if this is statistically significant. Taxane-containing regimens appear to achieve higher clinical and pathological response rates compared to non-taxane-containing regimens; however, the reported differences were only statistically significant in the NSABP B-27 trial. BCT is performed at least as often, after taxane-containing neoadjuvant chemotherapy is given compared to standard neoadjuvant chemotherapy. Patient preferences will influence the decision to have breast cancer therapy performed.

Toxicity data is reported differently between trials. Febrile neutropenia was reported most consistently between trials with higher rates reported in the taxane-containing arms compared to the control arms. Grade III or IV stomatitis, myalgia, and arthralgia appear to be more common in taxane-containing arms. Grade III or IV nausea, vomiting and granulocytopenia appear to be more common in non-taxane-containing arms. For some of these outcomes the number of events are small and not commonly reported between trials, and therefore it is difficult to determine whether the toxicity profiles differ between the taxane- and non-taxane-containing regimens.

# REFERENCES

1. Ferguson T, Wilcken N, Vagg R, Ghersi D and Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database of Systematic Reviews*. 2007; Issue 4: Art. No.: CD004421. DOI: 10.1002/14651858.CD004421.pub2. .
2. Buzdar AU, Singletary SE, Theriault RL, *et al*. Prospective evaluation of paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. *J Clin Oncol*. 1999;17(11):3412-7.
3. Dieras V, Fumoleau P, Romieu G, *et al*. Randomized parallel study of doxorubicin plus paclitaxel and doxorubicin plus cyclophosphamide as neoadjuvant treatment of patients with breast cancer. *J Clin Oncol*. 2004;22(24):4958-65.
4. Malamos N, Kosmas C, Antonopoulos MJ, *et al*. Prospective randomized study of neoadjuvant chemotherapy (NACT) with paclitaxel/epirubicin (PE) versus fluorouracil/epirubicin/cyclophosphamide (FEC) in operable stage II-IIIa breast cancer (BC). *Ann Oncol*. 1998;9(4).
5. Bear HD, Anderson S, Smith RE, *et al*. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2006;24(13):2019-27.
6. Evans TR, Yellowlees A, Foster E, *et al*. Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an anglo-celtic cooperative oncology group study. *J Clin Oncol*. 2005;23(13):2988-95.
7. Learn PA, Yeh IT, McNutt M, *et al*. HER-2/neu expression as a predictor of response to neoadjuvant docetaxel in patients with operable breast carcinoma. *Cancer*. 2005;103(11):2252-60.
8. Lee HG, Lee JJ, Jung KH, *et al*. Phase III randomized trial of primary chemotherapy with doxorubicin/cyclophosphamide (AC) vs docetaxel/capecitabine (TX) for stage II/III breast cancer (BC): Interim analysis. *J Clin Oncol ASCO Meeting*. 2004;22(14S suppl 15):607.
9. Smith IC, Heys SD, Hutcheon AW, *et al*. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol*. 2002;20(6):1456-66.
10. Hutcheon AW, Heys SD and Sarkar TK. Docetaxel primary chemotherapy in breast cancer: a five year update of the Aberdeen trial. *Breast Cancer Res Treat*. 2003;82(suppl 1):s6.
11. Bear HD, Anderson S, Brown A, *et al*. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2003;21(22):4165-74.
12. Nowak AK, Wilcken NR, Stockler MR, Hamilton A and Ghersi D. Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. *Lancet Oncol*. 2004;5(6):372-80.
13. Trudeau M, Sinclair S, Clemons M, Shelley W and members of the Breast Cancer Disease Site Group. *The role of taxanes in neoadjuvant chemotherapy for women with non-metastatic breast cancer (practice guideline report #1-20)*. Cancer Care Ontario, 2004.
14. Trudeau M, Sinclair SE and Clemons M. Neoadjuvant taxanes in the treatment of non-metastatic breast cancer: A systematic review. *Cancer Treat Rev*. 2005;31(4):283-302.

15. Felici A, Bria E, Ferretti G, *et al.* Taxanes as neoadjuvant chemotherapy (NAC) for breast cancer (BC): pooled analysis of 3120 patients (pts) enrolled in 10 randomized trials (RCTs). *J Clin Oncol ASCO Meeting*. 2005;23(16S suppl 1):682.
16. Buzdar AU, Hortobagyi GN, Asmar L, *et al.* Prospective randomized trial of paclitaxel alone versus 5-fluorouracil doxorubicin/cyclophosphamide as induction therapy in patients with operable breast cancer. *Semin Oncol*. 1997;24(5 SUPPL. 17):S17-34.
17. National Cancer Institute NCT00017095. Available online:  
<http://www.clinicaltrials.gov/ct2/show/NCT00017095?term=neoadjuvant+and+taxane+and+breast&rank=6> Access date: May 2007
18. National Cancer Institute NCT00314977.  
<http://clinicaltrials.gov/ct2/show/NCT00314977?term=neoadjuvant&rank=4> Access date: May 2007

# APPENDICES

## Appendix 1: Database search results

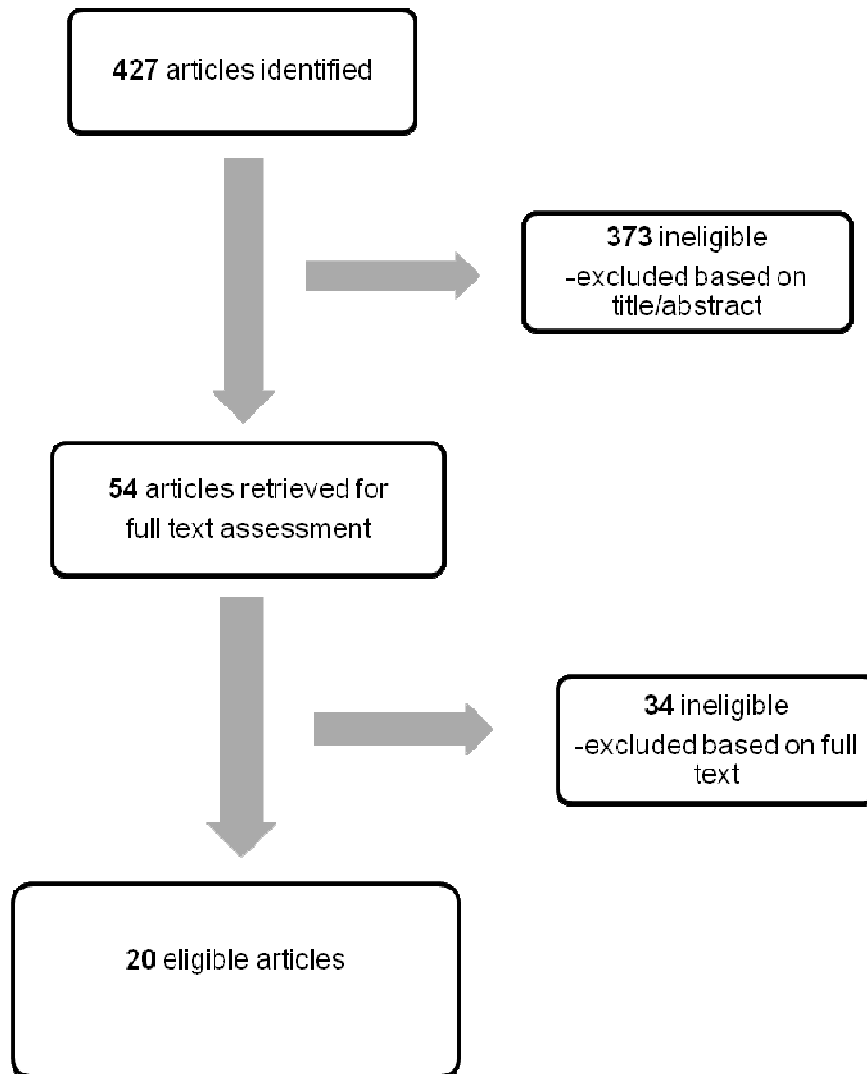
Source	Results/Retrievals
Medline (Ovid)	106
CINAHL (Ovid)	11
EBM Reviews (Ovid)	60
Embase	296
Pubmed	158
Additional Papers (sourced from reference lists and conference sites)	5

## Appendix 2: Search terms used in search strategies

Key areas	Search Terms
<b>Breast Cancer</b>	("breast neoplasms/" or "breast cancer" or "breast carcinoma" or (breast adj5 cancer))
<b>Neoadjuvant chemotherapy</b>	("induction chemotherapy" or "primary chemotherapy" or "preoperative chemotherapy" or "pre-operative chemotherapy" or "neoadjuvant chemotherapy" or "neo-adjuvant chemotherapy" or "neoadjuvant therapy/" or "neoadjuvant therapy" or "neo-adjuvant therapy" or ((neoadj\$ or neo-adj\$) and chemotherapy))
<b>Taxanes</b>	(taxiods/ or taxane\$ or paclitaxel/ or paclitaxel or taxol or docetaxel or taxotere)
<b>Randomized trials</b>	("randomized controlled trial" or "randomized controlled trials" or "randomised controlled trial\$" or "random\$" or "random allocation" or "controlled clinical trial" or "double blind method" or "single blind method" or "meta-analysis/" or "meta-analysis" or "meta analysis")

Notes: \* / indicates Mesh terms, \$ indicates truncated terms and adj5 indicates Boolean terms

**Appendix 3: Flowchart of Inclusion/Exclusion process**



#### Appendix 4: Sites searched

Country	Acronym	Organisation	Website
Australia	ACTR	Australian Clinical Trials Registry	<a href="http://www.actr.org.au/">http://www.actr.org.au/</a>
	ANZBCTG	Australian New Zealand Breast Cancer Trials Group	<a href="http://www.anzbctg.org/">http://www.anzbctg.org/</a>
	NICT	National Institute of Clinical Trials	<a href="http://www.nhmrc.gov.au/nics/asp/index.asp?">http://www.nhmrc.gov.au/nics/asp/index.asp?</a>
Canada	CCO	Cancer Care Ontario	<a href="http://www.cancercare.on.ca/">http://www.cancercare.on.ca/</a>
International	HTAi	Health Technology Assessment International	<a href="http://www.htai.org/">http://www.htai.org/</a>
Scotland	SIGN	Scottish Intercollegiate Guidelines Network	<a href="http://www.sign.ac.uk/">http://www.sign.ac.uk/</a>
UK	CRD	Centre for Reviews and Dissemination	<a href="http://www.york.ac.uk/inst/crd/">http://www.york.ac.uk/inst/crd/</a>
	CCT	Current Controlled Trials	<a href="http://www.controlled-trials.com/">http://www.controlled-trials.com/</a>
	NICE	National Institute for Health and Clinical Excellence	<a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a>
	NRR	National Research Register	<a href="http://www.nrr.nhs.uk/">http://www.nrr.nhs.uk/</a>
US		ClinicalTrials.gov	<a href="http://www.clinicaltrials.gov/">http://www.clinicaltrials.gov/</a>
	NCI	National Cancer Institute Clinical Trials	<a href="http://www.cancer.gov/clinicaltrials">http://www.cancer.gov/clinicaltrials</a>
	NGC	National Guideline Clearinghouse	<a href="http://www.guideline.gov/">http://www.guideline.gov/</a>