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## The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer Practice Guideline Report #1-20

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### SUMMARY

#### Guidelines Questions

In women with non-metastatic breast cancer who are candidates for neoadjuvant chemotherapy (refer to second bullet under “Qualifying Statements” section below):

1. Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes (clinical response, pathologic response, breast conservation, disease-free survival, or overall survival) relative to other neoadjuvant regimens?
2. Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to adjuvant taxane-containing regimens?
3. What is the preferred dose and schedule for neoadjuvant taxane administration?
4. What are the harms associated with neoadjuvant taxane-containing regimens?

#### Recommendations

- When neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or doxorubicin and cyclophosphamide (AC) chemotherapy regimen is planned for a woman with non-metastatic breast cancer, a neoadjuvant taxane (paclitaxel or docetaxel) should also be offered. Based on evidence from clinical trials, the following regimens are recommended:
  - Paclitaxel (80mg/m<sup>2</sup>), administered weekly for 12 weeks prior to the anthracycline-based regimen.
  - Docetaxel (100mg/m<sup>2</sup>), administered every three weeks for four cycles following the anthracycline-based regimen.
- There is no evidence at this time to suggest that one taxane is superior to the other in the neoadjuvant setting.

#### Qualifying Statements

- Since disease-free and overall survival data are limited, the recommendations for neoadjuvant taxane chemotherapy are often based on pathologic and clinical complete-response data.
- Neoadjuvant therapy is not the standard of care for operable breast cancer but is usually given to improve the likelihood of breast conservation for large operable breast cancer or to increase the possibility of operability for locally advanced or inflammatory breast cancer.

- There is no evidence in the neoadjuvant setting for the use of taxanes after optimally dosed anthracycline-based regimens, such as 5-fluorouracil, epirubicin, and cyclophosphamide (FEC-100 or CEF).
- The recommended schedule for paclitaxel therapy (i.e., weekly) is based on two trials of weekly versus three-weekly regimens. There were no direct comparisons available for docetaxel; therefore, the recommended schedule (i.e., three-weekly) is based on that which showed improved efficacy in trials comparing a docetaxel-containing regimen with a non-docetaxel regimen. The suggested doses for paclitaxel and docetaxel are those associated with the recommended schedule.
- While neoadjuvant paclitaxel and docetaxel are recommended in sequence with a standard anthracycline-based regimen, it may be appropriate to switch to an anthracycline-based regimen from paclitaxel or to docetaxel from an anthracycline-based regimen earlier if the patient's disease progresses while on the initial regimen.
- Tumours that fail to respond to two cycles of neoadjuvant therapy are likely resistant (in terms of subsequent pathologic complete response rates) to chemotherapy, including taxane-anthracycline combinations, vinorelbine, and capecitabine. For these patients, a novel therapy may be considered.
- The data supporting neoadjuvant taxane therapy are maturing. While results to date do not support an increase in adverse events relative to other settings, physicians should monitor patients carefully for toxicity, especially hematologic toxicity, neurologic toxicity (with paclitaxel), and hand-foot syndrome (with docetaxel).
- There is at present no literature to support the use of adjuvant taxane-based therapy for residual tumour found after neoadjuvant anthracycline-based therapy.
- This practice guideline report is based upon the reported neoadjuvant literature and cannot be extrapolated to endorse the use of adjuvant docetaxel after adjuvant anthracyclines. Studies exploring that sequence of treatments are underway.

### **Key Evidence**

- Nine randomized paclitaxel trials (five phase III and four phase II) were identified. Three trials compared neoadjuvant paclitaxel-containing regimens to other neoadjuvant regimens, one compared a neoadjuvant paclitaxel-containing regimen to a paclitaxel-containing adjuvant regimen, and five evaluated a neoadjuvant paclitaxel dose and/or schedule.
  - One of three trials with comparative data showed significantly improved complete pathologic response with neoadjuvant paclitaxel and epirubicin therapy compared with neoadjuvant 5-fluorouracil, epirubicin, and cyclophosphamide therapy (n=30).
  - Improved rates of breast conservation and nodal involvement at surgery were reported with neoadjuvant therapy in the only trial comparing neoadjuvant with adjuvant paclitaxel (n=923).
  - Of the five paclitaxel trials evaluating neoadjuvant dose and/or schedule, three reported statistically significant differences. The first detected improved pathologic and clinical complete response rates with weekly cisplatin, epirubicin, and paclitaxel therapy versus three-weekly epirubicin and paclitaxel therapy (n=130). The second reported superior pathologic complete response with weekly paclitaxel therapy followed by 5-fluorouracil, doxorubicin, and cyclophosphamide compared with three-weekly paclitaxel followed by 5-fluorouracil, doxorubicin, and cyclophosphamide (n=236). The third (n=475) reported superior pathologic complete response and breast conservation rates with sequential paclitaxel and epirubicin therapy compared with combination therapy.

- Nine randomized docetaxel trials (six phase III and three phase II) were identified. Seven trials compared neoadjuvant docetaxel-containing regimens to other neoadjuvant regimens, and two trials evaluated neoadjuvant docetaxel dose and/or schedule.
  - Of six docetaxel trials comparing a neoadjuvant docetaxel-containing regimen to other neoadjuvant regimens, two reported significant differences. The first reported improved clinical response, breast conservation, disease-free survival, and overall survival rates with neoadjuvant docetaxel therapy compared with neoadjuvant cyclophosphamide, vincristine, doxorubicin, and prednisolone in patients who received and responded to initial cyclophosphamide, vincristine, doxorubicin, and prednisolone (n=145). There was a trend towards improved complete pathologic response. A second trial demonstrated improved complete breast response, overall clinical response, and pathologic node status in women receiving neoadjuvant doxorubicin and cyclophosphamide followed by docetaxel compared with those receiving neoadjuvant doxorubicin and cyclophosphamide alone (n=2,255). Disease-free and overall survival was not reported.
  - Of two trials evaluating docetaxel dose and/or schedule, one (n=288) detected improved pathologic complete response and breast conservation with longer combination epirubicin and docetaxel therapy (six versus three cycles).
- One practice guideline was identified. The Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer report 15, *Treatment for Women with Stage III or Locally Advanced Breast Cancer*, endorsed the use of neoadjuvant anthracycline-based chemotherapy. As of September 2004, the Committee felt that there were insufficient data to make definitive recommendations concerning the use of taxane-containing regimens in locally advanced breast cancer; however, this was subsequently questioned.

### **Related Guidelines**

Practice Guidelines Initiative's Practice Guideline Report #1-3: *The Role of the Taxanes in the Management of Metastatic Breast Cancer*.

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## **PREAMBLE: About Our Practice Guideline Reports**

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.<sup>1</sup> The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

### Reference:

<sup>1</sup> Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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## FULL REPORT

### I. QUESTIONS

In women with non-metastatic breast cancer who are candidates for neoadjuvant chemotherapy:

1. Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes (clinical response, pathologic response, breast conservation, disease-free survival, or overall survival) relative to other neoadjuvant regimens?
2. Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to adjuvant taxane-containing regimens?
3. What is the preferred dose and schedule for neoadjuvant taxane administration?
4. What are the harms associated with neoadjuvant taxane-containing regimens?

### II. CHOICE OF TOPIC AND RATIONALE

Breast cancer is the most frequently diagnosed cancer among Canadian women. In 2004, it is estimated that 21,200 new cases and 5,200 deaths will occur as a result of the disease (1). Since 1993, incidence rates have stabilized and mortality rates have declined; in part due to the widespread development and use of adjuvant (postoperative) systemic therapy.

Neoadjuvant chemotherapy, also known as primary, induction, or preoperative chemotherapy, has been used in the treatment of locally advanced breast cancer (LABC) for many years (2,3). Improvements in clinical and pathologic response rates and breast conservation in these patients have led to the use of neoadjuvant chemotherapy in the treatment of patients with less advanced, operable breast cancer (4,5). Several practical and theoretical advantages provided the rationale for this approach over adjuvant chemotherapy. They included the following: 1) the response to treatment can be directly assessed by pathologic examination of the surgical specimen; 2) primary tumour and lymph node metastases may be down-graded to increase the possibility of operability (LABC) and breast conservation surgery (LABC and large operable breast cancer); 3) the efficacy of systemic therapy can be assessed in vivo; 4) the rapid growth of metastatic foci after removal of the primary tumour is potentially limited; 5) the emergence of chemo-resistant clones is potentially decreased; 6) tumour vasculature is more likely to be left intact; and 7) molecular markers of sensitivity and resistance to chemotherapy can be assessed using surgical specimens (6,7).

In general, anthracycline-based neoadjuvant regimens increased the likelihood of primary tumour and/or axillary lymph node response and breast conservation relative to adjuvant regimens (8-10). While clinical and pathologic response are correlated with overall and disease-free survival (DFS), studies have failed to show a direct survival benefit for neoadjuvant versus adjuvant anthracycline-based therapy (9-11). Thus, other active chemotherapy agents, particularly the taxanes, were considered for incorporation into anthracycline-based neoadjuvant chemotherapy regimens.

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*. In the adjuvant setting, randomized trials have shown improved disease-free and overall survival with the addition of paclitaxel or docetaxel to anthracycline-based regimens, in sequence (12,13) or in combination (14).

This practice guideline was developed to review the evidence for the use of taxanes as neoadjuvant treatment for women with non-metastatic breast cancer and make recommendations for their use.

### **III. METHODS**

#### **Guideline Development**

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (15). Evidence was selected and reviewed by two medical oncologist members and one research methodologist member of the PGI's Breast Cancer Disease Site Group (Breast Cancer DSG). Members of the Breast Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on neoadjuvant taxane chemotherapy developed through systematic reviews and evidence synthesis. The body of evidence in this report is comprised of randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

#### **Literature Search Strategy**

MEDLINE was searched to September 2004 using a disease-specific medical subject heading (MeSH) term ("breast neoplasms"), treatment-specific title or abstract terms ("induction chemotherapy" or "primary chemotherapy" or "neoadjuvant chemotherapy" or "preoperative chemotherapy"), and an agent-specific MeSH term ("taxoids"). The Excerpta Medica database (EMBASE) was also searched up to September 2004 using a disease-specific Excerpta Medica Tree (EMTREE) term ("breast cancer"), treatment specific keywords ("induction chemotherapy" or "primary chemotherapy" or "neoadjuvant chemotherapy" or "preoperative chemotherapy"), and agent-specific EMTREE terms ("paclitaxel" or "docetaxel"). These terms were then combined with the search terms for the following publication types: practice guideline, randomized controlled trial, systematic review, and meta-analysis.

Issue 3 (2004) of the Cochrane Library and online conference proceedings from the American Society of Clinical Oncology ([http://www.asco.org/ac/1,1003,\\_12-002095,00.asp](http://www.asco.org/ac/1,1003,_12-002095,00.asp); 1999-2004) and the San Antonio Breast Cancer Symposium (<http://www.sabcs.org/SymposiumOnline/index.asp#abstracts>; 2001-2003) were also searched. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

#### **Inclusion Criteria**

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

- A neoadjuvant taxane-containing regimen was evaluated using any of the publication types listed in the search strategy (practice guideline, randomized controlled trial, systematic review, or meta-analysis).

- Reported outcomes included rates of clinical response, pathologic response, breast conservation, DFS, or overall survival.
- 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. These data often appear first in meeting abstracts and may not be published for several years (16).

### **Exclusion Criterion**

Trials published in a language other than English were excluded.

### **Synthesizing the Evidence**

The trials of neoadjuvant taxane therapy were too clinically heterogeneous to pool.

## **IV. RESULTS**

### **Literature Search Results**

Eighteen randomized trials (17-37) and one practice guideline (38) were eligible for inclusion in this systematic review of the evidence and are summarized in Tables 1a to 3 (pages [pgs.] 14-18). No relevant systematic reviews or meta-analyses were found.

### **Randomized Controlled Trials**

The randomized controlled trials identified for inclusion in this guideline report, summarized in Tables 2 (pgs. 15-16) and 3 (pgs. 17-18) as well as Appendix A, included nine randomized paclitaxel trials (17-19,30-35) and nine randomized docetaxel trials (20-29,36,37). Of note, the results of the Aberdeen trial were uniquely reported in four sources (23-26). Randomized controlled trial characteristics, study quality, and efficacy outcomes will be described below according to guideline question, with the exception of question 4.

### ***Interpreting the Evidence***

The definitions of pathologic and clinical response of the primary tumour and/or nodes varied from study to study. Those variations have a substantive impact on how the evidence was interpreted. Across the 18 randomized controlled trials eligible for inclusion (17-37), three different definitions of clinical response (Table 1a, pg. 15), two different definitions of pathologic response involving the primary tumour (Table 1b, pg. 15), and two different methods of assessing axillary lymph node involvement at surgery (Table 1c, pg. 15) were used. In a study by Chollet et al, pathologic complete response rates were 20% or 40% depending on whether lymph node response and the presence of ductal carcinoma in situ (DCIS) was or was not included in the classification, respectively (39). Furthermore, complete pathologic response rates were 26%, 13%, and 15% or 19%, 9%, and 10% in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial, depending on whether the presence of DCIS was included or not, respectively (22). Thus, it is essential that the pathologic, clinical, and node-specific response outcomes used in each trial be considered when interpreting individual study outcomes.

### ***Clinical Response (Table 1a, pg. 15)***

Of 16 trials that measured and reported clinical response (17-32,34,36,37), the NSABP B-27 and the Anglo-Celtic Cooperative Oncology Group (ACCOG) were the only groups to use the more exclusive clinical response criteria, where primary tumour and node response are included in the definition of complete and partial clinical response (22). The remaining trials defined clinical response according to the Unio Internationalis Contra Cancrum (UICC) criteria, where only primary tumour response in the breast is considered (40).

### *Pathologic Response (Table 1b, pg. 15)*

Ten trials explicitly defined complete and partial pathologic responses (17,22,25,27,30,32-35,37). Two trials excluded DCIS as well as invasive disease from their definition of complete pathologic responses (34,37). Two included lymph node response in their definition (34,35).

### *Node Response (Table 1c, pg. 15)*

Twelve trials measured and reported axillary lymph node involvement (17,20,21,23-26,30,31,33-37). As previously mentioned, the Green et al M.D. Anderson and the Romieu et al trials were the only studies to include lymph node response in their definition of pathologic response (34,35). Three studies measured and reported pathologic node response separate from primary tumour response (21,23-26). The seven remaining trials reported pathologic nodal involvement without attempting to account for response attributable to neoadjuvant chemotherapy.

## **Question 1: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to other neoadjuvant regimens?**

### *Trial characteristics*

Treatment arms, patient eligibility criteria, and patient characteristics are summarized in Table 2 (pgs. 15-16). Due to the complexity of and differences in treatment arms, they will be described in detail below.

For both the paclitaxel and docetaxel trials, neoadjuvant chemotherapies were followed by local surgical therapy. Radiotherapy, adjuvant chemotherapy, and hormone therapy were sometimes administered, often at the treating physician's discretion. More detailed treatment data, including dose and schedule, are described in Appendix A.

### Paclitaxel (three trials)

The M.D. Anderson trial reported by Buzdar et al compared neoadjuvant paclitaxel alone with neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) (17). Poulillart et al evaluated paclitaxel in combination with doxorubicin and doxorubicin in combination with cyclophosphamide (AC) (18). Malamos et al administered paclitaxel and epirubicin compared to 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) (19).

### Docetaxel (seven trials)

Two trials randomized patients based on their response to initial chemotherapy. In the Aberdeen trial, four cycles of cyclophosphamide, vincristine, doxorubicin, and prednisolone (CVAPr) were given to the entire sample (23-26). Responders (women exhibiting a complete or partial clinical response) were randomized to receive further CVAPr or docetaxel alone, whereas non-responders received docetaxel. Similarly, in the German Pre-operative Adriamycin Docetaxel-TRIO Trial (GEPAR-TRIO), docetaxel, doxorubicin, and cyclophosphamide in combination (TAC) was given to the entire sample; after two cycles of TAC, responders were given further TAC, while non-responders were randomized to receive either further TAC or vinorelbine and capecitabine in combination (27).

The NSABP B-27 study evaluated the effect on response of adding neoadjuvant docetaxel to neoadjuvant doxorubicin and cyclophosphamide (22). This trial included three arms; doxorubicin and cyclophosphamide were administered to the entire sample followed by neoadjuvant docetaxel (arm i), adjuvant docetaxel (arm ii), or no further neo- or adjuvant chemotherapy (arm iii). Arms ii and iii were combined for the analyses.

Three studies evaluated docetaxel in combination with doxorubicin. The first compared neoadjuvant docetaxel and doxorubicin to neoadjuvant cyclophosphamide and doxorubicin (20), the second compared doxorubicin and docetaxel with FAC (28), and the third evaluated neoadjuvant epirubicin and docetaxel against neoadjuvant FEC (29).

Lee et al compared combination docetaxel/capecitabine with combination doxorubicin/cyclophosphamide therapy (21).

### *Study quality*

#### Paclitaxel (three trials)

Only one (17) of the three studies (18,19) that evaluated neoadjuvant taxane and non-taxane regimens was a phase III design. Both randomized phase II trials were reported in abstract form, and the results for one (19) were interim (accrual ongoing). Since abstracts describe little in the way of methodology, the more detailed discussion on study quality in this section and those following will focus on full reports only.

The strengths of the M.D. Anderson trial reported by Buzdar et al include: enough patients were accrued to detect clinically meaningful differences in outcomes; potential confounding due to patient age, tumour size, and node status was controlled for by stratification prior to randomization; and intention-to-treat analysis was used to avoid bias due differential rates in patient drop-out (17). Criticisms of the report include: the method of randomization was not described; blinding to treatment was not employed; and the p-value criterion or confidence interval (CI) calculation was not adjusted for multiple comparisons. Also of note, the M.D. Anderson trial was supported by a pharmaceutical company research grant.

#### Docetaxel (seven trials)

Five (20-26,28) of seven (27,29) docetaxel studies were phase III randomized trials. The methods and findings of five were published in abstract form only (20,21,27-29), three of which reported interim rather than final analyses (21,28,29).

While the Aberdeen trial did analyze outcomes on an intention-to-treat basis, it failed to report adequate power to detect meaningful differences, stratification prior to randomization, and adjustment to the p-value criterion or CI calculation to compensate for the analysis of several outcome variables (23-26). The Aberdeen trial was funded by a pharmaceutical company.

The strengths of the NSABP B-27 trial include: the sample size was adequate to detect meaningful differences (while statistical power was not reported the study was very large [n=2,411]) and potential confounding due to node status, tumour size, and estrogen-receptor status was controlled for. Possible criticisms include the failure to adjust the p-value criterion or CI calculation to account for the analysis of several outcome variables and the exclusion of patients who did not complete their treatment. Support for the trial was from a government source.

### *Efficacy outcomes*

Available efficacy data are summarized in Table 3 (pgs. 17-18). Key findings are described below under the headings *Response*, *Breast conservation*, and *Survival*.

#### Response

##### Paclitaxel (three trials)

Three studies evaluated neoadjuvant paclitaxel therapy relative to other regimens. The smallest trial (n=30, accrual ongoing) reported a statistically significant improvement in pathologic complete response (pCR) with paclitaxel and epirubicin therapy compared to FEC therapy (25% versus [vs.] 0%; p-value not reported) but no difference in pathologic partial response (pPR) (19). In the Pouillart et al trial (n=247), accrual into the AC arm (but not the doxorubicin and paclitaxel arm) was stopped prematurely due to a lack of response. While p-values were not reported, rates of pCR and clinical overall response appeared higher with doxorubicin and paclitaxel compared with AC (18). Of note, the Buzdar et al M.D. Anderson trial (n=174)

reported rates of pCR which appeared to favour FAC over paclitaxel alone (difference, 8%; 95% CI, -18.5 to 1.5%; p-value not reported) (17).

#### Docetaxel (seven trials)

While not significant at the 5% level, the Aberdeen trial results (n=97) suggested improved pCR with CVAPr followed by docetaxel versus CVAPr followed by CVAPr (31% vs. 15%; p=0.06). Overall clinical response was also higher in the first arm (85% vs. 64%; p=0.001) (26). The ACCOG trial found equivocal rates of pCR but improved clinical overall response with doxorubicin and docetaxel versus AC (71% vs. 61%; p=0.06) (20). Lee et al (n=65, accrual ongoing) (21), Bouzid et al (n=362, accrual ongoing) (28), and Luporsi et al (n=50, accrual ongoing) (29) reported no significant differences in pathologic or clinical response rates at the time of their interim analyses.

In the NSABP B-27 trial (n=2,411), a pCR occurred in 26% of patients who received neoadjuvant docetaxel in addition to AC (arm i) compared to 15% in the AC followed by surgery and adjuvant docetaxel group (arm ii) and 13% in the AC followed by surgery alone group (arm iii) (p<0.001 for arm i vs. arms ii and iii) (22). Clinical overall response followed the same pattern, with improved rates in the neoadjuvant docetaxel arm (p<0.001 for arm i vs. arms ii and iii).

Of four trials that measured and reported axillary lymph node involvement, only the NSABP B-27 trial reported significant differences. Women who received neoadjuvant docetaxel after AC were more likely to be node negative at the time of surgery compared with women who received AC alone (58% vs. 51%; p<0.001) (22).

#### Breast conservation

##### Paclitaxel (three trials)

Two (17,18) trials reported rates of breast-conserving surgery that appeared to favour neoadjuvant paclitaxel. In the M.D. Anderson trial reported by Buzdar et al, 46% of women who received paclitaxel underwent breast-conserving surgery compared with 35% of women who received FAC (p-value not reported). In the Pouillart et al trial, 56% and 45% of women who received doxorubicin and paclitaxel and AC underwent breast-conserving surgery, respectively (p-value not reported).

##### Docetaxel (seven trials)

Six (20-22,25,27,29) trials reported rates of breast conservation. In the Aberdeen trial, patients with tumours that responded to four cycles of CVAPr and who were randomized to docetaxel, were more likely to undergo breast conservation compared with patients who were randomized to receive further CVAPr (67% vs. 48%; p<0.01) (25). Two of the four remaining trials reported rates of breast conservation that appeared to favour the docetaxel treatment arm; however, p-values were not reported (27,29). The Lee et al, NSABP B-27, and ACCOG trials did not detect significant differences in breast-conservation rates (20-22).

#### Survival

##### Paclitaxel (three trials)

DFS was assessed in one trial; no significant difference between paclitaxel alone or FAC was detected (17). Overall survival was not reported in any of the trials investigating paclitaxel.

##### Docetaxel (seven trials)

Three trials reported disease-free and/or overall survival data (20,23,26,28). At 38 months, the Aberdeen trial reported significantly higher overall survival rates in CVAPr-responders who received docetaxel compared with those who received further CVAPr (97% vs. 84%; p=0.02) (23). At a median follow-up of 65 months, the difference was still statistically significant (93% vs.

78%;  $p=0.04$ ) (26). DFS was also significantly higher among CVAPr-responding women who received neoadjuvant docetaxel (90% vs. 77%;  $p=0.03$ ) (23).

At a median follow-up 32 months, the ACCOG trial detected no significant differences in DFS (75% vs. 69%,  $p=NS$  [not statistically significant]) or overall survival (86% vs. 84%,  $p=NS$ ) with docetaxel and doxorubicin versus AC, respectively (20). Similarly, Bouzid et al reported no significant difference between the median number of months progression free in the doxorubicin and docetaxel arm compared with the FAC arm (8.3 months vs. 6.9 months;  $p$ -value not reported) (28).

**Question 2: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to adjuvant taxane-containing regimens?**

*Treatment characteristics*

Treatment arms, patient eligibility criteria, and patient characteristics are summarized in Table 2 (pgs. 15-16). Treatment arms are also described below.

Paclitaxel (one trial)

In the European Cooperative Trial in Operable Breast Cancer (ECTO) trial, neoadjuvant doxorubicin and paclitaxel followed by cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) was compared to adjuvant doxorubicin and paclitaxel followed by CMF, or adjuvant doxorubicin alone followed by CMF (30).

Docetaxel (no trials)

As previously described, the NSABP B-27 trial randomized patients to three treatment arms, two of which, when compared, will provide data on the effect of neoadjuvant versus adjuvant docetaxel (22). Since only pooled response data for arms ii and iii are available, the impact of neoadjuvant versus adjuvant therapy cannot be determined. It is likely that future NSABP B-27 publications will provide arm-specific follow-up data that compare docetaxel in those settings.

*Study quality*

The ECTO trial is a phase III design, the results for which are available in abstract form only.

*Efficacy outcomes*

Efficacy outcomes are summarized in Table 3 (pgs. 17-18). The ECTO trial ( $n=892$ ) found significantly different rates of nodal involvement at surgery; 61% of patients who received neoadjuvant paclitaxel and doxorubicin were node-negative at surgery compared with 38% of patients who received no neoadjuvant chemotherapy ( $p=0.0001$ ) (30). Breast conservation was more likely in women who received neoadjuvant paclitaxel and doxorubicin compared with no neoadjuvant chemotherapy (71% vs. 35%;  $p<0.0001$ ) (30).

**Question 3: What is the preferred dose and schedule for neoadjuvant taxane administration?**

*Treatment characteristics*

Treatment arms, patient eligibility criteria, and patient characteristics are summarized in Table 2. Treatment arms are also described below.

Paclitaxel (five trials)

The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) trial evaluated high-dose sequential versus standard-combination paclitaxel regimens (33). Specifically, three cycles of epirubicin ( $150\text{mg}/\text{m}^2$ , every 2 weeks [q2w]) followed by three cycles of paclitaxel ( $250\text{mg}/\text{m}^2$ , q2w) were compared with four cycles of three-weekly epirubicin ( $90\text{mg}/\text{m}^2$ ) and paclitaxel ( $175\text{mg}/\text{m}^2$ ) in combination (33).

The Southern Italy Cooperative Oncology Group (SICOG) 9908 trial and the Green et al M.D. Anderson trial compared lower-dose, weekly paclitaxel regimens with higher-dose three-weekly regimens (31,35). Specifically, the SICOG 9908 trial randomized women to receive 12 weekly cycles of cisplatin (30mg/m<sup>2</sup>), epirubicin (50mg/m<sup>2</sup>), and paclitaxel (120mg/m<sup>2</sup>) in combination or four three-weekly cycles of epirubicin (90mg/m<sup>2</sup>) and paclitaxel (175mg/m<sup>2</sup>) in combination (31). The M.D. Anderson Green et al study administered weekly paclitaxel (150mg/m<sup>2</sup> or 80mg/m<sup>2</sup>) followed by FAC versus three-weekly paclitaxel (225mg/m<sup>2</sup>) followed by FAC (35).

Romieu et al evaluated four and six cycles of doxorubicin and paclitaxel (200mg/m<sup>2</sup>, q3w) (34) whereas Stearns et al administered three cycles of doxorubicin followed by three cycles of paclitaxel therapy (250 mg/m<sup>2</sup> or 175 mg/m<sup>2</sup>, q3w) or the reverse (32).

#### Docetaxel (two trials)

The Austrian Breast Cancer Study Group (ABCSG)-14 trial compared six versus three cycles of three-weekly epirubicin (75mg/m<sup>2</sup>) and docetaxel (75mg/m<sup>2</sup>) (36). Miller et al evaluated four cycles of three-weekly doxorubicin (75mg/m<sup>2</sup>) and docetaxel (100mg/m<sup>2</sup>) combination therapy or three cycles each of two-weekly doxorubicin (56mg/m<sup>2</sup>) and docetaxel (75mg/m<sup>2</sup>) in sequence (37).

#### *Study quality*

##### Paclitaxel (five trials)

Three (31,33,35) of the five (32,34) trials were phase III designs. Only one trial was fully published (32). The SICOG 9908 and AGO trials reported interim rather than final analyses (31,35). Of note, 160 women are enrolled in the SICOG 9908 trial; however only 130 had undergone surgery at the time of analysis.

The strengths of the Stearns et al trial include control for potential confounding due to menopausal status and lesion stage and intention-to-treat analyses (32). Potential criticisms include the method of randomization was not reported, the sample size estimation was not described, the treatment was not blinded, and the p-value criterion or CI calculation was not adjusted for the analysis of several outcome variables. Of note, the trial was funded by (investigator-initiated) pharmaceutical company grants and government grants.

#### Docetaxel (two trials)

The ABCSG-14 trial is a phase III design, published in abstract form (36), whereas the Miller et al trial is a randomized phase II design, fully published in a peer-reviewed journal (37).

Miller et al reported sample size estimation and power to detect differences (37). Potential confounding due to the method of biopsy and tumour size was controlled for by stratification prior to randomization. Treatments were not blinded, and the method of randomization was not reported. No adjustments were made to the p-value criterion or CI calculation to account for the multiple comparisons that arise from the analysis of several outcome variables. Support for the trial came from a pharmaceutical company research grant.

#### *Efficacy outcomes*

Available efficacy data are summarized in Table 3 (pgs. 17-18). Key findings are described below under the headings *Response* and *Breast conservation*.

#### Response

##### Paclitaxel (five trials)

The SICOG 9908 trial (n=130) reported significantly higher rates of pCR (16% vs. 4%, p=0.03) and cCR (29% vs. 15%, p=0.05) with 12 cycles of lower-dose weekly cisplatin, epirubicin, and paclitaxel combination therapy versus four cycles of higher-dose three-weekly epirubicin and

paclitaxel (31). Similarly, the M.D. Anderson trial by Green et al (n=118) found significantly improved pCR rates, defined according to the Chevallier classification system, in weekly versus three-weekly paclitaxel followed by FAC (29% vs. 14%,  $p<0.01$ ) (35).

The AGO trial (n=475; accrual ongoing) detected significantly higher rates of pCR in the dose-dense sequential therapy arm compared to the standard therapy arm (18% and 10%, respectively;  $p=0.03$ ) (33). Romieu et al (n=232) reported pCR rates of 17% versus 24% (Sataloff classification) and 11% versus 16% (Chevallier classification) in patients who received four and six cycles of doxorubicin and paclitaxel, respectively (p-values not reported) (34). Clinical response was 32% versus 20% in the six-cycle group and four-cycle groups, respectively (p-value not reported). Stearns et al (n=29) reported no significant differences in complete and partial pathologic responses when paclitaxel preceded doxorubicin or vice versa (10% vs. 7% and 7% vs. 17%, respectively; p-values not reported) (32).

Node response was reported in two trials (31,33). Untch et al reported rates of 51% and 42% at the time of surgery in their dose-dense sequential and standard dose arms, respectively ( $p=0.098$ ) (33). The SICOG 9908 trial reported that 17 women in the weekly arm versus 14 women in the three-weekly arm were node negative at the time of surgery (31).

#### Docetaxel (two trials)

In the ABCSG-14 trial (n=288), the rate of pCR was higher in the six-cycle epirubicin-docetaxel arm versus the three-cycle arm (19% vs. 8%;  $p=0.0045$ ). Miller et al (n=40) did not detect any significant differences in clinical or pathologic response rates between the combination versus sequential doxorubicin and docetaxel chemotherapy arms (37).

The ABCSG-14 trial reported significantly higher rates of node negativity at surgery with six versus three three-weekly cycles of epirubicin and docetaxel (57% vs. 43%;  $p=0.02$ ) (36). In the Miller et al trial, 19% of women who received combination therapy were node negative at surgery compared with 53% of women who received sequential therapy (p-value not reported) (37). On average, 2.17 versus 4.81 nodes were positive in the combination and sequential groups, respectively ( $p=0.037$ ).

#### Breast Conservation

##### Paclitaxel (five trials)

Two trials reported comparative breast conservation data. The AGO trial detected a higher rate in women who received dose-dense sequential epirubicin and paclitaxel compared with standard-dose epirubicin and docetaxel (66% vs. 55%;  $p=0.016$ ) (33). In the Romieu et al trial, breast conservation was achieved in 64% of patients who received six cycles of doxorubicin and docetaxel compared with 61% of patients who received only four cycles (p-value not reported).

##### Docetaxel (two trials)

While there was a slight trend towards improved rates of breast conservation in the ABCSG-14 trial, the rates of breast conservation in the six- and three-cycle groups were not significantly different at the 5% level (76% vs. 67%;  $p=0.1$ ) (36). In the Miller et al trial, 19% of women who received doxorubicin and docetaxel in combination underwent breast conservation compared with 37% of women who received sequential therapy ( $p=NS$ ) (37).

#### **Question #4: What are the harms associated with neoadjuvant taxane-containing regimens?**

The adverse events assessed were inconsistent across the trials, and p-values were rarely reported. Often trials administered supportive agents, such as antibiotics, antiemetics, or growth factor to prevent or alleviate adverse events due to chemotherapy. A comprehensive description of all agents administered is beyond the scope of this document; however, given the relevance

of neutropenia, the use of growth factor support will be noted in the following summaries. No trials reported quality of life data.

The following sections highlight differential rates of hematologic, cardiac, neurologic, gastrointestinal, and other toxicity in the paclitaxel and docetaxel trials.

### *Paclitaxel*

#### Hematologic toxicity

##### Neutropenia/febrile neutropenia

Neutropenia data was available for seven (17,30-35) of the nine paclitaxel trials (18,19). Neoadjuvant taxane therapy appeared to be associated with higher rates of grade 3 and/or 4 febrile neutropenia in two trials; however, p-values were not reported (17,30).

In the Buzdar et al M.D. Anderson trial, 53% of women receiving paclitaxel (250mg/m<sup>2</sup> q3wx4) versus 21% of those receiving FAC experienced neutropenic fever. Granulocyte colony-stimulating factor (G-CSF) was administered if patients had neutropenic fever in a previous cycle or was used prophylactically (17). Women receiving paclitaxel were more likely than those receiving FAC to receive G-CSF (56% vs. 25%; p-value not reported).

In the ECTO trial, 9% of women receiving doxorubicin and paclitaxel (200mg/m<sup>2</sup> q3wx4) followed by CMF experienced febrile neutropenia compared with 5% in those receiving doxorubicin alone followed by CMF(30).

##### Anemia

Anemia data was reported in three trials (31,33,34), one of which detected differential rates (31). The SICOG 9908 trial reported “substantially more frequent” severe anemia in lower-dose cisplatin-epirubicin-paclitaxel (120mg/m<sup>2</sup> q1wx12) arm than in the higher-dose three-weekly epirubicin-paclitaxel (175mg/m<sup>2</sup> q3wx4) arm.

##### Cardiotoxicity

One (18) of four (17,30,34) trials reporting on cardiotoxicity data detected a slight trend towards more adverse cardiac events with neoadjuvant taxane therapy. Pouillart et al reported abnormal left ventricular fraction values in 8% and 5% of the women receiving a neoadjuvant doxorubicin and paclitaxel (200mg/m<sup>2</sup> q3wx4) combination versus those receiving AC, respectively (18). One patient in the doxorubicin-cyclophosphamide arm experienced congestive heart failure.

##### Neurotoxicity

Three (17,30,31) of six trials (32-34) reported neurotoxicity rates that appeared different (p-values not reported). The Buzdar et al M.D. Anderson trial reported grade 2 paresthesias in 46% of women receiving paclitaxel (250mg/m<sup>2</sup> qw3x4) versus 8% of those receiving FAC (17). Severe neurotoxicity was less common, with only 5% and 1% experiencing grade 3 paresthesias, respectively.

Similar to the M.D. Anderson trial findings, grade 2 neurotoxicity occurred in 23% and 5% of women in the ECTO trial who received doxorubicin and paclitaxel (200mg/m<sup>2</sup> q3wx4) followed by CMF or doxorubicin alone followed by CMF therapy (30). Grade 3 neurotoxicity rates were 2% and 0%, respectively.

Peripheral neuropathy was “substantially more frequent” in the SICOG 9908 lower-dose weekly cisplatin-epirubicin-paclitaxel (120mg/m<sup>2</sup> q1wx12) arm than in the higher-dose three-weekly epirubicin-paclitaxel (175mg/m<sup>2</sup> q3wx4) arm (31).

##### Gastrointestinal toxicity

Two (17,31) of three trials (32) that reported on gastrointestinal toxicity appeared to find differential rates of gastrointestinal toxicity. In the Buzdar et al M.D. Anderson trial, rates of grade 3 stomatitis (16.9% vs. 13%), nausea (21% vs. 10%), vomiting (7% vs. 2%), and diarrhea

(16% vs. 3%) appeared to be higher in the FAC group than in the paclitaxel (250mg/m<sup>2</sup>, q3wx4) group, respectively (44). Conversely, gastrointestinal toxicity was “substantially more frequent” in the SICOG 9908 cisplatin-epirubicin-paclitaxel (120mg/m<sup>2</sup> q1wx12) arm than in the higher-dose three-weekly epirubicin-paclitaxel (175mg/m<sup>2</sup> q3wx4) arm (31).

#### Other toxicities

The M.D. Anderson trial by Buzdar et al reported grade 3 infection rates of 9% and 5% in the paclitaxel (250mg/m<sup>2</sup>, q3wx4) and FAC arms, respectively.

Of note, the M.D. Anderson trial by Green et al found lower rates of toxicity in the 80mg/m<sup>2</sup> weekly arm compared with the 150mg/m<sup>2</sup> weekly arm (personal communication: Green, 2002). No trials reported any incidents of death due to toxicity.

#### *Docetaxel*

##### Hematologic toxicity

##### Neutropenia/febrile neutropenia

Six (21,22,25,27,28,37) of nine (20,29,36) trials reported differential rates of neutropenia for the regimens each compared. Lee et al lower detected rates of grade 3 and/or 4 neutropenia in the docetaxel (75mg/m<sup>2</sup>) and capecitabine arm (77%), with the AC arm (94%) (p-values not reported) (21).

In the NSABP B-27 trial, febrile neutropenia was significantly more frequent in the neoadjuvant docetaxel and AC arm compared with the AC-only arm (21% vs. 7%, p-value not reported). Rates of G-CSF support were approximately the same (21 vs. 18% respectively, p-value not reported) (22).

In the Aberdeen trial, Grade 3 or 4 granulocytopenia (p=0.006) was more common in patients who received eight cycles of CVAPr compared with those who received CVAPr followed by four cycles of docetaxel (100mg/m<sup>2</sup> q3wx4) (25).

In the GEPAR-TRIO trial, grade 3 or 4 neutropenia seemed to occur more frequently in the non-responders who received TAC followed by vinorelbine and capecitabine compared with non-responders who received vinorelbine and capecitabine alone (76% vs. 33%; p-value not reported) (27).

Bouzid et al reported higher rates of grade 3 or 4 neutropenia (71% vs. 25%; p-value not reported) and febrile neutropenia (10% vs. 0%; p-value not reported) with doxorubicin and docetaxel (75mg/m<sup>2</sup> q3wx4) than with FAC (28).

Miller et al reported significantly more granulocytopenia in their combination doxorubicin and docetaxel arm (100mg/m<sup>2</sup>) than in their sequential doxorubicin and docetaxel arm (75mg/m<sup>2</sup>) (grade 3: 10% vs. 37% and grade 4: 76% vs. 37%, respectively; p<0.05 for grade 3 and 4 events) (37). In both arms, G-CSF was administered once daily on days 2 to 11 of both treatment cycles.

##### Leukopenia

Two trials reported leukopenia rates (25,37). The Aberdeen trial reported more grade 3 or 4 leukopenia in patients who received CVAPr for eight cycles compared with those who switched to docetaxel (100mg/m<sup>2</sup> q3wx4) after four cycles (p=0.029) (25). In the Miller et al trial, leukopenia was more common with the combination arm (docetaxel 100mg/m<sup>2</sup> q3wx4) than with the sequential arm (docetaxel 75mg/m<sup>2</sup> q2wx3) (grade 3: 43% vs. 32% and grade 4: 38% vs. 11%, respectively; p<0.05 for grade 3 and 4 events combined) (37).

##### Neurotoxicity

The NSABP B-27 was the only docetaxel trial to report rates of neurotoxicity (22). Grade 3 neurosensory and neuromotor events and grade 4 neuromotor and neurocortical events were very infrequent and non-differential between groups.

### Cardiotoxicity

Rates of adverse cardiac events were not reported for any of the trials.

### Gastrointestinal toxicity

Four trials reported gastrointestinal toxicity data (21,22,25,28). Nausea, vomiting, diarrhea, and stomatitis were infrequent, and toxicity rates were similar between groups in each trial.

### Other toxicities

Lee reported the occurrence of hand-foot syndrome in 8% of women receiving docetaxel and capecitabine (21). No women receiving AC experienced hand-foot syndrome. Miller reported a trend towards more grade 3 and 4 hand-foot syndrome (21% vs. 0%, p-value not reported) with sequential doxorubicin and docetaxel (75mg/m<sup>2</sup> q2wx3) than in their combination doxorubicin and docetaxel arm (75mg/m<sup>2</sup> q3wx4), respectively (37).

In the NSABP B-27 trial, more women receiving neoadjuvant docetaxel in addition to AC required more dose reductions (19%) compared with those receiving AC alone (2%) (22). Deaths were more frequent in the neoadjuvant docetaxel arm (0.4% vs. 0.1%; p-value not reported).

In the Aberdeen trial, two women in the CVAPr followed by docetaxel arm died of neutropenic sepsis. Women who switched to docetaxel after CVAPr were more likely to receive a higher percentage of the total intended drug dose than were patients who continued to receive CVAPr (p=0.002) (25).

**Table 1a: Definitions of clinical response used in eligible trials.**

Source (Reference)	Clinical Complete Response	Clinical Partial Response
NSABP (22)	Clinical absence of primary tumour and node involvement	≥50% reduction of primary tumour and node involvement
Sataloff (41)	Clinical absence of primary tumour and node involvement	Complete primary tumour response with partial node response OR partial tumour response with complete node response OR partial response in both primary tumour and node involvement
UICC Criteria (40)	Clinical absence of primary tumour	≥50% reduction of primary tumour

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; UICC, Unio Internationalis Contra Cancrum

**Table 1b: Definitions of pathologic response used in eligible trials.**

Source (Reference)	Pathologic Complete Response	Pathologic Partial Response
Chevallier (42)	Pathologic absence of all primary tumour and node involvement	DCIS with no nodal involvement OR DCIS with stromal alteration
Sataloff (41) or Miller/Payne (43)	Pathologic absence of <i>invasive</i> primary tumour	Up to 90% reduction in primary tumour

**Table 1c: Definitions of axillary lymph node outcomes used in eligible trials.**

Source (Reference)	Pathologic Complete Response	Pathologic Partial Response	Pathologic Node Involvement
Sataloff (41)	Previously node-positive converted to node-negative after neoadjuvant chemotherapy	Pathologic evidence of partial node response	Not reported
(17,20,30,31,33,36,37)	Not reported	Not reported	Histological presence of involved nodes at surgery

**Table 2: Characteristics of eligible trials (18 trials)**

Trial (ref.)	Phase	N per arm		Treatment arms <sup>b</sup>	Eligibility criteria	Patient characteristics
<b>Q1: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to other neoadjuvant regimens?</b>						
<i>Paclitaxel</i>						
M.D. Anderson (17) (Buzdar, 1999)	III	87 87	i ii	[P q3wx4]→LT→[FAC q3wx4]→RT→HT [FAC q3wx4]→LT→[FAC q3wx4]→RT→HT	• T1-3,N0-1,M0	<ul style="list-style-type: none"> <li>• T1,2,3: 8,64,28%</li> <li>• N0,1,2: 38,61,1%</li> <li>• Stage IIa,b,III: 34,49,17%</li> <li>• ER+,-,uk: 58,34,8%</li> </ul>
<sup>a</sup> Pouillart, 1999 (18)	II	180 67	i ii	[A+P q3wx4]→LT→RT→HT [A+C q3wx4]→LT→RT→HT	• T2-3,N0-1,M0	<ul style="list-style-type: none"> <li>• T2,3: 62,38%</li> <li>• HR+:66%</li> </ul>
<sup>a</sup> Malamos, 1998 (19)	II	16/NR <sup>c</sup> 14/NR	i ii	[E+P q3wx3]→LT→[E+P q3wx3]→RT→HT [FEC q3wx3]→LT→[FEC q3wx3]→RT→HT	• Operable BC	NR
<i>Docetaxel</i>						
<sup>a</sup> ACCOG (20) (Evans, 2004)	III	183 180	i ii	[A+D q3wx6]→LT→RT→HT [A+C q3wx6]→LT→RT→HT	<ul style="list-style-type: none"> <li>• Operable BC ≥3cm</li> <li>• LABC</li> <li>• IBC</li> </ul>	<ul style="list-style-type: none"> <li>• 8% LA, inoperable</li> <li>• 15% inflammatory</li> <li>• 77% large operable</li> </ul>
<sup>a</sup> Lee, 2004 (21)	III	33/NR <sup>c</sup> 32/NR	i ii	[D+X q3wx4]→LT→RT→HT [A+C q3wx4]→LT→RT→HT	<ul style="list-style-type: none"> <li>• Stage II/III, N+</li> <li>• Previously untreated</li> </ul>	<ul style="list-style-type: none"> <li>• Stage II: 56%</li> <li>• ER+: 54%</li> <li>• HER2 3+:28%</li> </ul>
NSABP B-27 (22)	III	752 772 762	i ii iii	[A+C q3wx4] +HT→[D q3wx4]→LT→RT [A+C q3wx4] +HT→LT→[D q3wx4]→RT [A+C q3wx4] +HT→LT→RT	• T1-3,N0-1,M0	• T≥4cm:45%
Aberdeen (23-26)	III	48 47 50	i ii iii	(R-)→[D q3wx4]→LT [CVAPr q3wx4] (R+)→[D q3wx4]→T (R+)→[CVAPr q3wx4]→LT	<ul style="list-style-type: none"> <li>• T≥3cm or</li> <li>• T3-4,N2</li> </ul>	<ul style="list-style-type: none"> <li>• T2,3,4: 36,42,22%</li> <li>• N0,1,2: 74,14,12%</li> <li>• Stage I,II,III,uk: 17,38,41,4%</li> <li>• ER+,PR+: 61,31%</li> </ul>
<sup>a</sup> GEPAR-TRIO (27)	II	107 24 20	i ii iii	(R+)→[D+A+C q3wx4]→LT [D+A+C q3wx2] (R-)→[D+A+C q3wx4]→LT (R-)→[N+X q3wx4]→LT	<ul style="list-style-type: none"> <li>• T≥2cm or</li> <li>• LABC</li> </ul>	• 89% operable
<sup>a</sup> Bouzid, 2001 (28)	III	198/NR <sup>c</sup> 164/NR	i ii	[A+D q3wx4]→LT [FAC q3wx4]→LT	• Stage IIIa or b	NR
<sup>a</sup> Luporsi, 2000 (29)	II	25/NR <sup>c</sup> 25/NR	i ii	[E+D q3wx6]→LT [FEC q3wx6]→LT	<ul style="list-style-type: none"> <li>• T2-4</li> <li>• Non-IBC</li> </ul>	NR
<b>Q2: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to adjuvant taxane-containing regimens?</b>						
<i>Paclitaxel</i>						
<sup>a</sup> ECTO (30) (Gianni, 2002)	III	270/NR <sup>c</sup> 622/NR	i ii iii	[A+P q3wx4]→[CMF q4wx4]→LT LT→[A q3wx4]→[CMF q4wx4] LT→[A+P q3wx4]→[CMF q4wx4]	• T>2cm	NR

Trial (ref.)	Phase	N per arm		Treatment arms <sup>b</sup>	Eligibility criteria	Patient characteristics
<b>Q3: What is the preferred dose and schedule for neoadjuvant taxane administration?</b>						
<i>Paclitaxel</i>						
<sup>a</sup> SICOG 9988 (31) (Comella, 2004)	III	140/160 <sup>c</sup>	i ii	[Cis+E+P q1wx12]→LT [E+P q3wx4]→LT	<ul style="list-style-type: none"> <li>T4 and/or N3</li> <li>≤70 years</li> <li>Previously untreated</li> </ul>	NR
Stearns, 2003 (32)	II	15 14	i ii	[A q2wx3]→[P q2wx3]→LT→CT→HT→RT [P q2wx3]→[A q2wx3]→LT→CT→HT→RT	<ul style="list-style-type: none"> <li>T3-4</li> </ul>	<ul style="list-style-type: none"> <li>Stage IIIa,b,IV: 48,35,17%</li> </ul>
<sup>a</sup> AGO (33) (Untch, 2002)	III	242/NR <sup>c</sup> 233/NR	i ii	[E q2wx3]→[P q2wx3]→LT→[CMF q4wx3 +RT] [E+P q3wx4]→LT→[CMF q4wx3 +RT]	<ul style="list-style-type: none"> <li>T&gt;3cm or IBC</li> </ul>	NR
<sup>a</sup> Romieu, 2002 (34)	II	232	i ii	[A+P q3wx6]→LT [A+P q3wx4]→LT	<ul style="list-style-type: none"> <li>T2-3,N0-1,M0</li> </ul>	<ul style="list-style-type: none"> <li>T2,3: 50. 49%</li> <li>N0,1: 43, 57%</li> <li>HR+: 66%</li> </ul>
<sup>a</sup> M.D. Anderson (35) (Green, 2002)	III	51 67 68 50	i ii iii iv	N+ [P q1w for 3wks, 1wk break x4]→[FACx4]→LT N- [P wx12]→[FACx4]→LT N- [P 3wx4]→[FACx4]→LT N+ [P 3wx4]→[FACx4]→LT	<ul style="list-style-type: none"> <li>T1-3,N0-1,M0</li> </ul>	NR
<i>Docetaxel</i>						
<sup>a</sup> ABCSG-14 (36) (Steger, 2004)	III	288	i ii	[E+D q3wx6]→LT [E+D q3wx3]→LT	<ul style="list-style-type: none"> <li>T1-4<sub>a-c</sub>,N+/-M0</li> </ul>	NR
Miller, 1999 (37)	II	21 19	i ii	[A+D q3wx4]→LT [A q2wx3]→[D q2wx3]→LT	<ul style="list-style-type: none"> <li>≥2cm and</li> <li>Stage II or III</li> </ul>	<ul style="list-style-type: none"> <li>N+: 57%</li> </ul>

<sup>a</sup>Published abstract; <sup>b</sup>for full trial dosing and scheduling information please see Appendix A; <sup>c</sup>trial is ongoing (number evaluable/number accrued)

Abbreviations: A, doxorubicin; ABCSG Austrian Breast Cancer Study Group; ACCOG Anglo-Celtic Cooperative Oncology Group; AGO Arbeitsgemeinschaft Gynäkologische Onkologie; BC, breast cancer; C, cyclophosphamide; Cis, cisplatin; cm, centimetre(s); CT, chemotherapy; D, docetaxel; E, epirubicin; ECTO European Cooperative Trial in Operable Breast Cancer; ER+, estrogen-receptor positive; ER-, estrogen-receptor-negative; F, fluorouracil; GEPAR German Pre-operative Adriamycin Docetaxel Trial; HR+, hormone-receptor-positive; HT, hormone therapy; IBC, inflammatory breast cancer; LA, locally advanced; LT, local surgical therapy; M, methotrexate; N per arm, number of patients per arm; N, vinorelbine; N+, node positive; N-, node negative; NR, not reported; NSABP National Surgical Adjuvant Breast and Bowel Project; P, paclitaxel; Pr, prednisolone; PR+, progesterone-receptor-positive; R+, responders; R-, non-responders; RT, radiotherapy; SICOG Southern Italy Cooperative Oncology Group; uk, unknown; V, vincristine-; w, wks, week(s); X, capecitabine.

**Table 3: Response and Survival Data (18 trials).**

Trial (ref.)	N per arm	Treatment arms <sup>b</sup>	F/U (mo.)	Tumour response				Node response			BCS (%)	DFS (%)	OS (%)	
				pCR(%)	pPR(%)	cCR(%)	cPR(%)	pCR(%)	pPR(%)	N- at LT(%)				
<b>Q1: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to other neoadjuvant regimens?</b>														
<i>Paclitaxel</i>														
M.D. Anderson (17) (Buzdar,1999)	87 87	i P ii FAC	23	8 16	NR	27 24	53 55	NR	NR	44 37	46 35	94 89	NR	
<sup>a</sup> Pouillart, 1999 (18)	180 67	i A+P ii A+C	NR	16 10	NR		14 9		NR	NR	NR	56 45	NR	NR
<sup>a</sup> Malamos, 1998 (19)	16/NR <sup>c</sup> 14/NR	i E+P ii FEC	NR	<b>25<sup>d</sup></b> <b>0</b>	56 57	31 0	56 50	NR	NR	NR	NR	NR	NR	NR
<i>Docetaxel</i>														
<sup>a</sup> ACCOG (20) (Evans, 2004)	183 180	i A+D ii A+C	32	21 24	NR	20 17	50 44	NR	NR	34 39	20 20	75 69	86 84	
<sup>a</sup> Lee, 2004 (21)	33/NR <sup>c</sup> 32/NR	i D+X ii A+C	NR	15 6	NR	3 3	85 72	27 29	NR	NR	NR	64 56	NR	NR
NSABP B-27 (22)	752 772 762	i A+C→D→LT ii A+C→LT→D iii A+C→LT	NR	<b>26<sup>d</sup></b> <b>15</b> <b>13</b>	NR		<b>91<sup>d</sup></b> <b>85</b> <b>86</b>		NR	<b>58<sup>d</sup></b> <b>50</b> <b>51</b>	NR	64 62	NR	NR
Aberdeen (23-26)	47 50	ii CVAPr→D iii CVAPr→CVAPr	38/65	31 <sup>e</sup> 15	42 <sup>e</sup> 40		<b>85<sup>de</sup></b> <b>64</b>	2 <sup>e</sup> 8	12 <sup>e</sup> 8	NR	<b>67<sup>de</sup></b> <b>48</b>	<b>90<sup>de</sup></b> <b>77</b>	<b>97<sup>de</sup>/93<sup>df</sup></b> <b>84/78</b>	
<sup>a</sup> GEPAR-TRIO (27)	24 20	ii TAC iii N+X	NR	7 3	NR		25 25	NR	NR	NR	61 56	NR	NR	
<sup>a</sup> Bouzid, 2001 (28)	198/NR <sup>c</sup> 164/NR	i A+D ii FAC	8.3	NR	NR	11 9	61 55	NR	NR	NR	NR	NR	NR	NR
<sup>a</sup> Luporsi, 2000 (29)	25/NR <sup>c</sup> 25/NR	i E+D ii FEC	NR	24 24	NR		84 72	NR	NR	NR	85 69	NR	NR	
<b>Q2: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to adjuvant taxane-containing regimens?</b>														
<i>Paclitaxel</i>														
<sup>a</sup> ECTO (30) Gianni, 2002	270/NR <sup>c</sup> 622/NR	i A+P→CMF→LT ii LT→A→CMF iii LT→A+P→CMF	NR	23 NA	NR NA	52 NR		NR	NR	NR	<b>61<sup>b</sup></b> <b>38</b>	<b>71<sup>d</sup></b> <b>35</b>	NR	NR

Trial (ref.)	N per arm	Treatment arms <sup>b</sup>	F/U (mo.)	Tumour response				Node response			BCS (%)	DFS (%)	OS (%)
				pCR(%)	pPR(%)	cCR(%)	cPR(%)	pCR(%)	pPR(%)	N- at LT			
<b>Q3: What is the preferred dose and schedule for neoadjuvant taxane administration?</b>													
<i>Paclitaxel</i>													
<sup>a</sup> SICOG 9988 (31) (Comella, 2004)	130/160 <sup>c</sup>	i [w Cis+E+P] ii [3w E+P]	NR	<b>16<sup>d</sup></b> <b>4</b>	NR	<b>29<sup>d</sup></b> <b>15</b>	59 62	NR	NR	n=17 n=14	NR	NR	NR
Stearns, 2003 (32)	15 14	i A→P ii P→A	24	10 7	7 17	10 3	3 17	NR	NR	NR	44	NR NR	NR
<sup>a</sup> AGO (33) (Untch, 2002)	242/NR <sup>c</sup> 233/NR	i E→P ii E+P	NR	<b>18<sup>d</sup></b> <b>10</b>	NR	NR	NR	NR	NR	51 42	<b>66<sup>d</sup></b> <b>55</b>	NR NR	NR
Romieu, 2002 (34) <sup>a</sup>	232	i A+P x6 ii A+P x4	NR	24 17	16 11	NR	32 20	NR	PRs included node response	NR	64 61	NR NR	NR
<sup>a</sup> M.D. Anderson (35) (Green, 2002)	50 68 51 67	i + wP→FAC ii -: wP→FAC iii -: 3wP→FAC iv +: 3wP→FAC	NR	28 29 13 14	<b>29<sup>d</sup></b> <b>15</b>	NR	NR	NR	PRs included node response	NR	NR	NR NR	NR
<i>Docetaxel</i>													
<sup>a</sup> ABCSG-14 (36) (Steger, 2004)	288	i [E+D x6] ii [E+D x3]	NR	<b>19<sup>d</sup></b> <b>8</b>	NR	NR	NR	NR	NR	<b>57<sup>d</sup></b> <b>43</b>	76 67	NR	NR
Miller, 1999 (37)	21 19	i A+D ii A→D	98 105	5 16	5 0	10 32	71 58	NR	NR	19 53	19 37	NR NR	NR

<sup>a</sup>Published abstract; <sup>b</sup>for full trial dosing and scheduling information please see Appendix A; <sup>c</sup>trial is ongoing (number evaluable/number accrued); <sup>d</sup>difference is statistically significant at or below the 5% level; <sup>e</sup>at 38 months of follow-up; <sup>f</sup>at 65 months of follow-up.

Abbreviations: A, doxorubicin; ABCSG Austrian Breast Cancer Study Group; ACCOG Anglo-Celtic Cooperative Oncology Group; AGO Arbeitsgemeinschaft Gynäkologische Onkologie; BCS, breast conserving surgery; C, cyclophosphamide; cCR, clinical complete response; Cis, cisplatin; cPR, clinical partial response; D,T, docetaxel; DFS, disease-free-survival; E, epirubicin; ECTO European Cooperative Trial in Operable Breast Cancer; F, fluorouracil; GEPAR German Pre-operative Adriamycin Docetaxel Trial; LR, local recurrence; LT, local surgical therapy; M, methotrexate; N per arm, number of patients per arm; N, vinorelbine; N+, node positive; N-, node negative; N- at BCS, node negative at time of breast conserving surgery; NA, not applicable; NSABP National Surgical Adjuvant Breast and Bowel Project; NR, not reported; OS, overall survival; P, paclitaxel; pCR, pathologic complete response; pPR, pathologic partial response; PRs, partial response(s); Pr, prednisolone; SICOG Southern Italy Cooperative Oncology Group; V, vincristine; w, week(s); X, capecitabine.

## **Practice Guideline**

In 2004, the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer published a practice guideline report, *Treatment for Women with Stage III or Locally Advanced Breast Cancer* (38). The objective of the practice guideline was to define the optimal treatment for these women. MEDLINE and CANCELIT databases were systematically searched to June 2002. A non-systematic search was used to update the literature through December 2003. The quality of the evidence was rated using methods described by Sackett et al (45).

In their consideration of neoadjuvant chemotherapy, eleven trials were reviewed (17,22,25,46-52), three of which evaluated neoadjuvant taxane therapy, alone (17) or in combination with an anthracycline regimen (22,25). Based on those data, as well as evidence from the adjuvant and metastatic settings, the Steering Committee recommended that patients with operable stage IIIA disease should be offered anthracycline-based chemotherapy, either pre- or postoperatively. Acceptable regimens included six cycles of FAC, CAF, CEF, or FEC. The Steering Committee felt that there were insufficient data to make definitive recommendations concerning the use of taxane-containing regimens in LABC.

## **V. DISEASE SITE GROUP INTERPRETIVE SUMMARY AND CONSENSUS**

In the context of current clinical practice, the Breast Cancer DSG discussed the evidence for neoadjuvant taxanes in the treatment of women with non-metastatic breast cancer. The DSG agreed that the primary goal for treatment in this population is to achieve the longest survival with the best quality of life, using a treatment with acceptable toxicity. The following sections summarize the Breast Cancer DSG's interpretation of the evidence and consensus.

### **Question 1: Do taxane-containing regimens improve clinically meaningful outcomes relative to other neoadjuvant regimens?**

Since many of the eligible trials are not yet mature, disease-free and overall survival data are sparse. One (23-26) of four trials (17,20,28) providing such data reported a significant improvement in DFS with neoadjuvant taxane therapy; specifically, docetaxel was associated with a larger proportion of disease-free women at follow-up than was CVAPr. The same trial also found significantly longer overall survival at follow-up with taxane therapy. DFS rates in the three trials with non-significant results appeared to favour neoadjuvant taxane-containing therapy.

In the absence of survival data, the Breast Cancer DSG chose to consider pathologic and clinical complete response as surrogate markers for survival in non-metastatic breast cancer. One (19) of three (17,18) relevant paclitaxel trials with comparative data showed significantly improved complete pathologic response with neoadjuvant paclitaxel therapy. While the trial was very small (n=30), epirubicin and paclitaxel in combination was superior to standard FEC therapy. While the remaining two trials did not report statistically significant findings, the direction in one (18) was towards improved responses.

Two (22-26) of seven (20,21,27-29) relevant docetaxel trials detected significant differences in pathologic and/or clinical response. By far the largest and most rigorous, the NSABP B-27 study clearly demonstrated improved complete pathologic breast response, overall clinical response, and node status in women receiving neoadjuvant docetaxel in addition to AC compared with those receiving only AC (22). In the Aberdeen trial, complete pathologic response was 31% compared with 15% in the docetaxel and CVAPr arms, respectively (p=0.06) (23-26). That same trial also showed improved clinical response and breast conservation with neoadjuvant docetaxel therapy. Of note, GEPAR-TRIO patients who failed to respond to two cycles of neoadjuvant TAC therapy failed to improve with either further TAC therapy or vinorelbine and capecitabine therapy (27).

The Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer practice guideline endorsed the use of neoadjuvant anthracycline-based chemotherapy. In their opinion, there were insufficient data to make definitive recommendations concerning the use of taxane-containing regimens in LABC. Only three trials evaluating neoadjuvant taxanes were included in their review, compared with a total of 18 in this review (38).

Based on the ten trials that compared a neoadjuvant taxane-containing regimen to one without a taxane (17-29), the Breast Cancer DSG agreed that breast and/or node response rates as well as breast-conservation rates are improved in patients taking neoadjuvant taxanes in addition to neoadjuvant anthracycline-based chemotherapy. The Breast Cancer DSG concluded that women with non-metastatic breast cancer who have large primary cancers or locally advanced or inflammatory disease and who could therefore benefit significantly from maximizing local response rates should be offered neoadjuvant taxane therapy, in sequence with an anthracycline regimen, as a treatment option.

**Question 2: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to adjuvant taxane-containing regimens?**

In the ECTO trial, comparative response data were not reported; however, the number of women who received breast-conserving surgery was significantly higher in the arm that received neoadjuvant paclitaxel and doxorubicin compared with the pooled results from women who received adjuvant doxorubicin or adjuvant paclitaxel and doxorubicin (30). Furthermore, women in the neoadjuvant docetaxel arm were more likely to be node-negative at the time of their surgery.

While preliminary data is positive, there is insufficient evidence at this time to recommend administering taxanes in the neoadjuvant versus the adjuvant setting; thus neoadjuvant taxanes are currently recommended only for those women who are felt by their physicians to be candidates for neoadjuvant chemotherapy.

**Question 3: What is the preferred dose and schedule for neoadjuvant taxane administration?**

*Sequential versus combination therapy / longer versus shorter chemotherapy*

The AGO trial detected superior pathologic complete response and breast-conservation rates with neoadjuvant epirubicin and paclitaxel sequential therapy compared with combination therapy (33). While non-significant, the Miller et al trial also suggested that sequential therapy with an anthracycline followed by a taxane is more effective than combination therapy (37). In both trials, a total of six sequential cycles (q2wx3→q2wx3) were compared with four combination cycles (q3wx4). Furthermore, the taxane and anthracycline doses were higher in the sequential arms than in the combination arms. Thus, the longer duration and/or increased dose of taxane and anthracycline therapy may have been at least partly responsible for the effect. Two trials support this theory. Romieu et al directly compared six- and four-cycle (three-weekly) doxorubicin-docetaxel regimens; although significance testing was not reported, results appeared to favour the six-cycle regimen (34). The ABCSG-14 trial compared three and six cycles of epirubicin and doxorubicin. Rates of pathologic complete response and breast conservation were significantly improved in the longer-therapy arm. While preliminary, these data suggest that six cycles of taxane therapy, in sequence with an anthracycline, are superior to combination therapy and/or fewer cycles.

*Weekly versus three-weekly schedules*

While the majority of eligible trials administering taxanes used a three-weekly taxane schedule, two administered weekly paclitaxel (31,35). In the SICOG 9908 trial, the rates of pathologic and clinical complete response were significantly improved with weekly cisplatin,

epirubicin, and paclitaxel (120mg/m<sup>2</sup>) combination therapy compared with three-weekly epirubicin and paclitaxel (175mg/m<sup>2</sup>) combination therapy. The M.D. Anderson trial by Green et al showed superior pathologic complete response with weekly paclitaxel therapy at 150mg/m<sup>2</sup> (q1w for three weeks followed by a one-week break) or 80mg/m<sup>2</sup> (every week for 12 weeks) followed by FAC compared with three-weekly paclitaxel at 225mg/m<sup>2</sup> followed by FAC (35). While still immature, these data suggest that paclitaxel should be administered weekly. There is insufficient evidence to recommend a weekly regimen for docetaxel; therefore the standard three-weekly regimen is recommended.

#### *Order of administration*

Stearns et al reported mixed results when doxorubicin followed by paclitaxel was compared with the reverse, likely due to the very small sample size (32). The Green et al M.D. Anderson trial was the only study to administer the taxane (paclitaxel) prior to the anthracycline-based regimen (35). While there was no comparison of sequence order between arms, weekly paclitaxel prior to the anthracycline was shown to improve pathologic complete response. Therefore neoadjuvant paclitaxel should be administered prior to a standard anthracycline-based regimen, such as FAC. There is no evidence as yet showing improved pathologic complete response when weekly paclitaxel is administered after anthracycline-cyclophosphamide chemotherapy.

Since the trials showing improved outcomes with neoadjuvant docetaxel, particularly the Aberdeen (23-26) and NSABP B-27 (22) studies, administered docetaxel after the anthracycline-based regimen, neoadjuvant docetaxel should be given following a standard anthracycline-containing regimen.

#### *Dose*

Paclitaxel doses ranged from 80mg/m<sup>2</sup> to 250mg/m<sup>2</sup> and docetaxel doses were either 75mg/m<sup>2</sup> or 100mg/m<sup>2</sup>. In general, larger doses were prescribed for sequential, three-weekly schedules. Since three-weekly docetaxel after an anthracycline is recommended, the higher dose (100mg/m<sup>2</sup>) should be administered. Conversely, weekly paclitaxel followed by an anthracycline is recommended. In the only sequential weekly trial, paclitaxel was administered at 150mg/m<sup>2</sup> (weekly for three weeks followed by a one-week break in node-positive women) or 80mg/m<sup>2</sup> (weekly for twelve weeks in node-negative women) (35). Pathologic complete response rates for the two weekly groups were equivalent; however, toxicity was less for the 80mg/m<sup>2</sup> group. Therefore, the Breast Cancer DSG members agreed that 80mg/m<sup>2</sup> is a reasonable dose for weekly therapy, regardless of nodal status.

Overall, paclitaxel should be administered weekly, at 80mg/m<sup>2</sup>, for 12 weeks, prior to a standard anthracycline-based regimen. Four cycles of docetaxel should be administered every three weeks, at 100mg/m<sup>2</sup>, following a standard anthracycline-based regimen. Examples of standard anthracycline-based regimens include FAC or AC. FAC and AC may not be ideal; the role of optimal anthracycline regimens, such as FEC, in sequence with taxanes has yet to be studied in the neoadjuvant setting.

#### **Question 4: What are the adverse effects associated with neoadjuvant taxane-containing regimens?**

Adverse effects were inconsistently reported throughout the trials. In general, hematologic toxicity, in particular neutropenia and febrile neutropenia, was more common with a taxane-containing regimen. Neurotoxicity may be associated with neoadjuvant paclitaxel and hand-foot syndrome may be associated with neoadjuvant docetaxel. There was little evidence to suggest that other adverse events occur more frequently with a neoadjuvant taxane. As the trials mature, more data on the adverse effects of neoadjuvant taxanes will be available; until then, physicians should monitor patients closely.

## **VI. ONGOING TRIALS**

The Physician Data Query database ([http://www.cancer.gov/search/clinical\\_trials/](http://www.cancer.gov/search/clinical_trials/)) was searched for additional ongoing trials. One relevant randomized trial of taxanes in the neoadjuvant setting was located. Designed as a large multicentre randomized trial, the EORTC-10994 study will compare neoadjuvant FEC with neoadjuvant docetaxel and epirubicin followed by radiotherapy and surgery (53). Women with locally advanced, inflammatory, or large operable breast cancer are eligible to enter the study. The accrual of 1,440 patients will be completed by the year 2006. The information was last updated in September 2003.

## **VII. IMPLICATIONS FOR POLICY**

In March 2004, the Breast Cancer DSG submitted funding requests to the Policy Advisory Committee (PAC). Based on current evidence, neoadjuvant paclitaxel and docetaxel, when given in sequence with an anthracycline, improve operability and tumour response rates. This finding, by extension, may translate into improved disease-free and overall survival for women with non-metastatic, large primary, locally advanced, and/or inflammatory disease. Therefore, the Breast Cancer DSG advised that women who elect to receive these agents prior to local therapy should receive reimbursement through the New Drug Funding Program.

The PAC decided that there was sufficient evidence to support the reimbursement of docetaxel (100mg/m<sup>2</sup>, q3wx4) following a doxorubicin-based regimen for the neoadjuvant treatment of women with non-metastatic breast cancer. The Committee determined that the data supporting the use of paclitaxel in the neoadjuvant setting and the use of docetaxel following epirubicin was weaker; therefore, the PAC concluded that paclitaxel-containing regimens and docetaxel following epirubicin should not be reimbursed at this time.

## **VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT**

### **Draft Recommendations**

Based on the evidence reviewed, the Breast Cancer DSG drafted the following recommendations:

#### ***Target Population***

These recommendations apply to women with non-metastatic breast cancer who are candidates for neoadjuvant chemotherapy (refer to second bullet under “Qualifying Statements” section below).

#### ***Recommendations***

- When neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or doxorubicin and cyclophosphamide (AC) chemotherapy regimen is planned for a woman with non-metastatic breast cancer, a neoadjuvant taxane (paclitaxel or docetaxel) should also be offered. Based on evidence from clinical trials, the following regimens are recommended:
  - Paclitaxel (80mg/m<sup>2</sup>), administered weekly for 12 weeks prior to the anthracycline-based regimen.
  - Docetaxel (100mg/m<sup>2</sup>), administered every three weeks for four cycles following the anthracycline-based regimen.
- There is no evidence at this time to suggest that one taxane is superior to the other in the neoadjuvant setting.

#### ***Qualifying Statements***

- Since disease-free and overall survival data are limited, the recommendations for neoadjuvant taxane chemotherapy are often based on pathologic and clinical complete-response data.

- Neoadjuvant therapy is not the standard of care for operable breast cancer but is usually given to improve the likelihood of breast conservation for large operable breast cancer or to increase the possibility of operability for locally advanced or inflammatory breast cancer.
- There is no evidence in the neoadjuvant setting for the use of taxanes after optimally dosed anthracycline-based regimens, such as 5-fluorouracil, epirubicin, and cyclophosphamide (FEC-100 or CEF).
- The recommended schedule for paclitaxel therapy (i.e., weekly) is based on two trials of weekly versus three-weekly regimens. There were no direct comparisons available for docetaxel; therefore, the recommended schedule (i.e., three-weekly) is based on that which showed improved efficacy in trials comparing a docetaxel-containing regimen with a non-docetaxel regimen. The suggested doses for paclitaxel and docetaxel are those associated with the recommended schedule.
- While neoadjuvant paclitaxel and docetaxel are recommended in sequence with a standard anthracycline-based regimen, it may be appropriate to switch to an anthracycline-based regimen from paclitaxel or to docetaxel from an anthracycline-based regimen earlier if the patient's disease progresses while on the initial regimen.
- Tumours that fail to respond to two cycles of neoadjuvant therapy are likely resistant (in terms of subsequent pathologic complete response rates) to chemotherapy, including taxane-anthracycline combinations, vinorelbine, and capecitabine. For these patients, a novel therapy may be considered.
- The data supporting neoadjuvant taxane therapy are maturing. While results to date do not support an increase in adverse events relative to other settings, physicians should monitor patients carefully for toxicity, especially hematologic toxicity, neurologic toxicity (with paclitaxel), and hand-foot syndrome (with docetaxel).
- There is at present no literature to support the use of adjuvant taxane-based therapy for residual tumour found after neoadjuvant anthracycline-based therapy.
- This practice guideline report is based upon the reported neoadjuvant literature and cannot be extrapolated to endorse the use of adjuvant docetaxel after adjuvant anthracyclines. Studies exploring that sequence of treatments are underway.

### **Practitioner Feedback**

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

### **Methods**

Practitioner feedback was obtained through a mailed survey of 113 practitioners in Ontario (57 medical oncologists, 20 surgical oncologists, 35 surgeons, and one medical resident). 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 30, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer DSG reviewed the results of the survey.

### **Results**

Sixty-three responses were received out of the 113 surveys sent (56% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 60% indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 4.

**Table 4. Practitioner responses to eight items on the practitioner feedback survey.**

Item	Number <sup>a</sup> (%) <sup>b</sup>		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.	38 (100%)	0	0
There is a need for a clinical practice guideline on this topic.	33 (87%)	5 (13%)	0
The literature search is relevant and complete.	33 (87%)	4 (11%)	1 (3%)
The results of the trials described in the report are interpreted according to my understanding of the data.	30 (79%)	7 (18%)	1 (3%)
The draft recommendations in this report are clear.	32 (84%)	2 (5%)	4 (11%)
I agree with the draft recommendations as stated.	26 (68%)	8 (21%)	4 (11%)
This report should be approved as a practice guideline.	24 (63%)	10 (26%)	3 (8%)
	<b>Very likely or likely</b>	<b>Unsure</b>	<b>Not at all likely or unlikely</b>
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	26 (70%)	9 (24%)	1 (3%)

<sup>a</sup>For some items, numbers may not total 38 due to missing responses.

<sup>b</sup>For some items, percentages may not total 100 due to rounding error.

### **Summary of Written Comments**

Fourteen respondents (37%) provided written comments. The main criticisms of the written comments were:

1. Paclitaxel should be allowed prior to or after anthracycline combination chemotherapy. The data does not support the conclusion that paclitaxel prior to anthracycline combination chemotherapy is more effective than paclitaxel after anthracycline-combination chemotherapy.
2. Granulocyte-colony stimulating factor is needed when adding docetaxel following an anthracycline-based regimen.
3. The guideline recommends that a taxane be offered if a neoadjuvant anthracycline-based regimen is planned. Yet the caveat that the anthracycline regimens in the published randomized trials “may not” be the most efficacious is included. Indeed most would regard them as inferior to regimens such as CEF or FEC-100. It does not follow logically to recommend that a taxane should be offered if anthracycline based therapy (all such therapies lumped together) is being considered. Perhaps in the “draft recommendation”

should qualify more specifically the anthracycline regimens (i.e. those used in the quoted studies which are “CMF-like”). For newer generation anthracycline regimens the “taxane should be offered” statement seems ungrounded; for example, if, after 4 cycles of FEC-100 you achieve a CR, should you offer a taxane?

4. The guideline does not deal with the approach that I use in clinical practice and which I think is used by many experienced oncologists. I start with either CAF or CEF. If the tumour response is excellent (CR) with one of these regimens, then I continue up to six cycles of chemotherapy, and then follow with local management. If there is a partial or no response after three cycles of CEF/CAF, I then proceed with a taxane; either paclitaxel or docetaxel every three weeks. If there is a good response with a taxane, then I will give up to six cycles followed by local management. The current draft of the guideline recommends the "blanket" use of a taxane, but does not deal with the patient who has a CR to a dose-intense anthracycline regimen. I feel that the guideline should allow for the approach that I describe here. I think that high quality level I evidence is required to change practice. I certainly agree with draft guideline that there is a role for taxanes as neoadjuvant chemotherapy; however I do not feel that the evidence is so compelling to change current practice where dose-intense anthracycline is given and taxane added if no complete response.

### **Modifications/Actions**

1. While weekly paclitaxel prior to an anthracycline-based regimen (FAC) was shown to improve pathologic complete response (35), there is currently no evidence showing improved pCR when weekly paclitaxel is administered after an anthracycline-based regimen. Furthermore, three-weekly paclitaxel, given pre- or post-anthracycline, has not yielded improved pCR rates. The Breast Cancer DSG felt that, at this time, the only sequential paclitaxel regimen supported by the data is paclitaxel followed by an anthracycline-based regimen. In order to make clear the lack of evidence for paclitaxel following the anthracycline combination chemotherapy, the following statement was added to the *Order of administration* section of the *Interpretive Summary*: “There is no evidence as yet showing improved pathologic complete response when weekly paclitaxel is administered after an anthracycline-based regimen.”
2. There is no evidence to support primary prophylaxis with G-CSF when administering three-weekly docetaxel following an anthracycline-based regimen; therefore it cannot be recommended. However, the Breast Cancer DSG members agree that, given the high rates of febrile neutropenia in the NSABP B-27 trial (22), prophylactic G-CSF with three-weekly docetaxel is a reasonable precaution.
3. The Breast Cancer DSG agreed that the recommendation should be more specific. Therefore the wording of the recommendation was changed from “when a neoadjuvant anthracycline-based regimen is planned...” to “when neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or doxorubicin and cyclophosphamide (AC) chemotherapy regimen is planned....”
4. While the Breast Cancer DSG agreed that CEF or CAF are standards of care, there is currently no data to support recommending either regimen followed by a taxane in the neoadjuvant setting. Given the available evidence, summarized in this practice guideline, the Breast Cancer DSG agreed that AC followed by three-weekly docetaxel and weekly paclitaxel followed by AC are new standards of care. The Breast Cancer DSG agreed to add the following sentence to a qualifying statement in order to emphasize the lack of evidence for the dose-escalated anthracycline-based regimens: “There is no evidence in the neoadjuvant setting for the use of taxanes after dose-escalated anthracycline-based regimens, such as 5-fluorouracil, epirubicin, and cyclophosphamide (FEC-100 or CEF).”

## **Practice Guidelines Coordinating Committee Approval Process**

The practice guideline report was circulated to members of the PGCC for review and approval. Nine of fifteen members of the PGCC returned ballots. All nine PGCC members approved the practice guideline report as written.

## **IX. PRACTICE GUIDELINE**

This practice guideline report reflects the integration of the draft recommendations with feedback obtained from the external review process. The report has been approved by the Breast Cancer DSG.

### **Recommendations**

- When neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or doxorubicin and cyclophosphamide (AC) chemotherapy regimen is planned for a woman with non-metastatic breast cancer, a neoadjuvant taxane (paclitaxel or docetaxel) should also be offered. Based on evidence from clinical trials, the following regimens are recommended:
  - Paclitaxel (80mg/m<sup>2</sup>), administered weekly for 12 weeks prior to the anthracycline-based regimen.
  - Docetaxel (100mg/m<sup>2</sup>), administered every three weeks for four cycles following the anthracycline-based regimen.
- There is no evidence at this time to suggest that one taxane is superior to the other in the neoadjuvant setting.

### **Qualifying Statements**

- Since disease-free and overall survival data are limited, the recommendations for neoadjuvant taxane chemotherapy are based on pathologic and clinical complete-response data.
- Neoadjuvant therapy is not the standard of care for operable breast cancer but is usually given to improve the likelihood of breast conservation for large operable breast cancer or to increase the possibility of operability for locally advanced or inflammatory breast cancer.
- The anthracycline-cyclophosphamide regimens administered in the neoadjuvant taxane trials (and thus recommended in this practice guideline report) may not be the most efficacious. There is no evidence in the neoadjuvant setting for the use of taxanes after optimally dosed anthracycline-based regimens, such as 5-fluorouracil, epirubicin, and cyclophosphamide (FEC-100 or CEF).
- The recommended schedule for paclitaxel therapy (i.e., weekly) is based on two trials of weekly versus three-weekly regimens. There were no direct comparisons available for docetaxel; therefore, the recommended schedule (i.e., three-weekly) is based on that which showed improved efficacy in trials comparing a docetaxel-containing regimen with a non-docetaxel regimen. The suggested doses for paclitaxel and docetaxel are those associated with the recommended schedule.
- While neoadjuvant paclitaxel and docetaxel are recommended in sequence with a standard anthracycline-based regimen, it may be appropriate to switch to an anthracycline-based regimen from paclitaxel or to docetaxel from an anthracycline-based regimen earlier if the patient's disease progresses while on the initial regimen.
- Tumours that fail to respond to two cycles of neoadjuvant therapy are likely resistant to chemotherapy, including taxane-anthracycline combinations, vinorelbine, and capecitabine. For these patients, a novel therapy may be considered.
- The data supporting neoadjuvant taxane therapy are maturing. While results to date do not support an increase in adverse events relative to other settings, physicians should monitor

patients carefully for toxicity, especially hematologic toxicity, neurologic toxicity (with paclitaxel), and hand-foot syndrome (with docetaxel).

- There is at present no literature to support the use of adjuvant taxane-based therapy for residual tumour found after neoadjuvant anthracycline-based therapy.
- This practice guideline report is based upon the reported neoadjuvant literature and cannot be extrapolated to endorse the use of adjuvant docetaxel after adjuvant anthracyclines. Studies exploring that sequence of treatments are underway.

### **Related Guidelines**

Practice Guidelines Initiative's Practice Guideline Report #1-3: *The Role of the Taxanes in the Management of Metastatic Breast Cancer*.

### **X. CONFLICTS OF INTEREST**

The members of the Breast Cancer DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. Two (MT, MC) of the guideline lead author reported related research involvement and funding from Aventis Pharmaceuticals. One author (MT) reported related research involvement and funding from Bristol-Myers Squibb as well as the receipt of honoraria from both companies. In addition, several DSG members reported related research involvement with these companies.

### **XI. JOURNAL REFERENCE**

- Trudeau M, Sinclair SE, Clemons M. Neoadjuvant taxanes in the treatment of non-metastatic breast cancer: a systematic review. *Cancer Treat Rev*. 2005;31:283-302. *Cancer Treatment Review* is available online at: <http://www.elsevier-international.com/journals/ctrv/>.

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For a complete list of the Breast Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at: [http://www.cancercare.on.ca/access\\_PEBC.htm](http://www.cancercare.on.ca/access_PEBC.htm).

## Appendix A. Detailed dose and schedule data for eligible randomized controlled trials.

First Author, Year (Ref)	Treatment Arms (as in Table 1)	Additional dose and scheduling information
<b>Q1: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to other neoadjuvant regimens?</b>		
<i>Paclitaxel</i>		
M.D. Anderson (17) (Buzdar, 1999)	i [P q3wx4]→LT→[FAC q3wx4]→RT→HT ii [FAC q3wx4]→LT→[FAC q3wx4]→RT→HT	CT: F=500mg/m <sup>2</sup> (d1&4), A=50mg/m <sup>2</sup> (over 72 hrs), C=500mg/m <sup>2</sup> (d1), P=250mg/m <sup>2</sup> (over 24 hrs) (if indicated) RT: 50 Gy (9 to 10 Gy per week), 10- to 15-Gy boost (if≥50yrs and ER+) T=5yrs HT:
<sup>a</sup> Pouillart, 1999 (18)	i [A+P q3wx4]→LT→RT→HT ii [A+C sq3wx4]→LT→RT→HT	CT: A=60mg/m <sup>2</sup> (bolus), P=200mg/m <sup>2</sup> (over 3 hrs), C=600mg/m <sup>2</sup> (bolus) RT: NR HT: (if HR+)
<sup>a</sup> Malamos, 1998 (19)	i [E+P q3wx3]→LT→[E+P q3wx3]→RT→HT ii [FEC q3wx3]→LT→[FEC q3wx3]→RT→HT	CT: E=75mg/m <sup>2</sup> (bolus d1), P=200mg/m <sup>2</sup> (over 3 hrs d1), F=600 mg/m <sup>2</sup> (d1), C=600mg/m <sup>2</sup> (d1) RT: NR HT: Pre-menopausal: LHRH=1 year, T=5 yrs or PD, Post-menopausal: T=5 yrs
<i>Docetaxel</i>		
<sup>a</sup> ACCOG (20) (Evans, 2004)	i [A <sub>1</sub> +D q3wx6]→LT→RT→HT ii [A <sub>2</sub> +C q3wx6]→LT→RT→HT	CT: A <sub>1</sub> =50mg/m <sup>2</sup> , D=75mg/m <sup>2</sup> , A <sub>2</sub> =60mg/m <sup>2</sup> C=600mg/m <sup>2</sup> RT: (if indicated) HT: (if ER+) T
<sup>a</sup> Lee, 2004 (21)	i [D+X q3wx4] →LT→RT→HT ii [A+C q3wx4] →LT→RT→HT	CT: D=75mg/m <sup>2</sup> (d1), X=1000mg/m <sup>2</sup> (bid d1-14), A=60mg/m <sup>2</sup> (d1), C=600mg/m <sup>2</sup> (d1) RT: NR HT: (if indicated) T
NSABP B-27 (22)	i [A+C q3wx4] +HT→[D q3wx4]→LT→RT ii [A+C q3wx4] +HT→LT→[D q3wx4]→RT iii [A+C q3wx4] +HT→LT→RT [CVAPr q3wx4]	CT: A=60mg/m <sup>2</sup> , C=600mg/m <sup>2</sup> , D=100mg/m <sup>2</sup> RT: NR HT: T=20mg/d for 5 yrs
Aberdeen (23-26)	i (R-)→[D q3wx4]→LT ii (R+)→[D q3wx4]→LT iii (R+)→[CVAPr q3wx4]→LT	CT: C=1000mg/m <sup>2</sup> (bolus), A=50mg/m <sup>2</sup> , V=1.5mg/m <sup>2</sup> (over 21d), D=100mg/m <sup>2</sup> (over 1 hr); Pr=40mg/day
<sup>a</sup> GEPAR-TRIO (27)	[D+A+C q3wx2] i (R+)→[D+A+C q3wx4]→ LT ii (R-)→[D+A+C q3wx4]→ LT iii (R-)→[N+X q3wx4]→ LT	CT: D=75mg/m <sup>2</sup> (d1), A=50mg/m <sup>2</sup> (d1), C=500mg/m <sup>2</sup> (d1), N=25mg/m <sup>2</sup> (d1&8), X=2000mg/m <sup>2</sup> (d1-14)
<sup>a</sup> Bouzid, 2001 (28)	i [A+D q3wx4]→LT ii [FAC q3wx4]→LT	CT: A=50mg/m <sup>2</sup> (over 15min), D=75mg/m <sup>2</sup> (over 1h), F=500 mg/m <sup>2</sup> (bolus), C=500mg/m <sup>2</sup> (bolus)
<sup>a</sup> Luporsi, 2000 (29)	i [E+D q3wx6]→LT ii [FEC q3wx6]→LT	CT: F=500mg/m <sup>2</sup> , E=100mg/m <sup>2</sup> , C=500mg/m <sup>2</sup> , D=75mg/m <sup>2</sup>
<b>Q2: Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to taxane-based adjuvant regimens?</b>		
<i>Paclitaxel</i>		
ECTO (30) <sup>a</sup> (Gianni, 2002)	i [A <sub>1</sub> +P q3wx4]→[CMF q4wx4]→LT ii LT→[A <sub>2</sub> q3wx4]→[CMF q4wx4] iii LT→[A <sub>1</sub> +P q3wx4]→[CMF q4wx4]	CT: A <sub>1</sub> =75mg/m <sup>2</sup> , P=200mg/m <sup>2</sup> (over 3 hrs), CMF=(d1&8), A <sub>2</sub> =60mg/m <sup>2</sup>

First Author, Year (Ref)	Treatment Arms (as in Table 1)	Additional dose and scheduling information
<b>Q3: What is the preferred dose and schedule for neoadjuvant taxane administration?</b>		
<i>Paclitaxel</i>		
<sup>a</sup> SICOG 9988 (31) (Comella, 2004)	i [Cis+E <sub>1</sub> +P <sub>1</sub> q1wx12]→LT ii [E <sub>2</sub> +P <sub>2</sub> q3wx4]→LT	CT: Cis=30mg/m <sup>2</sup> , E <sub>1</sub> =50mg/m <sup>2</sup> , P <sub>1</sub> =120mg/m <sup>2</sup> , E <sub>2</sub> =90mg/m <sup>2</sup> , P <sub>2</sub> =175mg/m <sup>2</sup> A=45mg/m <sup>2</sup> (d1&2), P=250mg/m <sup>2</sup> (over 3 hrs) Midway into accrual reports suggested that higher doses were more toxic and not beneficial compared with standard doses, Thus, for patients 21 to 29, the regimen was changed to: A=60mg/m <sup>2</sup> (d1), P=175mg/m <sup>2</sup> . Postoperative CT was administered if indicated.
Stearns, 2003 (32)	i [A q2wx3]→[P q2wx3]→LT→CT→HT→RT ii [P q2wx3]→[A q2wx3]→LT→CT→HT→RT	CT: (if indicated) RT: (if HR+) HT: (if HR+)
<sup>a</sup> AGO (33) (Untch, 2002)	i [E <sub>1</sub> q2wx3]→[P <sub>1</sub> q2wx3]→LT→[CMF q4wx3]→RT ii [E <sub>2</sub> +P <sub>2</sub> q3wx4]→LT→[CMF q4wx3]→RT	CT: E <sub>1</sub> =150mg/m <sup>2</sup> , P <sub>1</sub> =250mg/m <sup>2</sup> , E <sub>2</sub> =90mg/m <sup>2</sup> , P <sub>2</sub> =175mg/m <sup>2</sup> , CMF=500/40/6000mg/m <sup>2</sup> (d1+8) RT: (mandatory)
<sup>a</sup> Romieu, 2002 (34)	i [A+P q3wx6] →LT ii [A+P q3wx4] →LT	CT: A=60mg/m <sup>2</sup> , P=200mg/m <sup>2</sup>
<sup>a</sup> M.D. Anderson (35) (Green, 2002)	i N+[P <sub>1</sub> q1w for 3wks, 1wk break x4]→[FACx4]→LT ii N-[P <sub>2</sub> wx12]→[FACx4]→LT iii N-[P <sub>3</sub> 3wx4]→[FACx4]→LT iv N+[P <sub>3</sub> 3wx4]→[FACx4]→LT	CT: P <sub>1</sub> =150 mg/m <sup>2</sup> /wk (for 3 wks followed by a one wk break for 4 cycles), P <sub>2</sub> =80 mg/m <sup>2</sup> /wk (for 12 wks), P <sub>3</sub> =225 mg/m <sup>2</sup> (over 24 hrs q3w x4 cycles)
<i>Docetaxel</i>		
<sup>a</sup> ABCSG-14 (36) (Steger, 2004)	i [E+D q3wx6] →LT ii [E+D q3wx3] →LT	CT: E=75mg/m <sup>2</sup> (d1), D=75mg/m <sup>2</sup> (d1)
Miller, 1999 (37)	i [A <sub>1</sub> +D <sub>1</sub> q3wx4]→LT ii [A <sub>2</sub> q2wx3]→[D <sub>2</sub> q2wx3]→LT	CT: A <sub>1</sub> =75mg/m <sup>2</sup> , D <sub>1</sub> =100mg/m <sup>2</sup> , A <sub>2</sub> =56mg/m <sup>2</sup> , D <sub>2</sub> =75mg/m <sup>2</sup>

<sup>a</sup>Published abstract.

Abbreviations: A, doxorubicin; ABCSG Austrian Breast Cancer Study Group; ACCOG Anglo-Celtic Cooperative Oncology Group; AGO Arbeitsgemeinschaft Gynäkologische Onkologie; C, cyclophosphamide; CT, chemotherapy; d, day; D, docetaxel; E, epirubicin; ECTO European Cooperative Trial in Operable Breast Cancer; ER+, estrogen-receptor-positive; F, fluorouracil; hrs, hours; GEPAR German Pre-operative Adriamycin Docetaxel Trial; HR+, hormone-receptor-positive; HT, hormone therapy; LHRH, leutenizing-hormone-releasing hormone; LT, local surgical therapy; M, methotrexate; mg/d, milligrams per day; mg/m<sup>2</sup>, milligrams per metre squared, N, vinorelbine; N+, node positive; N-, node negative; NSABP National Surgical Adjuvant Breast and Bowel Project; NR, not reported; P, paclitaxel; PD, progression of disease; Pr, prednisolone; q#wx#, treatment given in a # week cycle for # cycles; R+, responders; R-, non-responders; RT, radiotherapy; SICOG Southern Italy Cooperative Oncology Group; T, tamoxifen; w, week(s); X, capecitabine; yrs, years; →, followed by.

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