**Evidence-based Series 1-7 Version 2 - Education and Information**

**Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer**

*Members of the Breast Cancer Disease Site Group*

Evidence-based Series 1-7 Version 2 was put in the Education and Information Section in March 2015. The Breast Disease Site Group (DSG) made the decision that EBS 1-7 Version 2 will not be updated as it has been replaced by EBS 1-21- Optimal Systematic Therapy for Early Female Breast Cancer that include the more recent literature. The recommendations in EBS 1-7 Version 2 will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document

**(PEBC Assessment & Review Protocol)**

**Evidence-based Series (EBS) 1-7 Version 2**, the resulting review report, consists of the following 5 parts:

1. Guideline Report Overview
2. Section 1: Clinical Practice Guideline
3. Section 2: Systematic Review
4. Section 3: Guideline Development and External Review
5. Document Assessment and Review Tool

and is available on the [CCO Web site](http://www.cancercare.on.ca/) on the PEBC Breast Cancer DSG page

**Release Date: September 30, 2011**

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at [http://www.cancercare.on.ca/](http://www.cancercare.on.ca/) or contact the PEBC office at:

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Evidence-based Series 1-7 Version 2

Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer

Guideline Review Summary

Review Date: September 16, 2011

The 2006 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by Cancer Care Ontario’s Program in Evidence-based Care in January 2006 and was modified in December 2006. In July 2011, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Clinical Practice Guideline and Evidentiary Base in this version are the same as in the December 2006 version.

Update Strategy

Using the Document and Assessment Review Tool, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Compared with a standard anthracycline-based regimen (e.g., doxorubicin and cyclophosphamide [AC], 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC], 5-fluorouracil, epirubicin, and cyclophosphamide [500/100/500mg/m2] [FEC-100], or cyclophosphamide, epirubicin, 5-fluorouracil [75/60/100mg/m2] [CEF]), does a concurrent taxane-anthracycline regimen improve clinically meaningful outcomes (disease-free and overall survival)?
2. Compared with an anthracycline-based regimen, does a sequential taxane-anthracycline regimen improve clinically meaningful outcomes?

3. Compared with a standard (three-weekly) anthracycline-taxane regimen, does a dose-dense (two-weekly) regimen improve clinically meaningful outcomes?

4. Compared with an anthracycline-based regimen, does a non-anthracycline taxane regimen improve clinically meaningful outcomes?

5. What are the harms associated with adjuvant taxane regimens?

**Literature Search and New Evidence**

The new search (2006-April 2011) yielded 18 references representing two meta-analysis and 14 RCTs, of which 11 RCTs were already included in the existing guideline. Three randomized controlled trials (RCTs) (one abstract and two full text publications) are potentially new studies. Brief results of these publications are shown in the Document and Assessment Review Tool at the end of this report.

**Impact on Guidelines and Its Recommendations**

The new evidence supports the existing recommendations and increases support for taxane-containing regimens over anthracycline alone. Hence, the Breast Cancer DSG ENDORSED the 2006 recommendations on adjuvant taxane therapy for women with early-stage, invasive breast cancer.
Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Clinical Practice Guideline


A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)


Report Date: December 15, 2006

Guideline Questions
1. Compared with a standard anthracycline-based regimen (e.g., doxorubicin and cyclophosphamide [AC], 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC], 5-fluorouracil, epirubicin, and cyclophosphamide [500/100/500mg/m²] [FEC-100], or cyclophosphamide, epirubicin, 5-fluorouracil [75/60/100mg/m²] [CEF]), does a concurrent taxane-anthracycline regimen improve clinically meaningful outcomes (disease-free and overall survival)?
2. Compared with an anthracycline-based regimen, does a sequential taxane-anthracycline regimen improve clinically meaningful outcomes?
3. Compared with a standard (three-weekly) anthracycline-taxane regimen, does a dose-dense (two-weekly) regimen improve clinically meaningful outcomes?
4. Compared with an anthracycline-based regimen, does a non-anthracycline taxane regimen improve clinically meaningful outcomes?
5. What are the harms associated with adjuvant taxane regimens?

Target Population
Women with T 1-3, operable, node-positive breast cancer.
Recommendations and Key Evidence

SUMMARY RECOMMENDATION

The following taxane-containing regimens are considered reasonable treatment options for the target population:

- Six cycles of three-weekly docetaxel, doxorubicin, and cyclophosphamide (DAC) (75/50/500 mg/m²)
- Four cycles of doxorubicin and cyclophosphamide (AC) (60/600 mg/m²) followed by four cycles of paclitaxel (175 mg/m² or 225 mg/m² every three weeks or 175 mg/m² every two weeks with granulocyte colony-stimulating factor [G-CSF]).
- Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m²). These regimens are recommended over their non-taxane-containing counterparts (six cycles of FAC, four cycles of AC, or six cycles of FEC-100), as they have been shown to be superior in efficacy.

Qualifying Statements

- Taxane-containing counterparts to other commonly used non-taxane anthracycline regimens (e.g., CEF) have not yet been evaluated by randomized clinical trials. However, these non-taxane-containing regimens remain reasonable treatment options.

Six cycles of three-weekly DAC (75/50/500 mg/m²) is recommended over six-cycles of three-weekly FAC (500/50/500 mg/m²).

- In the analysis of the Breast Cancer International Research Group (BCIRG) 001 trial (1), (n=1,491) women receiving six cycles of three-weekly DAC experienced improved disease-free survival (DFS) (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.59 to 0.88, absolute difference at five years 7%, p<0.001) and overall survival (OS) (HR 0.70, 95% CI 0.53 to 0.91, absolute difference at five years 6%, p=0.0080) at a median follow-up of 55 months compared with women receiving six cycles of three-weekly FAC.

Qualifying Statements

- There are no data comparing epirubicin-based regimens such as FEC-100 or CEF to their epirubicin-containing and taxane-containing counterparts. There is also no evidence directly comparing 1) doxorubicin, cyclophosphamide, and a taxane to FEC-100 or CEF or 2) FAC to FEC-100 or CEF. Therefore, there are no grounds on which to base a recommendation as to which of FEC-100, CEF, or DAC may be preferable. However, in the case of FEC-100, see the recommendations for sequential anthracycline-taxane regimens below.

- Data is available from the European Cooperative Trial in Operable Breast Cancer (ECTO) in abstract form (2,3). This trial reported a significant benefit for the combination of doxorubicin and paclitaxel followed by CMF compared to doxorubicin alone followed by CMF. As neither of these regimens is commonly used in Ontario, no specific recommendation is made based on this trial.

- A meta-analysis of DFS and OS was conducted on five trials (1-8) of concurrent anthracycline-taxane regimens compared to their non-taxane containing counterparts. For DFS, the estimated summary HR was 0.82 (95% CI 0.71 to 0.94), with little statistical heterogeneity (x² test for heterogeneity p=0.16, I²=39.1%). For OS, the estimated summary HR was 0.84 (95% CI 0.66 to 1.08), with evidence of statistical heterogeneity (x² test for heterogeneity p=0.02, I²=65.1%). Based on the pattern of greater toxicity found in the studied concurrent regimens and the lack of a consistent OS benefit, no specific statement regarding the general value of using a taxane concurrently with an anthracycline-based regimen can be made at this time.
The inclusion of a taxane in sequence with an anthracycline-based regimen should be considered. The following regimens have been specifically studied in comparison to their non-anthracycline-containing counterparts and are recommended.

- Four cycles of three-weekly AC (60/600 mg/m²) followed by four cycles of three-weekly paclitaxel (175 mg/m² or 225 mg/m²) is recommended over four cycles of three-weekly AC alone (60/600 mg/m²).
- Three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m²) is recommended over six cycles of FEC-100 alone.

- A meta-analysis of DFS and OS was conducted on six trials (7-15) of sequential anthracycline-taxane regimens compared to their non-taxane-containing counterparts. For DFS, the estimated summary HR was 0.80 (95% CI 0.75 to 0.86), and for OS, it was 0.83 (95% CI 0.76 to 0.91). There was no statistical heterogeneity in either estimate (I²=0% for both estimates).

- At median follow-ups of 69 and approximately 64.6 months, DFS was improved in both the Cancer and Leukemia Group B (CALGB) 9344 trial (9) (n=3,170) (HR 0.83, 95% CI 0.73 to 0.94, absolute difference at five years 5%, p=0.0023) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 (13) (n=3,060) (HR 0.83, 95% CI 0.72 to 0.95, absolute difference at five years 4%, p=0.006) trial with the addition of four cycles of three-weekly paclitaxel (175mg/m² or 225mg/m²) following AC (60-90/600mg/m²). The CALGB 9344 trial detected improved OS (HR 0.82, 95% CI 0.71 to 0.95, absolute difference at five years 3%, p=0.0064) with the addition of paclitaxel, whereas the NSABP B-28 trial did not (HR 0.93, 95% CI 0.78 to 1.12, absolute difference at five years 0%, p=0.46). In unplanned subgroup analyses of the CALGB 9344 trial, the DFS benefit was most pronounced among women whose tumours were hormone receptor-negative, whereas in the NSABP B-28 trial, the opposite was true.

- In the Programmes d'Actions Concertées Sein (PACS) 01 trial (14,15) (n=1999), after a planned median follow-up of 60 months, five-year DFS was improved with a three-cycle FEC-100, three-cycle docetaxel regimen as opposed to a six-cycle FEC-100 regimen (absolute difference 5.1%; p=0.014).

**Qualifying Statements**
- The El Grupo Español de Investigación en Cáncer de Mama (GEICAM) 9906 trial (10,11) interim analysis published abstract reported a significant DFS benefit for FEC followed by paclitaxel compared to FEC alone. As these results are from an interim analysis, and the trial was not reported to have stopped early due to effect, no recommendation is made regarding this regimen at this time.
- The Breast International Group (BIG) 2-98 trial primary analysis published abstract reported a significant DFS benefit for doxorubicin followed by docetaxel followed by CMF compared to doxorubicin alone followed by CMF. As neither of these regimens is commonly used in Ontario, no specific recommendation is made based on this trial.
- Four cycles of three-weekly paclitaxel (250mg/m²) followed by four cycles of three-weekly to four-weekly FAC (500/50/500 mg/m²) (taxane [T]→FAC) may not be different from eight cycles of three-weekly to four-weekly FAC; however, data are only available from one small randomized trial (n=524) for which only the DFS was reported. In the M.D. Anderson Cancer Center (MDACC) trial (12) (n=524), there was a trend towards improved DFS (absolute difference, 3%; p=0.09) with four cycles of paclitaxel followed by four cycles of FAC versus eight cycles of FAC at a median follow-up of 60 months. OS was not reported.
Women in the target population should be considered for dose-dense therapy with doxorubicin and cyclophosphamide followed by paclitaxel. In practice, four cycles of two-weekly AC (60/600 mg/m\(^2\)) followed by four cycles of two-weekly paclitaxel (175 mg/m\(^2\)) (AC→T) is more commonly used due to a shorter duration of treatment.

G-CSF (days three to 10 of each cycle [a total of seven doses] at 5 μg/kg rounded to either 300 μg or 480 μg total dose) should be given in combination with four cycles of two-weekly AC→T to prevent neutropenia.

- In the Intergroup (INT) C9741 trial (16-18) (n=1,973), DFS was significantly improved in women who received G-CSF and four cycles of two-weekly A→T→C or AC→T compared with women who received the same regimens every three weeks at a median follow-up of 69 months (HR 0.80, 95% CI 0.62 to 0.96, p=0.018). At a median follow-up of 36 months, the absolute difference in four-year DFS was 7% (p=0.010).

**Qualifying Statements**
- To date no trial has investigated the relative efficacy of dose-dense AC→T with either standard anthracycline-based regimens (i.e., FEC-100, CEF), taxane-containing counterparts to those regimens, or other dose-dense regimens. Therefore, there are no grounds on which to base a recommendation as to which of these various regimens should be preferred.

Four cycles of three-weekly docetaxel and cyclophosphamide (75/600 mg/m\(^2\)) (DC) is recommended over four cycles of three-weekly AC (60/600 mg/m\(^2\)).

- In the U.S. Oncology (USON) 9735 trial (19-21), DFS was significantly improved in women treated with DC versus those treated with AC (HR 0.67, absolute difference at five years 6%, p=0.015). No significant difference was reported in OS (HR 0.76, absolute difference at five years 3%, p=0.131).

**Qualifying Statements**
- To date, no trial has compared a taxane-only regimen to either a concurrent or sequential anthracycline/taxane regimen, so there are no grounds on which to base a recommendation preferring one of these options.

Prophylactic G-CSF should be considered in patients receiving concurrent anthracycline/taxane regimens.

Women receiving an adjuvant anthracycline-taxane regimen should be closely monitored for febrile neutropenia. In those who experience febrile neutropenia while receiving DAC, G-CSF should be administered with subsequent docetaxel infusions. Alternatively, a dose reduction should be considered.

The Breast Cancer DSG considers the following G-CSF regimen to be reasonable for either prophylaxis for or treatment of febrile neutropenia: day three to ten of each cycle (a total of seven doses) at 5 μg/kg rounded to either 300 μg or 480 μg total dose.

Women receiving a taxane regimen should also be monitored for other toxicities, including diarrhea, stomatitis, amenorrhea, asthenia, myalgia, paresthesia, and leukopenia.

- Among trials of concurrent taxane-anthracycline therapy versus non-taxane anthracycline therapy, hematologic toxicity, particularly febrile neutropenia, was considerably higher on the taxane-containing arm. Rates of febrile neutropenia on the taxane-containing arm ranged from 24.6% to 40.8%, while, on the non-taxane-containing arm, they ranged from 2.5 to 10%. In the BCIRG 001 trial (1) of DAC versus FAC, grade 3+ neutropenia (65.5% versus [vs.] 49.3%, p<0.001), grade 3+ anemia (4.3% vs. 1.6%, p=0.003), and febrile
neutropenia (24.7% vs. 2.5%, p<0.001) were all significantly more frequent with DAC therapy. With regard to non-hematologic toxicity, grade 3+ nausea and vomiting were generally more frequent in the non-taxane-containing arm, while stomatitis/mucositis, diarrhea, and myalgia/arthralgia were more frequent in the taxane-containing arm.

- Among trials of sequential taxane-anthracycline therapy versus non-taxane anthracycline therapy, hematologic toxicity was mixed. The GEICAM 9906 trial (10-11) of FEC→T versus FEC found significantly less frequent grade 3+ neutropenia (20.5% vs. 30%, p=significant), grade 3+ leucopenia (7.4% vs. 10.6%, p=significant), and febrile neutropenia (5.1% vs. 9.3%, p=0.004) in patients receiving FEC→T. In contrast, the PACS 01 trial (14,15) of FEC→D versus FEC found more frequent febrile neutropenia on the taxane arm (4.6% vs. 1%, p=0.001). The CALGB 9344 trial (9) reported fewer occurrences of hematologic toxicity during the paclitaxel cycles of the AC→T arm than during the equivalent cycles of AC in the AC-only arm. With regard to grade 3+ non-hematologic toxicity, only the GEICAM 9906 trial (10-11) reported a significant difference, with the rate of mucositis being significantly higher in patients receiving FEC→T compared to FEC (3% vs. 5.4%, p=significant). Additionally, the MDACC trial (12) reported a higher rate of grade 3+ myalgia in patients treated with T→FAC compared to patients treated with FAC (1.5% vs. 12.5%), but a significance test was not reported. The PACS 01 trial (14-15) reported significantly more moderate to severe edema (4.8% vs. 0.3%, p=0.001) and moderate to severe nail disorders (10.3% vs. 1.0%, p<0.001) during the docetaxel cycles of the FEC→D regimen than in the equivalent cycles of the FEC-alone regimen.

- The INT C9741 trial (16-18) of dose-dense versus standard sequential doxorubicin and paclitaxel therapy reported a lower rate of grade 3+ neutropenia (5.9% vs. 12%, significance test not reported) with dose-dense AC→T versus standard AC→T. Also, grade 2+ anemia was significantly higher in patients receiving dose-dense AC→T (23%, p<0.0001) compared to patients receiving standard AC→T (8%). It is important to note that patients receiving dose-dense therapy in this trial received G-CSF prophylaxis.

- In the USON 9735 trial (19-21) of DC versus AC, docetaxel-related side effects, such as paresthesia, edema, weight gain, rash, and arthralgia, were more common with DC, whereas more anemia, vomiting, and stomatitis were associated with AC. Grade 3 and 4 leukopenia, infections, asthenia, and hair loss were similar. Febrile neutropenia was significantly more common among patients treated with DC compared to those treated with AC (6% vs. 3%, p=0.03).

Qualifying Statement

- It is the expert opinion of the Breast Cancer DSG that pegylated G-CSF may be a reasonable alternative to G-CSF in conjunction with non-dose-dense chemotherapy. If used, an appropriate dose is 6 mg, given once 24 hours after completion of chemotherapy.

Related Topics

Practice guidelines published by the PEBC on related topics (available at: http://www.cancercare.on.ca/):
- PG #1-8: Adjuvant Systemic Therapy for Node-Negative Breast Cancer.
- PG #1-20 The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer.
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REFERENCES


Evidence-based Series #1-7: Section 2

Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: A Systematic Review


A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Please see the EBS 1-7 Guideline Review Summary and the Document and Assessment Review Tool for a summary of updated evidence published between 2006 and 2011.

Report Date: December 15, 2006

QUESTIONS
1. Compared with a standard anthracycline-based regimen (e.g., doxorubicin and cyclophosphamide [AC], 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC], 5-fluorouracil, epirubicin, and cyclophosphamide [500/100/500mg/m²] [FEC-100], or cyclophosphamide, epirubicin, 5-fluorouracil [75/60/100mg/m²] [CEF]), does a concurrent taxane-anthracycline regimen improve clinically meaningful outcomes (disease-free and overall survival)?
2. Compared with an anthracycline-based regimen, does a sequential taxane-anthracycline regimen improve clinically meaningful outcomes?
3. Compared with a standard (three-weekly) anthracycline-taxane regimen, does a dose-dense (two-weekly) regimen improve clinically meaningful outcomes?
4. Compared with an anthracycline-based regimen, does a non-anthracycline taxane regimen improve clinically meaningful outcomes?
5. What are the harms associated with adjuvant taxane regimens?

INTRODUCTION
Breast cancer is the most frequently diagnosed cancer in Canadian women (1). During the year 2006 in Canada, an estimated 22,200 women will have been diagnosed with breast cancer, and 5,300 women will have died from the disease. Since 1993, breast cancer incidence rates have stabilized, and mortality rates have dropped (1). This decline in mortality, as well as a similar drop in disease recurrence, is largely due to the increased use of screening mammography and the widespread development and use of adjuvant systemic chemotherapy.
Three types of chemotherapy regimens predominate: standard-dose anthracycline doublets and triplets, escalated-dose epirubicin combinations, and anthracycline-taxane combinations. The taxanes (e.g., paclitaxel and docetaxel) comprise the class of mitotic inhibitors and are considered to be among the most powerful chemotherapy agents. Paclitaxel (Taxol®, Bristol-Myers Squibb) was initially isolated from the bark of the Pacific yew, Taxus brevifolia, in 1971. Docetaxel (Taxotere®, Aventis), a semi-synthetic analogue of paclitaxel, was subsequently synthesized from the needles of the European yew, Taxus baccata.

Due to the relatively recent emergence of taxanes, there is considerable uncertainty about their role, particularly in the adjuvant setting. Therefore, the Breast Cancer Disease Site Group (DSG) decided to develop a practice guideline on adjuvant taxane therapy for women with early-stage invasive breast cancer. Other adjuvant systemic guidelines are being developed concurrently. The Breast Cancer DSG anticipates combining those reports, at some point, to form a comprehensive practice guideline on adjuvant systemic therapy for early-stage invasive disease.

METHODS
This systematic review was developed by Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (2,3). Evidence was selected and reviewed by one member of the PEBC Breast Cancer DSG and one methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on adjuvant taxane therapy for women with early-stage, invasive breast cancer. The body of evidence in this review is primarily comprised of randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Breast Cancer DSG published as part of this evidence-based series. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy
MEDLINE (1966 to May 2006), EMBASE (1980 to May 2006), and the Cochrane Library (to May 2006) databases were searched. The MEDLINE and EMBASE search strategies are described in Table 1. The American Society of Clinical Oncology (ASCO) (1995 to 2006) and the San Antonio Breast Cancer Symposium (SABCS) (2001 to 2005) online conference proceedings were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Table 1: MEDLINE and EMBASE search strategies according to disease, treatment, and study design terms.

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<th>MEDLINE SEARCH STRATEGY</th>
<th>EMBASE SEARCH STRATEGY</th>
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<tr>
<td>DISEASE</td>
<td>BREAST NEOPLASMS[MeSH]</td>
<td>BREAST CANCER[DT]</td>
</tr>
<tr>
<td>STUDY DESIGN</td>
<td>META-ANALYSIS[PT] OR RANDOMIZED CONTROLLED TRIAL[PT]</td>
<td>META-ANALYSIS OR RANDOMIZED CONTROLLED TRIAL</td>
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</tbody>
</table>

Abbreviations: cb, drug combination; cm, drug comparison; dt, drug therapy; exp, explode; MeSH, medical subject heading; pt, publication type.
Inclusion Criteria
Articles were eligible for inclusion in this systematic review of the evidence if they met the following criteria:

- An adjuvant taxane regimen was evaluated in a phase III randomized controlled trial. Meta-analyses of phase III randomized controlled trials were also eligible.
- Reported outcomes included disease-free survival (DFS), overall survival (OS), or toxicity.
- Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. Those data often appear first in meeting abstracts and may not be published for several years (4).

Exclusion Criteria
Due to a lack of available translation resources, articles published in a language other than English were excluded.

Synthesizing the Evidence
When clinically homogeneous results from two or more trials were available, the data were pooled using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview © Update Software). Since hazard ratios (HR), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (5), those were extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CI), using the methods described by Parmar et al (5). A random effects model was used for all pooling.

Statistical heterogeneity was calculated using the $\chi^2$ test for heterogeneity and the $I^2$ percentage. A probability level for the $\chi^2$ statistic less than or equal to 10% (p≤0.10) and/or an $I^2$ greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95% CI. An HR >1.0 indicates that patients receiving a taxane had a higher probability of experiencing the presence of disease or death (DFS) or death (OS); conversely, an HR <1.0 suggests that patients receiving a taxane experienced a lower probability of an event.

RESULTS
Literature Search Results
Twenty-three randomized controlled phase III trials were identified (6-40) that met the inclusion and exclusion criteria. Of these trials, sixteen (6-10,12,15-17,19-22,24-28,30,31,33-40) reported DFS data; the remaining seven reported only toxicity data. Sixteen of these trials (7-11,13,16-18,21-24,27-37,39,40) have to date only been reported in abstract form and not in the peer-reviewed literature. The treatment arms and patient characteristics of these trials are summarized in Table 2, and other details about the trials are summarized in Table 3.

Outcomes
The DFS and OS data for each of the trials that reported this data is reported in Table 4. Key data regarding toxicity is reported in Tables 5 and 6. Additional relevant data from each trial is summarized below.
Table 2. Included trials of taxane containing regimens in the adjuvant therapy of breast cancer: information on size, year, and regimen.

<table>
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<tr>
<th>Trial</th>
<th>Concurrent/Sequential</th>
<th>Yrs. of Enroll.</th>
<th>Tmt. Arms (Pts)</th>
<th>Pt. Char.</th>
<th>Treatment Details</th>
<th>Other Systemic Therapy</th>
<th>G-CSF use</th>
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<td>BCIRG 001 (6)</td>
<td>Concurrent</td>
<td>1997 to 1999</td>
<td>DAC (745) FAC (746)</td>
<td>Ages 18 to 70, N+, no prior therapy with anth or tax.</td>
<td>DAC: A (50 mg/m²), C (500 mg/m²), D (75 mg/m²) on day 1 every 21 days for 6 cycles. FAC: A (50 mg/m²), F (500 mg/m²), C (500 mg/m²) on day 1 q 21 days for 6 cycles.</td>
<td>Tamoxifen (20 mg/day for 5 years) to ER+ patients.</td>
<td>Prophylaxis with G-CSF not permitted. G-CSF mandatory in patients with febrile neutropenia.</td>
</tr>
<tr>
<td>ECOG 2197 (7,8) [abstract]</td>
<td>Concurrent</td>
<td>1998 to 2000</td>
<td>(2889) AD AC</td>
<td>1-3 N+ or N- with tumour &gt; 1 cm.</td>
<td>AD: A (60 mg/m²), D (60 mg/m²) q 3 wks for 4 cycles. AC: A (60 mg/m²), C (600 mg/m²) q 3 wks for 4 cycles.</td>
<td>Tamoxifen for 5 years to ER+ and/or PR+ patients.</td>
<td>“per ASCO guidelines”</td>
</tr>
<tr>
<td>ECTO (9,10) [abstract]</td>
<td>Concurrent</td>
<td>1996 to 2002</td>
<td>AT–CMF (451) A–CMF (453)</td>
<td>Tumour ≥ 2 cm (T2-T3, N0-N1, M0).</td>
<td>AT–CMF: A (60 mg/m²), T (200 mg/m²) q 3 wks for 4 cycles followed by C (600 mg/m²), M (40 mg/m²), F (600 mg/m²) on days 1 and 8 q 4 weeks for 4 cycles. A–CMF: A (75 mg/m²) q 3 wks for 4 cycles followed by C, M, F as arm above.</td>
<td>Tamoxifen (20 mg/day for 5 years); originally offered to all patients after 30 June 2000 only to ER+ and/or PR+.</td>
<td>NR</td>
</tr>
<tr>
<td>GEICAM 9805 (11) [abstract]</td>
<td>Concurrent</td>
<td>1990 to NR</td>
<td>DAC (520) FAC (520)</td>
<td>Ages 18 to 70, High-risk N-</td>
<td>DAC: A (50 mg/m²), C (500 mg/m²), D (75 mg/m²) on day 1 every 21 days for 6 cycles. FAC: A (50 mg/m²), F (500 mg/m²), C (500 mg/m²) on day 1 q 3 wks for 6 cycles.</td>
<td>Tamoxifen (20 mg/day for 5 years) to ER+ and/or PR+ patients.</td>
<td>Initially, none reported. Amended after 224 patients enrolled to require prophylactic G-CSF.</td>
</tr>
<tr>
<td>Kümmel et al (12)</td>
<td>Sequential</td>
<td>1996 to 2000</td>
<td>ET–CMF (116) EC–CMF (115)</td>
<td>≥ 4 positive lymph nodes</td>
<td>ET–CMF (DD): E (90 mg/m²), T (175 mg/m²) q 14 days for 4 cycles followed by C (600 mg/m²), M (40 mg/m²), F (600 mg/m²) q 14 days for 3 cycles. EC–CMF: E, C q 21 days for 4 cycles followed by C, M, F q 21 days for 4 cycles, dosages as arm above.</td>
<td>Tamoxifen (20 mg/day for 5 years) to ER+ and/or PR+ patients.</td>
<td>G-CSF to all patients on ET–CMF (DD) arm, others received “if required.”</td>
</tr>
<tr>
<td>PACS 04 (13)</td>
<td>Sequential</td>
<td>NR</td>
<td>ED (1492) FEC (1518)</td>
<td>Age &lt; 65 years, N+, M0</td>
<td>ED: E (75 mg/m²), D (75 mg/m²) for 6 cycles. FEC: F (500 mg/m²), E (100 mg/m²), C (500 mg/m²) for 6 cycles.</td>
<td>Tamoxifen to hormone receptor positive patients. HER2/neu positive patients randomized to 1 year trastuzumab (6 mg/kg q 3 weeks) or observation.</td>
<td>G-CSF prophylaxis not planned.</td>
</tr>
<tr>
<td>RAPP-01 (14)</td>
<td>Sequential</td>
<td>1999 to 2003</td>
<td>AD (311) AC (316)</td>
<td>Ages 18 to 70, high risk N- or N+ ≤ 3.</td>
<td>AD: A (50 mg/m²), D (75 mg/m²) q 3 wks for 4 cycles. AC: A (60 mg/m²), C (600 mg/m²) q 3 wks for 4 cycles.</td>
<td>NR</td>
<td>Recommended only for grade 3 or 4 febrile neutropenia with temperature &gt;38°C and requiring antibiotics.</td>
</tr>
<tr>
<td>CALGB 9344 (15)</td>
<td>Sequential</td>
<td>1994 to 1999</td>
<td>AC–T (1590) AC (1580)</td>
<td>N+</td>
<td>AC–T: A (60/75/90 mg/m²)⁶, C (600 mg/m²) q 21 days for 4 cycles, followed by T (175 mg/m²) q 21 days for 4 cycles. AC: A, C as arm above.</td>
<td>Not mandated by protocol. 94% of hormone receptor positive and 21% of hormone receptor negative patients received tamoxifen.</td>
<td>Given routinely to patients receiving 90 mg/m² A, but only after febrile neutropenia to other patients.</td>
</tr>
<tr>
<td>Trial</td>
<td>Yrs. of Enroll.</td>
<td>Tmt. Arms (Pts)</td>
<td>Pt. Char.</td>
<td>Treatment Details</td>
<td>Other Systemic Therapy</td>
<td>G-CSF use</td>
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<tr>
<td>GEICAM 9906</td>
<td>2000 to 2002</td>
<td>FEC–T (634)</td>
<td>Ages 18 to 70, T1-3, pN1, M0</td>
<td><strong>FEC–T</strong>: F (600 mg/m²), E (90 mg/m²), C (600 mg/m²) on day 1 q 3 wks for 4 cycles, followed by T (100 mg/m²) q wk for 8 wks. F, E, C as arm above for 6 cycles.</td>
<td>Tamoxifen for 5 years to hormone receptor positive patients.</td>
<td>NR</td>
<td></td>
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<tr>
<td>(16,17,39)</td>
<td></td>
<td>FEC (614)</td>
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<tr>
<td>[abstract]</td>
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<tr>
<td>GOIM 9902</td>
<td>1999 to 2005</td>
<td>D–EC (376) EC (374)</td>
<td>Ages 18 to 70, pT1-3, pN1, M0</td>
<td><strong>D–EC</strong>: D (100 mg/m²) on day 1 q 21 days for 4 cycles, followed by E (120 mg/m²) C (600 mg/m²) on day 1 q 21 days for 4 cycles. E, C as arm above for 4 cycles.</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>(18) [abstract]</td>
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<tr>
<td>MDACC (19)</td>
<td>1994 to 1998</td>
<td>T–FAC (265) FAC (259)</td>
<td>T1-3, N0-1, M0.</td>
<td><strong>T–FAC</strong>: T (250 mg/m²) q 3 wks for 4 cycles, followed by F (500 mg/m² day 1 and 4), A (50 mg/m² continuous 72 hr infusion day 1-3), C (500 mg/m² day 1) q 3 to 4 wks for 4 cycles. FAC: F, A, C as arm above for 8 cycles.</td>
<td>Tamoxifen for 5 years to ER+ patients.</td>
<td>Given only to patients with febrile neutropenia.</td>
<td></td>
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<tr>
<td>NSABP B-28</td>
<td>1995 to 1998</td>
<td>AC–T (1531) AC (1529)</td>
<td>cT1-3, cN0-1, cM0</td>
<td><strong>AC–T</strong>: A (60 mg/m²), C (600 mg/m²) q 21 days for 4 cycles, followed by T (225 mg/m²) q 21 days for 4 cycles. AC: A, C as arm above for 4 cycles.</td>
<td>Tamoxifen (20 mg/day for 5 years) to ER+ and/or PR+ patients.</td>
<td>Prophylaxis with G-CSF not permitted. G-CSF mandatory after cycle with prolonged neutropenia, febrile neutropenia, or grade 3 to 4 infection.</td>
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<tr>
<td>(20) [abstract]</td>
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<tr>
<td>PACS 01</td>
<td>1997 to 2000</td>
<td>FEC–D (1003)</td>
<td>Age 19 to 64, T1-3, N+ (at least 5 nodes), M0</td>
<td><strong>FEC–D</strong>: F (500 mg/m²), E (100 mg/m²), C (500 mg/m²) q 21 days for 3 cycles, followed by D (100 mg/m²) q 21 days for 3 cycles. F, E, C, as arm above for 6 cycles.</td>
<td>Tamoxifen (20 mg/day for 5 years) to hormone receptor positive patients.</td>
<td>Prophylaxis with G-CSF not permitted. G-CSF prescribed in case of febrile neutropenia or delay in initiation at day 21. G-CSF not allowed for first D cycle.</td>
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<tr>
<td>(21,22) [abstract]</td>
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<td>FEC (996)</td>
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<tr>
<td>TACT (23)</td>
<td>NR (4192)</td>
<td>FEC–D</td>
<td>NR</td>
<td><strong>FEC–D</strong>: F, E, C for 4 cycles, followed by D for 4 cycles, dose and cycle length NR. F, E, C for 8 cycles, dose and cycle length NR. E–CMF: E for 4 cycles, followed by C, M, F for 4 cycles, dose and cycle length NR.</td>
<td>Yes, with regards to quality of life.</td>
<td>NR</td>
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<tr>
<td>[abstract]</td>
<td></td>
<td>FEC E–CMF</td>
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<tr>
<td>Taxit216</td>
<td>1998 to 2002</td>
<td>E–D–CMF (486)</td>
<td>N+</td>
<td><strong>E–D–CMF</strong>: E (120 mg/m²) on day 1 q 21 days for 4 cycles, followed by D (100 mg/m²) on day 1 q 21 days for 4 cycles, followed by C (600 mg/m²), M (40 mg/m² IV), F (600 mg/m²) on day 1 &amp; 8 q 28 days for 4 cycles. E–CMF: As arm above, except no D delivered between E and C, M, F cycles.</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>(24) [abstract]</td>
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<td>E–CMF (486)</td>
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<td>Dose-dense</td>
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<tr>
<td>INT C9741</td>
<td>1997 to 1999</td>
<td>A–T–E (484) AC–T–E (DD) (493)</td>
<td>T0-3, N1-2, M0.</td>
<td><strong>A–T–E</strong>: A (60 mg/m²) q 3 wks for 4 cycles followed by T (175 mg/m²) q 3 wks for 4 cycles followed by C (600 mg/m²) q 3 wks for 4 cycles. <strong>A–T–E(DD)</strong>: As A–T–E except q 2 wks instead of q 3 wks.</td>
<td>Tamoxifen (20 mg/day for 5 years) recommended but not required for hormone receptor positive cancers and all postmenopausal patients.</td>
<td>G-CSF given in all DD arms.</td>
<td></td>
</tr>
<tr>
<td>(25,26,38)</td>
<td></td>
<td>AC–T (501) AC–T (DD) (495)</td>
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</tbody>
</table>
## Treatment Details

<table>
<thead>
<tr>
<th>Trial</th>
<th>Yrs. of Enroll.</th>
<th>Tmt. Arms (Pts)</th>
<th>Pt. Char.</th>
<th>Treatment Details</th>
<th>Other Systemic Therapy</th>
<th>G-CSF use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Anthracycline</strong></td>
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<tr>
<td>USON 9734 (27,28,40) [abstract]</td>
<td>1997 to 1999</td>
<td>DC (506) AC (510)</td>
<td>Age &gt; 18 years, stage I, II, or operable stage III</td>
<td>AC: D (75 mg/m²), C (600 mg/m²) q 3 wks for 4 cycles. AC: A (60 mg/m²), C (600 mg/m²) q 3 wks for 4 cycles.</td>
<td>Tamoxifen to hormone receptor positive patients.</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Other Trials</strong></td>
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</tr>
<tr>
<td>BCIRG 005 (29) [abstract]</td>
<td>2000 to 2003</td>
<td>DAC (1649) AC–D (1649)</td>
<td>N+, HER2/neu negative</td>
<td>DAC: D (75 mg/m²), A (50 mg/m²), C (500 mg/m²) q 3 wks for 6 cycles. AC–D: D (60 mg/m²), C (600 mg/m²) q 3 wks for 4 cycles followed by D (100 mg/m²) q 3 wks for 4 cycles.</td>
<td>Hormonal therapy for 5 years to ER+ and/or PR+ patients.</td>
<td>G-CSF given as primary prophylaxis in some patients, protocol NR</td>
</tr>
<tr>
<td>BIG 2-98 (30,31) [abstract]</td>
<td>1998 to 2001</td>
<td>AD–GMF (481) A–D–GMF (487) A–GMF (960) AC–GMF (959)</td>
<td>Age &gt; 18 and &lt; 70 years, T1-3, N+</td>
<td>AD–GMF: A (50 mg/m²), D (75 mg/m²) for 4 cycles followed by C (100 mg/m²/ day 1-14), M (40 mg/m²/day 1 &amp; 8), F 600 mg/m²/ day 1 &amp; 8) q 28 days for 3 cycles. A–D–GMF: A (75 mg/m²) for 3 cycles followed by D (100 mg/m²) for 3 cycles followed by C, M, F as above. A–GMF: A (75 mg/m²) q 3 wks for 4 cycles followed by C, M, F as above. AC–GMF: A (60 mg/m²), C (600 mg/m²) for 4 cycles followed by C, M, F as above.</td>
<td>“received hormone-(receptor+)...therapy per local guideline.”</td>
<td>NR</td>
</tr>
<tr>
<td>Fountzilas et al (32) [abstract]</td>
<td>2000 to 2005</td>
<td>ET–GMF (521) E–T–GMF (538)</td>
<td>N+</td>
<td>ET–GMF: E (83 mg/m²), T (187 mg/m²) q 3 wks for 4 cycles followed by C, M, F q 2 wks for 3 cycles. E–T–GMF: E (110 mg/m²) q 2 wks for 3 cycles followed by T (250 mg/m²) q 2 wks for 3 cycles followed by C (840 mg/m²), M (57 mg/m²), F (840 mg/m²) q 2 wks for 3 cycles.</td>
<td>“...appropriate hormonal treatment [was] administered.”</td>
<td>G-CSF support provided in E–T–GMF arm.</td>
</tr>
<tr>
<td>INT E1199 (33,37) [abstract]</td>
<td>1999 to 2002</td>
<td>(4988) AC–T1, AC–T2, AC–T3, AC–D2</td>
<td>T1-3, N1-2, or T2-3, NO</td>
<td>AC: Same in all arms. A (60 mg/m²), C (600 mg/m²) q 3 wks for 4 cycles. T1: T (175 mg/m²) q 3 wks for 4 cycles. T2: T (175 mg/m²) q 3 wks for 4 cycles. T3: T (80 mg/m²) q wk for 12 wks. D: (100 mg/m²) q 3 wks for 4 cycles. D: D (35 mg/m²) q wk for 12 wks.</td>
<td>Hormonal therapy (either tamoxifen 20 mg/day or AI or tamoxifen followed by AI) for 5 years to ER+ and/or PR+ patients.</td>
<td>NR</td>
</tr>
<tr>
<td>Lambert-Falls et al (34) [abstract]</td>
<td>2000 to 2005</td>
<td>ETax (308) EC–Tax (309)</td>
<td>N+</td>
<td>ETax: E (75 mg/m²) and either T (175 mg/m²) or D (75 mg/m²), at physician’s discretion, q 21 days for 8 cycles. EC–Tax: E (90 mg/m²), C (600 mg/m²) q 21 days for 4 cycles followed by either T (175 mg/m²) or D (75 mg/m²), at physician’s discretion, q 21 days for 4 cycles.</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Loesch et al (35,36) [abstract]</td>
<td>2000 to 2002</td>
<td>AT–T (914) AC–T (916)</td>
<td>Age ≥ 18 years, (T1-3, N1-2, T2, N0, MO), or (T1c, N0, MO, ER-/PR-)</td>
<td>AT–T: A (50 mg/m²), T (200 mg/m²) q 3 wks for 4 cycles followed by T (80 mg/m²) q wk for 12 wks. AC–T: A (60 mg/m²), C (600 mg/m²) q 3 wks for 4 cycles followed by paclitaxel (175 mg/m²) q 3 wks for 4 cycles.</td>
<td>Tamoxifen for 5 years to hormone receptor positive patients.</td>
<td>NR</td>
</tr>
</tbody>
</table>

* The ECTO trial also included an additional preoperative AT–GMF arm that is not relevant to this document and is not reported here.
Additional details taken from a separate reference (41) that did not meet the inclusion criteria.

Additional details taken from an abstract of earlier results (42,43).

Patients were randomized to dose of A.

Abbreviations: → followed by; A, doxorubicin; AI, aromatase inhibitor; anth; anthracyclines; ACCOG, Anglo-Celtic Cooperative Oncology Group; BCIRG, Breast Cancer International Research Group; BIG, Breast International Group; C, cyclophosphamide; CALGB, Cancer and Leukemia Group B; D, docetaxel; DD, dose dense; E, epirubicin; ECOG; Eastern Cooperative Oncology Group; ECTO, European Cooperative Trial in Operable Breast Cancer; ER+, estrogen-receptor positive; F, fluorouracil; G-CSF, granulocyte colony-stimulating factor; GEICAM, El Grupo Español de Investigación en Cáncer de Mama; GOIM, Gruppo Oncologico Dell’italia Meridionale; INT, Intergroup; IV, intravenously; KPS, Karnofsky performance scale; M, methotrexate; MDACC, the University of Texas M. D. Anderson Cancer Center; N-, node negative; N+, node positive; NSABP, National Surgical Adjuvant Breast and Bowel Project; PACS, Programmes d’Actions Concertées Sein; PR+, progesterone-receptor positive; q, every; RAPP, Reposant sur des Arguments Pronostiques et Prédictifs; T, paclitaxel; TACT, Taxotere as Adjuvant Chemotherapy Trial; tax, taxanes; USON, U.S. Oncology; wks, weeks.
Table 3. Included trials of taxane containing regimens in the adjuvant therapy of breast cancer: information on trial design and execution.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of Trial and Analysis</th>
<th>Method of Randomization</th>
<th>Primary Outcomes</th>
<th>Expected Effect, Power, and Planned Sample Size</th>
<th>Achieved Sample Size?</th>
<th>ITT?</th>
<th>Correction for multiple analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent</td>
<td></td>
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<tr>
<td>BCIRG 001 (6)</td>
<td>Multicentre, Interim</td>
<td>Stratified by institution and number of positive nodes</td>
<td>DFS</td>
<td>27% reduction in risk of relapse, 97% power, 590 events</td>
<td>No, interim analysis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ECOG 2197 (7,8)</td>
<td>Multicentre, Primary</td>
<td>Stratified by nodal status, hormone receptor status, menopausal status</td>
<td>DFS</td>
<td>25% reduction in DFS hazard rate, 83% power, 2778 patients</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ECTO (9,10) [abstract]</td>
<td>Multicentre, NR</td>
<td>Done centrally using minimization algorithm to balance by tumour size, tumour grade and hormone receptor status.</td>
<td>FFP</td>
<td>30% FFP difference, 80% power, 450 patients per arm</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>GEICAM 9805 (11)</td>
<td>Multicentre, Interim, Safety only</td>
<td>Stratified by study center and menopausal status.</td>
<td>NR</td>
<td>N/A</td>
<td>NA, interim safety analysis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kümmel et al (12)</td>
<td>Multicentre, Primary</td>
<td>Permutated block randomization, stratified by center.</td>
<td>DFS</td>
<td>60% vs. 75% DFS at 5 years, 80% power, 121 patients per arm</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>PACS 04 (13)</td>
<td>Multicentre, Preliminary, safety only</td>
<td>Central randomization, stratified by age, tumour grade and hormone receptor status.</td>
<td>DFS</td>
<td>10% difference in 5-year DFS (one-sided alpha 5%), 80% power, 350 patients per arm</td>
<td>No, study terminated early due to serious adverse events</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sequential</td>
<td></td>
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<tr>
<td>CALGB 9344 (15)</td>
<td>Multicentre, Interim</td>
<td>Central randomization, stratified by nodal status.</td>
<td>DFS</td>
<td>No, interim analysis</td>
<td>NR</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>GEICAM 9906 (16,17,39)</td>
<td>Multicentre, Interim</td>
<td>Stratified by menopausal status, nodal status, center status.</td>
<td>DFS</td>
<td>No, planned interim analysis at 202 events</td>
<td>Yes</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>GOIM 9902 (18)</td>
<td>Multicentre, Toxicity only</td>
<td>Stratified by center, age, hormone receptor status, and nodal status.</td>
<td>DFS</td>
<td>N/A</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MDACC (19)</td>
<td>Single center, Primary</td>
<td>Stratified by age, tumour status, and nodal status.</td>
<td>5-year response</td>
<td>Absolute difference of 15% in five year response based on 60% DFS in FAC arm, 80% power, 518 patients</td>
<td>Yes</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Trial</td>
<td>Type of Trial and Analysis</td>
<td>Method of Randomization</td>
<td>Primary Outcomes</td>
<td>Expected Effect, Power, and Planned Sample Size</td>
<td>Achieved Sample Size?</td>
<td>ITT?</td>
<td>Correction for multiple analysis?</td>
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<tr>
<td>NSABP B-28 (20)</td>
<td>Multicentre, Primary</td>
<td>Stratified by nodal status, tamoxifen administration, type of surgery. Randomized using biased coin minimization algorithm.</td>
<td>DFS and OS</td>
<td>25% reduction in mortality rate, 80% power, 3050 patients</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PACS 01 (21,22)</td>
<td>Multicentre, Primary</td>
<td>Stratified by center, age, nodal status</td>
<td>5-year DFS</td>
<td>Absolute difference of 7.5% in five year DFS based on 65% DFS in FEC arm, 90% power, 2000 patients</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>TACT (23) [abstract]</td>
<td>Multicentre, Quality of Life only</td>
<td>Dynamic balancing algorithm with center, nodal status, ER status and menopausal status as balancing factors</td>
<td>DFS</td>
<td>HR 0.70 based on 5 yr DFS of 65% in non-D arm, 80% power, 480 pts per arm and 250 events</td>
<td>Yes</td>
<td>NA</td>
<td>NR</td>
</tr>
<tr>
<td>Taxit216 (24) [abstract]</td>
<td>Multicentre, Primary</td>
<td>Dynamic balancing algorithm with center, nodal status, ER status and menopausal status as balancing factors</td>
<td>DFS</td>
<td>HR 0.70 based on 5 yr DFS of 65% in non-D arm, 80% power, 480 pts per arm and 250 events</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Dose-dense</strong></td>
<td></td>
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</tr>
<tr>
<td>INT C9741 (25,26,38)</td>
<td>Multicentre, updated after primary</td>
<td>Stratified by nodal status and age</td>
<td>DFS</td>
<td>33% difference in hazard for either DD arms or concurrent vs. sequential, 90% power, 1584 pts</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td><strong>Non-Anthracycline</strong></td>
<td></td>
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<tr>
<td>USON 9734 (27,28,40)</td>
<td>Primary</td>
<td>Stratified by nodal status and age</td>
<td>DFS</td>
<td>10% improvement in DFS with taxane arm given 80% DFS in that arm, 90% power, 1016 patients</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Other Trials</strong></td>
<td></td>
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</tr>
<tr>
<td>BCIRG 005 (29)</td>
<td>Multicentre, Interim, Safety only</td>
<td>Stratified by nodal status and hormone receptor status</td>
<td>DFS</td>
<td>Absolute difference of 5%, 80% power, planned sample size NR</td>
<td>No, interim analysis</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>BIG 2-98 (30,31)</td>
<td>Multicentre, Primary</td>
<td>Unbalanced randomization 2:1 in favour of taxane arms, stratified by center, nodal status, and age</td>
<td>DFS (Taxane vs. non taxane)</td>
<td>Exp. Effect NR, Power NR, 1215 events</td>
<td>No, relapse rate slower than expected, protocol modified for final analysis at 810 events or 5 years, whichever comes first</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Systematic Review

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of Trial and Analysis</th>
<th>Method of Randomization</th>
<th>Primary Outcomes</th>
<th>Expected Effect, Power, and Planned Sample Size</th>
<th>Achieved Sample Size?</th>
<th>ITT?</th>
<th>Correction for multiple analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fountzilas et al (32) [abstract]</td>
<td>NR, Safety only</td>
<td>NR</td>
<td>DFS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>INT E1199 (33,37) [abstract]</td>
<td>Multicentre, Interim</td>
<td>Stratified by hormonal status, nodal status, tumour size, and type of surgery</td>
<td>DFS (both T vs. D and 3 week vs. weekly)</td>
<td>17.5% reduction in failure in either T vs. D or 3 week vs. weekly comparison; 86% power; 1042 events</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lambert-Falls et al (34) [abstract]</td>
<td>Primary</td>
<td>NR</td>
<td>DFS</td>
<td>0.10 increase in probability of DFS a 3 yrs for the ETax arm; 90% power, 300 patients per arm</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Loesch et al (35) [abstract]</td>
<td>Preliminary</td>
<td>Stratified by hormone receptor status and nodal status</td>
<td>DFS</td>
<td>25% decrease in HR of recurrence; 90% power, 1830 patients</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>

A Additional details taken from a separate reference (41) that did not meet the inclusion criteria.
B Additional details taken from an abstract of earlier results (42,43).
C Two-sided alpha value of 5% unless otherwise noted.

Abbreviations: BCIRG, Breast Cancer International Research Group; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; ECTO, European Cooperative Trial in Operable Breast Cancer; ER, estrogen receptor; Exp., expected; FFP, freedom from progression; GEICAM, El Grupo Español de Investigación en Cáncer de Mama; MDACC, the University of Texas M. D. Anderson Cancer Center; NA, not applicable; NR, not reported; OS, overall survival; PACS, Programmes d'Actions Concertées Sein; RAPP, Reposant sur des Arguments Pronostiques et Prédictifs; vs., versus.
### Table 4. Outcome measures from included trials of taxane containing regimens in the adjuvant therapy of breast cancer.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median f/u (months)</th>
<th>Arm&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DFS Estimate</th>
<th>Comparison</th>
<th>OS Estimate</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concurrent</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BCIRG 001 (6)</td>
<td>55</td>
<td>DAC vs. FAC</td>
<td>5 yrs: 75% vs. 68%</td>
<td>HR 0.72 (95% CI 0.59 to 0.88), p=0.001</td>
<td>5 yrs: 87% vs. 81%</td>
<td>HR 0.70 (95% CI 0.53 to 0.91), p=0.008</td>
</tr>
<tr>
<td>ECOG 2197 (7,8)</td>
<td>59</td>
<td>AD vs. AC</td>
<td>4 yrs: 87% vs. 87%</td>
<td>HR 0.93&lt;sup&gt;b&lt;/sup&gt; (95% CI 0.80 to 1.16), p=0.70</td>
<td>4 yrs: 94% vs. 93%</td>
<td>HR 0.92 (95% CI 0.71 to 1.18)</td>
</tr>
<tr>
<td>ECTO (9,10) [abstract]</td>
<td>43</td>
<td>AT–CMF vs. A–CMF</td>
<td>NR</td>
<td>HR 0.66, p=0.012&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 yrs: 91% vs. 87%</td>
<td>HR 0.71, p=0.16</td>
</tr>
<tr>
<td>Kümmel et al (12)</td>
<td>38.4</td>
<td>ET–CMF (DD) vs. EC–CMF</td>
<td>4 yrs: 64% vs. 58%</td>
<td>HR 0.76 (95% CI 0.47 to 1.22), p=0.12</td>
<td>4 yrs: 85% vs. 75%</td>
<td>HR 0.57 (95% CI 0.30 to 1.10), p=0.092</td>
</tr>
<tr>
<td><strong>Sequential</strong></td>
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<tr>
<td>CALGB 9344 (15)</td>
<td>69</td>
<td>AC–T vs. AC</td>
<td>5 yrs: 70% vs. 65%</td>
<td>HR 0.83 (95% CI 0.73 to 0.94), p=0.0023</td>
<td>5 yrs: 80% vs. 77%</td>
<td>HR 0.82 (95% CI 0.71 to 0.95), p=0.0064</td>
</tr>
<tr>
<td>GEICAM 9906 (16,17,39) [abstract]</td>
<td>47</td>
<td>FEC–T vs. FEC</td>
<td>86.9% vs. 79.2%</td>
<td>36% risk reduction, p=0.0009</td>
<td>94.5% vs. 91.8%</td>
<td>26% risk reduction, p=0.1375</td>
</tr>
<tr>
<td>MDACC (19)</td>
<td>60</td>
<td>T–FAC vs. FAC</td>
<td>4 yrs: 86% vs. 83%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HR 0.70 (95% CI 0.47 to 1.07), p=0.09&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>NSABP B-28 (20)</td>
<td>64.6</td>
<td>AC–T vs. AC</td>
<td>5 yrs: 76% vs. 72%</td>
<td>HR 0.83 (95% CI 0.72 to 0.95), p=0.006</td>
<td>5 yrs: 85% vs. 85%</td>
<td>HR 0.93 (95% CI 0.78 to 1.12), p=0.46</td>
</tr>
<tr>
<td>PACS 01 (21,22)</td>
<td>59.7</td>
<td>FEC–D vs. FEC</td>
<td>5 yrs: 78.3% vs. 73.2%</td>
<td>HR 0.83 (95% CI 0.69 to 0.99), p=0.014&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5 yrs: 90.7% vs. 86.7%</td>
<td>HR 0.77 (95% CI 0.59 to 1.00), p=0.017&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Taxit216 (24)</td>
<td>53</td>
<td>E–CMF vs. E–CMF</td>
<td>5 yrs: 74% vs. 67%</td>
<td>HR 0.80 (95% CI 0.62 to 1.03), p=0.079</td>
<td>NR</td>
<td>HR 0.74 (95% CI 0.51 to 1.07), p=0.10</td>
</tr>
<tr>
<td><strong>Dose-dense</strong></td>
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<tr>
<td>INT C9741 (25,26,38)</td>
<td>78</td>
<td>DD&lt;sup&gt;f&lt;/sup&gt; vs. Standard&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>HR 0.80 (95% CI 0.67 to 0.95)&lt;sup&gt;e&lt;/sup&gt;, p=0.012</td>
<td>NR</td>
<td>HR 0.85&lt;sup&gt;f&lt;/sup&gt; (95% CI 0.68 to 1.05), p=0.12</td>
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<tr>
<td><strong>Non-Anthracycline</strong></td>
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<tr>
<td>USON 9734 (27,28,40) [abstract]</td>
<td>66</td>
<td>DC vs. AC</td>
<td>5 yrs: 86% vs. 80%</td>
<td>HR 0.67, p=0.015</td>
<td>5 yrs: 90% vs. 87%</td>
<td>HR 0.76, p=0.131</td>
</tr>
<tr>
<td><strong>Other Trials</strong></td>
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<tr>
<td>BIG 2-98 (30,31)</td>
<td>62.2</td>
<td>Taxane&lt;sup&gt;e&lt;/sup&gt; vs. non-taxane&lt;sup&gt;e&lt;/sup&gt;</td>
<td>HR 0.86 (95% CI 0.74 to 1.00), p=0.051</td>
<td>HR 0.92 (95% CI 0.75 to 1.13), p=0.34</td>
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<tr>
<td></td>
<td></td>
<td>AD–CMF vs. AC–CMF</td>
<td>HR 0.93 (95% CI 0.75 to 1.14), p=0.48</td>
<td>HR 1.16 (95% CI 0.94 to 1.45), p=0.17</td>
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<tr>
<td></td>
<td></td>
<td>A–D–CMF vs. A–CMF</td>
<td>HR 0.83 (95% CI 0.69 to 1.00), p=0.047</td>
<td>HR 0.82 (95% CI 0.61 to 1.02), p=0.069</td>
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<tr>
<td></td>
<td></td>
<td>AD–CMF vs. AD–CMF</td>
<td>HR 0.83 (95% CI 0.69 to 1.00), p=0.047</td>
<td>HR 0.80 (95% CI 0.63 to 1.02), p=0.069</td>
<td></td>
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<tr>
<td>INT E1199 (33,37)</td>
<td>46.5</td>
<td>T vs. D</td>
<td>NR</td>
<td>HR 0.985, p=0.83</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td>3 week vs. weekly</td>
<td>NR</td>
<td>HR 1.043, p=0.54</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Trial</td>
<td>Median f/u (months)</td>
<td>Arm(^A)</td>
<td>DFS Estimate</td>
<td>Comparison</td>
<td>OS Estimate</td>
<td>Comparison</td>
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<tr>
<td>Lambert-Falls et al (34)</td>
<td>30</td>
<td>ETax vs. EC–Tax</td>
<td>16% vs. 18%</td>
<td>NR</td>
<td>9.4% vs. 11.0%</td>
<td>NR</td>
</tr>
<tr>
<td>Loesch et al (35, 36)</td>
<td>36</td>
<td>AT–T vs. AC–T</td>
<td>3 yrs: 88.4% vs. 84.6%</td>
<td>HR 0.74, p=0.05</td>
<td>3 yrs: 94.6% vs. 91.6%</td>
<td>HR 0.65, p=0.005</td>
</tr>
</tbody>
</table>

Note: HRs less than one favour the first listed arm.

\(^A\) See table 2 for explanation of abbreviations.
\(^b\) The inverse of reported HR is provided here, in order for all HRs to be comparable across studies.
\(^c\) Recurrence free survival.
\(^D\) Reported p-value is log-rank adjusted p-value. p-value for HRs: DFS p=0.041, OS p=0.50.
\(^E\) Freedom from progression.
\(^F\) The DD arm is the combination of the A–T–C(DD) and AC–T(DD) arms. The standard arm is the combination of the A–T–C and AC–T arms.
\(^G\) The taxane arm is the combination of the A–D–CMF and AD–CMF arms. The non-taxane arm is the combination of the A–CMF and AC–CMF arms.
\(^H\) At 69 months median follow-up.

Abbreviations: \(^\rightarrow\) followed by; A, doxorubicin; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; CI, confidence interval; D, docetaxel; DFS, disease-free survival; F, fluorouracil; f/u, follow-up; FFP, freedom from progression; HR, hazard ratio; M, methotrexate; MDACC, the University of Texas M. D. Anderson Cancer Center; OS, overall survival; PACS, Programmes d’Actions Concertées Sein; T, paclitaxel; vs., versus.
Table 5. Severe hematologic toxicity in included trials of taxane containing regimens in the adjuvant therapy of breast cancer.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>Gr 3/4 Neutropenia</th>
<th>Gr 3/4 Thrombocytopenia</th>
<th>Gr 3/4 Leukopenia</th>
<th>Gr 3/4 Anemia</th>
<th>Febrile Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concurrent</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BCIRG 001 (6)</td>
<td>DAC vs. FAC</td>
<td>65.5% vs. 49.3%, p&lt;0.001</td>
<td>2.0% vs. 1.2%, p=0.23</td>
<td>NR</td>
<td>4.3% vs. 1.6%, p=0.003</td>
<td>24.7% vs. 2.5%, p&lt;0.001</td>
</tr>
<tr>
<td>ECOG 2197 (7,8) [abstract]</td>
<td>AD vs. AC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>28% vs. 10%, p=NR</td>
</tr>
<tr>
<td>GEICAM 9805 (11) [abstract]</td>
<td>DAC vs. DAC-G-CSF vs. FAC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>24.6% vs. 5.8% vs. 2.3% p=NR</td>
</tr>
<tr>
<td>Kümmel et al (12)</td>
<td>ET=GMF(DD) vs. EC=GMF</td>
<td>63% vs. 65%, p=NR</td>
<td>3% vs. 0%, p=NR</td>
<td>44% vs. 49%, p=NR</td>
<td>4% vs. 1%, p=NR</td>
<td>NR</td>
</tr>
<tr>
<td>PACS 04 (13)</td>
<td>ED vs. FEC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>31.4% vs. 10.3%, p=NR</td>
</tr>
<tr>
<td>RAPP-01 (14)</td>
<td>AD vs. AC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>40.8% vs. 7.1%, p&lt;0.001</td>
</tr>
<tr>
<td><strong>Sequential</strong></td>
<td></td>
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<td></td>
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<tr>
<td>GEICAM 9906 (16,17,39) [abstract]</td>
<td>FEC→T vs. FEC</td>
<td>20.5% vs. 30%, p=Sig</td>
<td>NR</td>
<td>7.4% vs. 10.6%, p=Sig</td>
<td>1% vs. 1%, p=NR</td>
<td>5.1% vs. 9.3%, p=0.004</td>
</tr>
<tr>
<td>GOIM 9902 (18) [abstract]</td>
<td>D–EC vs. EC</td>
<td>Gr 3, 21.3% vs. 29%, p=NR; Gr 4, 48.8% vs. 32.7%, p=NR</td>
<td>1.6% vs. 3.3%, p=NR</td>
<td>NR</td>
<td>Gr 3, 2.4% vs. 0%, p=NR</td>
<td>9.5% vs. 3.7%, p=NR</td>
</tr>
<tr>
<td>MDACC (19)</td>
<td>T–FAC vs. FAC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>17% vs. 9%, p=NR</td>
</tr>
<tr>
<td>PACS 01 (21,22) [abstract]</td>
<td>FEC→D vs. FEC</td>
<td>See text</td>
<td>0.4% vs. 0.3%, p=0.71</td>
<td>NR</td>
<td>0.7% vs. 1.4%, p=0.12</td>
<td>4.6% vs. 1%, p=0.001</td>
</tr>
<tr>
<td><strong>Dose-dense</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INT C9741 (25,26,38)</td>
<td>A–T–E</td>
<td>1.3%</td>
<td>0.2%</td>
<td>0%</td>
<td>0%</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>A–T–E(DD)</td>
<td>0.2%</td>
<td>0%</td>
<td>0.4%</td>
<td>0.2%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>AC–T</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
<td>0.2%</td>
<td>NR</td>
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<tr>
<td></td>
<td>AC–T(DD)</td>
<td>5.9%</td>
<td>0.8%</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
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<tr>
<td><strong>Non-anthracycline</strong></td>
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<tr>
<td>USON 9734 (27,28,40) [abstract]</td>
<td>DC vs. AC</td>
<td>59% vs. 55%, p=NR</td>
<td>&lt;1% vs. &lt;1%, p=NR</td>
<td>NR</td>
<td>&lt;1% vs. 1%, p=NR</td>
<td>6% vs. 3%, p=0.03</td>
</tr>
<tr>
<td><strong>Other Trials</strong></td>
<td></td>
<td></td>
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<tr>
<td>BCIRG 005 (29) [abstract]</td>
<td>DAC vs. AC–D</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>17.9% vs. 8.5%, p=NR</td>
</tr>
<tr>
<td>BIG 2-98 (30,31) [abstract]</td>
<td>AD–GMF</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>11.6% vs. 7.5%</td>
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<td>A–D–GMF</td>
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<td>NR</td>
<td>4.9%</td>
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<td>A–GMF</td>
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<td>3.5%</td>
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<td>AC–GMF</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6% vs. 4%, p=NR</td>
</tr>
</tbody>
</table>

Fountzilas et al [abstract] | ET–GMF vs. ET–GMF | 23% vs. 25%, p<0.05 | NR | 12% vs. 12%, p=NR | NR | 6% vs. 4%, p=NR |
<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms(^a)</th>
<th>Gr 3/4 Neutropenia</th>
<th>Gr 3/4 Thrombocytopenia</th>
<th>Gr 3/4 Leukopenia</th>
<th>Gr 3/4 Anemia</th>
<th>Febrile Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT E1199 (33,37)</td>
<td>AC→T(_1)</td>
<td>4%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td></td>
<td>AC→T(_1)</td>
<td>2%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>AC→D(_1)</td>
<td>46%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>AC→D(_1)</td>
<td>3%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1%</td>
</tr>
<tr>
<td>Loesch et al (35,36)</td>
<td>AT→T vs. AC→T</td>
<td>71% vs. 69%, p=NR</td>
<td>2% vs. 3%, p=NR</td>
<td>NR</td>
<td>2% vs. 3%, p=NR</td>
<td>7% vs. 7%, p=NR</td>
</tr>
</tbody>
</table>

\(^a\) See table 2 for explanation of abbreviations.
\(^b\) After 224 patients were enrolled, the protocol for the GEICAM 9805 study was changed to mandate G for all patients receiving TAC. Results were reported by TAC, with or without G-CSF (a non-randomized comparison) and FAC. Number of patients: 114 in TAC group, 416 in TAC-G group, and 520 in FAC group.
\(^c\) Grade 3 only.
\(^d\) At 36 months median follow-up.

Abbreviations: BCIRG, Breast Cancer International Research Group; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; GEICAM, El Grupo Español de Investigación en Cáncer de Mama; Gr, grade; MDACC, the University of Texas M. D. Anderson Cancer Center; NR, not reported; PACS, Programmes d’Actions Concertées Sein; RAPP, Reposant sur des Arguments Pronostiques et Prédictifs; Sig, significant; vs., versus.
Table 6. Severe non-hematologic toxicity in included trials of taxane containing regimens in the adjuvant therapy of breast cancer.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Concurrent/Sequential</th>
<th>Arms&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Nausea/Vomiting</th>
<th>Stomatitis/Mucositis</th>
<th>Infection</th>
<th>Diarrhea</th>
<th>Myalgia/Arthralgia</th>
<th>CHF</th>
<th>AML/MDS cases</th>
<th>Trmt-related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCIRG 001 (6)</td>
<td>DAC vs. FAC</td>
<td>5.1% vs. 9.5%, p=0.001/4.3% vs. 7.3%, p=0.013</td>
<td>7.1% vs. 2.0%, p=0.001/NR</td>
<td>3.9% vs. 2.2%, p=0.05</td>
<td>3.8% vs. 1.8%, p=0.02</td>
<td>0.8% vs. 0.5% vs. 0.3%, p=0.69</td>
<td>1.6% vs. 0.7%, p=0.09</td>
<td>2 vs. 1</td>
<td>2 vs. 1</td>
<td></td>
</tr>
<tr>
<td>ECOG 2197 (7,8) [abstract]</td>
<td>AD vs. AC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.01% vs. 0.006%, pNS</td>
<td>7 vs. 7</td>
<td>3 vs. 0</td>
<td></td>
</tr>
<tr>
<td>GEICAM 9805 (11) [abstract]</td>
<td>DAC vs. DAC-G&lt;sup&gt;2&lt;/sup&gt; vs. FAC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Kümmel et al (12)</td>
<td>ET→CMF(DD) vs. EC→CMF</td>
<td>Combined: 7% vs. 11%, p=NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Combined: 4% vs. 0%, p=NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>PACS 04 (13)</td>
<td>ED vs. FEC</td>
<td>Combined: vs. 7.5% vs. 13.2%, p=NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>RAPP-01 (14)</td>
<td>AD vs. AC</td>
<td>5.5% vs. 9.5%, p=0.05</td>
<td>NR/4.8% vs. 2.0%, p=0.04</td>
<td>NR</td>
<td>2.9% vs. 0.6%, p=0.03</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sequential</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 9344 (15)</td>
<td>AC→T vs. AC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2% vs. 1%, p=NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>GEICAM 9906 (16,17,39) [abstract]</td>
<td>FEC→T vs. FEC</td>
<td>5.4% vs. 5.8%, p=NS&lt;sup&gt;c&lt;/sup&gt;/7.4% vs. 9.6%, p=NS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR/6% vs. 5.4%, p=NS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>2% vs. 0%, p=NR</td>
<td>NR</td>
<td>NR</td>
<td>2 vs. 1</td>
<td></td>
</tr>
<tr>
<td>GOIM 9902 (18) [abstract]</td>
<td>D→EC vs. EC</td>
<td>Combined, 3.1% vs. 6.2%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2.8% vs. 0.4%, p=NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>MDACC (19)</td>
<td>T→FAC vs. FAC</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3.4% vs. 2.3%, p=NR</td>
<td>NR</td>
<td>1.5% vs. 12.5%, p=NR/0% vs. 0.4%, p=NR</td>
<td>0 vs. 0</td>
<td>0 vs. 0</td>
<td></td>
</tr>
<tr>
<td>PACS 01 (21,22) [abstract]</td>
<td>FEC→D vs. FEC</td>
<td>See text</td>
<td>5.9% vs. 4.0%, p=0.05/NR</td>
<td>1.6% vs. 1.6%, p=0.98</td>
<td>NR</td>
<td>NR</td>
<td>0 pts vs. 4 pts, p=NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Dose dense</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INT C9741 (25,26,38)</td>
<td>A→T→C</td>
<td>4.8%/2.9%</td>
<td>1.0%/NR</td>
<td>3.1%</td>
<td>1.3%</td>
<td>4.8%</td>
<td>NR</td>
<td>7 on DD&lt;sup&gt;f&lt;/sup&gt; vs. 3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>A→T→C&lt;sup&gt;(DD)&lt;/sup&gt;</td>
<td>7.1%/3.7%</td>
<td>1.2%/NR</td>
<td>3.9%</td>
<td>2.4%</td>
<td>5.1%</td>
<td>NR</td>
<td>7 on Standard&lt;sup&gt;f&lt;/sup&gt; vs. 2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AC→T</td>
<td>8.8%/8.0%</td>
<td>2.8%/NR</td>
<td>5.4%</td>
<td>2.4%</td>
<td>5.4%</td>
<td>NR</td>
<td>7 on Standard&lt;sup&gt;f&lt;/sup&gt; vs. 0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AC→T&lt;sup&gt;(DD)&lt;/sup&gt;</td>
<td>8.3%/6.1%</td>
<td>2.6%/NR</td>
<td>3.0%</td>
<td>1.0%</td>
<td>5.3%</td>
<td>NR</td>
<td>7 on Standard&lt;sup&gt;f&lt;/sup&gt; vs. 0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>Armsa</td>
<td>Nausea/Vomiting</td>
<td>Stomatitis/Mucositis</td>
<td>Infection</td>
<td>Diarrhea</td>
<td>Myalgia/Arthralgia</td>
<td>CHF</td>
<td>AML/MDS cases</td>
<td>Trmt-related deaths</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
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<td></td>
</tr>
<tr>
<td>USON 9734 (27,28,40)</td>
<td>DC vs. AC</td>
<td>2% vs. 7%, p=NR/1% vs. 5%, p=NR</td>
<td>NR</td>
<td>11% vs. 12%, p=NR</td>
<td>NR</td>
<td>1% vs. &lt;1%, p=NR/1% vs. 1%, p=NR</td>
<td>0 vs. 0</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Other Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCIRG 005 (29) [abstract]</td>
<td>DAC vs. AC-D</td>
<td>4.5% vs. 4.1%, p=NR/4.2% vs. 4.1%, p=NR</td>
<td>2.6% vs. 3.0%, p=NR/NR</td>
<td>2.9% vs. 3.1%, p=NR</td>
<td>NR</td>
<td>0.1% vs. 0.4%, p=NR</td>
<td>NR</td>
<td>1 vs. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIG 2-98 (30,31) [abstract]</td>
<td>AD-CMF</td>
<td>5.3%/4.1%, p=NR</td>
<td>4.4%/NR</td>
<td>6.4%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A-D-CMF</td>
<td>4.3%/4.4%, p=NR</td>
<td>7.1%/NR</td>
<td>5.9%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A-EMF</td>
<td>5.5%/8.0%, p=NR</td>
<td>5.3%/NR</td>
<td>4.9%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AC-EMF</td>
<td>9.1%/4.9%, p=NR</td>
<td>1.6%/NR</td>
<td>3.9%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fountzilas et al [abstract]</td>
<td>ET-CMF vs. E-T-CMF</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0 vs. 1</td>
<td></td>
</tr>
<tr>
<td>INT E1199 (33, 37) [abstract]</td>
<td>AC-T3</td>
<td>&lt;0.5%/NR</td>
<td>3%</td>
<td>4%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AC-T1</td>
<td>0%/NR</td>
<td>5%</td>
<td>13%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AC-D1</td>
<td>2.5%/NR</td>
<td>5%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Loesch et al (35,36) [abstract]</td>
<td>AT-T vs. AC-T</td>
<td>5% vs. 8%, p=NR/4% vs. 7%, p=NR</td>
<td>2% vs. 1%, p=NR/NR</td>
<td>NR</td>
<td>NR</td>
<td>7% vs. 8%, p=NR/6% vs. 6%, p=NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

a See table 2 for explanation of abbreviations.

b After 224 patients were enrolled, the protocol for the GEICAM 9805 study was changed to mandate G for all patients receiving TAC. Results were reported by TAC, with or without G (a non-randomized comparison) and FAC. Number of patients: 114 in TAC group, 416 in TAC-G group, and 520 in FAC group.

c Grade 3 only.

d The DD arm is the combination of the A-T-C(DD) and AC-T(DD) arms. The standard arm is the combination of the A-T-C and AC-T arms.

Abbreviations: BCIRG, Breast Cancer International Research Group; CHF, congestive heart failure; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony-stimulating factor; GEICAM, El Grupo Español de Investigación en Cáncer de Mama; MDACC, the University of Texas M. D. Anderson Cancer Center; NR, not reported; NS, not significant; PACS, Programmes d'Actions Concertées Sein; RAPP, Reposant sur des Arguments Pronostiques et Prédictifs; Sig, significant; Trmt, treatment; vs., versus.
Trials of concurrent anthracycline plus taxane regimens versus similar anthracycline-based regimens without taxane

Eight trials (6-14,30,31) were identified that compared a concurrent anthracycline and taxane regimen with a similar non-taxane anthracycline-based regimen. In addition to the data presented in Tables 2-6, additional details are provided below.

Breast Cancer International Research Group (BCIRG) 001 trial

The BCIRG 001 trial (6) also reported DFS data from several planned subgroup analyses (Table 7).

Table 7. DFS subgroup analyses from the BCIRG 001 trial.

<table>
<thead>
<tr>
<th>Subgroup Analysis</th>
<th>DFS HR (CI) (DAC vs. FAC)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 3 positive nodes</td>
<td>HR 0.61 (0.46 to 0.82)</td>
<td>0.15</td>
</tr>
<tr>
<td>4 or more positive nodes</td>
<td>HR 0.83 (0.63 to 1.08)</td>
<td></td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>HR 0.69 (0.49 to 0.82)</td>
<td>0.72</td>
</tr>
<tr>
<td>Positive</td>
<td>HR 0.72 (0.56 to 0.92)</td>
<td></td>
</tr>
<tr>
<td>HER2/neu status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>HR 0.76 (0.59 to 1.00)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>HR 0.60 (0.41 to 0.88)</td>
<td>0.41</td>
</tr>
<tr>
<td>Unknown</td>
<td>HR 0.72 (0.45 to 1.17)</td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>HR 0.66 (0.50 to 0.86)</td>
<td>0.34</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>HR 0.79 (0.59 to 1.07)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DAC, docetaxel plus doxorubicin plus cyclophosphamide; DFS, disease-free survival; FAC, fluorouracil plus doxorubicin plus cyclophosphamide; HR, hazard ratio.

In addition to the toxicity data reported in Tables 5 and 6, the BCIRG 001 trial reported significantly higher rates of overall amenorrhea in patients receiving DAC (61.7%) compared to patients receiving FAC (52.4%, p=0.007).

The BCIRG 001 trial measured quality of life using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30, version 2.0, and the breast cancer-specific QLQ-BR23, version 1.0. Patients were evaluated with the questionnaire at baseline; before cycles 3 and 5; 3 to 4 weeks after last cycle; and 6, 12, and 24 months after the last cycle. The baseline mean scores were 72 for both groups on the global health status subscale. The mean score at the end of treatment was 62 (61 to 64) in the DAC group and 69 (67 to 70) in the FAC group. At 6 months and beyond, the scores were similar in both groups and generally higher than at baseline.

Breast International Group (BIG) 2-98 trial

The BIG 2-98 trial (30,31) included a concurrent anthracycline-taxane arm, doxorubicin and docetaxel followed by cyclophosphamide, methotrexate, and fluorouracil (AD-CMF), and an appropriate comparison anthracycline-based arm, doxorubicin and cyclophosphamide followed by cyclophosphamide, methotrexate, and fluorouracil (AC-CMF). This trial is described under “Other Trials” in Tables 2-6, and, with additional details, found in the “Other Trials of Anthracycline and Taxane chemotherapy” section below.
Eastern Cooperative Oncology Group (ECOG) 2197 trial

In the ECOG 2197 trial (7,8), reported in abstract and presentation form at the 2005 ASCO Annual Meeting, no significant difference between the combination of docetaxel and doxorubicin (AD) and the combination of doxorubicin and cyclophosphamide (AC) was measured in any of the planned subgroup analysis, including analyses by nodal status, hormone-receptor status, and menopausal status.

In a separate planned analysis, DFS was analyzed by the estrogen and progesterone status, as shown in Table 8. This analysis suggests that taxane efficacy may be related to progesterone status.

Table 8. DFS by estrogen and progesterone status in the ECOG 2197 trial.

<table>
<thead>
<tr>
<th>Hormone receptor status</th>
<th>DFS HR (AD vs. AC) (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-/PR-</td>
<td>0.78 (0.59 to 1.04)</td>
</tr>
<tr>
<td>ER-/PR+</td>
<td>3.33 (1.05 to 10.00)</td>
</tr>
<tr>
<td>ER+/PR-</td>
<td>0.61 (0.36 to 1.04)</td>
</tr>
<tr>
<td>ER+/PR+</td>
<td>1.27 (0.91 to 1.72)</td>
</tr>
</tbody>
</table>

Reference: (7,8)
Note: The inverse of the reported HRs is reported here so that values less than 1 favour AD.
Abbreviations: AC, doxorubicin plus cyclophosphamide; AD, doxorubicin plus docetaxel; CI, 95% confidence interval; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

An earlier abstract from this study (44) from the 2003 ASCO Annual Meeting reported on measured left ventricular ejection fraction (LVEF) at baseline and post chemotherapy in 2,112 of the patients. This abstract reported no significant change in LVEF due to chemotherapy on either arm.

European Cooperative Trial in Operable Breast Cancer (ECTO)

In the ECTO trial (9,10), reported in abstract form at the 2005 ASCO Annual Meeting, no specific toxicity data were reported. However, the authors stated that cardiac effects were measured, but no significant differences in cardiac toxicity were found.

El Grupo Español de Investigación en Cáncer de Mama (GEICAM) 9805 trial

Efficacy results for this trial have not yet been published. The interim safety analysis reported in abstract form at the 2005 ASCO Annual Meeting (11), was an analysis of toxicity by three treatment categories; docetaxel, doxorubicin, and cyclophosphamide (DAC) without granulocyte colony-stimulating factor (G-CSF), DAC with G-CSF (DAC-G), and fluorouracil, doxorubicin, and cyclophosphamide (FAC). The DAC and DAC with G-CSF patients were not randomized; patients accrued early in the study did not receive G-CSF prophylaxis, but the study protocol was changed after enrolling 224 patients, and all patients accrued after the change received G-CSF. In addition to the data reported in Tables 5 and 6, the GEICAM 9805 trial also measured quality of life using the EORTC QLQ-C30, with measurements at baseline, after each chemotherapy cycle, and at 6, 12, and 24 months after completion of chemotherapy. During chemotherapy, quality of life was worse in patients receiving DAC compared to FAC (p=0.008), but no significant difference was measured between DAC-G and FAC.

Kümmel et al trial

The trial by Kümmel et al (12) included a dose-dense taxane and anthracycline arm. However, the comparison arm did not include a taxane, and so the results of this trial are reported here, instead of in the dose-dense versus standard dose section of this document.
Programmes d’Actions Concertées Sein (PACS) 04 trial
All relevant data from the PACS 04 trial (13), reported in abstract form at the 2006 ASCO Annual Meeting, are included in Tables 2-6.

Reposant sur des Arguments Pronostiques et Prédictifs (RAPP) 01 trial
The RAPP-01 trial (14) was stopped early due to three serious cases of life-threatening gastrointestinal infection (two fatal and one requiring surgery).

Meta-analysis
To estimate the overall effect of the addition of a concurrent taxane–anthracycline regimen to a non-taxane anthracycline-based chemotherapy regimen, a meta-analysis was conducted of both DFS and OS. Of the seven trials that included this comparison, five provided sufficient data on DFS and OS to be included in the meta-analyses—BCIRG 001, BIG 2-98, ECOG 2197, ECTO, and Kümmel et al. The results of these meta-analyses are shown in Figures 1 and 2.

Figure 1. Meta-analysis of DFS; concurrent anthracycline and taxane vs. anthracycline-based regimen.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>log[Hazard Ratio] (SE)</th>
<th>Hazard Ratio (random)</th>
<th>Weight %</th>
<th>Hazard Ratio (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG 001</td>
<td>-0.3285 (0.1020)</td>
<td>0.72 [0.59, 0.88]</td>
<td>25.88</td>
<td></td>
</tr>
<tr>
<td>BIG 2-98</td>
<td>-0.0726 (0.1068)</td>
<td>0.93 [0.75, 1.15]</td>
<td>24.65</td>
<td></td>
</tr>
<tr>
<td>ECOG 2197</td>
<td>-0.0726 (0.0948)</td>
<td>0.93 [0.77, 1.12]</td>
<td>27.81</td>
<td></td>
</tr>
<tr>
<td>ECTO</td>
<td>-0.4155 (0.1654)</td>
<td>0.66 [0.48, 0.91]</td>
<td>12.09</td>
<td></td>
</tr>
<tr>
<td>Kümmel</td>
<td>-0.2744 (0.2433)</td>
<td>0.76 [0.47, 1.22]</td>
<td>7.59</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.82 [0.71, 0.94]</td>
<td></td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 6.56, df = 4 (P = 0.16), I² = 39.1%
Test for overall effect: Z = 2.80 (P = 0.005)

Figure 2. Meta-analysis of OS; concurrent anthracycline and taxane vs. anthracycline-based regimen.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>log[Hazard Ratio] (SE)</th>
<th>Hazard Ratio (random)</th>
<th>Weight %</th>
<th>Hazard Ratio (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG 001</td>
<td>-0.3567 (0.1379)</td>
<td>0.70 [0.53, 0.92]</td>
<td>23.87</td>
<td></td>
</tr>
<tr>
<td>BIG 2-98</td>
<td>0.1484 (0.1106)</td>
<td>1.16 [0.93, 1.44]</td>
<td>26.60</td>
<td></td>
</tr>
<tr>
<td>ECOG 2197</td>
<td>-0.0834 (0.1296)</td>
<td>0.92 [0.71, 1.19]</td>
<td>24.70</td>
<td></td>
</tr>
<tr>
<td>ECTO</td>
<td>-0.3425 (0.2438)</td>
<td>0.71 [0.44, 1.14]</td>
<td>14.79</td>
<td></td>
</tr>
<tr>
<td>Kümmel</td>
<td>-0.5621 (0.3314)</td>
<td>0.57 [0.30, 1.09]</td>
<td>10.04</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.84 [0.66, 1.08]</td>
<td></td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 11.46, df = 4 (P = 0.02), I² = 65.1%
Test for overall effect: Z = 1.38 (P = 0.17)

The pooled estimate, using a random effects model, of the HR for DFS, concurrent anthracycline and taxane versus anthracyline combination, was 0.82 (95% CI 0.71 to 0.94), with little statistical heterogeneity (x² p=0.16, I²=39.1%). The pooled estimate for OS was 0.84 (95% CI 0.66 to 1.08), with evidence of statistical heterogeneity (x² p=0.02, I²=65.1%).
Trials of sequential anthracycline plus taxane regimens versus similar anthracycline-based regimens without taxane

Nine trials (15-24,30,31) were identified that compared a sequential anthracycline and taxane regimen with a similar non-taxane anthracycline-based regimen. In addition to the data presented in Tables 2-6, additional details are provided below.

BIG 2-98 trial

The BIG 2-98 trial (30,31) included a sequential anthracycline-taxane arm, doxorubicin followed by docetaxel followed by cyclophosphamide, methotrexate, and fluorouracil (A→D→CMF), and an appropriate comparison anthracycline-based arm, doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil (A→CMF). This trial is described under “Other Trials” in Tables 2-6, and, with additional details, is found in the “Other Trials of Anthracycline and Taxane chemotherapy” section below.

Cancer and Leukemia Group B (CALGB) 9344 trial

The CALGB 9344 trial (15), in addition to randomizing patients between eight cycles of doxorubicin and cyclophosphamide (AC) or four cycles of AC followed by four cycles of paclitaxel (AC→T), also randomized patients to three separate dosage levels of doxorubicin—60, 75, or 90 mg/m². No significant association between DFS or OS and the dose of doxorubicin was found nor was any interaction between dose of doxorubicin and paclitaxel therapy. All the other data presented in this document, unless otherwise noted, includes all the patients regardless of the doxorubicin dose level. In an unplanned subgroup analysis, DFS was significantly improved among hormone-receptor negative/unknown patients (HR 0.72, 95% CI 0.59 to 0.86), but not among hormone-receptor positive patients (HR 0.91, 95% CI 0.78 to 1.07).

The CALGB 9344 trial reported toxicity rates for the first four cycles of therapy, doxorubicin plus cyclophosphamide (AC), including all patients, versus the second four cycles of therapy of paclitaxel in the sequential arm, including approximately half the patients, rather than according to treatment (AC followed by paclitaxel vs. AC alone); furthermore, p-values for differences were not reported (15). Paclitaxel resulted in fewer occurrences of hematologic toxicity than did AC. Sixty-two percent of patients experienced at least one episode of granulocytopenia while receiving AC (A at 60 mg/m²) compared with 16% while receiving paclitaxel. The rates of infection, hospitalization, and most gastrointestinal side effects were also lower during the paclitaxel cycles. There was no difference in cardiotoxicity or secondary malignancies, including acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS) between the AC cycles and the paclitaxel cycles. Three deaths occurred, one during the AC therapy and two during the paclitaxel therapy.

GEICAM 9906 trial

All relevant data from the GEICAM 9906 trial (16,17,39), reported in abstract form at the 2005 SABCS, are included in Tables 2-6.

Gruppo Oncologico Dell’italia Meridionale (GOIM) 9902 trial

The GOIM 9902 trial (18), published in abstract form at the 2006 ASCO Annual Meeting, also reported the following toxicity rates in the docetaxel followed by epirubicin and cyclophosphamide arms (D→EC) versus the EC arm alone: grade 3/4 hypersensitivity reactions 4.3% versus 0%; grade 3/4 cardiac toxicity 0% versus 0.4%; grade 1-3 peripheral neuropathy 9.9% versus 0%. Significance tests were not reported.
M. D. Anderson Cancer Center (MDACC) trial

In the MDACC trial (19), a subgroup analysis found no significant difference in recurrence-free survival (RFS) by estrogen receptor (ER) status (p=0.07 for ER negative, p=0.39 for ER positive). It is important to note that the authors of this trial report state that the trial was planned with an assumption of a higher recurrence rate (66% four-year RFS in non-taxane arm) than was actually experienced, and, therefore, should be considered underpowered, even though sample size was met. In addition to the toxicity data described in Tables 5 and 6, the rate of chemotherapy-induced amenorrhea was 44% in the taxane-containing arm as compared to 57% in the non-taxane arm (p=0.2).

National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 trial

The NSABP B-28 trial (20) reported, in addition to the efficacy data shown in Table 3, that women who received AC→T experienced a significantly lower incidence of contralateral breast cancer than did those receiving AC alone (HR 0.53, 95% CI 0.29 to 0.98, p=0.039). The HR for experiencing a second non-breast cancer primary cancer was 0.72 (95% CI 0.46 to 1.08, p=0.11). Data from a subgroup analysis of the relationship between hormone receptor status and treatment arm are presented in Table 9.

Table 9. DFS and OS by hormone receptor status in the NSABP B-28 trial.

<table>
<thead>
<tr>
<th>Hormone Receptor Status</th>
<th>DFS HR (AC→T vs. AC) (CI)</th>
<th>OS HR (AC→T vs. AC) (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>HR 0.77 (0.65 to 0.92)</td>
<td>HR 0.94 (0.74 to 1.21)</td>
</tr>
<tr>
<td>Negative</td>
<td>HR 0.90 (0.72 to 1.12)</td>
<td>HR 0.90 (0.70 to 1.17)</td>
</tr>
</tbody>
</table>

Reference: (20)

Abbreviations: → followed by; AC, doxorubicin plus cyclophosphamide; CI, 95% confidence interval; HR, hazard ratio; NSABP, National Surgical Adjuvant Breast and Bowel Project; T, paclitaxel.

Toxicity rates in the NSABP B-28 trial were not reported by arm. Common grade 3+ toxicities, with rates, while on paclitaxel were neurosensory (16%), neuromotor (7%), arthralgia/myalgia (12%), and febrile neutropenia (3%). The rate of grade 3+ cardiac dysfunction was ~1.0% in both treatment arms. There were six cases of AML/MDS in patients treated with paclitaxel and two in patients not treated with paclitaxel.

An earlier abstract (45) from the 2003 ASCO Annual Meeting reported the following grade 3+ toxicity rates associated with AC chemotherapy, regardless of arm: febrile neutropenia (7%), nausea (6%), vomiting (5%), infection (3%), thromboembolic events (2%), stomatitis (2%). The following grade 3+ toxicity rates were associated with paclitaxel chemotherapy: neurotoxicity (19%), arthralgia/myalgia (11%), febrile neutropenia (2%), infection (2%), and thromboembolic events (2%).

PACS 01 trial

The PACS 01 trial (21,22), published in abstract and presentation form at the 2004 SABCS, reported additional efficacy data beyond that shown in Table 3, as shown in Table 10.

Table 10. Additional Efficacy Data from the PACS 01 Trial.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subgroup</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS HR</td>
<td>&lt; 50 years of age</td>
<td>0.98 (95% CI 0.77 to 1.25)</td>
</tr>
<tr>
<td>DFS HR</td>
<td>≥ 50 years of age</td>
<td>0.67 (95% CI 0.51 to 0.88)</td>
</tr>
<tr>
<td>DFS HR</td>
<td>1 to 3 positive nodes</td>
<td>0.76 (95% CI 0.58 to 1.00)</td>
</tr>
<tr>
<td>DFS HR</td>
<td>≥ 4 positive nodes</td>
<td>0.87 (95% CI 0.68 to 1.11)</td>
</tr>
<tr>
<td>IR, Distant Relapse</td>
<td>NA</td>
<td>17.7% vs. 21.8%, p=0.023</td>
</tr>
<tr>
<td>IR, Contralateral Breast Cancer</td>
<td>NA</td>
<td>2.4% vs. 3.0%, p=0.43</td>
</tr>
</tbody>
</table>
The PACS 01 trial also reported toxicity data by phase of chemotherapy, comparing the toxicity of the arms in the first three cycles, which were both fluorouracil, epirubicin, and cyclophosphamide (FEC), and the last three cycles, in which the taxane arm received docetaxel, and the non-taxane arm continued to received FEC. This additional toxicity data by cycle, as well as other data not included in Tables 5 and 6, is summarized in Table 11.

**Table 11. Toxicity data from the PACS 01 trial.**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cycle</th>
<th>FEC-D Rate</th>
<th>FEC Rate</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+ neutropenia</td>
<td>1 to 3</td>
<td>21.5%</td>
<td>21.0%</td>
<td>p=0.79</td>
</tr>
<tr>
<td></td>
<td>4 to 6</td>
<td>10.9%</td>
<td>20.2%</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Grade 3+ nausea/vomiting</td>
<td>1 to 3</td>
<td>10.1%</td>
<td>13.2%</td>
<td>p=0.031</td>
</tr>
<tr>
<td></td>
<td>4 to 6</td>
<td>1.6%</td>
<td>11.0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Moderate to severe edema</td>
<td>4 to 6</td>
<td>4.8%</td>
<td>0.3%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Moderate to severe nail disorders</td>
<td>4 to 6</td>
<td>10.3%</td>
<td>1.0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Chemotherapy-induced amenorrhea</td>
<td>All</td>
<td>68.4%</td>
<td>72.4%</td>
<td>p=0.13</td>
</tr>
</tbody>
</table>

Reference: (21, 22)

**Taxotere as Adjuvant Chemotherapy Trial (TACT)**

To date, only a quality of life analysis published in abstract form at the 2005 ASCO Annual Meeting is available from the TACT trial (23). The TACT trial involved three different treatments (FEC followed by docetaxel, FEC alone, and epirubicin followed by CMF). But it is not clear from the report whether patients were randomized to each regimen separately or whether patients were randomized to the taxane-containing arm or non-taxane containing arm and then the choice of FEC or epirubicin followed by CMF made in a non-random fashion for those randomized to no taxane. The EORTC ALA-C30, BR23, and Hospital Anxiety and Depression Scale (HADS) questionnaires were used to measure quality of life in this trial. Eight hundred and twenty-nine patients were involved—270 patients versus 265 for the comparison of FEC followed by docetaxel arm to FEC alone and 147 patients versus 148 for the comparison of FEC followed by docetaxel to epirubicin followed by CMF. FEC followed by docetaxel was associated with worse global quality of life scores (p=0.002 versus FEC, p=0.18 versus epirubicin followed by CMF) and decreased physical function scores (p=0.007 versus FEC, p=0.003 versus epirubicin followed by CMF), but the TACT trial report authors stated that the differences “did not appear clinically relevant”. No other significant differences in quality of life scores were reported.

**Taxit216 Trial**

All relevant data from the Taxit216 trial (24), published in abstract form at the 2006 ASCO Annual Meeting, are included in Tables 2-6.

**Meta-analysis**

To estimate the overall effect of the addition of a sequential taxane-anthracycline regimen to a non-taxane anthracycline-based chemotherapy regimen, a meta-analysis was conducted of both DFS and OS. Of the nine trials that included this comparison, seven provided sufficient data on DFS to be included in the meta-analysis—BIG 2-98, CALGB 9344, GEICAM 9906, MDACC, NSABP B-28, PACS 01, and Taxit216. Only six of these trials were
included in the analysis of OS; the MDACC trial did not provide OS data. The results of these meta-analyses are shown in Figures 3 and 4.

**Figure 3. Meta-analysis of DFS: sequential anthracycline and taxane vs. anthracycline-based regimen.**

![Meta-analysis of DFS](image)

**Figure 4. Meta-analysis of overall OS: sequential anthracycline and taxane vs. anthracycline-based regimen.**

![Meta-analysis of overall OS](image)

The pooled estimate, using a random effects model, of the HR for DFS, sequential anthracycline and taxane versus anthracycline combination, was 0.80 (95% CI 0.75 to 0.86), with no statistical heterogeneity ($x^2$ p=0.69, $I^2$=0%). The pooled estimate for OS was 0.83 (95% CI 0.76 to 0.91), also with no evidence of statistical heterogeneity ($x^2$ p=0.77, $I^2$=0%).

**Trials of dose-dense anthracycline plus taxane regimens versus standard dose regimens**

Only one trial (25,26) was identified that compared a dose-dense anthracycline and taxane regimen with an equivalent standard dose regimen. In addition to the data presented in Tables 2-6, additional details are provided below.

**The Intergroup (INT) C9741 Trial**

The primary analysis of the INT C9741 trial was reported in a peer-reviewed publication in 2003 (25) at 36 months median follow-up, and updated efficacy results at 69 months median follow-up have been published in abstract form at the 2005 SABCS (26,38). The INT C9741 trial had four treatment arms—doxorubicin followed by paclitaxel followed by...
cyclophosphamide (A→T→C), doxorubicin plus cyclophosphamide followed by paclitaxel (AC→T), and dose-dense versions of each of those regimens. For the most of the analyses reported to date, the two dose-dense arms were combined as were the two standard arms. The abstract also provided additional DFS and OS data analysed by estrogen receptor status, as shown in Table 12.

Table 12. DFS and OS data by estrogen receptor status from the INT C9741 trial.

<table>
<thead>
<tr>
<th></th>
<th>ER+</th>
<th>ER-</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>HR 0.86 (95% CI 0.67 to 1.11), p=0.26</td>
<td>HR 0.75 (95% CI 0.57 to 0.97), p=0.031</td>
</tr>
<tr>
<td>OS</td>
<td>HR 0.92 (95% CI 0.67 to 1.26), p=0.61</td>
<td>HR 0.77 (95% CI 0.57 to 1.03), p=0.073</td>
</tr>
</tbody>
</table>

Note: HRs presented as dose-dense regimen versus standard regimen. Reference: (26)

Abbreviations: CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; HR, hazard ratio; OS, overall survival.

At 36 months median follow-up, the incidence of contralateral breast cancer was significantly reduced on the dose-dense regimen (0.3%) versus the standard regimen (1.5%, p=0.0004). Grade 3+ cardiac function toxicity was reported by individual arm and not as dose-dense versus standard—A→T→C 1.3%, A→T→C (dose-dense) 0.8%, AC→T 0.4%, and AC→T (dose-dense) 0.2%, p-values not reported. An additional abstract (46) published at the 2005 ASCO Annual Meeting reported that grade 2 anemia or worse was most frequent on the dose-dense AC→T arm (23%), with rates for the other arms as follows: A→T→C 3%, dose-dense A→T→C 11%, and AC→T 8% (p<0.0001 for comparison).

In addition to the above trial, the PACS 06 randomized phase II trial (47), located during the literature search but not meeting the inclusion criteria, is reported here as it is relevant. This trial compared fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (500 mg/m²) for three cycles followed by docetaxel (100mg/m²) for three cycles as dose-dense (two week cycles with G-CSF) or standard (four-week cycles) therapy. Of the 74 patients recruited, 37 per arm, 14 (38%) exhibited dose-limiting toxicities (DLTs) in the dose-dense arm, versus three (8%) in the standard arm. Recruitment to the dose-dense arm was halted, in adherence to a preplanned stopping rule. Thirteen of the 14 DLTs on the dose-dense arm were skin/hand-foot syndrome.

**Trials of non-anthracycline taxane-based regimens versus non-taxane anthracycline-based regimens**

One trial (27,28) was identified that compared a non-anthracycline taxane-based regimen with a similar non-taxane anthracycline-based regimen. In addition to the data presented in Tables 2-6, additional details are provided below.

**The U.S. Oncology (USON) 9735 trial**

The USON 9735 trial was reported in abstract form at both the 2001 ASCO Annual Meeting and the 2005 SABCS (27,28,40). This trial also reported the results of an exploratory subgroup analysis of DFS with the following results (all hazard ratios expressed with a value less than zero favouring the taxane regimen: age < 50 years, HR 0.64 (95% CI 0.38 to 1.04); age ≥ 50 years, HR 0.73 (95% CI 0.48 to 1.10); hormone receptor negative, HR 0.64 (95% CI 0.38 to 1.04); hormone receptor positive, HR 0.71 (95% CI 0.47 to 1.08); node-negative, HR 0.73 (95% CI 0.42 to 1.27); node-positive, HR 0.67 (95% CI 0.45 to 0.98). With regards to all grades of toxicity, patients receiving DC experienced significantly (p<0.01) higher rates of edema (35% vs. 2%), myalgia (33% vs. 17%) and arthralgia (24% vs. 15%) versus those receiving AC; they experienced lower rates of nausea (53% vs. 81%) and vomiting (16% vs. 43%).
Other relevant trials

Six other trials (29-37) were identified that compared relevant taxane and/or anthracycline treatment regimens. In addition to the data presented in Tables 2-6, additional details are provided below.

BCIRG 005 trial
All relevant data from the BCIRG 005 trial (29), reported in abstract form at the 2005 SABCS, are abstracted in Tables 2-6.

BIG 2-98 trial
The BIG 2-98 trial (30,31) included four separate arms—two separate control arms (doxorubicin followed by CMF [A→CMF] and doxorubicin plus cyclophosphamide followed by CMF [AC→CMF]), a concurrent anthracycline-taxane arm (doxorubicin plus docetaxel followed by CMF [AD→CMF]), and a sequential anthracycline-taxane arm (doxorubicin followed by docetaxel followed by CMF [A→D→CMF]). The trial, therefore, addressed both sequential and concurrent taxane administration, as well as directly comparing concurrent and sequential regimens.

In addition to the results presented above and in Tables 2-6, the BIG 2-98 reported DFS data comparing A→D→CMF to A→CMF by nodal status (1-3 positive nodes, HR 0.85 [95% CI 0.58 to 1.23]; 4 or more positive nodes, HR 0.76 [95% CI 0.58 to 1.00]) and hormone receptor status (estrogen- and/or progesterone-receptor positive, HR 0.79 [95% CI 0.61 to 1.05]; hormone receptor negative, HR 0.79 (0.61 to 1.05)).

Fountzilas et al trial
The trial by Fountzillas et al (32), published in abstract form at the 2005 SABCS, was a direct comparison of a concurrent taxane-anthracycline regimen (epirubicin plus paclitaxel followed by CMF) to an equivalent sequential taxane-anthracycline regimen (epirubicin followed by paclitaxel followed by CMG). In addition to the data presented in Tables 2-6, the trial also reported that severe hypersensitivity reactions and peripheral neuropathy were significantly more profound in the sequential arm.

INT E1199 trial
The INT E1199 trial (33,37), published in abstract form at the 2005 SABCS, was a direct comparison of weekly and three-weekly schedules of docetaxel or paclitaxel following doxorubicin and cyclophosphamide. In addition to the data in Tables 2-6, the trial also reported the relative efficacy of the four arms. Using paclitaxel every three weeks as the comparator, the HRs, with 95% CIs, for the other arms were paclitaxel every week, 1.20 (0.99 to 1.46), p=0.06; docetaxel every three weeks, 1.13 (0.94 to 1.36), p=0.20; and docetaxel every week, 1.03 (0.85 to 1.23), p=0.78. The four-year DFS rates by arm were paclitaxel every three weeks, 80.5%; paclitaxel every week, 83.5%; docetaxel every three weeks, 83.1%; and docetaxel every week, 80.1%. The four-year OS rates by arm were paclitaxel every three weeks, 88.8%; paclitaxel every week, 91.7%; docetaxel every three weeks, 89.3%; and docetaxel every week, 88.9%. The incidence of grade 3/4 toxicity as the worst grade toxicity by arm was paclitaxel every three weeks, 24%/6%; paclitaxel every week, 24%/4%; docetaxel every three weeks, and 21%/50%; docetaxel every week, 39%/6%. The trial authors stated “...it is unlikely that either comparison [schedule or choice of taxane] could become significant after full planned information is obtained.”
Lambert-Falls et al trial

The trial by Lambert-Falls et al (34) was a comparison of a concurrent anthracycline-taxane regimen (epirubicin plus paclitaxel or docetaxel) versus a similar sequential regimen (epirubicin plus cyclophosphamide followed by paclitaxel or docetaxel). All relevant data from this trial are abstracted in Tables 2-6. No breakdown of toxicity by grade or arm and no statistical comparison of efficacy were provided. The trial authors concluded “both regimens are effective and well tolerated.”

Loesch et al trial

The trial reported by Loesch et al (35,36) was a comparison of doxorubicin plus paclitaxel followed by paclitaxel (AT→T) versus doxorubicin plus cyclophosphamide followed by paclitaxel (AC→T). No significant difference in cardiotoxicity was measured between the treatment arms. The rate of neuropathy was significantly higher in the AT→T arm (9%) versus the AC→T arm (4%, p<0.01).

Systematic Review

A systematic review by Nowak et al (48), covered both neoadjuvant and adjuvant chemotherapy with taxanes. It included five trials, all of which are included in this evidence-based series report—USON 9735, NSABP B28, BCIRG 001, CALGB 9344, MDACC. No meta-analysis was conducted, and there were no additional results beyond those presented here.

DISCUSSION

Question #1: Compared with an anthracycline-based regimen, does a concurrent taxane-anthracycline regimen improve clinically meaningful outcomes?

The evidence regarding the concurrent administration of taxane and anthracycline is mixed. Of the six trials (6-10,12,30,31) that reported efficacy data comparing concurrent anthracycline-taxane regimens against similar non-taxane anthracycline regimens, two reported significantly improved DFS with concurrent taxane (BCIRG 001, ECTO) and one reported significantly improved OS (BCIRG 001). A meta-analysis of these trials found significantly improved DFS with concurrent taxane administration, with little statistical heterogeneity (HR 0.82, 95% CI 0.72 to 0.94, I^2=39.1%), but no significant improvement and some statistical heterogeneity in OS (HR 0.84, 95% CI 0.66 to 1.08, I^2=65.1%).

Interestingly, planned subgroup analyses detected improved benefit with concurrent taxane, in the BCIRG 001 trial, in women with one to three positive nodes but not in women with four or more, although the interaction was not statistically significant. In addition, the ECOG 2197 trial found a non-significant trend (Table 8) that suggested the concurrent taxane regimen in that trial only improved DFS in patients who were progesterone-receptor negative, with progesterone-receptor positive patients experiencing non-significant reductions in DFS with the taxane. No recommendations can be made based on these analyses, but they provide a starting point for future trials.

When it was reported, hematologic toxicity was generally higher with concurrent taxane administration, particularly febrile neutropenia, which ranged from 24.6% to 40.8% in the concurrent arms versus 2.5% to 10.3% in the non-taxane arms in the included trials. Most other reported toxicities were also generally higher on the concurrent arms, with the exception of nausea and vomiting. Of particular note is the RAPP-01 trial (14), which was stopped early due to three serious cases of gastrointestinal infection on the concurrent arm.

At this time, it seems clear that the DAC regimen used in the BCIRG trial is superior to the FAC regimen in women with early-stage node-positive breast cancer. However, considering the increased toxicities and lack of DFS and OS improvements measured in the other trials, a general conclusion regarding concurrent taxane-anthracycline administration
cannot be made. Moreover, there is no data comparing “optimal” regimens such as FEC-100 (500/100/500 mg/m²) (49) or CEF (75/60/100 mg/m²) (50) to their epirubicin and taxane-containing counterparts, TEC-100 and CET, respectively. As well, the relative benefit of FAC therapy in comparison to FEC-100 or CEF therapy has not been tested, although FAC is a standard of care in some centres (e.g., MDACC). Therefore, there seem to be no grounds on which to base a recommendation as to which of the various anthracycline and taxane-anthracycline regimens (DAC, FEC-100, CEF, etc.) may be preferable.

Question #2: Compared with a standard anthracycline-based regimen, does a sequential taxane-anthracycline regimen improve clinically meaningful outcomes?

The evidence showing improved efficacy with the inclusion of a taxane in sequence with anthracycline-based chemotherapy is consistent and strong. Of the seven trials (15-17,19-22,24,30,31) that reported efficacy data comparing sequential anthracycline-taxane regimens against similar non-taxane anthracycline regimens, all but one (MDACC) reported significantly improved DFS and/or OS with sequential taxane. A meta-analysis of these trials found significantly improved DFS (HR 0.80, 95% CI 0.75 to 0.86) and OS (HR 0.82, 95% CI 0.76 to 0.91) for sequential taxane administration, with no statistical heterogeneity (I²=0% for DFS and OS).

Compared to the concurrent administration of taxane and anthracycline, the toxicity profile of sequential administration presents a more mixed picture. With respect to hematologic toxicity, no general impression can be formed regarding the superiority of either anthracycline only or sequential anthracycline-taxane. For example, in the GEICAM 9906 trial, significantly more febrile neutropenia was recorded in the FEC arm compared to the FEC followed by paclitaxel arm, but in the similar PAC 01 trial, febrile neutropenia was significantly higher in the FEC followed by docetaxel arm, and the overall rates were much lower in both arms (see Table 5 for details). The CALGB 9344 study reported lower hematologic toxicity for patients undergoing only taxane therapy than for patients undergoing anthracycline-combination therapy, and the PACS 01 trial reported a similar pattern of significantly lower rates of grade 3+ neutropenia in the last three cycles of therapy in patients receiving docetaxel compared to FEC. With respect to other toxicities, there seems to be no clinically relevant difference in any of the studies between sequential taxane versus a non-taxane regimen, although the PACS 01 trial did report significantly greater rates of edema and nail disorders during the taxane-only cycles of chemotherapy than during the FEC-only treatment in the same cycles, and, in the NSABP B-28 trial, grade 3+ neurotoxicity occurred in roughly 20% of patients during the paclitaxel cycles. It is important to note, however, that, in the results of the TACT trial, FEC followed by docetaxel was associated with significantly worse global quality of life and physical function scores.

Based on the evidence currently available, it seems likely that the incorporation of a taxane in sequence with an anthracycline-based regimen will improve the DFS efficacy of that regimen, regardless of its exact constituents.

Question #3: Compared with a standard (three-weekly) anthracycline-taxane regimen, does a dose-dense (two-weekly) regimen improve clinically meaningful outcomes?

In the INT C9741 trial, DFS was significantly improved at 69 months with dose-dense (two-weekly) doxorubicin and paclitaxel therapy (A→T→C or AC→T), with G-CSF support, versus standard (three-weekly) doxorubicin and paclitaxel therapy. As this is the only phase III trial as yet reported that compared dose-dense to standard regimens, no general conclusions can be drawn, but the dose-dense regimens used in the INT C9741 trial (with AC→T preferable due to shorter duration), with G-CSF support, should be considered superior to their standard counterparts.
Question #4: Compared with an anthracycline-based regimen, does a non-anthracycline taxane regimen improve clinically meaningful outcomes?

In the USON 9735 trial, there was a significant improvement in DFS, with an absolute difference of 5% (p=0.027), in patients receiving docetaxel and cyclophosphamide over patients receiving doxorubicin and cyclophosphamide. Both hematologic toxicities and non-hematologic toxicities were similar between the arms, with the only reported significant difference being less nausea and vomiting associated with the taxane regimen. Based on the results of this trial, docetaxel plus cyclophosphamide could be considered an alternative to doxorubicin and cyclophosphamide. However, there have as yet been no direct comparisons of other taxane-containing regimens to docetaxel and cyclophosphamide; in the absence of trials comparing these regimens, no conclusions can be drawn about whether one is preferable over the other.

Question #5: What are the harms associated with adjuvant taxane regimens?

As noted in the discussion above, hematologic toxicity was generally increased with a concurrent taxane-anthracycline regimen compared to a non-taxane-anthracycline regimen, while, with sequential taxane-anthracycline regimens, there is a more complex profile. In the three studies that directly compared a concurrent regimen to a similar sequential regimen (BCIRG 005, BIG 2-98, and Fountzilas et al), febrile neutropenia was less frequent with sequential versus concurrent therapy, although no significance tests were reported (see Table 5). However, febrile neutropenia was generally a concern in the taxane-containing arms of all the studies. In the non-randomized comparison reported from the GEICAM 9805 trial, G-CSF support, when given with DAC, led to reduced rates of febrile neutropenia (24.6% without G-CSF, 5.8% with G-CSF, significance test not reported). Future randomized studies evaluating that precaution are expected and should be monitored, but, at this time and at a minimum, patients receiving anthracycline-taxane therapy should be monitored for febrile neutropenia, and, if it occurs, either dose reduction or G-CSF support should be considered. Prophylactic G-CSF should be considered for use with concurrent anthracycline-taxane regimens.

In the INT C9741 trial, G-CSF was administered prophylactically in the dose-dense arms. As noted in Table 5, the incidence of neutropenia was lower in the dose-dense arms than in the standard arms. Therefore, prophylactic G-CSF should accompany dose-dense anthracycline-taxane therapy. The INT/CALGB 9741 trial used G-CSF on day three to ten of each cycle at 5 µg/kg, which could be rounded to either 300 or 480 µg total dose, on both arms. This dose should be considered a reasonable dose.

With regard to non-hematologic toxicities, stomatitis/mucositis, diarrhea, infection, myalgia/arthralgia, edema, and neuropathy were all important toxicities in the taxane-containing arms of the included studies, especially in studies with concurrent anthracycline therapy. Patients should be monitored for these toxicities.

Other Issues

There are several issues regarding the choice of anthracycline-taxane regimen that have been addressed at least in part by the preliminary results of several recent trials. First, results from three trials (BCIRG 005, BIG 2-98, and Fountzilas et al) are now available that directly compare sequential anthracycline-taxane regimens with similar concurrent regimens. The preliminary results of the BIG 2-98 trial have demonstrated that A→D→CMF provides a superior DFS benefit compared to AD→CMF, with a lower incidence of febrile neutropenia. The efficacy results of the BCIRG 005 trial, once released, will be of particular interest, as
this trial compares regimens (DAC vs. AC→D) that are more relevant in North America than are the regimens in the BIG 2-98 trial.

With regard to the provision of colony-stimulating factors, whether or not pegylated G-CSF can be used as an alternative to G-CSF warrants some discussion. Two recent practice guidelines (51,52) have both suggested that either agent may be used as prophylaxis or as a treatment for febrile neutropenia. In the 2006 ASCO recommendations (52), colony-stimulating factors are recommended generally, without specifying either G-CSF or pegylated G-CSF, with the caveat for pegylated G-CSF being that “the safety and efficacy of pegylated G-CSF has not yet been fully established in the setting of dose-dense chemotherapy.” This guideline also suggested that pegylated G-CSF should be given once as a 6 mg dose 24 hours after the completion of chemotherapy.

Another issue of concern is the choice of a specific taxane. The preliminary results of the INT E1199 trial suggest that, at least when given sequentially with AC, the choice of a taxane and of a taxane schedule (weekly or three weekly) has little effect on the efficacy of the regimen. However, this trial does suggest that three-weekly docetaxel, at least at the dose used in this trial (100 mg/m²) may have the least favourable hematologic toxicity profile of all the taxane/schedule choices available. The question of whether the efficacy of other sequential regimens (FEC→T or E→T→CMF) is also taxane independent has not yet been addressed in a randomized trial.

Finally, as a review of Tables 2-6 demonstrates, a considerable number of different taxane-anthracycline combinations have been or are being evaluated in randomized controlled trials, but at this time, direct comparisons are not available. For example, which of AC→T, FEC→D, DAC, and so on, are superior, or whether these regimens are essentially interchangeable with regard to efficacy, is still an open question. Until such time as these taxane-anthracycline combinations are compared directly in randomized trials, the choice of a particular regimen for a particular patient will remain a complicated one.

ONGOING TRIALS

The results from sixteen trials included in this systematic review [BCIRG 005 (29), BIG 2-98 (30,31), ECOG 2197 (7,8), ECTO (9,10), Fountzilas et al (32), GEICAM 9805 (11), GEICAM 9906 (16,17,39), GOIM 9902 (18), INT E1199 (33,37), Lambert-Falls et al (34), Loesch et al (35,36), PACS 01 (21,22), PACS 04 (13), TACT (23) Taxit216 (24), USON 9734 (27,28,40)] are, to date, only available in abstract form. Therefore, these results should be considered subject to change until they are fully published in the peer-reviewed literature.

In order to identify additional ongoing or unpublished trials, the U.S. National Cancer Institute Clinical Trials Database (http://www.cancer.gov/search клинических программ/) and the Cochrane Central Register of Controlled Trials were searched for trials that would likely be included in this systematic review if their results were published. These trials, as well as trials identified through ASCO and SABCS annual meeting abstracts, are summarized in Table 13.
Table 13. Ongoing or unreported phase III trials of adjuvant taxane chemotherapy.

<table>
<thead>
<tr>
<th>Protocol ID and NLM Identifier</th>
<th>First Published</th>
<th>Trial Sponsor</th>
<th>Projected Accrual</th>
<th>Trial Status</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN-NCIC-MA21, NCT00014222 (53)</td>
<td>2001 Apr 1</td>
<td>NCIC</td>
<td>2,100 patients</td>
<td>Closed</td>
<td>FEC: E, F on day 1-8 and C day 1-14 q 4 weeks for 6 cycles. EC→T: E, C on day 1 with G-CSF q 2 weeks for 6 cycles, followed by T on day 1 with G-CSF q 3 weeks for 4 cycles. AC→T: A, C on day 1 q 3 weeks for 4 cycles, followed by T on day 1 q 3 weeks for 4 cycles. Note: Patients with haemoglobin &lt;13.0 g/dL also received epoetin alfa on EC→T arm.</td>
</tr>
<tr>
<td>ICCG-C/14/96, NCT00010140 (54)</td>
<td>2001 Feb 1</td>
<td>ICCG</td>
<td>800 patients</td>
<td>Closed</td>
<td>E: E on day 1 and 8 q 4 weeks for 6 cycles. E→D: E on day 1 and 8 q 4 weeks for 3 cycles, followed by D on day 1 q 3 weeks for 3 cycles.</td>
</tr>
<tr>
<td>NSABP-B-30, NCT00003782 (55)</td>
<td>1999 Apr 1</td>
<td>NSABP</td>
<td>5,300 patients</td>
<td>Closed</td>
<td>AC→D: A, C q 3 weeks for 4 cycles, followed by D q 3 weeks for 4 cycles. AD: A, D q 3 weeks for 4 cycles. DAC: D, A, C q 3 weeks for 4 cycles.</td>
</tr>
<tr>
<td>GEICAM 2003-02, NCT00129389 (56)</td>
<td>NR</td>
<td>GEICAM</td>
<td>1,920 patients</td>
<td>Active</td>
<td>FAC: F (500 mg/m²), A (50 mg/m²), C (500 mg/m²) on day 1 q 3 weeks for 6 cycles. FAC→T: FAC as above for 4 cycles followed by T (100 mg/m²) q week.</td>
</tr>
<tr>
<td>NSABP-B-38, NCT00093795 (57)</td>
<td>2004 Sep 25</td>
<td>NSABP</td>
<td>4,800 patients</td>
<td>Active</td>
<td>DAC: D, A, C on day 1 q 3 weeks for 6 cycles. AC→T: A, C on day 1 q 2 weeks for 4 cycles, followed by T on day 1 q 2 weeks for 4 cycles. AC→TG: AC as above, followed by T, G on day 1 q 2 weeks for 4 cycles.</td>
</tr>
<tr>
<td>SWOG-50221, NCT00070564 (58)</td>
<td>2003 Sep 24</td>
<td>SWOG</td>
<td>4,500 patients</td>
<td>Active</td>
<td>AC₂→T₂: A, C on day 1 q 2 weeks for 6 cycles, followed by T on day 1 q 2 weeks for 6 cycles. AC₁→T₂: A, C on day 1 q week for 15 cycles, followed by T as in AC₂→T₂. AC₂→T₁: A, C as in AC₂→T₂, followed by T on day 1 q week for 12 cycles. AC₁→T₁: A, C as in AC₁→T₂, followed by T as in AC₁→T₂.</td>
</tr>
<tr>
<td>LMU-ADEBAR, NCT00047099 (59)</td>
<td>2002 Oct 1</td>
<td>LMU</td>
<td>446 patients</td>
<td>Active</td>
<td>FEC: F, E, on day 1 and B and C on day 1-14 q 4 weeks for 6 cycles. EC→D: E, C on days 1 q 3 weeks for 4 cycles followed by D on day 1 q 3 weeks for 4 cycles.</td>
</tr>
<tr>
<td>Protocol ID and NLM Identifier</td>
<td>First Published</td>
<td>Trial Sponsor</td>
<td>Projected Accrual</td>
<td>Trial Status</td>
<td>Arms</td>
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</tbody>
</table>
| CALGB-40101, NCT00041119 (60) | 2002 Jul 1     | CALGB         | 4,646 patients   | Active      | AC₂: A, C on day 1 q 2 weeks for 4 cycles.  
AC₄: A, C on day 1 q 2 weeks for 6 cycles.  
T₄: T on day 1 q 2 weeks for 4 cycles.  
T₆: T on day 1 q 2 weeks for 6 cycles. |

Abbreviations: C, cyclophosphamide; CALGB, Cancer and Leukemia Group B; D, docetaxel; E, epirubicin; F, fluorouracil; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; G, gemcitabine; G-CSF, granulocyte colony-stimulating factor; GEICAM, El Grupo Español de Investigación en Cáncer de Mama; ICCG, International Collaborative Cancer Group; LMU, Ludwig-Maximillians Universität München; NCIC, National Cancer Institute of Canada; NSABP, National Surgical Adjuvant Breast and Bowel Project; SWOG, Southwest Oncology Group; T, paclitaxel.

An abstract by Samuelkutty et al from the 2005 SABCS (61) was identified that reports on a retrospective survey of patients identified in a trial that compared epirubicin and cyclophosphamide followed by docetaxel to CEF or CMF. However, it is not clear from this abstract if patients were randomized to CEF or CMF or whether the choice was made by some other method. If there were randomization to the CEF and CMF arms, then the CEF versus epirubicin and cyclophosphamide followed by docetaxel comparison in this trial would be eligible for inclusion in this systematic review once any non-retrospective results are published.

CONFLICT OF INTEREST
The authors disclosed potential conflicts of interest relating to this evidence-based series. Two of the lead authors (AE, KP) reported receiving grants, other research support, or sponsorship for conference participation, from pharmaceutical companies that manufacture the aromatase inhibitors covered by this review.

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For a complete list of the Breast Cancer DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

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46. Citron ML, Berry DA, Cirrincione C, Livingston RB, Gradishar W, Perez E, et al. Dose-dense (DD) AC followed by paclitaxel is associated with moderate, frequent anemia compared to sequential (S) and/or less DD treatment: update by CALGB on Breast Cancer Intergroup Trial C9741 with ECOG, SWOG & NCCTG [abstract]. J Clin Oncol. 2005;23(16 Suppl):A620


Evidence-based Series #1-7: Section 3

Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer: Guideline Development and External Review - Methods and Results


A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)


Report Date: December 15, 2006

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.
The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- **Section 1: Clinical Practice Guideline.** This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

- **Section 3: Guideline Development and External Review: Methods and Results.** This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Breast Cancer DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on adjuvant taxane therapy for women with early-stage, invasive breast cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Practitioner Feedback

Following the review and discussion of the draft practice guideline and systematic review, the Breast Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the DSG.

<table>
<thead>
<tr>
<th>BOX 1: DRAFT RECOMMENDATIONS (sent for external review June 21, 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Population</strong></td>
</tr>
<tr>
<td>Women with T 1-3, operable, node-positive breast cancer.</td>
</tr>
</tbody>
</table>

**Question #1: Compared with an anthracycline-based regimen, does a concurrent taxane-anthracycline regimen improve clinically meaningful outcomes?**

**Draft Recommendation**

- Based on the evidence of one large randomized controlled trial, available in abstract only at this time, women with early-stage lymph node-positive breast cancer, are recommended to receive six cycles of three-weekly docetaxel, doxorubicin, and cyclophosphamide (TAC) \((75/50/500\text{mg/m}^2)\) over six-cycles of three-weekly 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) \((500/50/500\text{mg/m}^2)\).

**Qualifying Statement**

- There are no data comparing epirubicin-based regimens such as FEC-100 or CEF to their epirubicin- and taxane-containing counterparts. There is also no evidence directly comparing 1) doxorubicin, cyclophosphamide, and a taxane to FEC-100 or CEF or 2) FAC to FEC-100 or CEF. Therefore, the FEC-100 and CEF regimens should remain options for women with node-positive breast cancer, particularly when three or more axillary lymph nodes are involved.
Question #2: Compared with a standard anthracycline-based regimen, does a sequential taxane-anthracycline regimen improve clinically meaningful outcomes?

**Draft Recommendation**
- For women with early-stage lymph node-positive breast cancer, four cycles of three-weekly doxorubicin and cyclophosphamide (AC) (60/600mg/m²) followed by four cycles of three-weekly paclitaxel (175mg/m² or 225mg/m²) is recommended over four cycles of three-weekly AC alone (60/600mg/m²).
- For women with early-stage lymph node-positive breast cancer, three cycles of FEC-100 followed by three cycles of docetaxel (100 mg/m²) is recommended over six cycles of FEC-100 alone.

**Qualifying Statements**
- For women with early-stage breast cancer, four cycles of three-weekly paclitaxel (250mg/m²) followed by four cycles of three- to four-weekly FAC (500/50/500mg/m²) (taxane (T)→FAC) may be equivalent to eight cycles of three- to four-weekly FAC; however, data are only available from one small randomized trial (n=524) for which only disease-free survival was reported (see M. D. Anderson Cancer Centre [MDACC] evidence below).
- There is no data as of yet comparing concurrent to sequential anthracycline-taxane therapy (TAC vs. T→AC).

Question #3: Compared with a three-weekly anthracycline-taxane regimen, does a dose-dense regimen improve clinically meaningful outcomes?

**Draft Recommendations**
- Women with early-stage lymph node-positive breast cancer should be considered for dose-dense therapy. In practice, four cycles of two-weekly AC (60/600mg/m²) followed by four cycles of two-weekly paclitaxel (175mg/m²) (AC→T) is more commonly used due to a shorter duration of treatment.
- Granulocyte-colony stimulating factor (G-CSF) (days three to 10 of each cycle [a total of seven doses] at 5μg/kg rounded to either 300μg or 480μg total dose) should be given in combination with four cycles of two-weekly AC→T to prevent neutropenia.

Question #4: Compared with an anthracycline-based regimen, does a non-anthracycline taxane regimen improve clinically meaningful outcomes?

**Draft Recommendations**
- There is insufficient evidence at this time to make any evidence-based recommendations regarding non-anthracycline taxane regimens versus anthracycline-based regimens.

**Qualifying Statement**
- For women with early-stage breast cancer, four cycles of three-weekly docetaxel and cyclophosphamide (75/600mg/m²) (TC) may be equivalent to four cycles of three-weekly AC (60/600mg/m²); however, data are only available from one randomized trial with short follow-up (see US Oncology [USON] evidence below).

Question #5: What are the harms associated with taxane regimens?
Draft Recommendations

- Women receiving an adjuvant anthracycline-taxane regimen should be closely monitored for febrile neutropenia. In those who experience febrile neutropenia while receiving TAC, G-CSF (days 3 to 10 of each cycle [a total of seven doses] at 5μg/kg rounded to either 300μg or 480μg total dose) should be administered with subsequent docetaxel infusions. Alternatively, a dose reduction should be considered.
- Women receiving an anthracycline-taxane regimen should also be monitored for other toxicities, including diarrhea, stomatitis, amenorrhea, asthenia, myalgia, paresthesia, and leukopenia.
- Women receiving TC should be monitored for paresthesia, edema, weight gain, rash, and arthralgia.

Qualifying Statement

- Given the high rates of febrile neutropenia, prophylactic G-CSF use in women receiving TAC might be beneficial.

Methods

Practitioner feedback was obtained through a mailed survey of 109 practitioners in Ontario (77 medical oncologists and 32 radiation and/or surgical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on June 21, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer Disease Site Group DSG reviewed the results of the survey.

Results

Fifty-two responses were received out of the 109 surveys sent (48% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 28 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>28 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>28 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>25 (89%)</td>
<td>2 (7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>21 (75%)</td>
<td>5 (18%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>21 (75%)</td>
<td>4 (14%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>20 (71%)</td>
<td>6 (21%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>
Summary of Written Comments, with Modifications or Actions Taken in Response

Thirteen respondents (46%) provided written comments. The main points contained in the written comments were:

1. Abstracts should not be used as a basis for recommendations.
   The Breast Cancer DSG is of the opinion that, although abstracts and presentations from conferences are often incomplete reports of the results of clinical trials, including these reports in the clinical decision-making process is reasonable and there are circumstances where the evidence from the abstracts and presentations is so compelling that new clinical recommendations are warranted.

2. The investigators on the Intergroup/CALGB 9741 trial (3-5) may have reported that the survival benefit for the dose dense AC→T regimen had disappeared with longer follow-up, and, therefore, the evidence in favour of this regimen, used for the recommendation associated with Question 3, was no longer valid.
   A search was made of the CALGB Web site, and no new relevant publications regarding that trial were identified. A new abstract was identified, but that abstract dealt solely with anemia and stated that the trial “demonstrated superior DFS and OS” for the dose-dense regimen.

3. Comment is needed regarding the hormone-receptor status analysis in the Intergroup/CALGB 9741 trial (3-5).
   No detailed subset analysis could be identified in any of the published reports of that trial. However, a sentence describing the results by estrogen-receptor status was added to the results section for that trial.

4. The document did not consistently refer to the fully published results of the BCIRG 001 trial (6), still stating that results had only been published in abstract form in places.
   The document was corrected for consistency.

5. Conclusions should be based on risk and not on entry criterion. Some node-negative patients will be at higher risk than some node-positive patients. An overwhelming amount of evidence indicates that whether or not the patient has axillary nodes that are positive or negative, the proportionate reduction in mortality with a given treatment is the same.
   The recommendations and conclusions of this practice guideline cannot exceed the evidence available. Only two of the trials covered in this practice guideline included node-negative patients (MDACC (7) and USON 9735 (8-10)) The evidence of those trials alone is insufficient to draw any conclusions regarding this patient population.

6. Further comment regarding the toxicity of dose-dense regimens, especially hand-foot syndrome, is necessary.
   Rates of hand-foot syndrome were not reported by the INT/CALGB 9741 trial (3-5), and therefore, this toxicity cannot be addressed.

7. The definition of “early-stage” should be made explicit, so that the population covered by these recommendations is clear.
A definition of the target population was added to the guideline.

8. *It is too early to gauge the toxicity associated with the dose-dense regimens. More follow-up is needed.*

While the Breast Cancer DSG agrees that longer follow-up will provide more information, the DSG believes the current evidence is sufficient to support the conclusions and recommendations that have been made.

**Review By Report Approval Panel (RAP)**

The final evidence-based series report was reviewed and approved by the PEBC Report Approval Panel (RAP) in January 2006. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues. Overall, the Panel agreed the report was a comprehensive document that covered complex literature. Two key issues were identified by both reviewers:

- Given the range of treatment options identified, the reviewers felt that it would be helpful if the group could put the recommended options in context, for example, through the use of an algorithm or examination of trade-offs between recommended treatments. However, the reviewers also acknowledged that the evidence that would provide such a context might not be available.

- The reviewers suggested that the group consider conducting broader meta-analyses (e.g., class-specific comparisons or meta-analyses to explore potential sub-group effects).

**Final Review by the Breast Cancer DSG**

During the final review process by the Breast Cancer DSG, several members raised concerns similar to those raised by the RAP regarding the array of treatment options. These members felt strongly that some overall statement about adjuvant chemotherapy was necessary to make the recommendations useful to clinicians.

**Response to Review by the Breast Cancer DSG and the RAP**

In response to the feedback from the Breast Cancer DSG and the RAP, a summary recommendation was added that presented overall guidance regarding taxanes in adjuvant chemotherapy. A new meta-analysis was not conducted, as the authors felt that it would not provide sufficient additional evidence to warrant new recommendations. The Breast Cancer DSG also recognized the need for a future practice guideline that would combine all the current recommendations for adjuvant systemic therapy and provide guidance to clinicians in selecting appropriate regimens.

**Policy Implications and Original Release**

In 2005, a draft of the practice guideline and systematic review were provided to the Cancer Care Ontario’s Drug Quality Therapeutics Committee (DQTC) as part of that committee’s deliberations regarding the funding in Ontario of 5-fluorouracil, epirubicin, and cyclophosphamide (500/100/500 mg/m²) (FEC-100) for three cycles followed by docetaxel (100 mg/m²) for three cycles as an adjuvant chemotherapy regimen for breast cancer. The practice guideline and systematic review were approved and released to the public on January 16, 2006.
2006 Revision

As part of the process of preparing the systematic review of this document for publication in a peer-reviewed journal, a new literature search was conducted and the evidence-based updated to May 2006. In response to the considerable amount of new evidence that had become available, several changes were made to the practice guideline. The most important of these changes were:

- Based on new evidence and the results of a meta-analysis, a general recommendation regarding the use of a taxane sequentially with an anthracycline-based regimen was added.
- A general recommendation regarding the use of prophylactic G-CSF with concurrent anthracycline/taxane regimens was added.
- A qualifying statement regarding pegylated G-CSF was added.

The authors of the document agreed that these changes were not significant enough to warrant new RAP approval or practitioner feedback.

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca
REFERENCES


### EBS 1-7 Document Assessment and Review Tool

#### DOCUMENT ASSESSMENT AND REVIEW TOOL

| Number and title of document under review | 1-7 Adjuvant Taxane Therapy for Women with Early-stage, Invasive Breast Cancer |
| Date of current version | 15 December 2006 |
| Clinical reviewers | Dr. Yolanda Madarnas  
Dr. Mihaela Mates |
| Research coordinator | Chika Agbassi |
| Date initiated | 14 July 2010 |
| Date and final results / outcomes | 20 May 2011 - ENDORSED |

Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. *Is there still a need for a guideline covering one or more of the topics in this document as is?*  
   
   **Answer Yes or No, and explain if necessary:**
   
   **1. YES**  
   
   If No, then the document should be **ARCHIVED** with no further action; **go to 11**.  
   
   If Yes, then **go to 2**.

2. *Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search?*  
   
   **Answer Yes or No, and explain if necessary:**
   
   **2. NO**  
   
   If Yes, the document can be **ENDORSED** with no further action; **go to 11**.  
   
   If No, **go to 3**.

3. *Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?*  
   
   **Answer Yes or No, and explain if necessary, providing references of known evidence:**
   
   **3. NO**  
   
   If Yes, the document should be taken off the Web site as soon as possible. A **WARNING** should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons.  
   
   If No, **go to 4**.

4. *Do current resources allow for an updated literature search to be conducted at this time?*  
   
   **Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:**
   
   **4. YES**  
   
   - there is a designated research co-ordinator at the PEBC to carry out the literature search  
   
   If No, a **DEFERRAL** should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis.  
   
   If Yes, **go to 5**.

5a. Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The Document Assessment and Review process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this is what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be **ARCHIVED** (i.e., go back to Q1 of this form and answer NO).

- **Add node-negative patients to the target population**

**Original Questions:**

1. Compared with a standard anthracycline-based regimen (e.g., doxorubicin and cyclophosphamide [AC], 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC], 5-fluorouracil, epirubicin, and cyclophosphamide
1. [500/100/500mg/m²] [FEC-100], or cyclophosphamide, epirubicin, 5-fluorouracil [75/60/100mg/m²] [CEF]), does a concurrent taxane-anthracycline regimen improve clinically meaningful outcomes (disease-free and overall survival)?

2. Compared with an anthracycline-based regimen, does a sequential taxane-anthracycline regimen improve clinically meaningful outcomes?

3. Compared with a standard (three-weekly) anthracycline-taxane regimen, does a dose-dense (two-weekly) regimen improve clinically meaningful outcomes?

4. Compared with an anthracycline-based regimen, does a non-anthracycline taxane regimen improve clinically meaningful outcomes?

5. What are the harms associated with adjuvant taxane regimens?

**Target Population:**
Women with T 1-3, operable, node-positive and node-negative, early non-metastatic breast cancer.

5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

- No changes to inclusion or exclusion criteria

**Inclusion criteria:**
Articles were eligible for inclusion in this systematic review of the evidence if they met the following criteria:

- An adjuvant taxane regimen was evaluated in a phase III randomized controlled trial. Meta-analyses of phase III randomized controlled trials were also eligible.
- Reported outcomes included disease-free survival, overall survival, or toxicity.
- Clinical trial results were reported in either full papers or abstracts.

**Exclusion criteria:**
Due to a lack of available translation resources, articles published in a language other than English were excluded.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

**Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):**
Articles were eligible for inclusion in this systematic review of the evidence if they met the following criteria:

- An adjuvant taxane regimen was evaluated in a phase III randomized controlled trial. Meta-analyses of phase III randomized controlled trials were also eligible.
- Reported outcomes included disease-free survival, overall survival, or toxicity.
- Clinical trial results were reported in either full papers or abstracts.

**Exclusion criteria:**
Due to a lack of available translation resources, articles published in a language other than English were excluded.

**Search Period:**
- 2006 to April 14, 2011 (Medline + Embase)
- 2006 to April 2011 (ASCO Annual Meeting)
- 2006 to 2010 (San Antonio Breast Cancer Symposium)

**Brief Summary/Discussion of New Evidence:**
Of 377 total hits from Medline + Embase and 59 total hits from ASCO + San Antonio conference abstract searches, 18 references representing 2 meta-analysis and 14 RCTs were found, of which 11 RCTs were already included in the existing guideline (rows highlighted in grey in the Table). 3 RCTs (one abstract and two full text publications) are potentially new studies.
<table>
<thead>
<tr>
<th>Interventions (mg/m²)</th>
<th>Name of RCT (median F/U)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>D (100) q3W x 4→EC (75/700) q3W x 4 vs FEC(700/75/700) q3W for 6 cycles</td>
<td>HORG (62 mos)</td>
<td>Stage II-III Node +ve, Aged 18-75 yrs ECOG PS 0-2 (n=756)</td>
<td>*DFS, OS toxicity</td>
<td>DFS: The D-EC arm was significantly better than the FEC arm; 72.6% (95%CI; 63.8-81.3%) vs 67.2% (95%CI; 58.0-76.4%) p=0.041 Toxicity; hematologic and non-hematologic toxicities were significantly more in the D-EC arm. OS: No significant difference.</td>
<td>Polyzos A, et al 2010</td>
</tr>
<tr>
<td>D(100) q3W for 4cycles →FEC(600/60/600) q3W for 3cycles vs. Vinorelbine(25) q3W for 4cycles →FAC(600/60/600) q3W for 3cycles</td>
<td>FinHer (62mos)</td>
<td>Node +ve, or high risk Node +ve, Aged &lt;65 yrs WHO PS &lt;1 (n=1010)</td>
<td>DFS</td>
<td>DFS: when compared with the VIN arm, the D arm demonstrated significant improvement in distant DFS (HR = 0.66; 95%CI, 0.49 to 0.91) p=0.01.</td>
<td>Joensuu H, et al 2009</td>
</tr>
<tr>
<td>E(50)d1 and 8 q4W x 6 →D(100)q3W x 3 vs E(50)d1 and 8 q4W x 6</td>
<td>DEVA (64.7mos)</td>
<td>Post menopausal node +ve (n=803)</td>
<td>*DSF, *OS Toxicity</td>
<td>DFS rate was significantly better in the E-D arm; 79.5% against 72.7% in the E arm. HR= 0.68 (95%CI; 0.52-0.91) p= 0.008 OS rates were 88.9% for E-D and 81.8 with significant survival reduction in favour of the E-D (HR = 0.66; 95%CI, 0.46-0.94) p=0.02 Toxicity: E-D was more toxic than E.</td>
<td>Coombe RC et al 2010 [Abstract]</td>
</tr>
<tr>
<td>DAC (75/50/500) q3W for 4cycles vs FAC (500/50/500) q3W for 6 cycles</td>
<td>GEICAM 9805 (77mos)</td>
<td>High risk node +ve (n=1060)</td>
<td>*DFS, OS toxicity</td>
<td>DFS: D arm demonstrated a 30% reduction in risk of recurrence when compared with the FAC arm (HR = 0.68, 95% CI; 0.49 - 0.93) p=0.01. OS: The difference was not significant. Toxicity: Grade 3 and 4 AE were seen more in the D arm p=0.001</td>
<td>Martin M, et al 2010</td>
</tr>
<tr>
<td>A (75) q3W for 4cycles →CMF (600/40/600)q4W for 8cycles vs T (200) plus A (60) q3W for 4cycles →CMF q4W for 8cycles or neoadjuvant paclitaxel + doxorubicin (200/60mg/m²) q4W x 4 →CMF</td>
<td>ECTO (76 mos)</td>
<td>Stage II-III Node +ve, or high risk Node +ve, Age &gt;18 yrs, K-PS &gt;70, tumour ≥2 cm (n = 1355)</td>
<td>RFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC(600/600/600) q3W x 4 →D (100) q3W x 4, vs FEC(600/600/600) q3W x 8 or E (100) q3W for 4cycles →CMF(600/40/600)q4W x 4</td>
<td>TACT (62 mos)</td>
<td>Node +ve, or high risk Node +ve, Aged &gt;18y (n = 4162)</td>
<td>DFS, OS, toxicity</td>
<td>DFS and OS did not differ between the two arms Acute grade 3/4 AE occurred more in the D arm.</td>
<td>Ellis P, et al 2009</td>
</tr>
<tr>
<td>FEC(600/90/600) q3W x 4 →T(100) qW x 8 vs FEC(600/90/600) q3W x 6</td>
<td>GEICAM 9906 (66m)</td>
<td>Node +ve, Aged 18-75y. (n=2887)</td>
<td>*DSF OS</td>
<td>•Addition of T to FEC significantly reduced the risk of relapse by 23% (HR=0.77, 95%CI; 0.62-0.95) p=0.022. •Distant DFS was significantly better in the T arm; 83.8% vs. 78.1% (HR=0.70; 95%CI; 0.54-0.90) P= 0.006 •OS was not significantly different between arms.</td>
<td>Martin M et al 2008</td>
</tr>
<tr>
<td>D(60) plus A (60) q3W x 4 vs. AC(60/600) q3W x 4</td>
<td>ECOG 2197 (79.5 mos)</td>
<td>Node +ve, or Node -ve tumour &gt; 1 cm, Age ≤ 60y ECOG PS ≤ 1 (n = 2882)</td>
<td>RFS, OS toxicity</td>
<td>DFS and OS were not significantly different between arms. However, grade 3 neutropenia associated with fever was more in the D arm.</td>
<td>Goldstein LJ et al. 2008</td>
</tr>
<tr>
<td>FEC(600/90/600) q3W x 3 →D (100) q3W, vs FEC(600/90/600) q3W x 6</td>
<td>PACS 01 (60mos)</td>
<td>Node +ve, or Node -ve tumour &lt; 1 cm, WHO PS&lt;2 (n=1999)</td>
<td>*DSF, OS</td>
<td>DFS rate was better in D arm (78.4%) than in FEC arm (73.2%); p=0.012 With an OS rate of 90.7% vs 86.7% , the D arm demonstrated a 27% reduction the RR of death; p=0.017. Toxicity: there were fewer cardiac events (p=0.03) arm and fewer grade 3/4 toxicities in the D.</td>
<td>Roche H et al 2006</td>
</tr>
</tbody>
</table>
### Dose dense taxane based

| AC (60/600) q3Wx 4 vs. DC (75/600) q3W 4 | USON 9734 (84mos) | Stage II-III I-BC (n=1016) | DFS, OS, toxicity | DFS: DC arm was significantly better than AC arm; 81% vs. 75% (HR = 0.74, 95% CI; 0.56 - 0.98) p=0.033; OS was also significantly better in the DC arm; 87% vs. 82% (HR = 0.69, 95% CI; 0.50 - 0.97) p=0.032. Age did not affect the superiority of DC over AC; however, older women had more febrile neutropenia with DC and more anemia with AC. | Jones S et al 2009, Jones S et al 2006 |

### Sequential versus Concurrent

| T (175) q3W for 4cycles vs. A (50) plus T (200) q3W for 4cycles AC (60/600) q3W for 12W | 64mos | Stage II-IIIA PS 0-1 (n=1830) | *DFS, OS, toxicity | DFS and OS: There were no significant differences in between the two arms. Toxicity: There were significantly more leucopenia, anemia shortness of breath, N/V and grade 3-4 neutropenia in the weekly T arm (p<0.01 each). | Loesch D, et al 2010 |

### Meta analysis

| Anthracyline: taxane based vs. Anthracyline. | # of RCTs | Inclusion CRit | DFS, OS, Toxicity | Addition of taxane significantly reduced the risk of recurrence HR = 0.83 (95%CI; 0.79 - 0.87; p<0.0001) and the risk of death HR = 0.85 (95%CI; 0.79 - 0.91; p<0.0001). Taxane type did not influence the result. Seq adm seemed better than Cc adm. | De Laurentiis et al 2008 |

| Taxane based vs. non-taxane based | 12 RCTs | Stage I-IIIA | DFS, OS, Toxicity | Taxane containing regimen was better in OS and DFS; OS: HR = 0.81 (95%CI; 0.75-0.88; p<0.00001) Het p=0.71, DFS: HR = 0.81 (95%CI; 0.77 -0.86; p=0.00001) Het p=0.42. Toxicity (grade 3 or 4): There was no difference in cardiotoxicity: OR=0.90. | Ferguson T, et al 2010 |
### New References Identified (alphabetical order):


Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of
plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.
12. Loesch D, Greco FA, Senzer NN, Burris HA, Hainsworth JD, Jones S, et al. Phase III multicenter trial of doxorubicin
plus cyclophosphamide followed by paclitaxel compared with doxorubicin plus paclitaxel followed by weekly
paclitaxel as adjuvant therapy for women with high-risk breast cancer. Journal of Clinical Oncology. 2010 Jun
20;28(18):2958-65.
fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer. Journal of
the National Cancer Institute.. 2008 Jun 4;100(11):805-14.
relapse related to adjuvant taxane treatment in node-positive breast cancer? Results of the CNS substudy in the
by epirubicin/cyclophosphamide as adjuvant chemotherapy in women with axillary node-positive early breast
docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. Journal of Clinical

Literature Search Strategy:
Medline (Apr 25 2011)
1. meta-analysis as topic.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ul]
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical
summar$ or quantitative synthes$ or quantitative overview?).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyc$ or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or
cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$ or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp breast neoplasms/
40. (breast? or mammary).tw.
41. 39 and 40
42. 38 or 41
43. (early or invasive).tw.
44. non-metast$.tw.
45. (node-negative or node-positive or operable or non-metastatic or T1 or T2 or T3).tw.
46. or/43-45
47. 42 and 46
48. (adjuvant or neoadjuvant).tw.
49. (Paclitaxel or docetaxel or taxol or taxotere or abraxane).tw.
50. exp Paclitaxel/ or exp docetaxel/ or exp taxol/ or exp taxotere/ or exp abraxane/
51. (taxane derivative or taxane based).mp.
52. or/49-51
53. 48 and 52
54. 47 and 53
55. 37 and 54
56. (200605$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
57. 55 and 56

**Embase (Apr 25 2011)**

1. exp meta analysi$ or metaanaly$).tw.
2. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview$).tw.
3. (systematic adj (review$ or overview$)).tw.
4. exp review/ or review.pt.
5. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
6. (study adj selection).ab.
7. 5 and (6 or 7)
8. 9 or/1-4,8
9. (cochrane or embase or psychlit or psyclit or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
10. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
11. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
12. randomization/ or single blind procedure/ or double blind procedure/
13. (random$ control$ trial$ or rct or phase III or phase IV or phase 3 or phase 4$).tw.
14. or/12-14
15. (phase I or phase 2$).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
16. 16 and random$.tw.
17. (clinic$ adj trial$).tw.
18. (sing$ or doubl$ or treb$ or trip$).adj (blind$ or mask$ or dummy$).tw.
19. placebo/
20. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. or/18-22
23. practice guidelines/
24. practice guideline?.tw.
25. practice guideline.pt.
26. or/24-26
27. 9 or 10 or 11 or 15 or 17 or 23 or 27
28. exp (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
29. 28 not 29
30. limit 30 to english
32. limit 31 to human  
33. exp breast neoplasms/  
34. (cancer? or carcinoma? or neoplasm? or tumor?).tw.  
35. (breast? or mammary).tw.  
36. 34 and 35  
37. 33 or 36  
38. (early or invasive).tw.  
39. non-metastat$.tw.  
40. (node-negative or node-positive or operable or non-metastatic or T1 or T2 or T3).tw.  
41. or/38-40  
42. 37 and 41  
43. (adjuvant or neoadjuvant).tw.  
44. (Paclitaxel or docetaxel or taxol or taxotere or abraxane).tw.  
45. exp Paclitaxel/ or exp docetaxel/ or exp taxol/ or exp taxotere/ or exp abraxane/  
46. (TAXANE DERIVATIVE or taxane based).mp.  
47. or/44-46  
48. 43 and 47  
49. 42 and 48  
50. 32 and 49  
51. (200621S or 2007S or 2008$ or 2009$ or 2010$ or 201104$).ew.  
52. 50 and 51

**San Antonio Breast Cancer Symposium** - searched [www.sabcs.org](http://www.sabcs.org) with keywords: adjuvant taxane OR paclitaxel OR Docetaxel

### Go to 6.

6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?  

| 6.NO | If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 7. |

7. On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:  

| 7.YES; increases support for taxane-containing regimens over anthracycline alone | If Yes, the document can be ENDORSED. If No, go to 8. |

8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:  

| 8.Not applicable; guideline endorsed. | If Yes, a WARNING note will be placed on the web site. If No, go to 9. |

9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:  

| 9. Not applicable. | If Yes, the document update will be DEFERRED, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10. |

10. An update should be initiated as soon as possible. List the expected date of completion of the update:  

| 10. Not applicable. | An UPDATE will be posted on the Web site, indicating an update is in progress. |
11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.

| DSG Approval Date: | 16 Sept 2011 |
DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

**STEPS**

**Outcomes**

**Action**

**STEP 1: Initiation of the Document Assessment & Review process**

**STEP 2: First teleconference to determine:**
- the clinical relevance of the guideline,
- if a new literature search is needed, and
- if Yes, the search criteria.

1. Is there still a NEED for a guideline covering one or more of the topics in this document?
   - Yes
   - No

   **Archive**

2. Are all the current recommendations based on the current questions definitive* or sufficient§, and have less than 5 years elapsed since the latest search?
   - Yes to all
   - No

   **Endorse**

3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?
   - Yes
   - No

   **Warning**

4. Do current resources allow for an updated literature search to be conducted at this time?
   - Yes
   - No

   **Deferral**

5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

   **New search**

   **STEP 3: A new literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date.**
FLOW CHART (cont.)

**STEPS** | **Outcomes** | **Action**
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**STEP 4: Second teleconference to determine the ultimate status of the document**

6. Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?

| Yes | Archive |
| No |  |

7. Does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?

| Yes to all | Endorse |
| No |  |

8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?

| Yes | Warning |
| No |  |

9. Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?

| Yes | Deferral |
| No |  |

10. An update should be initiated as soon as possible. List the expected date of completion of the update.

| Yes | Update |
| No |  |

**STEP 5: Final outcome approval; Document Assessment & Review questions #11**

11. Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.

| RC emails draft for DSG approval |  |

Please note: No teleconference needed, IF the reviewer(s) complete and return the form with answers & explanations.
DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

*DEFINITIVE RECOMMENDATIONS* - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “Archived”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool (Appendix 2).

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.