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Evidence-Based Series #1–21

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

Optimal Systemic Therapy for Early Female Breast Cancer

Andrea Eisen, Glenn G. Fletcher, Sonal Gandhi, Mihaela Mates, Orit C. Freedman, Susan F. Dent, Maureen E. Trudeau, and members of the Early Breast Cancer Systemic Therapy Consensus Panel[1]

Report Date: September 30, 2014

An assessment conducted in January 2019 placed Evidence-based Series (EBS) 1-21 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-Based Series #1–21 contains 3 sections:

Section 1:	Guideline Recommendations
Section 2:	Evidentiary Base
Section 3:	EBS Development Methods and External Review Process

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[1] see Appendix A for a full list of participants

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Freedman OC, Fletcher GG, Gandhi S, Mates M, Dent SF, Trudeau ME, et al. Adjuvant endocrine therapy for early breast cancer: A systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline. Curr Oncol. 2015;22(Suppl 1):S95-113.

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LIST OF ABBREVIATIONS

CCO = Cancer Care Ontario
PEBC = Program in Evidence-Based Care
RAP = Report Approval Panel
RCT = randomized controlled trial

Disease Characteristics
DCIS = ductal carcinoma in situ
ER = estrogen receptor
ER− = ER negative
ER+ = ER positive
HER2 = human epidermal growth factor receptor 2
HER2− = HER2 negative
HER2+ = HER2 positive
HR− = hormone receptor negative
HR+ = hormone receptor positive
LABC = locally advanced breast cancer
LCIS = lobular carcinoma in situ
LVI = lymphovascular invasion
N0 = node negative (no positive lymph nodes)
N+ = node positive
PR = progesterone receptor
PR− = PR negative
PR+ = PR positive
TN = triple negative (PR−, ER−, HER2−)
RS = recurrence score

Treatments
ALND = axillary lymph node dissection
BCS = breast-conserving surgery
BCT = breast-conserving therapy (BCS + RT)
OA = ovarian ablation
OA/S = ovarian ablation and/or ovarian suppression
PMRT = postmastectomy radiation therapy
RT = radiation therapy
SLND = sentinel lymph node dissection

Outcomes
BCFI = breast cancer-free interval
BCFS = breast cancer-free survival rate
BMD = bone mineral density
cCR = clinically complete response
DDFS = distant disease-free survival rate
DFS = disease-free survival rate
DRFI = distant recurrence-free survival rate
EFS = event-free survival rate
HR = hazard ratio (95% confidence intervals may be in parentheses)
IDFS = invasive disease-free survival rate

LVEF = left ventricular ejection fraction
NNT = number needed to treat
OS = overall survival rate
pCR = pathologically complete response
QoL = quality of life
RFS = recurrence-free survival rate
RR = relative risk
TDR = time to distant recurrence

Systemic Therapy: Chemotherapy or Hormonal Therapy

A = doxorubicin (Adriamycin)
AC = doxorubicin (Adriamycin) + cyclophosphamide
AI = aromatase inhibitor
ANA = anastrozole (Arimidex)
C = cyclophosphamide
CAF = cyclophosphamide (oral) + doxorubicin (Adriamycin)(IV) + 5-fluorouracil (IV)
CEF = cyclophosphamide (oral) + epirubicin (IV) + 5-fluorouracil (IV)
CEX = cyclophosphamide + epirubicin + capecitabine
CMF = cyclophosphamide + methotrexate + 5-fluorouracil
ddAC = dose-dense AC
E = epirubicin
EC = epirubicin + cyclophosphamide
EXE = exemestane (Aromasin)
F = 5−fluoruracil
FAC = 5-fluorouracil + doxorubicin (Adriamycin) + cyclophosphamide (all IV)
FEC = 5-fluorouracil + epirubicin + cyclophosphamide (all IV)
FSH = follicle-stimulating hormone
G = gemcitabine
GCSF = granulocyte-colony stimulating factor
GnRH = gonadotropin-releasing hormone
GOS = goserelin (Zoladex)
H = trastuzumab (Herceptin)
LET = letrozole (Femara)
LHRH = luteinizing hormone-releasing hormone
M = methotrexate
OA = ovarian ablation
OA/S = ovarian ablation and/or ovarian suppression
P = paclitaxel
SERM = selective estrogen-receptor modulator
T = docetaxel (Taxotere) [less commonly abbreviated as D, with T referring to any taxane; this document generally uses "T" to refer to docetaxel]
TC = docetaxel (Taxotere) + cyclophosphamide
TAC = docetaxel (Taxotere) + doxorubicin (Adriamycin) + cyclophosphamide
TAM = tamoxifen
TCH = docetaxel (Taxotere) + carboplatin + trastuzumab (Herceptin) [*Note that TCH has a special meaning and does not follow convention in the other abbreviations]*
TH = docetaxel (Taxotere) + trastuzumab (Herceptin)
TX = docetaxel (Taxotere) + capecitabine
UFT = oral uracil and tegafur
X = capecitabine

Evidence-Based Series #1−21: Section 1

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

Optimal Systemic Therapy for Early Female Breast Cancer: Guideline Recommendations

Andrea Eisen, Glenn G Fletcher, Sonal Gandhi, Mihaela Mates, Orit Freedman, Susan Dent, Maureen Trudeau, and members of the Early Breast Cancer Systemic Therapy Consensus Panel

Report Date: September 30, 2014

1. QUESTION

What is the optimal adjuvant[1] systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered?

2. TARGET POPULATION

This guideline deals with female patients who are being considered for or are receiving systemic therapy for early-stage invasive breast cancer. The preferred definition of early breast cancer in this guideline is invasive cancers Stage I−IIA (T1N0−1, T2N0). Studies with cancer described as operable (no other description of stage) and some studies with both Stage I−IIA and operable Stage IIB−IIIA (sometimes considered locally advanced) are included.

3. INTENDED USERS

This guideline is directed toward clinicians (medical, radiation, and surgical oncologists and general practitioners) who participate in the care of patients with early breast cancer who are suitable for or receiving systemic therapy.

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[1] Several of the systemic therapies discussed in this guideline can be considered in the neoadjuvant setting. However, this guideline makes recommendations specifically for adjuvant therapy for the following reasons: a) there is significant variability within the patient population for whom neoadjuvant therapy may be considered (from early, operable breast cancer, to locally advanced breast cancer, which may have unique treatment needs) and b) our systematic review of the evidence focused on trials with disease-free survival (DFS) and overall survival (OS) as endpoints, and thus excluded several trials that used pathologically complete response (pCR) as a primary endpoint. Therefore, our recommendations represent only some of the data that may be relevant to neoadjuvant patients.

4. BACKGROUND

The systemic treatment of early-stage breast cancer involves decisions based on the characteristics of the patient and the disease. There are several guidelines that address specific issues of systemic therapy either in early breast cancer or in breast cancer generally. Because of the overlapping nature of the guidelines and patient characteristics, it is difficult for the end-user to find the appropriate guideline and recommendations. The Breast Cancer Disease Site Group (DSG) determined it would be desirable to have one guideline covering all systemic treatments for early breast cancer, and to have an associated user-friendly chart, matrix, or decision tree based on disease and patient characteristics.

This led to the development of a consensus panel of Ontario breast cancer oncologists. Utilizing the expertise of these clinicians from throughout the province, the available evidence was evaluated to create guidelines to ensure standardization of best practices.

5. SUMMARY OF METHODS (see Sections 2 and 3 for details)

A systematic review was conducted based on a literature search of MEDLINE and EMBASE for the period 2008 to March 2012. Guidelines were also identified from the SAGE Directory of Cancer Guidelines. Identified systematic reviews, meta-analyses, and practice guidelines were used to identify earlier studies or as the full evidence base when there were no more recent studies. Relevant abstracts presented at large academic meetings were used to update included trials or identify ongoing trials. The Working Group summarized the evidence and drafted recommendations that were then circulated to members of the consensus group. The consensus group (including the Working Group members) consisted of medical oncologists from Ontario who either were members of the Breast Cancer DSG or were invited to ensure representation from all regional cancer centres and programs in Ontario.

A consensus panel process among the participants was used as the method to review and provide feedback on the draft recommendations. In doing so, the large amount of evidence and wide scope of the document could be managed, the current use of several chemotherapy regimens that do not have direct randomized controlled trial (RCT) comparisons and that may have differential benefits in specific subpopulations of patients could be debated and judged, differences in practice patterns among different centres and regions of Ontario could be taken into account, and gaps in evidence for certain practices could be more easily identified. The consensus process was envisioned as a way to engage the larger clinical community, promote greater standardization of practice, raise awareness of some of the challenging issues surrounding treatment decisions, and reveal practices that are not according to best evidence.

The draft recommendations were circulated to all consensus group members and voted on prior to the consensus meeting of November 23, 2012 using a 5–point Likert scale (strongly disagree, disagree, undecided, agree, strongly agree). Consensus was defined as at least 80% agreement (agree or strongly agree) and no strong disagreement. Recommendations without consensus from the initial questionnaire were presented, discussed, revised, and voted on at the consensus meeting.

This section provides the final set of recommendations and key supporting evidence. Section 2 provides the evidence summary on which the recommendations were informed. Section 3 and Appendix B provide more detail about the consensus methods and the processes undertaken in this project, the original recommendations distributed to the consensus

participants, the original feedback received from the survey, and the feedback received at the meeting. In the final recommendations, cross-referencing to tables in Section 2 or other evidence was removed from the recommendation boxes and placed with the qualifying statements and key evidence.

6. RECOMMENDATIONS AND KEY EVIDENCE

The most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview (1) confirms the benefit of adjuvant chemotherapy vs none in improving outcomes in early breast cancer. The EBCTCG found similar relative benefit for all subgroups, although the absolute magnitude of benefit depended on baseline risk.

In all recommendations it is assumed that patient preference is considered and that final treatment is determined in consultation between the patient and the doctor. This is mentioned more explicitly in a few recommendations in which the balance between risk and benefit is less clear overall or for certain patient groups.

RECOMMENDATIONS 1−7. PATIENT/DISEASE CHARACTERISTICS AND RECURRENCE RISK

Recommendations for adjuvant systemic therapy in breast cancer are mostly guided by patient and disease characteristics. In general, these factors help stratify patients into low-, intermediate-, and high-risk categories (2-4). The evidence review focused on guidelines, meta-analyses, and phase III clinical studies evaluating the impact of adjuvant systemic therapies on disease-free and/or overall survival rates; a systematic review specifically on patient and disease stratification factors was not performed. The recommendations for risk stratification were created by:

- Extraction of information from clinical practice guidelines found by our systematic review.
- Assessment of patient and disease factors evaluated or addressed in clinical trials included in our systematic review.
- Initial expert consensus on additional relevant factors that may not have been specifically addressed in the reviewed guidelines and clinical trials.

R1. The following disease characteristics (histopathological parameters) are considered relevant (either prognostic or predictive) when making a decision regarding adjuvant systemic therapies for breast cancer:

- **Lymph node status**
- **T stage**
- **Estrogen receptor (ER) status**
- **Progesterone receptor (PR) status**
- **Human epidermal growth factor receptor 2 (HER2) status**
- **Tumour grade**
- **Presence of tumour lymphovascular invasion (LVI)**

Qualifying Statements

- Progesterone Receptor Status. The EBCTCG meta-analysis (5) (see Table 4 in Section 2 of this guideline) found that PR status was not an important independent factor for

determining response to endocrine therapy with tamoxifen. The consensus panel members cautioned that PR status in the studies used for the EBCTCG meta-analysis may have been analyzed by older pathological methods and may not be as well-standardized as ER analysis. ER−PR+ is very rare, such that a pathological result with this profile usually requires re-testing and confirmation. The method used to ascertain ER and PR is important, and positivity should be determined according to CCO/ASCO/CAP guidelines (6-9). Disease response of patients with ER−PR+ cancer to other endocrine agents besides tamoxifen was not addressed in the EBCTCG meta-analysis. Nonetheless, PR status may still have prognostic value even if it is not deemed useful in determining tamoxifen response.

- LVI. LVI predicted worse outcome in some studies (10,11) and may therefore be useful as a prognostic factor. According to the St. Gallen Consensus Conference (4,12) it is not sufficient to decide chemotherapy. The panel wondered whether LVI results are reproducible among various laboratories.

Other Characteristics without Consensus

- Ki-67. Ki-67 is currently considered more clinically useful in other cancers, such as lymphoma. There is generally poor analytical reproducibility of Ki-67 in breast cancer between various centres because testing methods are not standardized and no clear cut-off values have been defined. Some studies show a prognostic role for Ki-67, and it is incorporated in some molecular gene signatures, such as Oncotype DX. Finally, it is not prospectively validated. It is premature to recommend its use as a standard parameter for patient risk stratification, although it may be evaluated in clinical trials.
- Intrinsic Subtypes. Intrinsic breast cancer subtypes (luminal A, luminal B, HER2 enriched, basal, and normal) have been established to correlate with prognosis. There exist several retrospective analyses describing the response to various systemic treatments by these subtypes. However, the utility of these subtypes beyond measurement of ER, PR, HER2, and grade is not clear. At this point, the use of these subtypes in clinical decision making outside of a clinical trial is not recommended.

R2. The following risk stratification tools may be used in determining the utility of certain systemic therapies in patients with early-stage breast cancer:

- **Oncotype DX score (for HR+, N0 or $N1_{mic}$ or ITC, and HER2 negative cancers)**
- **Adjuvant! Online (www.adjuvantonline.com)**

Qualifying Statements

- The Oncotype DX assay analyzes expression of a panel of 21 genes using real time reverse transcription-polymerase chain reaction (RT-PCR). It has been compared with other molecular tests in the Molecular Oncology Advisory Committee (MOAC) report (13). Oncotype DX includes 5 reference genes and 16 genes found to correlate with distant relapse in hormone receptor positive (HR+) breast cancer. The test was initially validated in three independent patient trial cohorts. Tested tumours are stratified as low, intermediate, or high recurrence score (RS), and each individual score is associated with a distinct 10−year distant relapse rate, assuming five years of endocrine therapy with

tamoxifen. The additional benefit of chemotherapy varies by RS, whereby low scores have little to no benefit, and high scores have the most benefit (14). The utility of chemotherapy in the intermediate RS zone is less clear at this juncture, although a phase III clinical trial (TAILORx) may help address this once reported. The test is most useful in patients with estrogen/progesterone receptor positive, HER2 and lymph node negative cancer; studies have retrospectively evaluated the use of Oncotype DX in patients with lymph node positive cancer; however, they were not entirely robust from a statistical standpoint (15,16).

- Oncotype DX is not consistently funded by health authorities across Canada. The consensus panel agreed the test is useful in selecting patients with ER/PR positive, HER2 negative, lymph node negative cancer, or patients with lymph node micrometastasis in whom the additional benefit of chemotherapy over endocrine therapy alone is unclear.
- Prognostic information for Adjuvant! Online comes from the Surveillance, Epidemiology and End Results (SEER) cancer information database of the United States and was validated by Olivotto et al (17). There is good overall correlation with some exceptions. In the UK validation (18), patients did worse than predicted by Adjuvant! Online; this may relate to differences in the health system. There is good correlation between Adjuvant! Online and Oncotype DX in patients with mid-risk of recurrence, but poor correlation at the high and low ends.
- Several participants considered Adjuvant! Online a good tool to help explain risk and treatment options to patients but do not use it for decision making because it does not include other factors that need to be considered, such as HER2 status. Risks are dependent on the comorbidity the user enters.

R3. The following patient factors should be considered in making adjuvant systemic therapy decisions:

- **Age**
- **Menopausal status**
- **Medical comorbidities (including validated tools used to measure health status)**

Qualifying Statements

- The consensus panel agreed that age should not be a sole factor in selecting patients for chemotherapy. Advanced age in the absence of other medical comorbidities should not be used as an independent criterion to not recommend chemotherapy. Younger age may be correlated more often with aggressive tumour biology or subtypes, and may also predict response to certain treatments, but should not be an independent factor in determining candidacy for chemotherapy. Desire to spare fertility in younger patients and desire to avoid certain adverse effects in older patients may impact selection of treatment. Age has been used as a surrogate for menopausal status in some clinical studies (see Recommendations 15–25 on Endocrine Therapy).

R4. **In those patients in whom chemotherapy would likely be tolerated and is acceptable to the patient, adjuvant chemotherapy should be considered for patients with the following tumour characteristics (in no particular order):**

- **Lymph node positive: one or more lymph nodes with a macro-metastatic deposit (>2 mm)**
- **ER– with T size >5mm**
- **HER2+ tumours**
- **High-risk lymph node negative tumours with T size >5 mm and another high-risk feature (see next recommendation, R5)**
- **Adjuvant! Online 10–year risk of death from breast cancer >10%**

Qualifying Statements

- The consideration of disease factors for selecting patients to receive chemotherapy was based on review of existing guidelines and models of risk stratification, as outlined in the introduction. The Adjuvant! Online 10–year risk of death was considered by the panel at two cut-offs: 10% and 15%. There was strong consensus for 15%, and less robust consensus for using a 10% cut-off. Therefore, either a 10% or 15% 10–year risk of death according to the Adjuvant! Online model is a reasonable threshold for considering chemotherapy.

R5. **When considering lymph node negative tumours with T>5mm, the following should be considered <u>high-risk</u> features (thus considered candidates for chemotherapy):**

- **Grade 3**
- **Triple negative (ER–, PR–, and HER2–)**
- **LVI positive**
- **An Oncotype DX recurrence score (RS) that is associated with an estimated distant relapse risk of 15% or more at 10 years**
- **HER2+**

Qualifying Statements

- The panel reached consensus for considering all these features as high risk; therefore, patients with tumours possessing these characteristics should be considered for adjuvant chemotherapy. As previously noted, these features were derived from review of existing guidelines and models of risk stratification.

R6. **Patients with the following disease characteristics may <u>not</u> benefit from adjuvant chemotherapy:**

- **T <5 mm, lymph node negative and <u>no</u> other high-risk features (see R5)**

R7. **Adjuvant chemotherapy may <u>not</u> be required in patients with HER2–, strongly ER+ and PR+ breast cancer with any of the following additional characteristics:**

- **Lymph node positive with micrometastasis (<2 mm) only, <u>*or*</u>**
- **T <5mm, <u>*or*</u>**
- **An Oncotype DX RS with an estimated distant relapse risk of less than 15% at 10 years**

Qualifying Statements (Recommendations 6 and 7)

- Cut-offs for degree of estrogen receptor expression do not formally exist. The generally accepted degree of strong estrogen receptor positivity is >90% and this was used for the consensus question. Refer to local pathology policy in regards to degree of estrogen expression.
- Few RCTs have addressed the role of systemic chemotherapy in female patients with good prognosis early-stage breast cancers. In addition, there is limited data available on the benefit of systemic therapy in patients with lymph node positive micrometastatic (≤2 mm) disease. The IBCSG 23−01 trial concluded that axillary dissection could be avoided in patients with early breast cancer and limited sentinel-node involvement (micrometastasis only), thus eliminating complications of axillary surgery with no adverse effect on survival rates (19). In this trial more than 60% of patients received adjuvant endocrine treatment alone with excellent five-year disease-free survival rate (DFS) and overall survival rate (OS).
- Sentinel node micrometastases has been associated with an adverse prognosis in some long-term follow-up studies. Retrospective data have shown some benefit of systemic therapy in patients with micrometastatic disease. Until the results of prospective RCTs are available, the potential role of systemic therapy should be discussed with each patient (20).
- Prognostic tools such as Adjuvant! Online and Oncotype DX may be used to assist healthcare providers in determining the potential benefit of chemotherapy.
- The potential benefit of adjuvant systemic therapy is modest for patients with small (<1 cm) node negative breast cancer that is endocrine sensitive and HER2 negative, and these patients may be considered for endocrine therapy alone [see NCCN Guideline (3)].
- Although the majority of the consensus group agreed that patients with lymph node positive breast cancer with micrometastasis only (<2 mm) and no other high-risk features may not need adjuvant chemotherapy, 25% disagreed or were undecided and consensus was not reached. However, consensus was reached about potentially omitting chemotherapy when patients were found to have lower-risk (see R7) strongly ER/PR positive disease. There was disagreement as to whether lymph node micrometastasis alone is a high- or low-risk factor. Lymph node positivity with micrometastasis alone is therefore not included in the recommendation.

RECOMMENDATIONS 8−14. SELECTION OF OPTIMAL ADJUVANT CHEMOTHERAPY REGIMENS

R8.	**In patients who can tolerate it, using an anthracycline-taxane containing regimen is considered the optimal strategy for adjuvant chemotherapy, particularly in those patients deemed to be high risk.**

Key Evidence

- Aggregate data from several phase III clinical studies, as well as meta-analyses, have established the superiority of many anthracycline-taxane-based regimens compared with other chemotherapy (see Tables 2 and 3 in the Evidence Summary).
- The 2012 EBCTCG meta-analysis (1) highlights that anthracycline-taxane regimens that do

not alter the number of anthracycline cycles (e.g., AC×4→T×4) are superior to the anthracycline alone (e.g., AC×4). Although the EBCTCG found no significant differences in outcomes if the anthracycline treatments were truncated and a taxane was added instead (e.g., FEC×3→T×3), compared with simply increasing the number of anthracycline treatments (FEC×6), longer-term follow-up of the included studies (see Table 3) suggests benefit for taxanes exists. The PACS 01 trial of FEC×3→T×3 vs FEC×6 found improved survival rates at eight years for the anthracycline-taxane combination (21).

- Truncating the number of anthracycline cycles when adding a taxane can mitigate certain important adverse effects such as cardiotoxicity and leukemia, which occur more frequently with more cycles of anthracyclines [e.g., PACS 01 (22), review by Trudeau et al (23), and recent meta-analysis (24)]. Individual trial data supports the following regimens: FEC×3→T×3 (superior to FEC×6) [PACS 01 (21,22,25-27)], AC×4→T×4 (superior to AC×4) [NSABP B27 (28)], TAC×6 (superior to FAC×6) [BCIRG 001 (29-31)]. AC×4→P×4 administered every three weeks is an option in selected cases but was found to be inferior to AC×4→P administered weekly [ECOG 1199 (32)], CEF, and dose-intense EC→P [MA.21 (33)].

R9. For patients in whom a taxane is contraindicated, an optimal-dose anthracycline regimen (doxorubicin ≥240 mg/m^2 or epirubicin ≥360 mg/m^2) is recommended.

Key Evidence

- Anthracyclines have been established to be superior to some non-anthracycline chemotherapy regimens (Table 2 in Evidence Summary).
- Studies included in the EBCTCG 2012 meta-analysis (1) indicate that in general, anthracycline-based regimens are superior to non-anthracycline non-taxane regimens, provided that an optimal anthracycline cumulative dosage is achieved (defined as total epirubicin dosage of >360 mg/m^2 or doxorubicin dosage of >240 mg/m^2). These studies provide evidence for use of the following regimens:
    - CEF×6, or CAF×6, are superior to CMF×6 (with oral cyclophosphamide)
    - AC×4 is superior to CMF×6 (with IV cyclophosphamide), but equivalent to CMF×6 (with oral cyclophosphamide) (34,35).
    - CEF×6 resulted in improved survival rates compared with CMF×6 in a trial by Kimura et al (not included in the 2012 meta-analysis), although the difference was not statistically significant (36).
    - The utility of FEC_{100}×6 is evidenced by the FASG 05 trial in mostly patients with locally advanced breast cancer (LABC) (37) illustrating its superiority to FEC_{50}×6. However, it is unclear if the FEC_{100} regimen is comparable to CEF×6 or CAF×6. Although the total cumulative dosage of epirubicin in this regimen is >360 mg/m^2, the 2012 meta-analysis suggests that it may be equivalent to AC×4.

R10. The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen is <u>not</u> recommended for adjuvant chemotherapy.

Key Evidence

- The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen does not improve rates of DFS or OS and is more toxic (38,39) (see Table 3 in Section 2).

R11. In patients older than 65 years, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of adjuvant AC or CMF (oral cyclophosphamide).

Key Evidence

- In patients older than 65 years, adjuvant capecitabine was found to be inferior to CMF (oral cyclophosphamide)×6 and AC×4 (40) (see Table 1 in Section 2).

R12. CMF (with oral cyclophosphamide) is an acceptable chemotherapy regimen for patients in whom an anthracycline and taxane is contraindicated.

Key Evidence

- CMF chemotherapy has been found to be better than no chemotherapy in the adjuvant setting (41) (see Table 1 in Section 2: Evidentiary Base). CMF×6 (with oral cyclophosphamide) has been found to be no worse than AC×4 in the adjuvant setting (40).

R13. The following adjuvant chemotherapy regimens can be used for patients with early-stage breast cancer (also see R14 for non-anthracycline regimens):

- FEC×3→T×3 (superior to FEC×6)
- AC×4→T×4 (superior to AC×4)
- TAC×6 (superior to FAC×6)
- AC×4→P administered weekly
- Dose-dense, dose-intense EC→P
- Dose-dense AC→P (every 2 weeks)

Key Evidence and Qualifying Statements

- Phase III clinical studies have shown improved outcomes from the adjuvant anthracycline and the anthracycline-taxane-based regimens listed in R13 (see Tables 2 and 3 in the Evidence Summary).
- FEC followed by weekly paclitaxel was not included in the initial questionnaire. It was discussed at the meeting and participants were asked to add it to the answer sheet for the second round of voting. Four of sixteen participants did not answer this question at that round; therefore, consensus was not reached. Of those who voted, 11 agreed and 1 was undecided.
- Exploratory subgroup analysis suggests that the superiority of FEC→T over FEC_{100} may be restricted to subgroups such as postmenopausal patients or those aged >50 years (27). Some anthracycline-taxane regimens have been compared (AC→T, TAC, ddAC→P), showing comparable efficacy; FEC→T has not been directly compared with any other such regimen. Nonetheless, there is no clear data to show the superiority of any of these

anthracycline-taxane regimens over another, and a recent analysis found no difference in patient outcomes when evaluated by these regimens, including FEC→T (42). As such, they all remain reasonable options for adjuvant treatment in the absence of any prospective, randomized studies showing otherwise.

- Consensus was not reached on the use of CEF (5 of 16 disagreed or were undecided). This regimen may have a role in a subgroup of patients with very high risk of recurrence and good health who can tolerate it, although there are regimens with likely similar efficacy and lower risk of adverse effects.

Anthracycline vs Anthracycline-Taxane-Based Regimens

- The 2012 EBCTCG meta-analysis (1) highlights that anthracycline-taxane regimens that do not alter the number of anthracycline cycles (e.g., AC×4→T×4), are superior to the anthracycline alone (e.g., AC×4). Although the EBCTCG found no significant differences in outcomes if the anthracycline treatments were truncated and a taxane was added instead (e.g., FEC×3→T×3), compared to simply increasing the number of anthracycline treatments (FEC×6), longer-term follow-up of the included studies (see Table 3) suggests benefit for taxanes exists. The PACS 01 trial of FEC×3→T×3 vs FEC×6 found improved survival rate at eight years for the anthracycline-taxane combination (21).
- Truncating the number of anthracycline cycles when adding a taxane can mitigate certain important adverse effects, which are increased with more cycles of anthracyclines, including cardiotoxicity and leukemia [e.g., PACS 01 (22), review by Trudeau et al (23), and the recent meta-analysis by Petrelli (24)]. In addition, individual trial data supports the following regimens: FEC×3→T×3 (superior to FEC×6) [PACS 01 (21,25-27)], AC×4→T×4 (superior to AC×4) [NSABP B27 (28)], and TAC×6 (superior to FAC×6) [BCIRG 001 (29-31)].

Taxane-Based Regimens Compared With One Another

- The 2012 EBCTCG meta-analysis (1) did not include several studies evaluating particular taxane-based regimens to others. Individual RCTs support the use of the following: AC→P weekly [ECOG1199 (32)], dd AC→P [CALGB 9741 (43)], AC×4→T×4 [NSABP B30 (44-46) and BCIRG 005 (47)], TAC×6 [BCIRG 005 (47) and NSABP B-38 (38,48)], dd AC→P [NSABP B-38 (38,48)]. TAC×4 was found to be inferior in NSABP B30 (44-46).
- AC×4→P×4 administered every three weeks is an option in selected cases but was found to be inferior to AC×4→P administered weekly [ECOG 1199 (32)], CEF, and dose-intense EC→P [MA.21 (33)].
- Although there has been no direct comparison of FEC×3→T×3 vs optimal doxorubicin-taxane based regimens, a recent retrospective "real-world" analysis of patient outcomes in Ontario using propensity matching found equivalent rate outcomes for FEC×3→T×3 vs dd AC→P (42).

R14. TC (docetaxel/cyclophosphamide) is an adjuvant regimen that can be used when an anthracycline is <u>not</u> preferred.

Key Evidence and Qualifying Statements

- The US Oncology 9735 study found superiority of TC×4 over AC×4 (49) (see Table 3 in Section 2: Evidentiary Base). How a taxane regimen such as TC compares to an anthracycline-taxane regimen is unclear. TC vs TAC is being compared in the ongoing and interrelated NSABP B46, USOR (USON) 06–090, and NSABP B49 trials (see clinicaltrials.gov/ct2/show/NCT01547741, clinicaltrials.gov/ct2/show/NCT00887536).
- Patients who may have contraindications to anthracycline therapy (such as risk factors for cardiac disease) may be good candidates for a regimen such as TC. In recommending chemotherapy to patients who have moderate or intermediate risk disease, the omission of an anthracycline (such as by using TC) may also be reasonable to spare these patients the risk of cardiotoxicity.

RECOMMENDATIONS 15–25. ADJUVANT ENDOCRINE THERAPY

R15. For the purpose of selecting adjuvant endocrine therapy, the most reliable definitions of menopause are:

- **Bilateral oophorectomy**
- **At least 12 months of amenorrhea prior to initiation of chemotherapy or tamoxifen**
- **In female patients age ≤60 years who experience amenorrhea secondary to chemotherapy or tamoxifen, defining menopause is difficult and care must be taken when initiating an aromatase inhibitor (AI)**

Key Evidence and Qualifying Statements

- Caution must be employed in defining menopause in patients who have had a previous hysterectomy with ovaries left in place. In these patients, levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) measured prior to receiving chemotherapy/tamoxifen may be useful in determining menopausal status.
- The definition of menopause varied across studies, with most studies using a cut-off of age 50 or 60 years.
- Accurate identification of postmenopausal status is crucial if AI therapy is used because AIs cause a reflex increase in gonadotropin secretion in premenopausal patients (50).
- The incidence of chemotherapy-induced amenorrhea is dependent on the regimen used and the age of the patient (51,52).
- Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with chemotherapy-induced amenorrhea (53). In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen (54).

R16. Adjuvant endocrine therapy should be considered in all patients with ER+ cancer, defined by the ASCO/CAP guidelines as ER immunohistochemistry (IHC) staining ≥1%, taking into consideration overall disease risk, patient preference, and potential adverse effects.

Key Evidence and Qualifying Statements

- Evidence is summarized in Section 2 of this guideline (see Subsection 4.3)
- This recommendation follows the ASCO/CAP guidelines (6-9).
- Discussion at the consensus meeting acknowledged that the benefit of hormone-targeted therapy was greater in patients with higher ER levels.

R17. Consensus was not reached on whether to administer adjuvant endocrine therapy in patients with ER− but PR+ tumours. See Section 3 for details.

R18. Tamoxifen for five years has been the standard of care, but tamoxifen for up to ten years is a reasonable option for premenopausal patients with ER+ tumours, regardless of chemotherapy use.

Key Evidence and Qualifying Statements

- Evidence on tamoxifen use is summarized in Section 2 of this guideline (see Subsection 4.3.1).
- Tamoxifen for five years improves DFS and OS rates in the adjuvant setting, in both pre and postmenopausal patients. Five years of tamoxifen monotherapy is superior to two to three years.
- The ATLAS trial (55) included 12,894 female patients and found that extending tamoxifen duration in ER+ patients to 10 years further reduced the risk of breast cancer recurrence (617 vs 711 cases, −2.80% difference, p=0.002), breast cancer mortality (p=0.01), and overall mortality (639 vs 722 deaths, −2.48% difference, p=0.01). For all ER groups combined (ER+, ER−, or unknown) there was an increased incidence of pulmonary embolus (41 vs 21 cases, difference of 0.31%, p=0.01) and endometrial cancer (116 vs 63 cases, difference of 0.82%, p=0.0002), although this did not result in a significant difference in mortality from these causes (10 vs 8 deaths, p=0.69 and 17 vs 11, p=0.29, respectively). There was an decrease in ischemic heart disease (127 vs 163 cases, −0.56% difference, p=0.02,) and lower rate of death due to myocardial infarction or other vascular causes (178 vs 205 deaths, difference −0.43%, p=0.10).
- The aTTOM trial (56) also found that extending tamoxifen to ten years compared with five years reduced recurrence (p=0.003) and breast cancer mortality rates (p=0.05), with little effect on non-breast cancer mortality rates(457 vs 467 deaths, RR=0.94). There was an increase in endometrial cancer occurrence (102 vs 45 cases, RR=2.2, p<0.0001) and death (37 vs 20 deaths, 1.1% vs 0.6%, p=0.02). Combined results with the ATLAS trial gave enhanced statistical significance for extended tamoxifen benefit for recurrence (p<0.0001), breast cancer mortality (p=0.002), and OS (p=0.005). The proportional reduction in recurrence rates was unaffected by age or nodal status.
- The benefit of tamoxifen in improving DFS and OS rates remained even when initiated more than two years after definitive surgery or adjuvant chemotherapy (57,58); therefore, patients should be offered tamoxifen even when a delay occurred after surgery or adjuvant chemotherapy.

- Identifying menopause by amenorrhea or hormone levels post-chemotherapy and/or while on tamoxifen is unreliable (see Recommendation 15).

R19. Ovarian ablation or suppression is a reasonable treatment option for premenopausal patients with ER+ tumours who refuse or are not candidates for any other systemic therapy.

Key Evidence and Qualifying Statements

- Refer to Table 12 in the Evidentiary Base (Section 2).
- Ovarian ablation (OA) can be achieved through surgery or radiation, and ovarian suppression can be achieved with luteinizing hormone-releasing hormone (LHRH) agonists.

R20. In premenopausal patients with ER+ tumours (treated with or without chemotherapy) the addition of ovarian ablation or suppression to tamoxifen is not the standard of care.

Some consensus panel participants disagreed with the recommendation because it did not make allowance for subgroups and could be misinterpreted to mean that ovarian ablation and/or suppression (OA/S) plus tamoxifen should not be used. Because they did not vote "strongly disagree" the recommendation passed the consensus rules and rewording was not considered.

Subsequent to completion of this guideline, additional results for the SOFT trial became available which indicate that for women who remain premenopausal after chemotherapy (as demonstrated by estradiol levels), ovarian function suppression in addition to tamoxifen reduces risk of breast cancer recurrence, which can be further reduced by the use of exemestane rather than tamoxifen (59).

Key Evidence and Qualifying Statements

- In early breast cancer, OA/S plus tamoxifen is not currently the standard of care for all premenopausal patients with ER+ cancer. Some of the authors consider this combination appropriate in certain subgroups such patients who are younger or at higher risk of recurrence. Use of an AI is addressed in R21. OA/S plus tamoxifen (60) or OA/S plus endocrine therapy (3) is the standard of care for metastatic breast cancer (both pre- and postmenopausal).
- In the LHRH-agonists meta-analysis (61) (see Table 12 in Section 2), comparisons of recurrence rates with and without LHRH subdivided by age (≤40 and >40 years) suggested a stronger (and beneficial) effect of LHRH in younger patients. LHRH + tamoxifen compared with tamoxifen alone improved the hazard ratio for recurrence by 32% in the ≤40 years subgroup (p=0.12) compared with an improvement of 2% (p=0.91) in the >40 years subgroup.
- The benefit for LHRH added to chemotherapy or any systemic therapy was statistically significant (p=0.01 and p=0.002 respectively) for the ≤40 years group (61). In younger female patients, chemotherapy is less likely to induce permanent amenorrhea, and this may explain the greater benefit of OA/S in younger patients. In addition, permanent

amenorrhea after treatment using modern non-CMF-based chemotherapy is less common than with older chemotherapy regimens. It is unclear whether benefit persists when tamoxifen is also used.

- Results from the SOFT and TEXT trials (see R21 and Table 8 of Section 2) suggest that OA/S + exemestane is better than OA/S + tamoxifen.
- The SOFT and TEXT found that patients deemed by their physicians as not requiring chemotherapy had a DFS rate of 96% with exemestane + OA/S and 93% with tamoxifen + OA/S, and suggested there may be patients at low risk of recurrence who do not require chemotherapy if they receive appropriate endocrine therapy.
- Additional results from the SOFT trial comparing tamoxifen plus ovarian suppression to tamoxifen alone were reported subsequent to this guideline completion (59,62). There was a benefit for the addition of ovarian suppression to tamoxifen (86.6% vs 84.7% DFS, p=0.10; p=0.03 after adjustment for prognostic factors). Most recurrences and thus greater benefit was found in those who received chemotherapy; there was no difference in DFS (93.4% vs. 93.3%) or OS (99.2% vs. 99.8%) in the subgroup of patients who had no prior chemotherapy. The benefit of ovarian function suppression plus exemestane was especially seen in the patient group under 35 years old. Ovarian function suppression plus exemestane or tamoxifen, compared to tamoxifen alone, was associated with more toxicity and adverse effect on QoL and these effects need to be considered when choosing between tamoxifen, tamoxifen plus ovarian suppression, and exemestane plus ovarian suppression (59,62-65).

R21. In premenopausal patients with ER+ tumours, treated with or without chemotherapy, ovarian ablation or suppression plus five years of an AI is <u>not</u> the standard of care.

Subsequent to completion of this guideline, additional results for the SOFT trial became available which indicate that for women who remain premenopausal after chemotherapy (as demonstrated by estradiol levels), ovarian function suppression in addition to tamoxifen reduces risk of breast cancer recurrence which can be further reduced by the use of exemestane rather than tamoxifen (59).

Key Evidence and Qualifying Statements

- Standard practice in Canada and the United States is to use tamoxifen in premenopausal patients, although European clinicians tend to favour an AI + ovarian suppression (66). OA/S + tamoxifen (60) or OA/S + endocrine therapy (3) is the standard of care for metastatic breast cancer (both pre- and postmenopausal).
- In postmenopausal patients, AIs have been found superior to tamoxifen (see R22, R24). It has been proposed that AIs would be better than tamoxifen in premenopausal patients, but this would require OA/S to reduce estrogen levels to postmenopausal levels.
- The SOFT and TEXT Trials (see Table 8 in Section 2) found that exemestane + OA/S to resulted in improved survival rates compared with tamoxifen + OA/S (DFS 91.1% vs 87.3%, HR=0.72, p=0.0002).
- The SOFT and TEXT also found that patients deemed by their physicians not to require chemotherapy experienced survival rates of 96% with exemestane plus OA/S and 93% with

tamoxifen plus OA/S, suggesting that some patients who are at low risk of recurrence might not require chemotherapy if they receive appropriate endocrine therapy.

- Additional results from the SOFT trial comparing tamoxifen plus ovarian suppression to tamoxifen alone were reported subsequent to this guideline completion (59,62). There was a benefit for the addition of ovarian suppression to tamoxifen (86.6% vs 84.7% DFS, p=0.10; p=0.03 after adjustment for prognostic factors). Most recurrences and thus greater benefit was found in those who received chemotherapy; there was no difference in DFS (93.4% vs. 93.3%) or OS (99.2% vs. 99.8%) in the subgroup of patients who had no prior chemotherapy. The benefit of ovarian function suppression plus exemestane was especially seen in the patient group under 35 years old. Ovarian function suppression plus exemestane or tamoxifen, compared to tamoxifen alone, was associated with more toxicity and adverse effect on QoL and these effects need to be considered when choosing between tamoxifen, tamoxifen plus ovarian suppression, and exemestane plus ovarian suppression (59,62-65).

R22. The optimal* adjuvant endocrine therapy for postmenopausal patients with ER+ tumours should include an AI.

Key Evidence and Qualifying Statements

- Evidence is summarized in Tables 6–9 of Section 2 (Evidence Summary).
- Studies consistently demonstrate that the use of an AI either alone or sequentially after tamoxifen therapy, compared with tamoxifen alone, reduces the risk of recurrence and improves DFS rate (67).
- The absolute gain in breast cancer endpoints is greater for patients with a poorer prognosis.
- EBCTCG 2010 did not report mortality rates so the survival rate data from the aggregated trials is not yet known.
- Some studies suggest that the relative benefit of tamoxifen or various AIs may depend on patient characteristics (e.g., nodal status, hormone receptor status), although this needs to be verified in future studies.

*Some consensus panel participants felt that the word "optimal" may not apply to all patients. The risk to benefit ratio of using tamoxifen vs AIs must be taken into account, recognizing the different side-effect profile of these medications.

R23. Tamoxifen for up to ten years is an acceptable treatment for postmenopausal patients with ER+ tumours treated with or without chemotherapy.

Key Evidence and Qualifying Statements

- Evidence on tamoxifen use is summarized in Section 2 of this guideline (see Subsection 4.3.1).
- Substantial and highly significant recurrence rate reduction and survival rate benefit were found in all subgroups of patients with ER+ cancer treated with tamoxifen: entry age, tumour grade and size, chemotherapy use and sequence with tamoxifen, and nodal status.

- The absolute risk reduction from tamoxifen depends on the absolute breast cancer risk.
- Although incorporating an AI into treatment improves DFS rate and reduces recurrence, tamoxifen alone may be appropriate in some patients. The risk-to-benefit ratio of using tamoxifen and AIs must be taken into account, recognizing the different adverse-effect profiles of these medications.
- Extended tamoxifen beyond 5 years is supported by the ATLAS (55) and aTTOM trials (56) (see Recommendation 18).

R24. For postmenopausal patients with ER+ breast cancer (treated with or without chemotherapy) the following are acceptable strategies for use of AIs:
- **Upfront for five years (instead of tamoxifen)**
- **As a switch after two to three years of tamoxifen (for a total of five years of endocrine therapy)**
- **As extended adjuvant therapy for five years, after completing five years of tamoxifen**

Key Evidence and Qualifying Statements

- Tables 6–8 in the Evidence Base (Section 2) summarize the phase III clinical studies that evaluated the role of AIs in postmenopausal patients with ER+ breast cancer. All the included studies detected a small benefit in absolute DFS rate and indicated that AIs can be administered in several strategies:
  - **Upfront** letrozole, anastrozole, or exemestane (68) for five years in lieu of tamoxifen therapy; BIG 1–98 found a small OS benefit as well.
  - **Switch strategy** (letrozole, exemestane, or anastrozole) after two to three years of tamoxifen therapy. The IES and ARNO trials found an OS benefit as well; however, these studies had a highly selected population. BIG 1–98 provided data for switching from letrozole to tamoxifen after two to three years or from tamoxifen to letrozole; both of these were found to be have similar outcomes as five years of letrozole.
  - **Extended adjuvant therapy** with three to five years of any AI after five years of tamoxifen therapy; this strategy had a small OS benefit in patients with lymph node positive cancer (MA.17).
  - **Delayed AI** with the initiation of letrozole at a median of 2.8 years after completing 5 years of tamoxifen.
- All consensus participants either disagreed (12 of 16) or were undecided (4 of 16) with giving AIs as extended adjuvant therapy for longer than five years, after completing five years of tamoxifen.
- Some studies suggest that relative benefit of tamoxifen or various AIs may depend on patient characteristics (e.g., nodal status, hormone receptor status) although this needs to be verified in future studies.

R25. In patients with ER+ tumours who do not receive adjuvant endocrine therapy immediately after surgery or chemotherapy, delayed endocrine therapy is still clinically beneficial.

Key Evidence and Qualifying Statements

- Evidence exists for the delayed initiation of both tamoxifen and AIs, as indicated in the Evidentiary Base (Section 2, Subsection 4.3).
- The relevant trials initiated endocrine therapy at a mean of two years from diagnosis.

RECOMMENDATIONS 26–34. ADJUVANT TARGETED THERAPY (HER2+ CANCERS)

R26. Only patients with HER2+ breast cancer (IHC 3+, ISH ratio ≥2, or 6+ HER2 gene copies per cell nucleus) should be offered adjuvant trastuzumab.

Key Evidence and Qualifying Statements

- Trastuzumab is the targeted therapy for HER2+ early-stage breast cancer that has been most fully evaluated in completed RCTs (69-73). The TEACH trial (see Table 15) compared lapatinib to placebo and found benefit in DFS but not OS rates. The effect was greater in patients with hormone receptor negative cancer, although adverse effects (diarrhea, rash, hepatobilliary effects) were also higher with lapatinib. The ALTTO trial compared lapatinib, trastuzumab, and their combinations but the lapatinib arm was discontinued for futility. The other arms detected no significant differences, although lapatinib had more adverse effects. Follow-up is ongoing. Although lapatinib and pertuzumab have been investigated in the setting of locally advanced and metastatic disease (74,75), no recommendation for these agents can be made at this time. The role of dual blockade with trastuzumab and pertuzumab is currently being evaluated in the ongoing APHINITY trial (http://clinicaltrials.gov/ct2/show/NCT01358877).
- The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) (76,77) define a positive HER2 result as IHC staining of 3+ (uniform, intense membrane staining of >10% of invasive tumour cells); an in situ hybridization (e.g., FISH, SISH or CISH) ratio (HER2 gene signals to chromosome 17 signals) of ≥2.0; or HER2 gene polysomy of ≥6.0 HER2 gene copies per nucleus. Equivocal results, defined as IHC 2+ or ISH equivocal based on single-probe ISH average HER2 copy number ≥4.0 and <6.0 signals/cell or based on dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number ≥4.0 and <6.0 signals/cells, should be reported as equivocal and reassessed using a reflex test (same specimen using the alternative test) or new test (new specimen, if available, using same or alternative test).

R27. Trastuzumab plus chemotherapy is recommended for all patients with HER2+ node positive breast cancer and for patients with for HER2+ node negative breast cancer greater than 1 cm in size.

Key Evidence and Qualifying Statements

- Phase III clinical studies have demonstrated improved DFS and OS with the addition of trastuzumab to chemotherapy compared with chemotherapy alone in HER2+ early breast cancer (see Table 14 in Evidentiary Base).
- The majority of adjuvant trastuzumab trials included patients with lymph node positive

breast cancer, or lymph node negative disease with one of the following high-risk features: ER–, grade 2 or 3, T ≥1cm, or age <35 years. Trastuzumab may still be considered in patients with HER2+ disease outside these features. Although most studies excluded patients with tumours <1 cm, the benefit of trastuzumab was equivalent in both node negative and node positive tumours in the HERA trial which included small N0 tumours (1 cm was the formal inclusion criteria, although 60 patients with tumours <1 cm were also enrolled). The BCIRG 006 trial (71,72) analysis by tumour size found benefit in tumours <1 cm, <2 cm, and ≥2 cm, but not for tumours 1–2 cm in size; however, interpretation is limited because of the small number of patients in each category. The review by Petrelli and Barni (78) concluded that patients with HER2+ tumours have a higher rate of recurrence and poorer survival rate than patients with HER2– cancer of the same size/stage, confirming that HER2 positivity itself is a risk factor. There does not appear to be a threshold according to tumour size, and size alone should not be the deciding factor in whether to administer trastuzumab to patients with tumours <1 cm. In Ontario, tumours <1 cm can be treated under the Evidence Building Program (EBP).

- The meta-analysis by Moja et al (Cochrane Collaboration) (79) found that the hazard ratio for trastuzumab-containing regimens vs chemotherapy alone was 0.66 for OS and 0.60 for DFS ($p<0.00001$ for both). The risk of congestive heart failure and left ventricular ejection decline were higher with trastuzumab (RR=5.11, $p<0.00001$ and RR=1.83, $p<0.0008$, respectively). In patients at high risk of recurrence without cardiac problems, there is clear survival rate benefit for trastuzumab.
- The benefit of adjuvant trastuzumab in the absence of cytotoxic chemotherapy is unknown because it has not been evaluated in clinical trials. Trastuzumab monotherapy vs trastuzumab + chemotherapy is being evaluated in elderly patients in the SAS BC07 (RESPECT) study (80).

R28. Trastuzumab therapy can be considered in small (≤1 cm) tumours as part of clinical studies or evidence-building programs (such as the one currently available in Ontario).

Key Evidence and Qualifying Statements

- Evidence for trastuzumab use is included in the Evidence Summary (Section 2, Subsection 4.4).
- Because most major phase III trials that confirmed the benefit of adjuvant trastuzumab did not include small (≤1 cm diameter) node negative breast cancer, there is little evidence from RCTs evaluating the effect of trastuzumab in tumours ≤1cm. HERA and BCIRG 006 as discussed in R27 are exceptions.
- Several retrospective case series of HER2 positive $pT_{1a/b}N_0M_0$ carcinoma seem to demonstrate that they have a higher risk of relapse compared with the HER2 negative counterpart (79).
- In the HERA trial (81), the subgroup of 510 patients with node negative disease and tumours ranging from 1.1 to 2.0 cm in diameter had similar three-year DFS rate benefit with trastuzumab as in the overall cohort (trastuzumab vs observation HR=0.53, 95% CI 0.26–1.07; all patients HR=0.64, 95% CI 0.54–0.76).
- The American trials found a similar trend with benefit in $pT_1N_0M_0$ tumours smaller than 2

cm. Although there has not been a confirmatory trial, there is no reason to think that high-risk pT1a/bN0M0 breast cancer cannot benefit from trastuzumab in the same way as more advanced stages of the disease. There does not appear to be a threshold according to tumour size, and size alone should not be the deciding factor in whether to administer trastuzumab to patients with tumours ≤1 cm. In Ontario, tumours ≤1 cm can be treated under the Evidence Building Program.

R29. Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.

Key Evidence and Qualifying Statements

- Evidence on use of trastuzumab + chemotherapy is provided in Table 14 of Section 2: Evidentiary Base. The majority of evidence exists for anthracycline-taxane-based regimens.
- Three large RCTs (>1000 patients) administered anthracycline/taxane combinations [AC→paclitaxel in NSABP B31 (82) and NCCTG N9831 (69,70,82-85), AC→docetaxel in BCIRG 006 (71,72)], whereas the BCIRG 006 trial also included a non-anthracycline containing arm [docetaxel + carboplatin + trastuzumab (TCH)]. Trastuzumab had a significant survival rate benefit in all these trials.
- The HERA trial (81) gave trastuzumab to any patient who received prior chemotherapy (neoadjuvant, adjuvant, or both). There was no randomization regarding the type of chemotherapy: 68% received anthracycline, 26% anthracycline + taxane, and 6% no anthracycline. When results were censored to account for cross-over to trastuzumab after unblinding, there was persistent DFS and OS rate benefit. This trial suggests there is benefit of trastuzumab in combination with any chemotherapy, but it did not address the issue of which chemotherapy is optimal.
- PEBC Guideline #1–17 (86) recommended that trastuzumab be used with an anthracycline instead of CMF.
- Because anthracyclines are known to be cardiotoxic, and anthracyclines + trastuzumab even more cardiotoxic, non-anthracycline regimens may be more appropriate in some patients. The BCIRG 006 trial (71,72) compared both AC→docetaxel/trastuzumab (AC→TH) and docetaxel/carboplatin/trastuzumab (TCH, a non-anthracycline regimen) to the AC→T control. TCH and AC→TH were both superior to AC→T. There was no significant difference in OS or DFS rates among trastuzumab regimens, although AC→TH seemed to have a stronger effect in some subgroups. TCH had a much lower incidence of cardiotoxicity and leukemia. Whether TCH is equivalent to AC→TH was not established as the trial was not designed to test for non-inferiority between the two trastuzumab-containing regimens.

R30. The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended because of the potential of increased cardiotoxicity.

Key Evidence and Qualifying Statements

- Anthracyclines are known to be cardiotoxic and anthracycline followed by trastuzumab even more cardiotoxic. Anthracyclines administered concurrently with trastuzumab in patients with metastatic breast cancer resulted in high rates (25%) of congestive heart failure. Concurrent use of trastuzumab + anthracycline has been explored in several small trials in the neoadjuvant setting without significant cardiotoxicity. Long-term results of these trials have yet to be reported; therefore, this approach should not be considered outside the context of a clinical trial.

R31. Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen.

Key Evidence and Qualifying Statements

- The evidence is summarized in the Evidentiary Base (Section 2, Subsection 4.4.2).
- There appears to be no significant differences in survival outcomes between concurrent or sequential taxane and trastuzumab; however, initiating the trastuzumab concurrently with the taxane is still generally preferred.
- Most adjuvant trials started trastuzumab sequentially after anthracyclines, either concurrently with or after the taxane, and administered it either weekly (2 mg/kg) or every three weeks (6 mg/kg) for one year (sometimes switching frequency at the end of the taxane cycles). All trials used a higher dosage (loading) for the first round (8 mg/kg for the 3–weekly schedule and 4 mg/kg for the weekly administration).
- NCCTG N9831 had both sequential and concurrent arms and there was a nonsignificant trend toward greater survival rate benefit with the concurrent arm (87). NSABP B31 and the HERA trial prescribed trastuzumab sequentially after chemotherapy whereas BCIRG 006 delivered trastuzumab concurrently with the taxane in the two relevant arms.

32. TCH (docetaxel/carboplatin/trastuzumab) is less cardiotoxic than AC→TH (doxorubicin/cyclophosphamide-docetaxel/trastuzumab) and is recommended for patients at higher risk for cardiotoxicity.

Key Evidence and Qualifying Statements

- Evidence exists for trastuzumab in combination with docetaxel and carboplatin (TCH), and this regimen was found to be similar to AC→TH (see Table 14 in the Evidence Summary). The BCIRG 006 trial (71,72) compared both AC→TH and TCH (a non-anthracycline regimen) to the AC→T control. TCH and AC→TH were both superior to AC→T. There was no significant difference in OS or DFS rates among trastuzumab regimens, although AC→TH seemed to have a stronger effect in some subgroups. TCH had much lower incidence of cardiotoxicity and leukemia. Whether TCH is equivalent to AC→TH was not established because the trial was not designed to determine non-inferiority between the two trastuzumab-containing arms.
- Because anthracyclines are known to be cardiotoxic, and anthracyclines + trastuzumab even more cardiotoxic, non-anthracycline regimens may be more appropriate in some patients.

R33. Phase III evidence for the addition of trastuzumab to some chemotherapy regimens such as TC (docetaxel/cyclophosphamide) does not exist. However, these regimens may be in use and are reasonable options, particularly to mitigate cardiotoxicity in certain patients.

Key Evidence and Qualifying Statements

- HERA (73,81,88,89) was a large phase III international RCT that randomized patients with HER2+ early breast cancer to one year vs two years vs no trastuzumab after completion of adjuvant systemic therapy (as per investigator choice). Patients experienced significant clinical benefit with the addition of trastuzumab to chemotherapy, regardless of the chemotherapy backbone. TC has not been formally evaluated with trastuzumab in the context of an RCT; however, given the results of the HERA trial (systemic therapy as per investigator choice), TC could be considered a reasonable systemic option in combination with trastuzumab, particularly in patients for whom there is a concern with regards to cardiotoxicity.

R34. Patients should be offered one year total of adjuvant trastuzumab, with regular cardiac functional assessments during this period.

Key Evidence and Qualifying Statements

- Current evidence suggests that the optimal duration of adjuvant trastuzumab is one year (see Subsection 4.4.2 of Section 2: Evidentiary Base). Data for shorter durations of trastuzumab are being evaluated.
- Trastuzumab therapy for one year total continues to be the standard of care for patients with early-stage HER2+ disease. Studies with regular cardiac monitoring discontinued trastuzumab if there was cardiotoxicity.
- Trastuzumab can be administered concurrently with [see NSABP B-31 and NCCTG N9831 (69,83,85,90)] or sequential to radiotherapy [HERA (73,88,89)].
- The recent HERA update (73) on one- vs two-year trastuzumab subgroups found no DFS or OS rate benefits for the longer treatment duration, but increased cardiotoxicity (based on the secondary cardiac endpoint).
- The PHARE trial is a phase III RCT comparing 6 vs 12 months of adjuvant trastuzumab. Results presented at ESMO 2012 (91,92) were inconclusive as to whether 6 months of trastuzumab was non-inferior to 12 months with a nonsignificant trend favouring 12 months. Further results after 3.5 years follow-up (93) also concluded that they failed to show that 6 months trastuzumab was non-inferior to 12 months trastuzumab, although there were significantly more cardiac events in the 12 month group (5.7% vs 1.9%).
- Two small trials [FinHER, 9 weeks trastuzumab (94,95); E-2198, 12 vs 52 weeks trastuzumab (96)] suggest trastuzumab may be beneficial when administered for shorter durations resulting in less cardiotoxicity than longer treatment. Results need to be confirmed in larger trials that are ongoing. The Short-HER and SOLD studies are looking at one year vs nine weeks trastuzumab and the Hellenic Group and PERSEPHONE trials are looking at one year vs six months trastuzumab. Based on the completed trials plus neoadjuvant trials that found trastuzumab + chemotherapy increased the pathologically

complete response (pCR) rate compared with chemotherapy alone, some have suggested that shorter trastuzumab therapy (even if not optimal for preventing recurrence) may be acceptable, particularly for those patients who cannot tolerate trastuzumab for one year.

- The NICE guideline (97) recommends that patients receiving trastuzumab should have cardiac functional assessments every three months during trastuzumab treatment, and trastuzumab should not be offered to patients with any of the following:
  - A left ventricular ejection fraction LVEF of <55%
  - A history of documented congestive heart failure
  - High-risk uncontrolled arrhythmias
  - Angina pectoris requiring medication
  - Clinically significant valvular disease
  - Evidence of transmural infarction on electrocardiograph (ECG)
  - Poorly controlled hypertension.

  Most of the clinical trials evaluating trastuzumab excluded these patients. Patients who develop cardiotoxicity during administration of trastuzumab should be treated and monitored closely by a knowledgeable multidisciplinary team (oncologists and cardiologists).

7. IMPLEMENTATION

As indicated in Section 2, the systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada and issues specific to other jurisdictions (including low- or middle-income countries) were not considered. The recommendations encompassed in this guideline are most applicable to the Ontario (and likely North American) oncology practice setting. Although the approval of drugs is under the auspices of Health Canada, funding for particular systemic therapy agents is handled provincially in Canada, and this may impact on the ability to receive public reimbursement for certain therapeutic agents in each province. Some treatments as recommended by this guideline are fairly resource-intensive (e.g., taxane chemotherapy and trastuzumab). As such, these treatments may only be sustainable in higher-income nations. One must consider the local practice setting, including resource constraints, when considering the implementation of systemic therapy recommendations. Guidelines by groups such as the Breast Health Global Initiative (98-100) may help users of this guideline to better choose the most resource-appropriate systemic therapies for their unique practice setting.

8. RELATED PEBC/CCO GUIDELINES

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

Optimal Systemic Therapy for Early Female Breast Cancer: Evidentiary Base

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Report Date: September 30, 2014

1. QUESTION

What is the optimal adjuvant[1] systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered?

2. INTRODUCTION

There are several guidelines that address specific issues of systemic therapy either in early breast cancer, or breast cancer generally. Because of the overlapping nature of the guidelines and patient characteristics, it is difficult for the end-user to find the appropriate guideline and recommendations. The Breast Disease Site Group (DSG) determined it would be desirable to have one guideline covering all systemic treatments for early breast cancer. It would also be useful to have an associated user-friendly chart, matrix, or decision tree, based on disease and patient characteristics. Such a matrix or decision tree is not part of the current three-part guideline but will be prepared at a later date.

[1] Several of the systemic therapies discussed in this guideline can be considered in the neoadjuvant setting. However, this guideline makes recommendations specifically for adjuvant therapy for the following reasons: a) there is significant variability within the patient population for whom neoadjuvant therapy may be considered (from early, operable breast cancer to locally advanced breast cancer, which may have unique treatment needs), and b) our systematic review of the evidence focused on trials with disease-free survival (DFS) and overall survival (OS) as endpoints, and thus excluded several trials that used pathologically complete response (pCR) as a primary endpoint. Therefore, our recommendations represent only some of the data that may be relevant to neoadjuvant patients.

3. METHODS

The initial plan was to consolidate recommendations from Program in Evidence-Based Care (PEBC)/Cancer Care Ontario (CCO) guidelines on systemic therapy for female breast cancer (86,101-107) according to pathology and menopausal status and to provide additional context and qualifying statements. After working on this approach, it was found that many relevant randomized controlled trials (RCTs) were not included in any of the guidelines under consideration, both because of topics covered and the dates of the literature searches. Updating all of the individual guidelines so they could be used in a summary guideline was considered unfeasible.

A different approach was used in which a literature search for recent publications was conducted. The starting point was selected to include studies or updates published after the literature searches in the PEBC guidelines and the NICE Guideline "Breast Cancer (Early and Locally Advanced): Diagnosis and Treatment" (97). These guidelines, along with other guidelines or systematic reviews identified in the literature search, would be used as a source of publications for RCTs that were published before the literature search. This was not strictly an update of the previous guidelines as the research questions in the current guideline were not the same, because relevant issues have changed and because the current guideline was designed to be broader in scope. For topics in which a recent guideline, meta-analysis, or systematic review was found that covered most of the published trials, additional RCTs found in the literature search are listed so that the evidence base is complete, but they are not discussed unless they result in additional or different conclusions.

The evidence-based series (EBS) guidelines developed by the CCO/PEBC use the methods of the Practice Guidelines Development Cycle (108,109). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member (GF) of the PEBC Early Breast Cancer Systemic Therapy Working Group, with input from the full group once initial screening was complete. The body of evidence in this review is primarily mature RCT data. The evidence forms the basis of the recommendations developed by the Early Breast Cancer Systemic Therapy Consensus Panel. This systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

3.1 LITERATURE SEARCH STRATEGY

A literature search on MEDLINE and EMBASE was conducted for the period from 2008 to March 5, 2012 and updated on May 12, 2014. The search was for articles on breast cancer plus systemic therapy (chemotherapy, hormonal/endocrine therapy, targeted agents, ovarian suppression/ablation), and was limited to RCTs, guidelines, systematic reviews, and meta-analyses. Although in most cases chemotherapeutic agents were indexed to terms such as adjuvant therapy and the studies would be found by the index terms, we also included individual chemotherapy agents or regimens considered relevant to Ontario. The full search strategy is provided in Appendix C. The SAGE Directory of Cancer Guidelines (available at www.cancerview.ca) was searched in May 2012 for current versions of guidelines published in 2008 or later. Most guidelines listed were evaluated using AGREE II instrument and no further appraisal of quality was undertaken for the current guideline on systemic therapy in early breast cancer. NICE (UK), SIGN (UK), ASCO (US), NCCN (US), National Health and Medical

Research Council (Australia), and the New Zealand Guidelines Group sites were searched in February 2012 for guidelines not yet indexed in SAGE.

3.2 STUDY SELECTION CRITERIA

Clinical trials were included if they included at least 100 female patients with early-stage breast cancer randomized to at least one systemic agents and with survival rate (generally overall survival rate (OS) or disease-free survival rate (DFS)) as one of the primary or secondary outcomes to be determined according to the study design. Studies had to define the patient population as early or operable breast cancer, or provide a description in the abstract, methods, or results indicating that patients with early breast cancer were the main group studied. When tumour size and nodal status were reported, these were translated to stage according to the AJCC Cancer Staging Manual, 6th edition (110,111). Studies in which the title or abstract indicated the trial focused on metastatic breast cancer (other than locoregional lymph nodes), advanced, locally advanced breast cancer (LABC), non-invasive cancers [ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)], or treatment of recurrence were excluded. Because of overlap between early and LABC definitions, studies in which the patients were referred to as LABC but also indicated the distribution of stages were evaluated more carefully. Because Stages IIB and IIIA are also considered early in some definitions, these were included if Stage IIA was part of the patient population and at least one-half the patients had Stages I–IIB cancer. Studies with mostly Stage III–IV were excluded. Studies were excluded that focused on evaluation of supportive care such as drugs to prevent nausea and vomiting, gonadotropin-releasing agents to prevent ovarian damage, erythropoiesis-stimulating agents, or autologous hematopoietic stem-cell transplantation (AHST). Studies on bisphosphonates to prevent metastasis or cancer recurrence were included (with a final decision deferred to later in the process); studies to treat bone metastasis were excluded because they did not meet the definition of early breast cancer. A decision to include or exclude studies of granulocyte-colony stimulating factor (GCSF) to prevent or treat neutropenia was deferred to later in the guideline process; therefore, these were included in the initial screening.

Clinical practice guidelines were considered relevant if recommendations were based on a systematic review of the literature or were consensus-based with reference to the clinical evidence. When multiple versions of a guideline were located, only the most recent guideline was retained.

3.3 ADDITIONAL STUDIES

Recent guidelines, systematic reviews, and meta-analyses were evaluated and the included studies were compared with those found in the literature search for this guideline. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published the fifth cycle meta-analysis at the end of 2011. It presented the latest update of individual patient meta-analysis for polychemotherapy based on RCTs worldwide and included data available up to mid-2010 (1). This gave extended follow-up and additional trials compared with the previous (fourth cycle) meta-analysis published in 2005 (112). Because portions of the data included were comprehensive and current, these were used as a basis for some of the comparisons and the original studies were not obtained. In other areas, the current literature review revealed major new studies or extended follow-up of previous studies that needed to be considered along with the older publications. Therefore publications before 2008 referenced in the

guidelines, reviews, or meta-analyses were obtained and compiled along with the newer data. For RCTs that were in progress, incomplete, or reported only as an abstract, additional targeted searches using MEDLINE, EMBASE, or Google were performed to find recent or complete reports where available.

3.4 SYNTHESIZING THE EVIDENCE

Meta-analyses performed in other publications are cited but no meta-analysis was conducted in the preparation of this guideline.

4. RESULTS AND DISCUSSION

The recommendations and justification in Section 1 are based on the following evidence and can be considered as conclusions for the evidentiary summary. The full recommendations are not reproduced here.

4.1 LITERATURE SEARCH RESULTS

The initial search in MEDLINE and EMBASE, after removal of duplicate citations, resulted in 7380 publications (6085 RCTs and 1295 systematic reviews and guidelines). After applying the inclusion/exclusion criteria in an initial screening (primarily by title and abstract), there were 253 articles representing 163 trials from the original search. A secondary screening of the titles by the Working Group reduced this to 216 articles; studies were eliminated if they were not relevant to Ontario (e.g., old drugs no longer used), duplicate publications, publications with exploratory analyses or correlations, and studies without survival rate endpoints. The literature search also resulted in 63 candidate clinical practice guidelines, of which 42 remained after discussion by the Working Group. Five of the guidelines by the PEBC and four others have been summarized or referred to in this evidentiary review. AGREE II ratings of the non-PEBC guidelines are provided in Appendix E. Of the trials (RCTs) found in the literature search, 46 were trials that had not been included in the guidelines, meta-analyses, or systematic reviews discussed in the following subsections.

The literature search update of May 2014 resulted in 5350 RCT/trial publications and 1714 systematic reviews or guidelines. After screening, there were 110 publications of RCTs and 96 guidelines/systematic reviews/meta-analyses. The new guidelines and systematic reviews were not used unless updates of those already included in the current guideline. After adding in publications from other sources (reference lists, targeted searches for publications of studies initially found only as abstracts) there were 516 publications of trials.

The EBCTCG (see www.ctsu.ox.ac.uk/research/meta-trials/ebctcg) is an international collaboration formed in 1985 to evaluate studies on early (operable) breast cancer. They obtain individual patient data for all relevant RCTs (studies conducted throughout the world except Japan and USSR in the initial analysis, but later expanded to include these). The initial analysis included hormonal and cytotoxic therapy, with updates every five years giving longer-term follow-up and with the scope expanded to include all aspects of early breast cancer management (chemotherapy, endocrine therapy, surgery, radiotherapy). Individual patient meta-analysis is considered the strongest evidence (113) and provides the most reliable and least biased means of addressing questions that are not answered in individual RCTs (114). The Cochrane Collaboration has withdrawn several reviews on topics covered by the EBCTCG (115-117) instead of updating them, stating this is because the EBCTCG reviews are based on

individual patient data, are of the highest quality, and represent the best available evidence on the effects of these treatments on relapse, second cancer and death. Several of the EBCTG meta-analyses (1,5,112,118,119) are referred to in the following sections of this guideline. Because the EBCTCG had strict inclusion criteria and protocols and included individual patient data for all studies, it was considered unnecessary and unfeasible to extract data from or evaluate the quality of the individual trials included by the EBCTCG. Some limitations of the EBCTCG data are discussed in the subsequent subsections.

Another group conducted an individual patient meta-analysis of luteinizing hormone-releasing hormone (LHRH) agonists in early breast cancer (61). Five systematic reviews and one non-systematic review are also discussed in the following sections. Quality assessment of the systematic reviews and meta-analyses using the AMSTAR tool (120) is provided in Appendix F.

Individual RCTs, along with the guidelines, reviews, and meta-analyses, were sorted into studies of chemotherapy, endocrine therapy for hormone receptor positive (HR+) cancers, targeted therapy for human epidermal growth factor receptor 2 positive (HER2+) cancers, bisphosphonates, and GCSF. Chemotherapy trials were further subdivided into major classes: antimetabolites including CMF [cyclophosphamide + methotrexate + fluorouracil] and its components, anthracyclines, taxanes, and other agents. The major endocrine therapies were tamoxifen, aromatase inhibitors, and ovarian suppression or ablation (by surgery or radiation). Trastuzumab for HER2+ cancers is the only biologic/targeted agent that was found to have sufficient evidence from RCTs.

Trials were only included in the literature search with ≥100 patients, with patients randomized to at least one systemic agent, and with survival rate data available as one of the primary or secondary outcomes. Most of the RTCs found in the literature search were already included and assessed in the reviews, guidelines, or meta-analyses discussed in this subsection, and there was therefore no additional quality assessment of these studies. Because assessment of study quality is based primarily on design of the study, quality assessment is done per trial and therefore updates were not assessed for trial quality. A summary of study/trial design and quality characteristics is provided in Appendix G for new RCTs (i.e., RCTs not included in the cited guidelines, reviews, or meta-analyses).

4.2 CHEMOTHERAPY

The EBCTCG analysis published in 2005 reported on unconfounded RCTs of adjuvant chemotherapy or hormonal therapy that began by 1995 (112). Chemotherapy trials were primarily CMF vs no chemotherapy or CMF vs anthracycline-based chemotherapy such as FAC [fluorouracil + doxorubicin + cyclophosphamide] or FEC [fluorouracil + epirubicin + cyclophosphamide] but did not include taxanes. The latest EBCTCG analysis on chemotherapy (1) compared taxanes vs anthracyclines, and anthracycline vs anthracycline or CMF, and included data for all RCTs that began during 1973–2003. Both of these meta-analyses are referred to extensively in the following sections.

4.2.1 Antimetabolites (CMF) and Anthracyclines (Doxorubicin and Epirubicin)

The EBCTCG meta-analyses (1,112) covered most of the trials that have been conducted for CMF and/or anthracyclines. Because these drugs are from an earlier generation of chemotherapy agents, most of the studies were performed several years ago (the studies listed by EBCTCG started in the period 1973–1997) and are complete except for

some long-term follow-up or exploratory analysis of specific subfactors. Extended follow-up is not expected to change the conclusions of the EBCTCG that were based on individual patient data for all trials conducted, whether or not they had been published. EBCTCG 2005 (112) concluded that 6 months of FAC or FEC reduced annual breast cancer death rate by approximately 38% for patients aged <50 years and 20% for patients aged 50–69 years at diagnosis. These are significantly more effective than CMF. EBCTCG 2012(1) concluded that standard AC×4 cycles (A 60 mg/m^2 + C 600 mg/m^2, given IV 3–weekly) and standard CMF (6 cycles of C 100 mg/m^2 [days 1–14] + M 40 mg/m^2 [days 1 and 8 IV] + F 500 mg/m^2 [days 1 and 8 IV], given 4–weekly) were equivalent, but anthracycline-based regimens such as CAF or CEF that have much higher cumulative dose than 4 cycles AC were superior to standard CMF. Compared with no chemotherapy, CAF (RR=0.64) also resulted in greater reduction in mortality rates than did 4 cycles AC (RR=0.78) or CMF (RR=0.76). The meta-analysis of all taxane-based or anthracycline-based regimens found that age, nodal status, tumour size or differentiation, estrogen receptor (ER) status, and tamoxifen use had little effect on proportional risk reductions.

Reports of relevant studies found in the current literature search are summarized in Table 1 (CMF or other antimetabolites) (39,40,121-144) and Table 2 (anthracyclines) (33,36,131,142,145-159). Table 1 includes 17 RCTs, of which 10 were not reported in the EBCTCG meta-analysis. Table 2 includes 13 studies, of which 7 were not included in the EBCGTC meta-analysis. The study by Muss et al (40) found that capecitabine monotherapy was inferior to either CMF or AC in the elderly population and, therefore, is not recommended for adjuvant therapy. Trials that examined the addition of gemcitabine or capecitabine to an anthracycline-taxane regimen are discussed in Section 4.2.2. Some studies (137,144) examined drugs not commonly used in Canada for the treatment of breast cancer and thus are not included in our recommendations. Cheang et al (148) evaluated the outcomes in the MA.5 study according to intrinsic subtype as determined by the PAM50 test. In this retrospective analysis, the HER2+ subtype appeared to gain most benefit from the anthracycline, but this was not significant, and trastuzumab was not provided in this trial.

Table 1. Antimetabolites: CMF, capecitabine, and gemcitabine.

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Amadori, 2008 (121) Update of Amadori, 2000(122)	1989–1993	CMF×6 or none after locoregional therapy (mastectomy or quadrantectomy + RT)	278	N0 (at least 10 nodes examined), high thymidine labeling index (TLI) ≥3.1%, age ≤70 y	64% ≤2 cm (Stage I)	42% premenopausal, 65% ER+, 50% PR+	Stratified pts according to cell proliferation evaluated by TLI	TLI 3.1%–4.4% (33.1% of pts), TLI 4.5–6.8% (33.8%), TLI >6.8 (33.1%) Relapse at median follow-up of 12 y, CMF vs control: Overall: HR=0.75 (95% CI 0.50–1.13), p=0.17, (NS) Pts who received full CMF dose: HR=0.59 (95% CI 0.36–0.95), p=0.03 TLI 3.1%–4.4%: HR=1.05 (95% CI 0.45–2.49), p=0.91 TLI 4.5%–6.8%: HR=0.30 (95% CI 0.12–0.72), p=0.01 TLI>6.8 %: HR=0.79 (95% CI 0.37–1.68), p=0.53, 25% of relapses occurred within 20 mo in control and within 93 mo in CMF group Death at median follow-up of 12 y, CMF vs control Overall: HR=0.80 (95% CI 0.48–1.33), p=0.38 Pts who received full CMF dose: HR=0.57 (95% CI 0.31–1.07), p=0.08 TLI 3.1%–4.5%: HR=0.86 (95% CI 0.29–2.57), p=0.78 TLI 4.5%–6.8%: HR=0.27 (95% CI 0.08–0.83), p=0.02 TLI>6.8 %: HR=0.71 (95% CI 0.30–1.73), p=0.46
Taucher, 2008 (123)	ABCSG-07 1991–1999	CMF timing: CMF×3 preoperative vs CMF×3 post-operative All received additional therapy determined by histological nodal status (3×CMF if N0 or 3×EC if N+) All had axillary dissection, BCS +RT or modified radical mastectomy (+RT at physician's discretion)	398	HR–1991–99; high-risk (N1) HR+ 1996–99	24% T1, 65% T2, 9% T3; N0–1, M0	9% ER+, 15% PR+ 64% N0, 49% premenopausal	Biopsy proven cancer and/or cN+	OS not affected by therapy group: HR=0.800 (95% CI 0.563–1.136), p=0.213 Recurrence after median follow-up 9 y: RFS: HR=0.7 (95% CI 0.52–0.96), p=0.024 favouring postop treatment, although rates of local recurrence (13.3 vs 8.2%, p=0.1) and distant metastases (30.5% vs 22.6%, p=0.07) for pre and postoperative groups were not significantly different

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Muss, 2009 (40)	CALGB 49907 2001–2006	Std chemotherapy (CMF×6 or AC×4) vs capecitabine×6 Axilla treated at discretion of patient and surgeon HR+ offered tamoxifen or AI after chemotherapy Trastuzumab recommended in last year (2006) for HER2+ tumours	633 (ended early due to safety)	Age ≥65 y	I, II, IIA, IIIB; >1 cm	10% HER2+, 67% HR+, 70% N+, 55% >2 cm	Operable, histologically confirmed adenocarcinoma	At median follow-up of 2.4 y: • RFS: 80% capecitabine, 89% std chemotherapy • OS: 88% capecitabine, 93% std chemotherapy Estimated at 3 y: • RFS: 68% capecitabine, 85% std chemotherapy, HR=2.09, p<0.001 • OS: 86% capecitabine, 91% std chemotherapy; HR=1.85, p=0.02 • HR− subgroup with capecitabine vs all others: risk of relapse HR=4.39 (95% CI 2.9–6.7, p<0.001); risk of death HR=3.76 (95% CI 2.23–6.34, p<0.001) • Adverse effects (grade 3–4 events): 70% CMF, 60% doxorubicin, 34% capecitabine • Adverse effects (hematological grade 3–4 effects): 52% CMF, 54% doxorubicin, 2% capecitabine
Kornblith, 2011 (124)	CALGB 49907 2001–2006	See preceding entry (QoL substudy)	350					Pts with capecitabine had significantly better QoL, role function, social function, appetite, and less systemic adverse effects, psychological distress, fatigue, nausea, vomiting or constipation; capecitabine was worse for hand-foot syndrome and diarrhea. QoL similar at 1 y. Concluded std chemotherapy is better than capecitabine to improve RFS and OS, and survival rate effects outweigh short-term adverse effects
Ejlertsen, 2010 (125)	DBCG 77B 1977–83	CMF (N=423) vs cyclophosphamide (N=424) vs levamisole (N=112) vs no adjuvant systemic therapy (RT only, N=187) CMF was oral C at 80 mg/m^2 on days 1–14, IV M at 30 mg/m^2 and F at 500 mg/m^2 on days 1–8; q28d×12); C only as for CMF but 130 mg/m^2; levamisole 5 mg/w×48 w	1146	Premenopausal; N+ or >5 cm or invasion of deep fascia with no distant metastasis	high-risk; 17% N0, 56% N1, 27% N2+; 25% T1, 37% T2, 13 % T3, 24% unknown	hormone receptor status unknown for 70% of pts; 22% HR+	All had mastectomy + axillary sampling or clearance before chemotherapy	Levamisole arm closed early (1979) due to adverse effects, and resulted in closure of control arm as well in 1981 10−y survival rates: CMF 62%, C 60%, L 41%, Control 46%; C vs control: HR=0.70, p=0.02; CMF vs control: HR=0.70, p=0.02, C vs CMF: no difference (HR=1.11, p=0.32) Invasive DFS: CMF 49%, C 56%, L 35%, Control 39% OS benefit persisted at 25−y follow-up when adjusted for baseline characteristics:

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		All received radiotherapy to chest wall and regional lymph nodes Endocrine therapy not permitted						C vs control: HR=0.66, p=0.002; CMF vs control: HR=0.59, p=0.0001
Ejlertsen, 2008 (126) (127)	DBCG 77B, 82B, 89B, 89D Results of all studies previously reported separately 1977–2001	Retrospective unplanned cross-trial comparison of higher-dose classic vs lower-dose IV CMF (CMF +RT dose and schedule) • **DBCG 77B**: see Ejlertsen 2010; used classic CMF • **DBCG 82B**: CMF +RT, CMF, CMF + tamoxifen • (IV CMF at 600, 40, 600 mg/m^2 q4w×8 except with delay after first cycle to administer RT) • **DBCG 89B**: HR+: RT + OA vs RT +CMF (CMF q3w×9) • **DBCG 89D**: HR−: RT + CMF vs RT + CEF; (CMF q3w×9); secondary randomization to pamidronate for 4 y permitted.	5652 (2113 received CMF + RT)	Premenopausal, N+	65% N1, 27% N2, 8% N3 43% T1 44% T2 9% T3		Data on those administered CMF combined from 4 studies of DBCG, N+ data only, exclude those on tamoxifen or OA	10−y survival rates after CMF were 48% with classic CMF, 45% administered every 4 w, 47% administered every 3 w; after adjusting in multivariate analysis was 30 % increase in risk of recurrence in 3− or 4−weekly regimen compared with classic CMF Effect was age dependent (p<0.01): pts aged <40 y did better in the 77 cohort, whereas those aged >50 y did better in 89 cohort, authors suggested may be endocrine effect because for those aged <40 y classic CMF resulted in 15% regular menses, whereas this was 47% in the 89 cohort; interpret with caution due to non-experimental design
Joensuu, 2012 (39)	FinXX, NCT00114816 2004−2007	Capecitabine TX×3→ CEX×3 vs T×3→ CEF×3	1500	N+ (89%), or N0 if >20 mm and PR− (11%)	44% pT1, 50% pT2, 5% pT3; [mostly IIA−IIB]	77% ER+, 62% PR+, 19% HER2+	Histologically confirmed invasive, excluded if had neoadjuvant chemotherapy	5−y RFS 87% for TX/CEX vs 84% for T/CEF, HR=0.79 (95% CI 0.60 to 1.04), p=0.087 56 pts assigned to TX→ CEX died during the follow-up compared to 75 pts assigned to T→ CEF, HR=0.73 (95% CI 0.52−1.04), p=0.08 In exploratory (subgroup) analyses, TX→ CEX improved breast cancer-specific survival rate (HR=0.64, p=0.027) and RFS rates (HR=0.64, 95% CI 0.43−0.96) in female pts with triple-negative disease and in female pts who had >3metastatic axillary lymph nodes at the time of diagnosis
Canney 2012, 2014 (128-130)	TACT2, CRUK/05/019 2005−2008	Accelerated E (aE) + pegfilgrastim vs E; then X vs classic CMF	4371 female pts, 20	N+ or high risk N0 invasive early breast cancer			1 y trastuzumab if HER2+; 5 y endocrine	• Median follow-up 61 mo, X vs CMF: • TTR events: 14.0% vs 14.4%, HR=0.98 (95% CI 0.84−1.15),p=0.79

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Velikova 2014 (131) [abstracts only]		E-CMF is control	men				therapy if HR+	•OS: HR=1.00 (95% CI 0.84–1.20) •DFS: HR0.99 (95% CI 0.86–1.15) •Fewer serious adverse effects (except diarrhea and PPE) and better global QoL with X than CMF •Concluded X non-inferior efficacy but superior tolerability •Median follow-up of 49 mo, aE vs E • TTR: 3–y recurrence rates 91.0% vs 90.9%, 5–y recurrence rates 86.4% vs 85.2%; HR=0.96 •OS 94.4% vs 95.4% at 5 y (p=0.23) •After 4 cycles, more nausea, vomiting, appetite loss, constipation, systemic adverse effects and deterioration of functioning (global QoL, role function) with aE than E, but these did not persist to 12 or 24 mo. •At end of 8 cycles, CMF had more adverse effects than with X (fatigue, dyspnea, insomnia, constipation, systemic side-effects, deterioration of functioning) and these (e.g., fatigue) often persisted to 24 mo •Impact on menstruation assessed at 18 mo for premenopausal aged <50 y (N=1622): E→ X has lower risk of permanent loss of menstrual function than E→ CMF (28% vs 69%); aE vs E had more short-term amenorrhea but effect lost by 18 m
Ohno 2013 (132)		Neoadjuvant FEC then randomized to TX vs T	477	Operable, age 20–70 y; T1C–3, N0, M0 >1 cm; or T1–3, N1, MO	43% IIA, 45% IIB, 11% IIIA	Excluded pts with disease progression on FEC	Relative dose intensity of T was lower in TX group due to adverse effects	Powered for pCR difference pCR 23% vs 24% (p=0.748) At median follow-up 4.5 y, 3–y DFS rates 92.7% vs 90.7%, HR=0.910 (95% CI 0.551–1.502); OS HR=0.671 (95% CI 0.303–1.488)
Pippen, 2011(133) O'Shaughnessy, 2010 (134)	US Oncology 1062 USON 01062 2002–2006	AC→ T vs AC→ TX AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4	2611	Resectable, early, high risk (N+, T1–3; or N0, T2+; or N0, >1 cm, HR–)			Tamoxifen or AI for 5 y if HR+; After 2005, HER2+ offered 1 y trastuzumab	• Median follow-up of 5 y, 304 events • DFS: HR=0.84 (95% CI 0.67–1.05), p=0.125 [endpoint not met] • Distant DFS favoured TX group: HR=0.80 (95% CI 0.63–1.02), p=0.067

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
[abstract]		AC→ TX: AC as in other arm→ TX (T: 75 mg/m^2 day 1, X: 825 mg/m^2 bid, days 1–14;) [4 cycles ?]						• OS: improvement with TX vs T: HR=0.68 (95% CI 0.51–0.92), p=0.011 • Subgroup analysis appeared to favour TX over T • Unplanned subset analysis of Ki-67 expression and DFS suggests benefit of X in more highly proliferative tumours (for Ki-67 >10%, hazard ratio for TX vs T is HR=0.70 (95% CI 0.50–0.98) for DFS and HR=0.52 (95% CI 0.33–0.82) for OS • Adverse events similar in both arms, except grade 3 hand-foot syndrome (3.8% T vs 18.1% TX), grade 3/4 stomatitis (4.5% vs 9.1%), diarrhea (2.9% vs 5.1%), and febrile neutropenia (13.1% vs 9.4%)
O'Shaughnessy, 2012 (135) [abstract]	USON 01062	See previous entry in table				2195 ductal 355 lobular or mixed		Exploratory analysis by histology: •ductal pts AC→ T vs AC→ XT: •no difference in DFS (HR=0.92, p=0.48) or OS (HR=0.75, p=0.07) •lobular/mixed AC→ XT vs AC→ T •DFS, HR=0.55, p=0.055 •OS, HR=0.38, p=0.04
Bermejo, 2013 (136)	GEICAM/2003–10 2004–2007	ET→ X vs EC→ T ET (90/75 mg/m^2)q3w×4→ X (1250 mg/m^2 bid d1–14) q3w×4 EC (90/600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4	1384	T1–3/N1–3 operable	66% N1, 25% N2, 9% N3	Stratified by site, menopausal status, number of nodes (1–3, 4–9, 9+), hormone receptor status	HER2+ pts excluded after first 803 pts recruited; 84% HR+, 11% HER2+	After median follow-up 6.6 y, survival rates at 5 y: •DFS: 82% EC→X vs 86% EC→T, HR=1.314 (95% CI 1.042–1.657), p=0.0208 •OS not different: HR=1.113 (95% CI 0.809–1.531), p=0.511 EC→X vs EC→T : Neutropenia 10% vs 19%, hand-foot syndrome 20% vs 2%, diarrhea 11% vs 3%
Watanabe, 2009 (137)	N-SAS BC 01 1996–2001	Oral uracil and tegafur (UFT) daily for 2 y vs CMF×6	707	N0, Stage I–IIIA	42% T1, 54% T2, 5% T3 [96% Stage I–IIA]	62% ER+ and/or PR+; 42% premenopausal	Authors considered "high risk" but no reason reported	RFS at 5 y: 88.0% CMF vs 87.8% UFT, HR=0.98 (95% CI 0.66–1.45), p=0.92 OS: 96.0% vs 96.2%, HR=0.81 for OS (95% CI 0.44 to 1.48), p=0.49 The adverse effects profiles differed between the two groups QoL scores were better for pts administered UFT than for those administered CMF (p<0.05 for social functioning, nausea/vomiting, constipation, systemic adverse effects, hair

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								loss)
Hara 2012 (138) [abstract]	N-SAS BC 01	See previous entry in table Subgroup of older pts (aged ≥65 y)	97					5-y RFS (UFT vs CMF): 93.0% vs 92.5%, HR=1.07 (95% CI 0.31–3.55) OS: 97.7% vs 98.1%, HR=1.07 (95% CI 0.15–10.25) Grade 3/4 leukopenia 0% vs 3.8%, neutropenia 4.8% vs 13.5%; grade 3/4 increased liver enzyme and nausea/vomiting less frequent with UFT; more elevated bilirubin and diarrhea observed in UFT arm; UFT better QoL scores
Ejlertsen, 2013 (139)	DBCG 82c 1982–1990	CMF (IV×9) + tamoxifen vs tamoxifen (30 mg/d for 1 y)	1445	Postmenopausal; N+, deep invasion, or >5 cm		55% N1, 34% N2+ 37% T1, 50% T2, 12% T3	Mastectomy + axillary sampling or clearance (level 1 + part of level II)	Analysis 20 y after recruitment closed; median follow-up 10 y DFS, 24 y OS DFS (CMFT vs CMF): HR=0.89 (95% CI 0.78–1.01), p=0.08 [ITT] DFS adjusted: HR=0.82 (95% CI 0.71–0.93), p=0.003 OS: no difference, HR=0.96 (95% CI 0.86–1.08), p=0.51
Colleoni 2011 (140) [abstract]	IBCSG 22–00	Study of low-dose maintenance/metronomic CM after surgery + chemo -Randomized to 12 mo CM vs no CM	1080 planned	ER–PR– (<10%), known HER2 status		Stratified by menopausal status, induction regimen	Concurrent trastuzumab permitted if HER2+	Ongoing
Wardley, 2008 (141)	tAnGo 2000–	EC→ G + P vs EC→ P E 90 mg/m^2 + C 600 mg/m^2 q3w×4→ [P 175 mg/m^2 q3h infusion day 1 and G 1250 mg/m^2 days 1 and 8] q3 w×4	3000		Substudy: 19% N0 35% N1 46% N2+	Substudy: 20% ER+ 15% PR+		Ongoing, no survival rate results
Earl, 2014 (142)	Neo-tAnGo	Neoadjuvant: EC→ P vs P→ EC vs EC→ PG vs PG→ EC Effect of gemcitabine and role of sequence (EC→ P vs P→ EC) Stratified by ER status, tumour size (50 mm cut-off), nodal status (N0/N+), inflammatory/locally	831	Early invasive, >2 cm; no previous chemo, RT, endocrine therapy T4 eligible	80% T2, 20% T3 50% N+	67% ER+ 51% PR+ 25% inflammatory or LABC; 57% premenopausal, 5% perimenopausal		Median follow-up 47 mo; first planned interim analysis found no significant difference in DFS or OS •DFS : EC→ P vs EC→ PG, HR=1.13 (95% CI 0.88–1.46), p=0.34 •DFS: P→ EC vs EC→ P, HR=0.84 (95% CI 0.65–1.09), p=0.18 •OS: EC→ P vs EC→ PG, HR=1.02 (95% CI 0.76–1.39), p=0.89 •OS: P→ EC vs EC→ P, HR=0.82

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		advanced (yes/no)						(95% CI 0.60–1.11), p=0.19 • pCR greater with P→ EC than EC→ P (20% vs 15%, p=0.03); G did not increase pCR • pCR was correlated with significant improvement in DFS (p<0.0001) and OS (p=0.0007)
Toi, 2012 (143) [abstract]	OOTR N0003	Neoadjuvant study FEC→ TX vs FEC→ T	504	Operable, T1C–3N0M0/ T1–3N1M0		Median 3.5 cm, 56% N+		Discontinued in 22% TX and 5% T groups (p<0.0001) Median follow-up 3.7 y, DFS 92% TX vs 91% T, HR=0.907 (95% CI 0.528–1.557), p=0.723 More hand-foot syndrome with TX (15% vs 2%) Concluded adding X to T not superiority to T alone following FEC
Schneeweiss 2011 (144)	2005–2007	Pemetrexed×4 vs cyclophosphamide×4 Doxorubicin + pemetrexed→ docetaxel vs doxorubicin + cyclophosphamide→ docetaxel	257	Operable T2–T4a–c, N0–2, M0	30% IIA, 46% IIB, 17% IIIA, 8% IIIB 39% N0 6% T1 38% T2 37% T3	66% HR+ 15% HER2+		Ongoing, no survival rate results

Abbreviations: AC, doxorubicin + cyclophosphamide; aE, accelerated epirubicin; AI, aromatase inhibitor; BCS, breast-conserving surgery; C, cyclophosphamide; CEF, cyclophosphamide + epirubicin+ fluorouracil; CEX, cyclophosphamide + epirubicin + capecitabine; CMF, cyclophosphamide + methotrexate + fluorouracil; DFS, disease-free survival rate; E, epirubicin; ER, estrogen receptor; EC, epirubicin + cyclophosphamide; F, 5–fluorouracil; FEC, fluorouracil + epirubicin + cyclophosphamide; G, gemcitabine; HR+, hormone receptor positive; HR–, hormone receptor negative; IDFS, invasive disease-free survival rate; ITT, intention to treat; LABC, locally advanced breast cancer; M, methotrexate; N0, node-negative; N+, nod-positive; OA, ovarian ablation; OS, overall survival rate; P, paclitaxel; pCR, pathologically complete response; PG, paclitaxel + gemcitabine; pts, patients; PR, progesterone receptor; QoL, quality of life; RFS, recurrence-free survival rate; RT, radiation therapy; T, docetaxel (Taxotere); TTR, time to recurrence; TX, docetaxel + capecitabine; TLI, thymidine labeling index; UFT, oral uracil and tegafur; X, capecitabine

* HER2, ER/PR, risk, menopausal status

Table 2. Anthracyclines: Doxorubicin and epirubicin.

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
de Azambuja, 2009 (145)	1988–1996	CMF vs EC vs high-dose EC (HEC) CMF×6 vs EC×8 vs HEC×8	777	N+ (≥10 nodes resected), age ≤70 y, operable breast cancer (mastectomy or lumpectomy + ALND)	60 % N1, 40% N2+ 43% pT1, 39% pT2, 2% pT3, 16% unknown	54% ER+, 30% ER–, 16% unknown; 58% premenopausal	Tamoxifen for 5 y if ER+ or unknown and postmenopausal; RT after BCS; PMRT depended on centre's policy	•15–y EFS was 45% for CMF, 39% for EC, 50% for HEC •HEC vs EC: HR=0.77 (95% CI 0.60–0.98), p=0.03 •HEC vs CMF: HR=0.90 (95% CI 0.7–1.15), p=0.39 •EC vs CMF: HR=0.86 (95% CI 0.67–1.09), p=0.21 •No difference in OS •Cardiac adverse effects more frequent with HEC than with CMF(p=0.006) but not more than with EC (p=0.21)
Kimura, 2010 (36)	1996–2000	CEF vs CMF post-surgery	294	N+, ALND, no previous systemic therapy or RT, exclude BCS	I–IIIA: 68% II, 25% IIIA; 32% N1, 42% N2, 26% N3; 11% T1, 64% T2, 17% T3	61% premenopausal, 53% ER+, 48% PR+	Tamoxifen for 2 y if ER+ or ER unknown; did not meet intended sample size of 700	• 5–y survival rate 77.1% for CEF and 71.4% for CMF, HR=0.79 (95% CI 0.50–1.24), p=0.24 • 5–y DFS 55.7% for CEF and 48.9% for CMF, HR=0.80 (95% CI 0.57–1.12), p=0.15 • Adverse drug reactions more common with CEF • Study had insufficient power to prove significance of trends
Amadori, 2011 (146)	1997–2004	E→ CMF vs CMF→ E (after radical resection)	878	Rapidly proliferating breast cancer (TLI >3% or histological grade 3 or S phase >10% or Ki-67 >20%); N1 or N0 and >1 cm	53% N0, 23% N1, 13% N2, 10% N3; 49% pT1, 46% pT2, 5% pT3–4	47% premenopausal, 62% ER+, 50% PR+, 44% HER2+	ER+ received tamoxifen for 5 y after chemotherapy, GnRH optional in premenopausal pts not achieving amenorrhea; RT administered after BCS; PMRT for pT3–4 tumours	At a median follow-up of 69 m: • 5–y OS 91% (88%–94%) for E→ CMF and 93% (90%–95%) for CMF→ E, with adjusted HR=0.88 (95% CI 0.58–1.35) • DFS 80% in both arms, adjusted HR=0.99 (95% CI 0.73–1.33) • Adverse events were similar, apart from a higher rate of neutropenia in the CMF→ E arm (12% vs 7. 5%, p=0.03). • No important differences in clinical outcome were observed between the two different sequences, making both a valid option in early breast cancer
Rocca 2014 (147)		See previous entry in table Amadori (146) E→ CMF vs CMF→ E vs CMF×6 (E×4 and CMF×4)	1066 (705 analyzed)				Combined E→ CMF and CMF→ E arms (E/CMF) Post-hoc analysis by tumour biomarkers HR,	E/CMF arms vs CMF: • DFS: 84% vs 73%, HR=0.54, p=0.0006 • OS: 94% vs 87%, HR=0.44, p=0.0009 Subgroup DFS, E/CMF vs CMF alone: •Ki-67 low: 89% vs 85%, HR=0.55, p=0.116

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
							Ki-67, HER2 for 705 pts	•Ki-67 high: 82% vs 68%, HR=0.53, p=0.002 •HER2−: 86% vs 74%, HR=0.50, p=0.001 •HER2+: 81% vs 71%, HR=0.64, p=0.147 •ER+: 86% vs 81%,, HR=0.61, p=0.047 •ER−: 81% vs 63%, HR=0.51, p=0.008 •PR+: 88% vs 82%, HR=0.65, p=0.151 •PR−: 81% vs 65%, HR=0.51, p=0.002 •ER+ and/or PR+: 85% vs 80%, HR=0.61, p=0.036 •Triple Negative: 85% vs 55%,, HR=0.33, p=0.0007 •ER−PR−HER2+: 75% vs 71%,, HR=1.10, p=0.840 •ER−PR−Ki-67 >20%: 82% vs 58%, HR=0.45, p=0.005
Cheang, 2012 (148)	NCIC.CTG MA.5 1989−1993	CEF + antibiotic prophylaxis vs CMF Prognostic impact of intrinsic subtype and interaction with treatment; determined by PAM50 gene-expression test	716	Premenopausal , N+	39% T1, 49% T2, 5% T3, 7% unknown 61% N1, 39% N2+		60% ER+, 28% ER−, 12% ER unknown 20% HER2+, 80% HER2− (HER2 measured only in subset with PAM50 test) <u>PAM50 determined Intrinsic subtype (N=476)</u> HER2−E (HER2 enriched) 22% Basal-like 20% Luminal B 23% Luminal A 31% Normal 4%	Multivariable regression results for intrinsic subgroups determined by PAM50, adjusted for clinicopathological variables •**Overall, CEF vs CMF (N=454)** •RFS: HR=0.87 (95% CI 0.67−1.12) •OS: HR=0.98 (95% CI 0.74−1.31) •**HER2−E** (N=105) •RFS HR=0.56 (95% CI 0.34−0.93) •OS HR=0.62 (95% CI 0.36−1.05) •**Non-HER2−E (N=350)** •RFS HR=1.02 (95% CI 0.76−1.38) •OS HR=1.22 (95% CI 0.86−1.74) •**Basal (N=94)** •RFS HR=1.12 (95% CI 0.60−2.08) •OS HR=1.32 (95% CI 0.71−2.46) •**Non-basal (N=361)** •RFS HR=0.80 (95% CI 0.60−1.06) •OS HR=0.90 (95% CI 0.65−1.25) •**Luminal B (N=110)** •RFS HR=0.76 (95% CI 0.47−1.24) •OS HR=0.83 (95% CI 0.46−1.50) •**Luminal A (N=145)** •RFS HR=1.14 (95% CI 0.70−1.88) •OS HR=1.71 (95% CI 0.91−3.22) •HER2−E and HER2+ status strongly predicted anthracycline sensitivity,

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								HER2+/HER2−E: 62% response to CEF, 22% response to CMF, p=0.0006
Bartlett, 2010 (149) Poole, 2006 (150)	NEAT, BR9601 1996−2001	E→ CMF vs classic CMF (NEAT) E→ modified CMF vs modified CMF (BR9601) Prospectively planned analysis of 1941 tumours by tissue microarrays for HER2, TOP2A, HER1−3, Ki-67, Ch17CEP (chromosome 17 centromere enumeration probe)	2391 (2021 NEAT, 370 BR9601)		28% N0 47% N1 25% N2−3 43% T1 50% T2 5% T3	48% premenopausal 9% perimenopausal 37% postmenopausal 6% unknown 50% ER+, 32% ER−, 18% unknown	Analyzed 1762 pts	Survival rate data reported in earlier publication (150), RFS and OS significantly higher with E-CMF: •2−y RFS 91% vs 85%, 5−y RFS 76% vs 69% •2−y OS 95% vs 92%, 5−y OS 82% vs 75%, p<0.001 for all •RFS HR=0.69 (95% CI 0.58−0.82), p<0.001 •OS HR=0.67 (95% CI 0.55−0.82), p<0.0001 favouring E-CMF •Independent prognostic factors were nodal status, tumour grade and size, ER status, vascular/lymphatic invasion; these did not significantly interact with effect of E-CMF •Adverse effects significantly higher with E-CMF but did not significantly affect QoL <u>2010 publication</u> • 21% were HER2 amplified, 10% TOP2A amplified, 11% TOP2A deleted, 23% Ch17CEP duplication, 61% high Ki-67 (>13%); • E-CMF significantly better for RFS (p=0.001−0.009) and OS for all categories (p=0.01−0.04) • HER2 amplification and TOP2A deletion were significant prognostic factors for RFS and OS • No significant interaction with anthracycline benefit for Ki-67, HER2, HER1−3, TOP2A • Ch17CEP duplication associated with significant improvement with anthracycline use • RFS: HR=0.92, (95% CI 0.72−1.18) normal vs HR=0.52 (95% CI 0.34−0.81) duplication, interaction p=0.04 • OS: HR=0.94 (95% CI 0.72−1.24) vs HR=0.57 (95% CI 0.36−0.92), interaction p=0.02
Earl, 2012 (151)	NEAT, BR9601	See previous entry in table	2391					•Median follow-up 7.4 y, E-CMF vs CMF, 5−y results •RFS: 78% vs 71%, HR=0.75

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								(95% CI 0.65–0.86), p<0.0001 •OS: 84% vs 78%, HR=0.76 (95% CI 0.65–0.89), p=0.0007
Earl, 2008 (152) Poole, 2006 (150)	NEAT 1996–2001	E→ CMF vs classic CMF QoL and adverse effects data	2021	Early stage	31% NO 45% N1 24% N2+ 44% T1 49% T2 5% T3	48% premenopausal 9% perimenopausal 37% postmenopausal 49% ER+, 32% ER–, 19% unknown	QoL substudy offered to all pts until 500 accrued, used EORTC QLQ-C30 and QLQ-BR23, and Women's Health Questionnaire at baseline, mid-chemotherapy, end of chemotherapy, 12 and 24 mo after baseline	• E-CMF vs CMF: 28% improvement in RFS and 30% OS • E-CMF produced low common adverse effects criteria (CTC) scores, although higher than CMF for nausea, vomiting, alopecia, constipation, stomatitis, infection (all p<0.001) and fatigue (p=0.03) • QoL over 2 y was equivalent despite minimally worse adverse effects for E-CMF during treatment • Conclude E-CMF is significantly more effective with no serious long-term adverse effects or QoL detriment
Van Nes, 2009 (153)	POCOB, EORTC 10902 1991–1999	FEC preoperative vs FEC postoperative	698	Early stage, T1c–T3, T4b; N0–1	59% pN+ 51% cN+ 14% cT1 58% cT2 27%c T3–4 37% pT0–1 42% pT2 11% pT3–4	42% ER+ 20% ER– 37% unknown 7% aged ≤35 y 48% aged 35–50 y 45% aged >50 y	Pts ≥50 y assumed postmenopausal and received tamoxifen for 2 y; BCS +RT or modified radical mastectomy	Median follow-up of 10 y: no statistically significant difference between the two treatment arms •OS: 66% postoperative, 64% preoperative, HR=1.09 (95% CI 0.83–1.42), p=0.54 •DFS: HR=1.12 (95% CI 0.90–1.39) p=0.30 •LRR: HR=1.16 (95% CI 0.77–1.74) •Preoperative chemotherapy was associated with an increase in BCT rates. BCT feasible due to tumour downsizing after preoperative chemotherapy was not correlated with higher LRR or worse OS compared with BCT which was feasible without downsizing of the tumour.
Canney 2012, 2014 (128-130); Velikova 2014 (131) [abstracts only]	TACT2, CRUK/05/019 2005–2008	Accelerated epirubicin (aE) + pegfilgrastim vs E; then X vs classic CMF E-CMF is control	4371 female pts, 20 male pts	N+ or high risk N0 invasive early breast cancer			1 y trastuzumab if HER2+; 5 y endocrine therapy if HR+	•Median follow-up 61 mo, X vs CMF: •TTR events: 14.0% vs 14.4%, HR=0.98 (95% CI 0.84–1.15),p=0.79 •OS: HR=1.00 (95% CI 0.84–1.20) •DFS: HR=0.99 (95% CI 0.86–1.15) •Fewer serious adverse effects (except diarrhea and PPE) and better global QoL with X than CMF •Concluded X non-inferior efficacy but

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								superior tolerability •Median follow-up of 49 mo, aE vs E • TTR: 3–y recurrence rates 91.0% vs 90.9%, 5–y recurrence rates 86.4% vs 85.2%; HR=0.96 •OS 94.4% vs 95.4% at 5 y (p=0.23) •After 4 cycles, more nausea, vomiting, appetite loss, constipation, systemic adverse effects and deterioration of functioning (global QoL, role function) with aE than E but these did not persist to 12 or 24 mo. •At end of 8 cycles, CMF had more adverse effects than X (fatigue, dyspnea, insomnia, constipation, systemic side-effects, deterioration of functioning) and these (e.g., fatigue) often persisted to 24mo •Impact on menstruation assessed at 18 mo for premenopausal aged <50 y (N=1622): E→ X had lower risk of permanent loss of menstrual function than E→ CMF (28% vs 69%); aE vs E had more-short term amenorrhea but effect lost by 18 m
Budd, 2011, 2013 (154,155) [abstracts]	SWOG S0221 2003–2012	AC vs ddAC, then second randomization to P(80 mg/m^2)q1w×12 vs P(175mg/m^2)q2w×6 **AC**=A(24 mg/m^2)q1w×15 + C(60mg/m^2)q1d + filgrastim **ddAC**=AC(60/600 mg/m^2) q2w×6 + pegfilgrastim	2716	N+ or high risk N0; operable				At first interim analysis after 2716 pts, a Cox model adjusted for paclitaxel arms had a HR=1.21 (95% CI 0.98–1.50, p=0.071) favouring ddAC; therefore, AC was stopped for futility. All subsequent pts received ddAC and then randomized to weekly or biweekly P
Lee, 2008 (156)	2002–2005	Neoadjuvant TX→ surgery→ AC vs Neoadjuvant AC→ surgery→ TX	204	N+, Stage II/III	Stage II/III 77% T1–2, 23% T3–4 69% N1, 31% N2–3	61% HR+ 34% HER2+ 47% HER2– 18% unknown	All received RT; tamoxifen or anastrozole if HR+	At median follow-up of 37 mo, no significant difference in DFS by treatment groups (p=0.932). Compared with AC, TX increased pCR in primary tumours (21% vs 10%, p=0.024) and clinical response (84% vs 65%, p=0.003). Fewer pts developed recurrence who achieved pCR in lymph nodes HR=0.189 (95% CI 0.044–0.815), p=0.025 in the multivariate analysis.

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								TX was associated with less nausea and vomiting, but more stomatitis, diarrhea, myalgia, and skin/nail changes than with AC
Burnell, 2010 (33)	MA.21 2000–2005	CEF vs dd EC→ P vs AC→ P Filgrastim and epoetin permitted with CEF or AC→ P, required with EC→ P; Prespecified interim analysis for RFS after 261 events at median follow-up of 30.4 m	2104	N+ or high risk N0 (≥1cm plus one or more of: ER–, grade 3, or lymphovascular invasion); age ≤60 y	28% N0, 43% N1, 22% N2, 6% N3 35% T1 55% T2 9% T3 1% T4	Premenopausal or early postmenopausal (age <60 y); 41% ER+ 11% HER2+, 70% HER2–, 19% unknown	Stratified by number of positive nodes, type of surgery, ER status; BCS +RT or mastectomy (PMRT permitted); ER+ received tamoxifen, AI allowed after Oct 2004; trastuzumab for 1 y for HER2+ was allowed after June 2005	3–y adjusted RFS for CEF, EC→ P, AC→ P were 90.1%, 89.5%, 85% (p=0.001); pairwise comparison: AC→ P vs CEF: HR=1.49 (95% CI 1.12–1.99), p=0.005 AC→ P vs EC→ P: HR=1.68 (95% CI 1.25–2.27), p=0.0006 EC→ P vs CEF: HR=0.89 (95% CI 0.64–1.22), p=0.46 Adverse effects: CEF, EC→ P compared with AC/P: febrile neutropenia: 22.3% CEF, 16.4% EC/P 4.8% AC/P (p=0.001); erythrocyte transfusion 23.8% CEF, 39.9% EC→ P, 1.6% AC/P (p<0.001); grade 3–4 cardiotoxicity higher in CEF (2.1%) vs 0.7% and 0.3% (p<0.001) AC→ P inferior for RFS but fewer adverse effects
Janni, 2012 (157); Schoenher r 2010 (158) [abstract]	ADEBAR (only in abstract form)	Dose-intensive $FE_{120}C$ vs $E_{90}C$→ T FE_{120} C: F 500 mg/m^2 days 1+8 + E 60 mg/m^2 days 1+8 + C 75 mg/m^2 days 1–14, q4w×6 $E_{90}C$→T: E 90 mg/m^2 + C 600 mg/m^2 q21d×4→ T 100mg/m^2 q21d×4	1502	N2+				Median 49.5 mo observation Events: HR=0.877 (95% CI 0.722–1.065), p=0.38 OS: HR=0.996 (95% CI 0.783–1.267), p=0.969 Different adverse effects profiles: FEC had more hematological adverse effects, more infection (20% vs 10%), required more GCSF (61% vs 39%) and erythropoietin stimulation (20% vs 8.7%), p<0.0001 Myalgia and arthralgia occurred significantly more often in the EC→ T-arm (12.3 vs 1.4%, p<0.0001). Neurological symptoms and dermal adverse effects were found almost exclusively in the EC→ T arm (3.9% vs 0.3%, 4.2% vs 0.8% p=0.0001)
Earl, 2014 (142)	Neo-tAnGo	Neoadjuvant: EC→ P vs P→ EC vs EC→ GP vs GP→ EC Effect of gemcitabine and	831	Early invasive, >2 cm; no previous chemo, RT, endocrine	80% T2, 20% T3 50% N+	67% ER+ 51% PR+ 25% inflammatory or LABC;		Median follow-up 47 mo; first planned interim analysis found no significant difference in DFS or OS • DFS • EC→ P vs EC→ PG, HR=1.13

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		role of sequence (EC→ P vs P→ EC) Stratified by ER status, tumour size (50 mm cut-off), nodal status (N0/N+), inflammatory/locally advanced (yes/no)		therapy T4 eligible		57% premenopausal, 5% perimenopausal		(95% CI 0.88–1.46), p=0.34; • P→ EC vs EC→ P HR=0.84 (95% CI 0.65–1.09), p=0.18 • OS • EC→ P vs EC→ PG HR=1.02 (95% CI 0.76–1.39), p=0.89; • P→ EC vs EC→ P HR=0.82 (95% CI 0.60–1.11), p=0.19 • pCR greater with P→ EC than EC→ P (20% vs 15%, p=0.03); G did not increase pCR • pCR was correlated with significant improvement in DFS (p<0.0001) and OS (p=0.0007)
Kerbrat, 2012 (159) [abstract]	PACS 05 2002–2006	FEC-100 q3w×6 vs FEC-100q3w×4 F 500 mg/m^2, E 100 mg/m^2, C 500 mg/m^2	1515	High-risk N0. Operable, N0, >1 cm and another poor prognostic factor (T >2 cm, HR–, SBR grade II or III, aged <35 y)			HR+ pts received 5 y hormonal therapy; after Aug 2005 excluded HER2+ pts	Median follow-up 73 mo PFS: 12.0% vs 14.0% No difference in DFS, DDFS, local relapse, OS More grade III and IV neutropenia after 6 cycles

Abbreviations: AC, doxorubicin (Adriamycin) + cyclophosphamide; aE, accelerated epirubicin; AI, aromatase inhibitor; ALND, axillary lymph node dissection; BCS, breast-conserving surgery; BCT, breast-conserving therapy (BCS + RT); CEF, cyclophosphamide + epirubicin + fluorouracil; CEX, cyclophosphamide + epirubicin + capecitabine; CMF, cyclophosphamide + methotrexate + fluorouracil; dd, dose-dense; ddAC, dose-dense AC; DFS, disease-free survival rate; DDFS, distant disease-free survival rate; E, epirubicin; EC, epirubicin + cyclophosphamide; EFS, event-free survival rate; ER, estrogen receptor; FEC, fluorouracil + epirubicin + cyclophosphamide; G, gemcitabine; GCSF, granulocyte-colony stimulating factor; GnRH, gonadotropin-releasing hormone; HEC, high-dose EC; HER2, human epidermal growth factor receptor 2; HER2–E, HER-2 enriched; HR, hazard ratio; HR+, hormone receptor positive; HR–, hormone receptor negative; IDFS, invasive disease-free survival rate; LABC, locally advanced breast cancer; LRR, locoregional recurrence; N0, node-negative; N+, node-positive; OS, overall survival rate; P, paclitaxel; PG, paclitaxel + gemcitabine; pCR, pathologically complete response; PMRT, postmastectomy radiotherapy; pts, patients; PR, progesterone receptor; QoL, quality of life; RFS, recurrence-free survival rate; RT, radiation therapy (radiotherapy); T, docetaxel (Taxotere); TLI, thymidine labeling index; TX, docetaxel + capecitabine; X, capecitabine.

*HER2, ER/PR, lymph node, risk, menopausal status

Intrinsic Subtypes: luminal A=(ER+ and/or PR+) and not (HER2+ or Ki-67^{high}); luminal B=(ER+ and/or PR+) and either (HER2+ and/or Ki-67^{high}); HER2=HER2+ and ER–; triple negative (TN)=PR– and ER– and HER2–; basal=TN and either (EGFR+ or cytokeratins 5/6+)

4.2.2 Taxanes: Docetaxel and Paclitaxel

In the current literature search, the largest number of RCTs was found for studies of taxanes (55 trials, 94 publications), mostly compared with anthracycline regimens, as seen in Table 3 (21,22,25-33,38,39,43-49,94,133-136,141,142,154-158,160-221). For adjuvant taxane use, recent reviews (222), systematic reviews (223) and meta-analyses (1,183,224,225) were consulted to identify RCTs that were not found by the literature search (primarily due to publication outside the search period). The EBCTCG individual patient meta-analysis was the most complete for the comparisons it included, and only two additional studies were found. Because these studies are relatively recent (those in the EBCTCG analysis commenced 1994–2003), reports of most of the trials (except those that are unpublished) were also found in the current literature search. The EBCTCG analysis did not cover neoadjuvant therapy, comparison of taxane to non-anthracyclines, and second-generation studies comparing taxane to a different dose or different taxane (docetaxel vs paclitaxel). For the second-generation studies, 14 RCTs were identified in the literature search and one additional study from the analysis by Qin (225). Gines (224) had included seven of the studies, and Arroyo (223) included two. For neoadjuvant studies, Cuppone (226) or PEBC/CCO Guideline #1–20 (105) identified nine studies, whereas the current search found three additional studies plus updates on four of the others.

Many of the studies identified in the EBCTCG and other reviews varied the dose or number of cycles of the anthracycline component such that they were different for the taxane and non-taxane arms. For some of the comparisons the taxane and anthracycline arms had equivalent outcomes. To account for this unexpected effect, the EBCTCG subdivided the studies by whether the only difference in the arms was the addition of taxane (unconfounded), or with differences in both the anthracycline and taxane component such that the contribution of taxane alone is less certain (confounded studies). Studies included those in which the anthracycline component was approximately double that used in the taxane arm (e.g., additional cycles of anthracycline were administered so that the total number of cycles of chemotherapy was the same in both arms), or studies in which the control arm had more anthracycline than the taxane arm but the amount was not close to being doubled. Studies were also subdivided according to whether taxane and anthracycline were administered concurrently or sequentially. The same categories are indicated in Table 3, along with the additional categories mentioned (neoadjuvant, taxane vs taxane, or without anthracycline). Outcome data are generally reported from the publication with the longest follow-up, although earlier data are sometimes also reported if more complete.

The EBCTCG analysis indicates that when anthracycline is equivalent in both arms, or anthracycline is increased but not near to doubled, then taxane regimens are superior. When anthracycline + taxane is compared with doubled anthracycline + taxane, the survival rate results are similar. Nonetheless, truncating the number of anthracycline cycles when adding a taxane can mitigate certain important adverse effects, which are increased with more cycles of anthracyclines, including cardiotoxicity and leukemia.

Although the EBCTCG analysis excluded comparisons of different taxanes or doses, these studies were found in the current search and have been included in Table 3. Based on the RCTs, AC→P weekly [ECOG 1199 (32)], dose-dense (dd) A→P [CALGB 9741 (43)], TAC×6 [BCIRG 5 (47), NSABP B-38 (38,48)], and dd EC→P [MA.21 (33)] are considered acceptable regimens, whereas TAC×4 was found to be inferior [NSABP B30 (45)]. In MA.21 (33), AC×4→ P×4 was found to be inferior to CEF and dd EC→P, and in CALGB 9741 (43) it was inferior to

dd AC→P, and thus is not recommended. Based on the FinHer study (94), vinorelbine is not recommended instead of docetaxel when followed by FEC and is therefore not recommended in the adjuvant setting. Additionally, several studies used the FEC regimen (25,94,157,158,183) with doses of epirubicin of <100 mg/m^2 and thus are not relevant to practice in Ontario.

The FinXX study (39) found improved breast cancer-specific survival rate and fewer local relapses with TX→CEX compared with T→CEF. However, the OS rates were not found to differ with statistical significance. In addition, the doses of both the taxane and anthracycline are considered non-standard in the Ontario setting. As such, the addition of capecitabine to an anthracycline-taxane regimen is not clearly beneficial.

ECOG 1199 (32) compared paclitaxel to docetaxel administered weekly or q3 weekly, and found that AC→ weekly paclitaxel provided the most benefit with the fewest adverse effects, but there was no direct comparison of AC→ weekly paclitaxel to AC→ q3 weekly docetaxel.

In NSABP B-38 (38,48), the addition of gemcitabine to ddAC→P did improve outcomes but increased adverse effects. In this trial, TAC×6 was found to be equivalent to ddAC→P, although with a different adverse effects profile. The trial by Kelly et al (210) demonstrated no benefit from the addition of capecitabine to an anthracycline -taxane regimen.

Sixteen publications of ten studies as summarized in Table 3 (28,142,156,195,196,201,211-221) evaluated the use of taxanes in the neoadjuvant setting. These were included because they met they search criteria used in the systematic review. However, as indicated in the footnote on the first page of Section 1, this guideline makes recommendations specifically for adjuvant therapy for the following reasons: a) there is significant variability within the patient population for whom neoadjuvant therapy may be considered (from early operable breast cancer, to LABC, which may have unique treatment needs), and b) our systematic review of the evidence focused on trials with DFS and OS rates as endpoints and thus excluded several trials that used pathologically complete response (pCR) as a primary endpoint. Therefore, our recommendations represent only some of the data that may be relevant to patients receiving neoadjuvant therapy.

Table 3. Taxanes: Paclitaxel and docetaxel.

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Taxane + anthracycline (sequential) vs same anthracycline regimen								
Rastogi, 2008 (28)	NSABP B-27 1995–2000	See neoadjuvant section later in this table						
Mamounas, 2005 (160)	NSABP B-28 1995–1998	AC vs AC→ P AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4 AC→ P: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ P (225 mg/m^2) q3w×4 • Before each P cycle, dexamethasone (20mg), diphenhydramine (50mg), and cimetidine (300mg) or ranitidine (50 mg) • All ER+ or PR+ pts or pts aged ≥50 y at time of surgery: tamoxifen (20mg/d) for 5 y beginning first day of AC cycle • Primary prophylaxis with GCSF not allowed, secondary prophylaxis mandated following a cycle complicated by prolonged neutropenia, febrile neutropenia, or grade 3–4 infection	3060	N+, cT1–3, cN0–1	70% N1 26% N2 4% N3 59% T1 32% 2.1–4 cm 8% ≥4 cm	66% ER+ 34% ER–/ borderline 61% PR+ 39% PR–/borderline	Tamoxifen for 5 y administered if age ≥50 y or HR+; RT after BCS, PMRT prohibited	5–y survival rates • DFS: 76% AC→ P vs 72% AC, RR=0.83 (95% CI 0.72–0.95), p=0.006 • OS: 85% for both groups, RR=0.93 (95% CI 0.78–1.12), p=0.46 • Subgroup analysis on the effect of paclitaxel according to hormone receptor status and tamoxifen administration did not find statistically significant interaction • Adverse effects with AC→ P were acceptable
Pusztai, 2009 (161)	NSABP B-28	See previous entry in table (160) Tau protein expression	1924					• No significant interaction between Tau expression and benefit from paclitaxel in total population or pts with ER+ or ER– cancer
Vici, 2012 (162)	GOIM 9902 1999–2005	EC vs T→ EC High-dose EC (E 120 mg/m^2, C 600 mg/m^2) in both arms EC: E (120 mg/m^2) + C (600 mg/m^2) q3w×4 T→ EC: T (100 mg/m^2) q3w×4→ E (120 mg/m^2) + C (600 mg/m^2) q3w×4	750	pN+ (at least 5 nodes removed), operable, T1–3	94% N1 4% N2 1% N3 41% T1 53% T2 6% T3	46% premenopausal 77% HR+ 28% HER2+	Tamoxifen for 5 y if HR+, starting Jan 2003 post-menopausal pts administered anastrozole for 5 y; RT for	Median follow-up 64 mo: report 5–y survival rates, T→ EC vs EC • DFS: 73.4% in both arms, HR=0.99 (95% CI 0.75–1.31), p=0.95 • DFS: no treatment differences between subgroups (T1 vs T2–3, ER and hormone receptor status) • OS: 90.7% T→ EC vs 89.5% EC, HR=0.84 (95% CI 0.54–1.31), p=0.45

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		Primary prophylaxis with GCSF not allowed; administered in subsequent cycles if treatment delay due to low granulocyte/platelet count or G4 febrile neutropenia					BCS, PMRT if 4+ positive nodes	• Adverse effects more common but manageable with T→ EC: G3–4 neutropenia (65% vs 54%, p=0.007); hypersensitivity (5.2% vs 0.3%, p<0.0001), reversible cardiotoxicity (1.4% vs 0.3%, p=0.23), skin (1.6% vs 0%, p=0.03), diarrhea (3.3% vs 0.3%, p=0.006) • Found no advantage of adding T to high-dose EC

Henderson, 2003 (163)	CALGB 9344 INT 0148
	
	1994–1999
		AC (A: 60, 75, or 90 mg/m^2) vs AC (A: 60, 75, or 90 mg/m^2)→ P
		
		AC: C (600 mg/m^2) + A (either: 60 mg/m^2 on day 1 or 75 or 90 mg/m^2 on days 1 or 2) q3w×4
		
		AC→ P: C (600 mg/m^2) + A (either: 60 mg/m^2 on day 1 or 75 or 90 mg/m^2 on days 1 or 2) q3w×4→ P (175 mg/m^2) q3w×4
		
		Filgrastim (5µg/kg/d) + ciprofloxacin (750 mg 2×daily) administered routinely to pts receiving A 90 mg/m^2; only after an episode of febrile neutropenia for other pts
			3121	Operable, N+	46% N1
					42% N2
					12% N3
					
					35% T1
					52% T2
					13% T3
						62% premenopausal
						66% HR+
						59% ER+
							Tamoxifen administered for 5 y to 94% of pts with HR+ cancer and 21% of pts with HR– cancer;
							RT for BCS, PMRT elective
								Median follow-up 69 mo, 5–y survival rates, AC→ P vs AC
								• DFS: 69%, 66%, 67% for increasing doses of A (no dose effect)
								• DFS: 70% AC→ P vs 65% AC, p=0.0023
								• OS: 80% AC→ P vs 77% AC, HR=0.82 (95% CI 0.71–0.95), p=0.0064
								• Unplanned subset analysis:
								  • ER–: HR=0.72 (95% CI 0.59–0.86)
								  • ER+: HR=0.91 (95% CI 0.78–1.07)
								  • Without tamoxifen: HR=0.69 (95% CI 0.57–0.84)
								  • With tamoxifen: HR=0.92 (95% CI 0.79–1.08)
								• Additional adverse effects from adding P were generally modest
								• P resulted in fewer hematological adverse effects (16% vs 62% granulocytopenia for lowest dose AC), less other adverse effects (nausea, vomiting, stomatitis, cardiotoxicity)
								• Higher doxorubicin doses vs lower doses resulted in significantly more dose reductions and delays (p<0.001) and cardiotoxicity (p=0.0032)

Sartor, 2005 (164)	CLGB 9344	See previous entry in table (163) Subgroups were records indicate patient received BCS +RT	169					5–y cumulative incidence of isolated LRR after BCS + RT: 3.7% AC→P vs 9.7% AC, p=0.04
Hayes, 2007 (165)	CLGB 9344	See previous entry in table (163) Randomly selected tissue blocks from subset of 1500 female pts from study; analyzed 1322 by IHC for HER2	1322					No interaction observed between HER2+ and doxorubicin doses HER2+ associated with significant benefit from paclitaxel, interaction HR=0.59, p=0.01, regardless of ER status Paclitaxel did not benefit HER2– ER+ cancers

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Berry, 2009 (166) [abstract]	CLGB 9344	See previous entry in table (163) HER2 and ER status from tissue microarrays from 2039 pathology blocks from the study, including 957 that were part of previous HER2 study (165); plus results of the previous study where samples not re-analyzed	2376					HER2 had significant interaction with P for RFS, p=0.001 RFS for P vs not P: • HER2− ER− : HR=0.89 (95% CI 0.79−0.99), p=0.027, N=681 • HER2− ER+ : HR=1.01 (95% CI 0.92−1.10), p=0.95, N=1342 • HER2+ ER− : HR=0.73 (95% CI 0.59−0.89), p=0.0018, N=192 • HER2+ ER+ : HR=0.77 (95% CI 0.65−0.92), N=277 • Results were similar for OS (not reported) • AC→ P in pts with N+ cancer improves outcome for HER2+ tumours and TN or double-negative tumours, but does not benefit ER+HER2− (which are majority of pts)
Lara, 2011 (167)	CLGB 9344	See previous entry in table (163) From trial, evaluated 1887 patient specimens for p53 expression using IHC antibodies (mAbs 1801 and D07)	1877			P53 expression: 23% by mAbs 1801 and 27% by mAbs D07, 92% concordance		• P53+ associated with worse OS with either antibody • P53 staining with mAb 1801 had significantly worse RFS • P53 not predictive of RFS or OS from either doxorubicin dose escalation or addition of paclitaxel
Cognetti, 2008 (168) [abstract]	TAXIT 216 1998−2002	E→ T→ CMF vs E→ CMF E→ CMF: E (120 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8, q4w×4 E→ T→ CMF: E (120 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4→ CMF	998	Early, N+				Median follow-up 62 mo, report 5−y survival rates, E→ T→ CMF vs E→ CM • DFS: 74% vs 68%, HR=0.82 (95% CI 0.64−1.03), p=0.13 • RFS: 76% vs 69%, HR=0.75 (95% CI 0.59−0.96), p=0.039 • OS: 90% vs 85%, HR=0.67 (95% CI 0.48−0.94), p=0.017
Taxane + anthracycline (sequential) vs more non-taxane (anthracycline) regimen								
Francis, 2008 (169)	BIG 02−98 1998−2001	A→ CMF (sequential control) vs AC→ CMF (concurrent control) vs A→ T→ CMF (sequential docetaxel) vs AT→ CMF (concurrent docetaxel) *In all arms, if oral C not tolerated,	2887	N+ (at least 8 nodes dissected), T1−3	54% N1 46% N2−3 92% pT1−2 7% pT3	54% premenopausal 76% HR+, 24% HR−	Tamoxifen administered for 5 y if HR+, from 2004 on allowed sequential AIs in post-	Analysis after 5 y • DFS: 73% A, 72% AC, 78% A→ T, 74% AT • DFS: T vs control: HR=0.86 (95% CI 0.74−1.00), p=0.051 • DFS: sequential T vs control: HR=0.79 (95% CI 0.64−0.98), p=0.035 • DFS: concurrent T vs control: HR=0.93

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		IV C (600 mg/m^2) used A→ CMF: A (75 mg/m^2) q3w×4→ C (100 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3 AC→ CMF: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ C (100 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3 A→ T→ CMF: A (75 mg/m^2) q3w×3→ T (100 mg/m^2) q3w×3→ C (100 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3 AT→ CMF: A (50 mg/m^2) + T (75 mg/m^2) q3w×4→ C (100 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3 Unbalanced randomization, ratio: 1:1:2:2 Ciprofloxacin administered during AT cycles; primary GCSF prophylaxis not permitted, but recommended with subsequent doses in cases of previous febrile neutropenia, grade 3–4 infection, delay >7 d due to neutropenia					menopausal pts and ovarian suppression in pre-menopausal; RT after BCS, PMRT according to institutional guidelines	(95% CI 0.75–1.14), p=0.48 • DFS: sequential T vs concurrent T: HR=0.83 (95% CI 0.69–1.00) [survival rate better with sequential T] • No heterogeneity of effect with regard to efficacy of T found in subgroups according to age, lymph node status or hormone status • Too early to report OS • Febrile neutropenia, severe asthenia, myalgias, diarrhea, skin adverse effects, and neurosensory adverse effects more common with T than in controls
Oakman 2013 (170)	BIG 02–98	See previous entry in table (169)	2887					Median follow-up 93.4 mo • DFS (T vs no T): HR=0.91 (95% CI 0.80–1.05), p=0.187 • DFS (sequential T vs sequential control): HR=0.81 (95% CI 0.67–0.99), p=0.036 • DFS (sequential A→ T vs concurrent AT): HR=0.84 (95% CI 0.72–0.99), p=0.035 • OS (sequential A→ T vs concurrent AT): HR=0.79 (95% CI 0.65–0.98), p=0.028 Better OS and DFS with A→ T compared with concurrent AT

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Fernandez-Cuesta, 2012 (171)	BIG 02–98 1998–2001	See previous entry in table (169) Retrospective analysis of TP53 mutations for 18% of pts; classified as wild type (no TP53 variations or variations which do not modify p53 protein) or mutant	520			17% mutants		P53 status had no significant predictive value for response to docetaxel P53 truncating mutations were uncommon (3.6%) but associated with poor prognosis
Martin, 2013 (172)	GEICAM/ 2003–02 2003–2008	FAC→ P vs FAC FAC (500/50/500 mg/m^2)q3w×4→ P (100 mg/m^2)q1w×8 vs FAC (500/50/500 mg/m^2) q3w×6	1925	T1–3, N0 and at least one high-risk factor (age <35 y, T2+, HR–, histological grade 2–3)	58% T1 40% T2	50% premenopausal	HER2+ pts excluded after 2005 (792 pts already recruited); 73% HR+, 9.4% HER2+	Median follow-up 63.3 mo • 5–y DFS: 93% vs 90.3%, HR=0.73 (95% CI 0.54–0.99), p=0.04 • OS: 97% vs 96%, HR=0.79 (95% CI 0.49–1.26), p=0.31 • 1 vs 7 deaths from cardiovascular disease Grade 3/4 adverse events: neutropenia 22% vs 25% (p=0.07), febrile neutropenia 2.7% vs 3.6% (p=0.22), fatigue 7.9% vs 3.4% (p<0.01), sensory neuropathy 5.5% vs 0% (p<0.01), myalgia 1.5% vs 0.2% (p<0.01), thrombosis/embolism 1.1% vs 0.1% (p<0.01)
Delbaldo, 2014 (173)	AERO-B2000 2000–2002	FEC_{100}→ P vs FEC_{100} FEC (500/100/500 mg/m^2)q3w**×4→** P(175 mg/m^2)q3w×4 vs FEC(500/100/500 mg/m^2)q3w**×6**	837	N+	Mean 4.3 positive nodes; 43% T1, 46% T2	73% ER+, 62% PR+	Planned 1000 pts, closed early due to slow accrual; RT according to standard practice of each centre; HR+ administered 5 y tamoxifen or AI	Median follow-up 108 mo DFS HR=0.99 (95% CI 0.77–1.26), p=0.91 OS HR=0.85 (95% CI 0.62–1.15), p=0.29 5–y DFS 78.4% FEC→ P vs 78.5% FEC 9–y DFS 62.5% FEC→ P vs 62.9% FEC 5–y OS 88.6% FEC→ P vs 86.1% FEC 9–y OS 77% FEC→ P vs 73.9% FEC Overall grade 3–4 adverse effects similar (58% FEC→ P vs 63% FEC, p=0.16); neuropathy 2.9% vs 0.2%, p=0.002; myalgia 3.2% vs 0.5%, p=0.003; cardiac 0.3% vs 0.5% (NS) May be lack of power to detect small benefits
Martín, 2008 (174)	GEICAM 9906 1999–2002	FEC×6 vs FEC×4→ P (eight 1– w courses) FEC: F (600 mg/m^2) + E (90 mg/m^2) + C (600 mg/m^2) q3w×6 FEC→ P: F (600 mg/m^2) + E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ P	1246	N+ (at least 6 nodes isolated), T1–3	62% N1, 38% N2–3 43% T1 52% T2 36% T3	54% premenopausal 82% HR+ (investigator report), 66% HR+ (central) 20% HER2+	Tamoxifen if ER+ or PR+, AIs allowed in menopausal pts after Sept 2005; RT after BCS, PMRT according to	At 5 y, FEC→ P vs FEC • DFS 78.5% in FEC→ P, 72.1% in FEC, p=0.006 • OS: 22% reduction, HR=0.78 (95% CI 0.57–1.06), p=0.110 • Risk of relapse: 23% reduction, HR=0.77 (95% CI 0.62–0.95), p=0.022 • No significant interaction between HER2 or hormone receptor status and paclitaxel

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		after three weeks no treatment P(100 mg/m^2) q1w×8 Primary GCSF prophylaxis not permitted, but mandatory for pts with at least one episode of febrile neutropenia or infection					institutional guidelines (mostly T3 or N2–3)	treatment
Martín, 2010 (175)	GEICAM 9906	See Martín, 2008 (174) Molecular predictors of efficacy					928 (74.5%) samples had evaluation of molecular subtype	At 7–y follow-up, FEC→ P vs FEC: • Benefit with FEC→P is now statistically significant • DFS 75% vs 68%, HR=0.75 (95% CI 0.61–0.93), p=0.007 • OS: 84% vs 79%, HR=0.74 (95% CI 0.56–0.96), p=0.026 • Benefit small in absolute terms, attempted to find subgroups that benefit more • Superiority of FEC→ P greater in HR–/HER2– (TN), particularly in subset with basal phenotype (TN and either EGFR+ or cytokeratins 5/6+) and for luminal A (p=0.034) • TN: FEC→ P reduced likelihood of relapse by 47% and yielded and absolute benefit of 18% DFS compared with FEC (74% vs 56%), p=0.015 • Basal (N=79): DFS 83% FEC→ P vs 57% FEC, p=0.018 • HR=0.33 (95% CI 0.12–0.87),p=0.024
Fountzilas, 2008 (176)	HE 10/00 2000–2005	Group A: Sequential E→ P→ CMF vs Group B: Concurrent E+P→ CMF E→ P→ CMF: E (110 mg/m^2) q2w×3→ P (250 mg/m^2) q2w×3→ C (840 mg/m^2) + M (57 mg/m^2) + F (840 mg/m^2) q2w×3 E+P→ CMF: E (83 mg/m^2) + P (187 mg/m^2) q3w×4→ C (840 mg/m^2) + M (57 mg/m^2) + F (840 mg/m^2) q2w×3 Cumulative dose almost identical in both groups Prophylactic GCSF for dose-dense	1121	T1–4, N1–2	48% N1 52% N2+ (median 3–4 positive nodes) 32% T1 57% T2 11% T3+	69% ER+, 61% PR+, 73% HR+ 46% premenopausal 33% HER2+	5 y tamoxifen for HR+, 2 y ovarian suppression if premenopausal, switched in 2004 to 2–3 y tamoxifen + 2–3 y exemestane; RT for BCS, PMRT if N2+and/or T3+	Group A (dose-dense) had more thrombocytopenia (1.1% vs 0%, p=0.03), severe sensory neuropathy (9.5% vs 2.1%, p<0.001), hypersensitivity (5.2% vs 1.4%, p<0.001), severe arthralgias/myalgias (3% vs 0.8%, p=0.01), and discontinuation of chemotherapy (6.5% vs 3%, p=0.003) Conclude rates of severe adverse effects low, but significantly increased with dose-dense sequential regimen (Group A)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		treatments						
Gogas, 2012 (177)	HE 10/00 2000–2005	See Fountzilas 2008 (176)						Median follow-up 76 mo; 5–y survival rates, Group A (sequential) vs B (concurrent) • DFS: 74% and 74%, p=0.78 • OS: 86% and 85%, p=0.45 • Subgroup by disease subtypes: no significant differences in response by hormone receptor status, HER2 status, TN • Conclude no DFS or OS benefit Group A vs B
Burnell, 2010 (33)	MA.21 2000–2005	CEF vs dd EC→ P vs AC→ P CEF: C (75 mg/m^2; days 1–14) + E (60 mg/m^2; days 1&8) + F (500 mg/m^2; days 1&8) q4w×6 EC→ P: E (120 mg/m^2) + C (830 mg/m^2) q2w×6→ P (175 mg/m^2) q3w×4 AC→ P: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4 Filgrastim and epoetin permitted with CEF or AC→ P, required with EC→ P; Prespecified interim analysis for RFS after 261 events at median follow-up of 30.4 mo	2104	N+ or high risk N0 (≥1cm plus one or more of: ER–, grade 3, or LVI); age ≤60 y	28% N0, 43% N1, 22% N2, 6% N3 34% T1 55% T2 9% T3 1% T4	Premenopausal or early post-menopausal (age <60 y); 41% ER+ 11% HER2+, 70% HER2–, 19% unknown	Stratified by number of positive nodes, type of surgery, ER status; BCS +RT or mastectomy (PMRT permitted); ER+ received tamoxifen, AI allowed after Oct 2004; trastuzumab for 1 y for HER2+ was allowed after June 2005	3–y adjusted RFS for CEF, EC/P, AC/P were 90.1%, 89.5%, 85% (p=0.001); pairwise comparison: • AC→ P vs CEF: HR=1.49 (1.12–1.99), p=0.005 • AC→ P vs EC/P HR=1.68 (1.25–2.27), p=0.0006 • EC→ P vs CEF: HR=0.89 (95% CI 0.64–1.22), p=0.46 Adverse effects: febrile neutropenia was 22.3% and 16.4% in CEF and EC→ P pts compared with 4.8% in AC→ P (p=0.001); erythrocyte transfusion 23.8%, 39.9%, 1.6% (p<0.001); grade 3–4 cardiotoxicity higher in CEF (2.1%) vs 0.7% and 0.3% (p<0.001); full adverse effects comparison listed AC→ P inferior for RFS but fewer adverse effects [see CALGB 9741 for higher-dose AC→ P (43)]
Polyzos, 2010 (178)	HORG 1995–2004	T→ EC vs FEC T→ EC: T (100 mg/m^2)→ E (75 mg/m^2) + C (700 mg/m^2) q3w×4 FEC: E (75 mg/m^2) + C (700 mg/m^2) + F (700 mg/m^2) q3w×6 Epirubicin dose 75 mg/m^2 was lower than used in other studies; prophylactic GCSF not permitted,	756	N+, ALND with at least 10 nodes removed, early, Stage II-IIIA	35% N1, 45% N2, 21%N3 53% T1, 40% T2, 5% T3, 3% unknown	71% ER+ and/or PR+ 20% ER–PR– 10% unknown 38% premenopausal	60%-70% HR+ and subsequently received adjuvant hormonal treatment; RT for all BCS, PMRT at physician discretion	Median follow-up of 5 y • Relapse: 28% T→ EC vs 33% FEC, p=0.181 • DFS 72.6% (63.8–81.3) and 67.2% (58.0–76.4%), p=0.041; • No difference in OS rates (83.8% vs 81.4%, p=0.533) • T→ EC had increase neutropenia requiring GCSF (90.5% vs 74.1%, p=0.0001) • T→ EC had higher significantly more stomatitis, diarrhea, hypersensitivity reactions, nail disorders, neurotoxicities

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		but allowed in subsequent courses if febrile neutropenia or grade 3–4 neutropenia or >7 d delay because of neutropenia						• Conclude: improved DFS in pts with N+ cancer at expense of increased but manageable myelotoxicity

Joensuu, 2009 (94)	FinHer
	
	2000–2003
		T→ FEC vs vinorelbine→ FEC
		
		T→ FEC: T (100 mg/m^2) q3w×3→ F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×3
		
		Vinorelbine→ FEC: Vinorelbine (25 mg/m^2; days 1,8,15) q3w×3→ F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×3
		
		Further randomization to receive trastuzumab if HER2+ (N=232, 2+ or 3+ on scale of 0–3+ by IHC, and 6+ gene copies)
		
		Prophylactic GCSF not recommended unless 1+ episodes of febrile neutropenia or severe infection
		Dose of T reduced from 100 to 80 mg/m^2 in Feb 2002 due to neutropenic fevers
			1010	N+ or high risk N0 (>2 cm and PR–)	56% >2 cm
					11% N0
					61% N1
					28% N2+
						72% ER+
						23% HER2+
							Tamoxifen for 5 y if HR+, amended Dec 2005 to allow switching to AI for post-menopausal pts after 2–3 y and to allow administration of AI for addition 2–3 y after completion of 5 y tamoxifen; RT according to each institutions guideline	5–y survival rates calculated
								OS=90.7% for entire series
								• T vs vinorelbine, HR=0.70 (95% CI 0.46–1.05), p=0.086
								DDFS rate (pts with only local recurrence were censored):
								• T vs vinorelbine: HR=0.66 (95% CI 0.49–0.91), p=0.010
								• Subgroup HER2+:
								  • Trastuzumab better than without: HR=0.65 (95% CI 0.38–1.12), p=0.12; adjusted for nodal metastases HR=0.57, p=0.047
								  • T + trastuzumab better than T, HR=0.32 (95% CI 0.12–0.89), p=0.029
								  • T + trastuzumab better than vinorelbine + trastuzumab, HR=0.31 (95% CI 0.11–0.83), p=0.020
								  • Vinorelbine ± trastuzumab HR=0.92 (95% CI 0.47–1.83), p=0.82
								  • Median left ventricular ejection fraction of trastuzumab-treated pts remained unaltered during 5–y follow-up
								• HER2– subgroup
								  • DDFS: 88.2% T vs 83.5% vinorelbine, HR=0.69 (95% CI 0.47–1.01), p=0.058
								• Docetaxel more favourable than vinorelbine overall, and subsets N0, N+,

Nitz, 2009(179) [abstract]	EC-Doc WSG/AGO AM02
	
	2000–2005
		EC→ T vs control (FEC, N=828 or CMF, N=175)
		
		EC→ T: E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4
		
		FEC: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×6
			2012	N1, intermediate risk	Median 2.0 cm	78% HR+		• Median follow-up 41 mo, estimated 5–y survival rates
								  • EFS: 91% vs 86%, p=0.005 (better in EC→ T arm)
								  • OS: 95% vs 90%, p=0.004 (better in EC→ T arm)
								  • EC→ T vs FEC: EFS 91% vs 85%, HR=0.58, p=0.004
								  • EC→ T vs FEC: OS 95% vs 91%, p=0.03

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		CMF: C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) q4w×6						• HR+ subgroup, HR=0.51 in favour of EC→T, p=0.007 • Conclude EC→ T is superior for EFS and OS over FEC

Huober, 2010(180)
Nitz, 2011 (181)
Gluz, 2011 (182) [abstracts]
	EC-Doc	See previous entry in table	2012 (772 for protein analysis)				• 20% HER2+
							• ≈25% Topo-II aberration (deletion or amplifica-tion)
							• 49% HER2+ and 14% HER2− tumours had Topo-II aberration
							• 65% TIMP-1
								• Median follow-up 64 mo: report 5−y survival rates
								• DFS 90% EC→ T vs 80% FEC, p=0.006
								• OS: 95% EC→ T vs 92% FEC, p=0.022
								• DFS highest in luminal A (97%), lowest in TN basal-like (72%)
								• Significant benefit of EC→ T vs FEC for DFS in pts with luminal B cancer: HR=0.41 (95% CI 0.22−0.77), p=0.004
								• In multivariate model, EC→ T vs FEC, HR=0.44 (95% CI 0.26−0.76), p=0.003
								• EC→ T better than FEC in HR− non-basal like, HR=0.385 (95% CI 0.14−1.07), p=0.057
								• Prospective WSG Plan B trial to validate these results
								• Ki-67 cut-off of 20% was significant regarding interaction with therapy (HR=0.467, p=0.02)
								• DFS for subgroups, EC→ T vs FEC
								  • HER2: HR=0.29 (95% CI 0.12−0.7) p=0.006
								  • HER2− : EC→ T vs FEC, not significant, p=0.18
								  • Topo-II aberration: HR=0.28 (95% CI 0.11−0.69), p=0.006
								  • Topo-II normal, not significant, p=0.16
								  • TIMP-1 immunoreactive: HR=0.57, p=0.025
								  • TIMP-1 negative, not significant, p=0.14
								  • In multivariate model, only high Ki-67 had significant therapy interaction

Taxane + anthracycline (sequential) vs doubled non-taxane (anthracycline) regimen								
Ellis, 2009 (183)	TACT CRUK01/001 ISRCTN79718493 2001−2003	FEC→ T vs control (either FEC or E→ CMF) FEC→ T: F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4	4162	pT1−3a, pN0−1 Early, N+ or high risk N0 (grade 3, HR−, or lympho-	34% T1 56% T2 9% T3 20% N0 44% N1 36% N2+	69% ER+ 31% ER− 20% HER2+ 65% HER2− 14% unknown	Tamoxifen for 5 y if HR+, from 2005 allowed AIs as an alternative; pts with	Median follow-up 62 mo, report survival rates at 5 y • DFS: 75.6% vs 74.3 %, HR=0.95 (95% CI 0.85−1.08), p=0.44 • OS: 82.5% vs 83%, HR=0.99 (95% CI 0.86−1.14), p=0.91 • No difference due to choice of control

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		FEC: F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×8 E→ CMF: E (100 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) q4w×4 GCSF used according to local practice		vascular invasion)			HER2+ allowed to enter trials assessing trastuzumab; RT after BCS, PMRT according to local guidelines	regimen • No strong evidence for differential effect by ER status or HER2 status • Exploratory analysis consistent with improvement with taxane for ER− HER2+ subgroup, DFS HR=0.78 (95% CI 0.55−1.09), DFS for pts with N+ cancer HR=0.70 (95% CI 0.49−1.00) • Acute grade 3 or 4 adverse events significantly greater in experimental group than in control group (p<0.0001), most frequent was neutropenia, leucopenia, lethargy; late adverse effects also more frequent with FEC→ T • In QoL substudy there was significantly greater impairment in experimental group for physical, role, emotional and social functioning, pain, fatigue, global QoL, but less nausea and vomiting; returned to close to baseline levels over 24 mo • Conclude: did not show any overall gain from addition of T to standard anthracycline therapy

Roche, 2006 (27)	PACS 01
	
	1997−2000
		FEC vs FEC→ T
		
		FEC: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×6
		
		FEC→ T: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×3→ T (100 mg/m^2) q3w×3
		
		Primary prophylaxis with GCSF prohibited; administered for subsequent cycles of FEC in case of low granulocyte/platelet count or febrile neutropenia
			1999	Operable, N+ (based on at least 5 nodes removed), Stage <T4a	62% N1
					38% N2+
					
					37% T1
					55% T2
					8% T3
						61% premenopausal
						79% HR+, 21% HR−
						74% ER+, 65% PR+
							Tamoxifen for 5 y if HR+ and post-menopausal (optional for pre-menopausal until Dec 1998, after which it was required), some centres also gave for HR−
							RT after BCS, PMRT to chest wall, supra-clavicular
								• Median follow-up 60 mo, report 5−y survival rates
								  • DFS: 78.4% FEC→ T vs 73.2% FEC, HR=0.80 (95% CI 0.67−0.96), p=0.012
								  • OS: 90.7% FEC→ T vs 86.7% FEC, HR=0.73 (95% CI 0.56−0.94), p=0.017
								  • In subgroup analysis for DFS, FEC→ T was better or equivalent in all groups; there was significant benefit of FEC→ T for female pts aged ≥50 y or postmenopausal, but not premenopausal or aged <50 y
								• Grade 3−4 neutropenia, need for hematopoietic growth factor, incidence of nausea/vomiting higher with FEC
								• Febrile neutropenia (fourth cycle), stomatitis, edema, nail disorders higher with FEC→ T
								• Fewer cardiac events after FEC→ T due to lower anthracycline cumulative dose

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
							area, internal mammary chain recommended following mastectomy but irradiation of the axilla prohibited	
Coudert, 2009 (21) [abstract] 2012 (22)	PACS 01	See previous entry in table (27)						Update at median follow-up of 92.8 mo, report 8−y survival rates • DFS: 70.2% FEC→ T vs 65.8% FEC, HR=0.85 (95% CI 0.73−0.99), p=0.036 • OS: 83.2% FEC→ T vs 78.0% FEC, HR=0.75 (95% CI 0.62−0.92), p=0.007 • Cardiac events 0.4% FEC→ T vs 2.1% FEC Confirms previous 5−y results

Penault-Llorca, 2009 (184)	PACS 01	See previous entry in table (27)
		Measured ER, PR, Ki-67, HER2 by IHC in 55% of original samples (N=1190), and selected those ER+ for further analysis
			798	ER+ subset		21% Ki-67 >20%
						9% HER2+
						62% PR+ >10%
								ER+ tumours (this study), median follow-up 58.7 mo
								• DFS, 5 y: 82% FEC→ T vs 77% FEC, p=0.11
								• Relapse, FEC→ T vs FEC:
								  • All: HR=0.82 (060−1.12), p=0.22
								  • Ki-67+ HR=0.51 (95% CI 0.26−1.01)
								  • Ki-67− HR=1.03 (95% CI 0.69−1.55)
								  • Hazard ratio for interaction with T HR=0.53 (95% CI 0.24−1.16), p=0.11
								  • No trend for interaction with T observed for HER2 or PR status

Jacquemier 2011 (26)	PACS 01	See previous entry in table (27)
		Prepared tissue microarray for 1099 of the cases that had IHC(184), and evaluated expression of ER, PR, Ki-67, HER2 and 30 additional proteins
			1099				Defined molecular subtypes:
							• luminal A (HR+, HER2−, Ki-67−),
							• luminal B (HR+, HER2−, Ki-67+),
							• HER2 over-expressing
								• In multivariate analysis, PR− and Ki-67+ remained associated with shorter DFS
								• Interaction of protein expression and FEC→ T only significant for Ki-67, p=0.012
								  • Ki-67+ HR=0.51 (95% CI 0.33−0.79), p=0.003
								  • Ki-67− HR=1.10 (95% CI 0.75−1.61), p=0.612
								• Molecular subtypes analyzed for docetaxel benefit on risk of relapse:
								  • Luminal B: 53% reduction, HR=0.47 (95% CI 0.22−1.01), p=0.05
								  • HER2 overexpressing: 34% reduction,

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
							• TN (HR−HER2−)	HR=0.66 (95% CI 0.37−1.19), p=0.14 • TN: 12% reduction, HR=0.88 (95% CI 0.49−1.57), p=0.67 • Luminal A: 16% higher with T, HR=1.16 (95% CI 0.73−1.84), p=0.52 • Interaction between benefit of T and each subtype was significant for luminal B (p=0.047), borderline for HER2 overexpressing (p=0.14) and not significant for TN (p=0.46) • Added value of molecular subtype compared with Ki-67 alone did not show any significant added predictive value
Ladoire, 2012 (25)	PACS 01	See previous entry in table (27) Assessed FOXP3 status in subgroup of 1097 pts by IHC	1097				37% FOXP3 expressed	Median follow-up 96 mo, FEC→ T vs FEC • OS shorter in pts with FOXP3− • For FOXP3−, OS shorter with FEC than FEC→ T • For FOXP3+, no difference between FEC and FEC→ T • Interaction between FOXP3 and treatment arm was not significant; however, the statistical power of the interaction test was 13%
Sakr, 2013 (185)	Mansoura University 2006−2010	FEC×3→ T×3 vs FEC×6 FEC (500/100/500mg/m^2) q3w×3→ T(100mg/m^2)q3w×3 vs FEC (500/100/500mg/m^2) q3w×6	657	Had surgery + AD with clear margins, high risk (T3−4 and/or N+)	34% T1, 51% T2, 7% T3 64% N1 36% N2+	79% HR+ 60% pre-menopausal	Almost all received RT, 78% received tamoxifen	Median 61 mo from randomization •5−y DFS 74% FEC vs 78% FEC→ T •Multivariate analysis found 17% reduction in relative risk of relapse with FEC→ T (p=0.034); difference found in N2+ subgroup (p=0.042) but not N1subgroup; benefit of FEC→ T in female pts aged ≤50 y (p=0.03) but not aged >50 y (p=0.65) Fewer cardiac events with FEC→ T (0.3% vs 1.8%, p=0.02), less nausea-vomiting (11.2% vs 19%, p=0.001), more edema (3.6% vs 0.3%, p=0.001), and nail disorders (5.1% vs 0.9%, p=0.001)
Coombes, 2011 (186)	DEVA 1997−2005	E vs E→ T E: E (50 mg/m^2; days 1&8) q4w×6 E→ T: E (50 mg/m^2; days 1&8) q4w×3→ T (100 mg/m^2; day 1)	803	Post-menopausal, N+, early	0.5% N0 66% N1 32% N2 1% unknown 44% T1	78% HR+ 19% HR− 3% unknown	Tamoxifen received by all pts, amended in 2001 to be omitted if	Median follow-up 64.7 mo, report 5−y survival rates for E→ T vs E • DFS: 79.5% vs 72.7%, HR=0.68 (95% CI 0.52−0.91), p=0.008 • OS: 88.9% vs 81.8%, HR=0.66 (95% CI 0.46−0.94), p=0.02

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		q3w×3 + dexamethasone 8mg orally 2×daily for 3 d each cycle Optional second random assignment of timing of tamoxifen (concurrently with chemotherapy or sequentially) in some centres, to be reported separately Prophylactic GCSF recommended in case of febrile neutropenia			49% T2 6% T3		HR− and in 2007 to allow AIs	• E→ T associated with greater adverse effects but no difference in QoL • Subgroup analysis found consistency with overall effect • T gave higher level of grade 3−4 adverse effects: febrile neutropenia (p<0.001), neutropenia (p<0.001), skin disorders (p=0.002), stomatitis(p=0.009), diarrhea (p=0.01), and myalgia/arthralgia (p=0.04); also higher level of neurological disorders of any grade and more persistent effects: peripheral neuropathy, edema, and nail abnormality • No significant differences in overall QoL • Overall, substitution of T for E for last 3 cycles improved DFS and OS but more adverse effects
Burnell, 2010 (33)	MA.21 2000−2005	CEF vs dose-dense EC→ P vs AC→ P CEF: C (75 mg/m^2; days 1−14) + E (60 mg/m^2; days 1&8) + F (500 mg/m^2; days 1&8) q4w×6 EC→ P: E (120 mg/m^2) + C (830 mg/m^2) q2w×6→ P (175 mg/m^2) q3w×4 AC→ P: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4 Filgrastim and epoetin permitted with CEF or AC→ P, required with EC→ P; Prespecified interim analysis for RFS after 261 events at median follow-up of 30.4 m	2104	N+ or high-risk N0 (≥1cm plus one or more of: ER−, grade 3, or lymphovas-cular invasion); age ≤60 y	28% N0, 43% N1, 22% N2, 6% N3 34% T1 55% T2 9% T3 1% T4	Premenopausal or early post-menopausal (<60 y old); 41% ER+ 11% HER2+, 70% HER2−, 19% unknown	Stratified by number of positive nodes, type of surgery, ER status; BCS +RT or mastectomy (PMRT permitted); ER+ received tamoxifen, AI allowed after Oct 2004; trastuzumab for 1 y for HER2+ was allowed after June 2005	3−y adjusted RFS for CEF, EC/P, AC/P were 90.1%, 89.5%, 85% (p=0.001); pairwise comparison: • AC→ P vs CEF: HR=1.49 (1.12−1.99), p=0.005 • AC→ P vs EC→ P HR=1.68 (1.25−2.27), p=0.0006 • EC→ P vs CEF: HR=0.89 (95% CI 0.64−1.22), p=0.46 Adverse effects: febrile neutropenia was 22.3% and 16.4% in CEF and EC→ P pts compared with 4.8% in AC→ P (p=0.001); erythrocyte transfusion 23.8%, 39.9%, 1.6% (p<0.001); grade 3−4 cardiotoxicity higher in CEF (2.1%) vs 0.7% and 0.3% (p<0.001); full adverse effects comparison listed AC→ P inferior for RFS but fewer adverse effects [see CALGB 9741 for higher-dose AC→ P (43)]
Janni, 2012 (157) Schoenherr, 2010 (158)	ADEBAR 2001−2005	$E_{90}C$→ T vs $FE_{120}C$ (dose-intensive anthracycline) EC→ T: E (90 mg/m^2) + C (600	1502	N2+			• Antibiotics administered in 10% ECT vs 20%	• At median follow-up 49.5 mo, **FEC vs EC→ T:** • Recurrence: 166 vs 193 events, HR=0.877 (95% CI 0.722−1.065), p=0.382 • OS: 131 vs 134 deaths, HR=0.996

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
[abstracts]		mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 FEC: F (500 mg/m^2; days 1&8) + E (60 mg/m^2; days 1&8) + C (75 mg/m^2; days 1&14) q4w×6					FEC • GCSF administered in 39% ECT vs 61% FEC • Erythro-poietin administered in 9% ECT vs 20% FEC	(95% CI 0.783–1.267), p=0.969 • Subgroup analysis found no significant difference between the two arms • Treatment stopped early due to adverse effects in 3.7% EC→ T and 8% FEC (p=0.0009) • Neutropenia grade 3–4 and febrile neutropenia similar in both groups • Hematological adverse effects significantly higher in FEC arm • Non-hematological adverse effects grade 3–4 seldom found in either arm • EC→ T had higher myalgia and arthralgia (12.3 vs 1.4%, p=0.0001), neurological symptoms (3.9% vs 0.3%), dermal adverse effects (4.2% vs 0.8%) • Conclude EC→ T is well tolerated feasible alternative to $FE_{120}C$
Albert, 2011 (187)	1994–1998	P→ FAC vs FAC P→ FAC: P (250 mg/m^2) q3w×4→ F (500 mg/m^2; days 1&4) + A (50 mg/m^2; days 1–3) + C (500 mg/m^2; day 1) q3w or q4w×4 FAC: F (500 mg/m^2; days 1&4) + A (50 mg/m^2; days 1–3) + C (500 mg/m^2; day 1) q3w or q4w×8	511	T1–3, N0–1	4% Stage 0, 17% Stage I, 43% Stage IIA, 30% Stage IIB, 5% Stage IIIA, 1% Stage IIB 31% N0, 38% N1, 28% N2+, 3% unknown	54% premenopausal 3% peri-menopausal 32% post-menopausal 11% surgical; 59% ER+, 37% ER–, 4% unknown; 58% PR+, 37% PR–, 6% unknown	Tamoxifen for 5 y if aged ≥ 50 y and ER+; RT after BCS, PMRT at discretion of physician	Median follow-up 124 mo, no difference in locoregional recurrence or death rates: • OS at 10 y: 78.4% in FAC arm vs 81.7% in P→ FAC, p=0.930 • No difference in OS between subgroups (BCT, mastectomy, PMRT, N+)
Taxane + anthracycline (concurrent) vs more non-taxane (anthracycline)								
Martín, 2005 (31)	BCIRG 001 1997–1999	TAC vs FAC TAC: A (50 mg/m^2) + C (500 mg/m^2) + T (75 mg/m^2) q3w×6 FAC: A (50 mg/m^2) + F (500 mg/m^2) + C (500 mg/m^2) q3w×6 Primary prophylaxis with GCSF not	1491	N+, T1–3; exclude advanced disease (T4, N2–3, M1)	62% N1 38% N2+ 41% T1 52% T2 7% T3	55% premenopausal 76% HR+ 22% HER2+, 15% unknown	Tamoxifen for 5 y administered if HR+; RT after BCS, PMRT according to institution guidelines	Median follow-up 55 mo; estimated 5–y survival rates • DFS: 75% TAC vs 68% FAC, p=0.001 • OS: 87% TAC vs 81% FAC, p=0.008 • Grade 3 or 4 neutropenia 65.5% vs 49.3 % (p<0.001), febrile neutropenia 24.7% vs 2.5% (p<0.001), infections 3.9% vs 2.2% (p=0.05)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		allowed; pts with one episode of febrile neutropenia or infection were administered GCSF in subsequent cycles						
Mackey, 2013 (188)	BCIRG 001	See previous entry in table	1491					Median follow-up 124 mo •DFS: 62% TAC vs 55% FAC, HR=0.80 (95% CI 0.68–0.93), p=0.0043 •OS (10 y): 76% TAC vs 69% FAC, HR=0.74 (95% CI 0.61–0.90), p=0.0020 •TAC improved DFS irrespective of nodal, hormone receptor, HER2 status (although not all statistically significant) •More serious adverse events during treatment phase with TAC than FAC (36% vs 9%); more sensory neuropathy during follow-up in TAC group (4% vs 1%, p<0.0001)
Hugh, 2009 (30)	BCIRG 001	See previous entry in table (31) Subtypes and response to docetaxel: • 14.5% Triple negative • 8.5% HER2 (HER2+, ER–, PR–) • 61.1% luminal B (ER+ and/or PR+ and either HER2+ and/or Ki-67^{high}) • 15.9% luminal A (ER+ and/or PR+ and not HER2+ or Ki-67 ^{high})	1350					• 3–y DFS (p values compared with luminal B) were 67% TN (p<0.001, HR=2.22), 68% HER2(p=0.0008, HR=2.12), 82% (referent luminal B), 91% luminal A (p=0.0027, HR=0.46) • Improved 3–y DFS with TAC was found in the luminal B group (p=0.025) and a combined ER+/HER– group treated with tamoxifen (p=0.041), with a marginal trend in the triple negatives (p=0.051) and HER2 (p=0.068) subtypes. • No DFS advantage was found in the luminal A population.
Dumontet, 2010 (29)	BCIRG 001	See previous entry in table (31) IHC assessment of biological markers	1350					• No interaction with Ki-67 and treatment allocation • Ki-67 and p53 protein, as well as microtubule-related parameters tau protein and tubulin III are independent prognostic factors but not predictive of docetaxel benefit
Francis, 2008 (169)	BIG 02–98 1998–2001	See previously in this table (Taxane + anthracycline [sequential] vs more non-taxane [anthracycline] regimen)						
Martín, 2010 (189)	GEICAM 9805	TAC vs FAC	1060	N0 (≥10 nodes examined),	51% T1 47% T2	53% premenopausal	Tamoxifen for 5 y if HR+; RT	Median follow-up 77 mo • DFS: 87.8% TAC vs 81.8% FAC (32%

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
	1999–2003	TAC: T (75 mg/m^2) + A (50 mg/m^2) +C (500 mg/m^2) q3w×6 FAC: F (500 mg/m^2) + A (50 mg/m^2) +C (500 mg/m^2) q3w×6 Primary prophylaxis with GCSF not permitted in original protocol, amended after 230 pts due to incidence of neutropenic fever in >25% of TAC group; all TAC pts then received GCSF; in FAC group received prophylactic antibiotics and GCSF in all remaining cycles if episode of febrile neutropenia or infection		T1–3, and at least one St Gallen risk factor (T2+, ER– and PR–, histological grade 2 or 3, age <35 y)	2% T3	65% HR+, 35% HR–	if BCS, PMRT if >5cm depending on institution guidelines	reduction), HR=0.68 (95% CI 0.49–0.93), p=0.01 • Benefit in subgroups (HR status, menopausal status, age, tumour size, grade) suggested benefit of TAC vs FAC is consistent with benefit in overall population • OS: 92.5% TAC vs 93.5% FAC, HR=0.76 (95% CI 0.45–1.26), not significant, but small number of events (need longer follow-up) • Grade 3 and 4 adverse events 28.2% for TAC and 17% for FAC (p<0.001); most TAC-induced adverse effects ameliorated with GCSF administered as primary prophylaxis
Goldstein, 2008 (190)	E2197 NCT00003519	AT vs AC AT: A (60 mg/m^2) + T (60 mg/m^2) q3w×4 AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4 Primary GCSF not used, received in pts with febrile neutropenia according to ASCO guidelines	2882	N1 or N0 with tumour >1 cm (at least 6 nodes removed)	66% N0 34% N1 43% T1 57% T2+ (75% ≤2.8 cm)	48% premenopausal or peri-menopausal 32% ER–PR– 3%ER–PR+ 11% ER+PR– 54% ER+PR+	Tamoxifen for 5 y if HR+; after June 2005 could switch to AI if post-menopausal; RT after BCS, PMRT at physician discretion	Median follow-up of 79.5 mo, 5–y survival rates reported • DFS: 85% both arms, HR=1.02 (95% CI 0.86–1.22), p=0.78 for AC vs AT • OS: 91% vs 92% • AT did not improve survival rate and was associated with more adverse effects
Sparano, 2012 (191) [abstract]	E2197 1998–2000	See previous entry in table	2883		Median T size 2.0 cm			Median follow-up 11.5 y, 10–y DFS, AC vs AT (HR >1 favours AT) Overall: HR=1.02 (95% CI 0.88–1.18), p=0.83 ER+: HR=0.91 (95% CI 0.76–1.10), p=0.34 ER–: HR=1.22 (95% CI 0.96–1.56), p=0.11 OS: HR=1.03 (95% CI 0.86–1.23), p=0.73 Still no significant difference in DFS or OS
Brain, 2009 (192) [abstract]	RAPP-01 1999–2003	AT vs AC AT: A (50 mg/m^2) + T (75 mg/m^2) q3w×4 AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4	627	Early, high-risk pN0 or limited pN+ (N1)	43% pN0	44% Ki-67 ≥25%	RT according to standard guidelines, endocrine treatment for 5 y if HR+	• Closed prematurely for adverse effects in 2003 • Median follow-up 64 mo • 5–y TTR 91% AT vs 90.9% AC, HR=0.91 (95% CI 0.54–1.52), p=0.71 • OS: 94.9 vs 94.3%

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		No prophylactic GCSF						

Del Mastro, 2008 (193)
 	
[abstract]
	GONO-MIG-5
	1996–2001
		FEC_{21} vs EP
		
		FEC: F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×6
		
		EP: E (90 mg/m^2) + P (175 mg/m^2) q3w×4
			1055	N+ (N1–2), operable	68% N1	22% HR–
						69% HR+
							Tamoxifen (20mg/d) for 5 y if HR+	• FEC vs EP: more nausea/vomiting (85% vs 76%, p=0.0001), mucositis (46% vs 37%, p=0.003), leukopenia (52% vs 40%, p=0.0002); less anemia (17% vs 25%, p=0.006), fever (7% vs 15%, p=0.0001), myalgia (1% vs 19%, p=0.0001), neurotoxicity (6% vs 38%, p<0.0001), allergic reaction (1% vs 5%, p=0.03)
								• Median follow-up 8.2 y
								  • EFS (5 y): 71% FEC vs 70% EP
								  • EFS (10 y): 46% both arms
								  • OS (5 y): 89% vs 88%
								  • OS (10 y): 72% vs 76%, p=0.8
								• Conclude different adverse effects profiles, no difference in survival rate

Roché, 2009 (194)
[abstract]
	PACS04
	2001–2004
		FEC vs ET
		
		FEC: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×6
		
		ET: E (75 mg/m^2) + T (75 mg/m^2) q3w×6
		
		GCSF mandatory for subsequent cycles after febrile neutropenia or treatment delay for neutropenia
			3010	N+	67% N1
					49% T2+
						48% post-menopausal
						62% ER+PR+
						20% ER–PR–
						19% HER2+
							RT after BCS; tamoxifen for 5 y if HR+, protocol amendments allowed sequential use of AIs; HER2+ secondarily randomized to 1 y trastuzumab or observation (see HER2+ table)	• FEC vs ET adverse effects: febrile neutropenia 2% vs 6.4% of cycles, grade 3–4 neutropenia 34% vs 9%, leucopenia 35% vs 47%, thrombopenia 1.7% vs 0.3%, nausea/vomiting 14% vs 8%
								• Median follow-up 59.3 mo; report 5–y survival rates
								  • DFS: 79.7% FEC vs 81.7% ET, HR=0.89 (95% CI 0.76–1.05), p=0.18
								  • Positive interaction was found and favoured ET for the HER2+ subgroup, p=0.01
								  • OS: 90.3% FEC vs 90.1% ET, HR=1.07 (95% CI 0.85–1.35), p=0.54

Gianni, 2009 (195); Zambetti, 2013 (196)	ECTO 1996–2002	See neoadjuvant section later in this table						
Taxane without anthracycline in one allocation								
Jones, 2009 (49)	US Oncology	AC vs TC	1016	Stage I-III, 1–7 cm,	48% NO 42% N1	69% HR+ 31% HR–	Tamoxifen for 5 y if HR+;	Median follow-up 7 y, 7–y survival rate results • DFS: 81% TC vs 75% AC, HR=0.74

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
	Research Trial 9735 1997–2000	AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4 TC: T (75 mg/m^2) + C (600 mg/m^2) q3w×4 Did not use prophylactic GCSF			10% N2+		RT after BCS, PMRT if N2+; HER2 status determined in 170 pts (emphasis on those who relapsed)	(95% CI 0.56–0.98), p=0.033 • OS: 87% TC vs 82% AC, HR=0.69 (95% CI 0.50–0.97), p=0.032 • TC was favoured in all subgroups: age, HER2 status, ER • Grade 3 and 4 adverse events: more anemia and febrile neutropenia in older pts and more febrile neutropenia with TC than AC; 3 late deaths in AC group probably related to treatment
Shulman 2014, 2012 (197,198)	CALGB 40101 2002–2010	P vs AC P: 80 mg/m^2 q1w×12 or 18 (N=287) or 175 mg/m^2 q2w×4 or 6(N=1653); AC; 60/600 mg/m^2 Randomized to 4 or 6 cycles (N=284 q3w, N=1647 q2w) Test of non-inferiority of T to AC (one-sided 95% CI of HR <1.30 for RFS)	3871 (4646 planned)	0–3 positive axillary nodes; operable	90% N0 65% T1 35% T2+	40% premenopausal, 68% HR+84% HER2–		Median follow-up 6.1 y RFS: HR=1.26 (1–05–1.53) favouring AC OS: HR=1.27 (1.00–1.62) favouring AC 5–y RFS 88% P vs 91% AC 5–y OS 94% P vs 95% AC OS, in table: 92% vs 94% The trial did not show non-inferiority of single agent P compared with AC Grade 3+ adverse effects (hemoglobin, neutropenia, vomiting, fatigue) higher with AC; neuropathy higher in P arm At median 5.3 y, 4–y RFS 90.9% vs 91.8% for 6 and 4 cycles, HR=1.03 (95% CI 0.84–1.28, p=0.77); OS 95.3% vs 96.3%, HR=1.12 (95% CI 0.84–1.49), p=0.44 Concluded 6 cycles not better than 4 cycles
Nitz, 2011 (199)	WSG Plan B 2009–2011+	TC×6 vs 4EC×4 -TC×4 Pts with HR+ N0–3 and RS11 receive endocrine therapy only (not included in randomization)	2296, ongoing	HER2–; N+ or high-risk N0 (pT2, HR–, G2–3, age 35 y, or high uPa/PAI-1)				Ongoing
Ortmann, 2011 (200)	SUCCESS-C	FEC×3→ T×3 vs TC×6	1452, Target 3547	HER2–				Ongoing
Nitz, 2009(179) [abstract]	WSG/AGO AM02	See previously in this table (179-182)						

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Mansi, 2010(201)	Anglo-Celtic (ACCOG) 1999–2002	See neoadjuvant section later in this table						
Second-generation studies, taxane vs taxane (different dose or docetaxel vs paclitaxel)								
Citron, 2003 (43)	CALGB 9741 1997–1999	I. A→ P→ C vs II. dd A→ P→ C vs III. AC→ P vs IV. dd AC→ P I. A→ P→ C: A (60 mg/m^2) q3w×4→ P (175 mg/m^2 IV over 3 hrs) q3w×4→ C (600 mg/m^2 IV) q3w×4 (33 w total) II. As I but each cycle q2w (22 w total) III. As I but C administered concurrently with A (total 21 w) IV. As II but C administered concurrently with A (total 14 w) Dose-dense (II and IV) received filgrastim days 3–10 of each cycle	1973	T0–3, N1–2, M0	59% N1, 29% N2, 12% N3 (median 3 positive nodes) 40% T1, 58% T2+ 2% unknown	49% premenopausal 65% ER+	70% of female pts received tamoxifen; recommended that tamoxifen 20 mg/d be administered for 5 y to all HR+; pre-menopausal and to all post-menopausal	Median follow-up 36 mo DFS: dd (q2w) vs q3w at 3 y: 85% vs 81% RR=0.74, p=0.010 DFS, q2w vs q3 w at 4 y: 82% vs 75%, p=0.0072 OS at 3 y, q2w vs q3w: 92% vs 90%, RR=0.69, p=0.013 • Treatment sequence (sequential A→ P→ C or concurrent AC→ P) was not significantly correlated with DFS (p=0.58) nor OS (p=0.48) • dd + filgrastim caused less grade 4 granulocytopenia, 3% and 9% for arms II and IV (q2w) vs 24% and 43% for arms 1 and 3 (q3 w) • Arm IV (AC→ P q2w) had higher rate of transfusions (13%) vs 0%, 3%, 4% on arms I, II, III • Concurrent regimens had higher Grade 3+ emesis (7% vs 3%, p=0.0002), later cardiotoxicity (2% vs 1%, p=0.11), severe neurotoxicity (4% vs 2%, p=0.005)
Budd, 2013, 2011 (154,155) [abstract]	SWOG S0221 2003–2012	dd AC→ P (80 mg/m^2)q1w×12 vs dd AC→ P (175mg/m^2)q2w×6 dd AC=AC (60/600 mg/m^2) q2w×6 + pegfilgrastim Initially was initial AC vs ddAC randomization then P randomization but AC→P arms were discontinued for futility after 2716 pts and remaining pts received ddAC AC=A(24 mg/m^2)q1w×15 + C(60mg/m^2)daily + filgrastim	3294	N+ or high risk N0; operable				• Powered to find DFS HR≤0.82 for weekly vs q2 weekly for each factor • HR=1.08 (95% CI 0.90–1.28), p=0.42 and therefore excluding the hypothesis that HR=0.82 • Estimated 5-y PFS 82% vs 81% for weekly P and ddP respectively

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Loesch, 2010 (202)	2000–2002	AC→ P vs AP→ P AC (60/600 mg/m^2)q3w×4→ P (175 mg/m^2) q3w×4 AP (50/200 mg/m^2)q3w×4→ P (80mg/m^2)q1w×12 No prophylactic hematopoietic growth factors permitted in cycle 1; use in subsequent cycles at physician's discretion	1830	High risk: N1–2 and T1–3, or N0 >2 cm or N0 >1cm and HR–	Stage I-III 6% Stage I 46% Stage IIA 35% Stage IIB 13% Stage IIIA 27% N0 46% N1 20% N2 8% N3	33% premenopausal 7% peri-menopausal 57% post-menopausal 52% ER+PR+ 10% ER+PR– 2% ER–PR+ 35% ER–PR– (HR–) 33% HER2+ 62% HER2– 21% TN	Premenopausal HR+ received 2–3 y tamoxifen (later increased to 5 y), Post-menopausal pts received 2–3 y tamoxifen which could be followed by AI at physicians discretion; RT after BCS, PMRT if N2+	• Median follow-up 64 mo, report 6–y survival rates (median survival not yet reached), no significant difference • DFS: 79% vs 80%, OS: 82% vs 87%, p=0.08 • Unplanned subgroup analysis for OS: HR– and TN groups favoured arm 2 (p=0.06 and p=0.07) • Both regimens equally effective and tolerable • Dose-dense P (arm 2) is as effective, but increased peripheral neuropathy
Swain, 2010a (45)	NSABP B30 NCT00003782 1999–2004	AC→ T vs AT vs ACT AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 AT: A (60 mg/m^2) + T (60 mg/m^2) q3w×4 ACT: A (60 mg/m^2) + C (600 mg/m^2) + T (60 mg/m^2) q3w×4 Doses modified in Sept 2000 after 5 deaths were reported with ACT. ACT: A 50 mg/m^2, C 500 mg/m^2, T 75 mg/m^2 AT: A 50 mg/m^2, T 75 mg/m^2; added primary prophylaxis with GCSF in these two treatment groups	5264	pN+, cN0–1, early, T1–3	65% N1 25% N2 8% N3 3% unknown 42% ≤2cm(T1) 40% 2–4 cm 15% >4 cm	45% pre- or peri-menopausal; 75% ER+	HR+ received tamoxifen for 5 y, starting October 2002 anastrozole was allowed in post-menopausal pts Pre-menopausal for menstrual history substudy	Median follow-up 73 mo, calculated 8–y survival rates • DFS: AC→ T 74% vs AT 69%, HR=0.80, p=0.001 • DFS: AC→ T 74% vs ACT 69%, HR=0.83, p=0.01 • OS: AC→ T 83% vs AT 79%, HR=0.83, p=0.03 • OS: AC→ T 83% vs ACT 79%, HR=0.86, p=0.09 • AT non-inferior to ACT for OS, HR=0.96 (95% CI 0.82–1.14) • No interaction between treatment effect and factors tested (age, hormone receptor status, nodes, tumour size, hormone therapy, menopausal status) • Increased incidence of grade 3 or 4 adverse events with AC→ T (65%) compared with AT (45%) or ACT (48%), including stomatitis, febrile neutropenia, infection, arthralgia, fatigue, and vomiting • Concluded AC→ T reduced mortality rates, and hypothesized that longer course and/or higher dose of T are important for maximum effect • Menstrual history substudy (N=2343): survival

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								rate higher in pts with amenorrhea for ≥6 mo in the 24 mo after randomization: DFS RR=0.70, p<0.001, OS HR=0.76, p=0.04 • No interaction for treatment, age, ER status
Swain, 2010b (46)	NSABP B30 NCT00003782	See previous entry in table (45) Reanalysis of menstrual history (MH) substudy to report 12−m landmark analysis	1885					12−m landmark analysis among female pts with amenorrhea compared with rest • Significant improvement in DFS (HR=0.65, p<0.001) and OS (HR=0.72, p=0.04) • ER+ subgroup: DFS HR=0.51, p<0.001; OS HR=0.52, p=0.002 • ER− subgroup: DFS HR=0.96, p=0.85; OS HR=1.08, p=0.76
Ganz, 2011 (44)	NSABP B30 NCT00003782 QoL 1999−2001	See previous entry in table (45) N=2145 in menstrual history (MH) substudy N=2111 in QoL substudy; calculated a trial outcome index (TOI) that summarizes physical and functional well-being scales and disease-specific items, 5− point difference is clinically meaningful, with a high score being better	5351 (2145, 2111)	MH substudy: pre-menopausal			MH substudy: 77% received tamoxifen QoL substudy: 79% received tamoxifen	Rate of prolonged amenorrhea at 12 mo differs significantly by treatment group: • 70% AC→ T, 38% AT, 58% TAC (p<0.001) • If exclude female pts with unknown status at 12 mo, 83% AC→ T, 47% AT, 67% TAC (p<0.001) • AC→ T had higher rate of prolonged amenorrhea to 12, 18, and 24 mo compared with AT; rates higher with tamoxifen • AT without tamoxifen had lowest rate of amenorrhea (20%-25% over the 24 mo of observation) • Information may be useful in younger female pts interested in preserving fertility, because AT may offer better chance of return of menses QoL Outcomes: • Over 24 mo, AC→ T had TOI 2.4 points lower than TAC; AT had TOI 1.0 points lower than TAC; differences are statistically significant but not clinically meaningful • At 6 mo, AC→ T had TOI ≈ 10 points lower than TAC or AT • TAC and AT pts TOI and symptoms severity score returned to baseline at 6 mo; AC→ T returned to baseline at 12 mo (p<0.001)
Eiermann, 2011 (47)	BCIRG 005	TAC×6 vs AC×4→ T×4	3298	N+ (cN0−1 but pN+, ALND of	41% pT1 51% pT2	48% premenopausal	96% received adjuvant	TAC associated with more febrile neutropenia and thrombocytopenia, AC→ T associate with

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
	2000–2003	TAC: T (75 mg/m^2) + A (50 mg/m^2) + C (500 mg/m^2) q3w×6 AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 Primary prophylaxis with GCSF allowed; recommend for secondary prophylaxis after an episode of febrile neutropenia or infection		at least 6 nodes), HER2–, T1–3	8% pT3 61% N1 28% N2, 11% N3	82% HR+	tamoxifen and/or AIs; 66% received RT	more sensory neuropathy, nail changes and myalgia; neutropenic infection similar in both groups At median follow-up 65 mo, estimated 5–y DFS & OS • DFS 79% in both groups: HR=1.0 (95% CI 0.86–1.16), p=0.98 • OS 88 and 89%: HR=0.91 (95% CI 0.75–1.11), p=0.37 • Conclude equally effective but different adverse effects profile
Poole, 2008 (203) [abstract] Wardley, 2008 (141)	tAnGo 2001–2004 safety substudy	EC→ PG vs EC→ P EC→ PG : E (90 mg/m^2 IV) + C (600 mg/m2) q3w×4→ P (175 mg/m2) + G (1250 mg/m^2 days 1 & 8) q3w×4 EC→ P (details not reported, assumed to be same as above without G)	3152 135 (safety sub-study)	Higher risk early	77% N+ 61% T2+	41% ER–, 37% PR–, 26% HER2+ (of 909 assayed)		Median follow-up 35 mo • DFS: HR=1.0 (95% CI 0.8–1.2), p=0.96 • OS: HR=1.1 (95% CI 0.9–1.4), p=0.35 • No subset where EC→ PG more effective, including by ER/PR status • Both regimens reported temporary reductions in pulmonary functions and transient transaminitis levels (not clinically significant); these were greater with EC→ PG but both well tolerated

Joensuu, 2012 (39)	FinXX
	NCT 0114816
		TX→ CEX vs T→ CEF
		
		TX→ CEX: T (60 mg/m^2) + X (900 mg/m^2; days 1–15) q3w×3→ C (600 mg/m^2) + E (75 mg/m^2) + X (900 mg/m^2; days 1–15) q3w×3
		
		T→ CEF: T (80 mg/m^2) q3w×3→ C (600 mg/m^2) + E (75 mg/m^2) + F (600 mg/m^2) q3w×3
		
		Prophylactic GCSF not scheduled
			1500	N+ or high risk N0 (T2+ and PR–)	11% N0
					61% N1
					28% N2+
					
					44% pT1
					50% pT2
					6% pT3–4
						44% pre-menopausal
						56% post-menopausal
						77% ER+, 62% PR+, 19% HER2+
							HR+ received adjuvant endocrine therapy for 5 y, premenopausal received tamoxifen and post-menopausal anastrozole; RT according to institutions practice; protocol amended May 2005 to allow trastuzumab for HER2+	Median follow-up 59 mo, calculated survival rates at 5 y, TX→CEX vs T→CEF
								• DFS: 86.6% vs 84.1%, HR=0.78 (95% CI 0.59–1.03), p=0.08
								• OS: 92.5% vs 89.9%, HR=0.73 (95% CI 0.52–1.04), p=0.080
								• TX→CEX arm had significantly fewer local relapses (8 vs 20, HR=0.39, p=0.024), deaths from breast cancer (42 vs 64, HR=0.64, p=0.027), and better breast-cancer specific survival, HR=0.64, (95% CI 0.44–0.95) p=0.027)
								• Exploratory subgroup analysis, TX→CEX vs T→CEF:
								  • RFS in N2 pts with N2 cancer (HR=0.64, 95% CI 0.43–0.96)
								  • RFS in pts with TN cancer (HR=0.48, 95% CI 0.26–0.88, p=0.018)
								• TX/CEX was associated with more

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								capecitabine-related adverse effects including stomatitis, hand-foot syndrome, nail changes, and diarrhea, whereas T/CEF was associated with more frequent neutropenia, febrile neutropenia, infection with neutropenia, myalgia, and amenorrhea, probably as a result of the higher docetaxel dose.

Sparano, 2008 (32)	E1199, ECO 1199 NCT00004125
	
	1999–2002
		AC→ P (q1w×12) vs AC→ P (q3w×4) vs AC→ T (q1w×12) vs AC→ T (q3w×4)
		
		AC→ P: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4
		
		AC→ P: AC as above→ P (80 mg/m^2) q1w×12
		
		AC→ T: AC as above→ T (100 mg/m^2) q3w×4
		
		AC→ T: AC as above→ T (35 mg/m^2) q1w×12
		
		P q3 w is considered standard therapy
		
		Colony-stimulating factors administered at physician discretion according to ASCO guidelines for pts who had an episode of febrile neutropenia or persistent neutropenia that prevented treatment on schedule
			4950	N+ (N1–2), T1–3; or N0 and high risk T2–3	12% N0
					56% N1
					32% N2–3
						70% HR+, 26% HR–, 4% unknown; 19% HER2+, 68% HER2–, 13% unknown	Tamoxifen for 5 y if HR+, modified June 2005 to allow switch to AI during or after the 5–y course; RT after BCS, PMRT at discretion of treating physician	• No significant difference in DFS between combined groups with P vs those with T (HR=1.03, p=0.61) or between weekly vs every 3 w (HR=1.06, p=0.33)
								• 5–y survival rates: compared with standard therapy (P every 3 w, OS 77%), HR >1 favours experimental therapy:
								  • P (weekly)
								  • DFS: HR=1.27 (1.03–1.57), p=0.006
								  • OS: HR=1.32 (1.02–1.72), p=0.01
								  • Grade 2–4 neuropathies more frequent with weekly P (27% vs 20%)
								  • T (every 3 w)
								  • DFS: HR=1.23 (1.00–1.52), p=0.02
								  • OS: HR=1.13 (95% CI 0.88–1.46), p=0.25
								  • T (weekly)
								  • DFS: HR=1.09 (95% CI 0.89–1.34), p=0.29
								  • OS: HR=1.02 (95% CI 0.80–1.32), p=0.80
								• Interaction of T and weekly schedule (q1w or q3w) was significant
								• In exploratory analysis, both HER2+ and HER2– subgroups did better on experimental treatment, but only significant for HER2– on weekly P (DFS, HR=1.33, p=0.009; OS, HR=1.34, p=0.03; not affected by hormone receptor status)
								• Overall, weekly P after AC improved DFS and OS

Schneider, 2012 (204)	E1199	See previous entry in table	4554					Median time to neuropathy after first dose of taxane was 3.0 mo (range 0–57 mo)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								Grade 2–4 neuropathy developed in 18%, 22%, 15%, 13% of pts in group P3 (P q3w), P1 (P q1w), D3 (T q3w), D1 (T q1w), respectively P1 vs P3, OR=1.34 (1.09–1.64), p=0.006 D1 vs P3 OR=0.73 (95% CI 0.58–0.92), p=0.008 D3 vs P3 OR=0.81 (95% CI 0.65–1.02), p=0.070

Watanabe, 2009 (205)
 	
[abstract, poster]
	N-SAS-BC02
	
	2000–2006
		a) (AC or EC)→ P vs
		b) (AC or EC)→ T vs
		c) P vs
		d) T
		
		(AC or EC)→ P: A (60 mg/m^2) or E (75 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4
		
		(AC or EC)→ T: (AC or EC) as above→ T (75 mg/m^2) q3w×4
		
		P: P (175 mg/m^2) q3w×8
		T: T (75 mg/m^2) q3w×8
			1060	N+ (SLNB or ALND); excluded ER+PR+ until June 2003	12% I
					40% IIA
					38% IIB
					10% IIIA
					
					64% <3 cm
					36% ≥3 cm
					
					58% N1
					26% N2
					16% N3
						56% ER+
						44% ER–
						44% PR+
						56% PR–
						
						HR+ : 20mg TAM or an AI for 5 y
							RT after BCS	Trial to test non-inferiority for DFS, median follow-up 46.5 mo
								• DFS: HR=0.81(95% CI 0.64–1.03), p=0.08 for T vs P (b or d) vs (a or c)
								• DFS: HR=1.26 (95% CI 0.99–1.60), p=0.67 for (taxane, c or d) vs (AC-taxane, a or b)
								  • HER2+: DFS HR1.85 (1.11–3.07), p=0.017
								  • HER2–: 1.11 (95% CI 0.85–1.46), p=0.44
								• Grade 3–4 adverse effects lowest in P arm
								• Neutropenic fever more frequent with T than P
								• Conclude DFS better with T than P
								• AC improves DFS in subset with HER2+ but not HER2–
								• Severe adverse effects greater with T than P

Shiroiwa, 2011 (206)	N-SAS BC 02 2001–2003	See previous entry in table	299 QoL sub-study	N+, Stage I-IIIA, excluded ER+PR+	55% N1 27% N2 18% N3 56% <3 cm 44% ≥3 cm	25% HER2+ 44% HER2– 34% unknown 39% HR+ 61% HR–	Utility scores for health-related QoL, range 0–1 (1 is perfect health)	• Utility scores significantly lower with T alone (group d) than AC (groups a and b) • AC-taxane had significantly higher utility score than taxane alone • No difference between T (b or d) vs P (a or c)
Shimozuma 2012 (207)	N-SAS BC02	See previous entry in table Study of chemotherapy-induced peripheral neuropathy (CIPN) and health-related QoL (HRQoL) assessment in first 300 pts						Author conclusions inconsistent with data, wide variation at baseline and inconsistency between groups, measured at end of cycle 6 but not cycle 8 (last cycle) so cumulative effect unknown; tests appear not sensitive enough to distinguish group differences
Swain, 2012, 2013 (38,48)	NSABP B-38 2004–2007	dd AC→ PG vs dd AC→ P vs TAC AC→ PG: A (60 mg/m^2) + C (600 mg/m^2) q2w×4→ P (175 mg/m^2) + G (2000 mg/m^2) q2w×4	4894	Operable, N+	65% N1	52% post-menopausal 80% HR+		Median follow-up 64 mo, reported 5–y survival rates • DFS: 80.6% AC→ PG vs 82.2% AC→ P (HR=1.1, p=0.27) and 80.1% TAC (HR=0.97, p=0.71) • DFS: AC→ P vs TAC, HR=0.89, p=0.14 • OS: 90.8% AC→ PG vs 89.1% AC→ P (HR=0.89, p=0.25) and 89.6% TAC (HR=0.90, p=0.32) • OS: AC→ P vs TAC, HR=1.01, p=0.92

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		AC→ P: AC as above→ P (175 mg/m^2) q2w×4 TAC: T (75 mg/m^2) + A (50 mg/m^2) + C (500 mg/m^2) q3w×6 Primary GCSF required; erythropoiesis-stimulating agents (ESA) used at investigator discretion						• Adverse effects for TAC, AC→ P, AC→ PG respectively: febrile neutropenia (grade 3–4, 8%, 2%, 2%, p<0.001); sensory neuropathy (grades 3–4, <1%, 7%, 6%, p<0.001), diarrhea (grade 3–4, Hgb <10 in 12%, 26%, 33% with ESA use in 35.2%, 46%, 51.6% and transfusions in 3.7%, 6.3%, 9.4%; death on treatment (N=13, 5, 7, p=0.2) • Conclude no significant differences in efficacy although adverse effects profiles differed
Pippen, 2011(133) O'Shaughnessy, 2010 (134) [abstracts]	US Oncology 1062 USON 01062 2002–2006	AC→ T vs AC→ TX AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 AC→ TX: AC as above→ TX (T: 75 mg/m^2 day 1, X: 825 mg/m^2 bid, days 1–14) [number of cycles not reported]	2611	Resectable, early, high risk (N+, T1–3; or N0, T2+; or N0, >1 cm, HR–)			Tamoxifen or AI for 5 y if HR+; After 2005, HER2+ offered 1 y trastuzumab	• Median follow-up of 5 y, 304 events • DFS: HR=0.84 (95% CI 0.67–1.05), p=0.125 [endpoint not met] • Distant DFS favoured TX group: HR=0.80 (95% CI 0.63–1.02), p=0.067 • OS: improvement with TX vs T: HR=0.68 (95% CI 0.51–0.92), p=0.011 • Subgroup analysis appeared to favour TX over T • Unplanned subset analysis of Ki-67 expression and DFS suggests benefit of X in more highly proliferative tumours (for Ki-67 >10%, hazard ratio for TX vs T is HR=0.70 (95% CI 0.50–0.98) for DFS and HR=0.52 (95% CI 0.33–0.82) for OS • Adverse events similar in both arms, except grade 3 hand-foot syndrome (3.8% T vs 18.1% TX), grade 3/4 stomatitis (4.5% vs 9.1%), diarrhea (2.9% vs 5.1%) and febrile neutropenia (13.1% vs 9.4%)
O'Shaughnessy, 2012 (135) [abstract]	USON 01062	See previous entry in table				2195 ductal 355 lobular or mixed		Exploratory analysis by histology: •Ductal pts AC→ T vs AC→ XT: •No difference in DFS (HR=0.92, p=0.48) or OS (HR=0.75, p=0.07) •Lobular/mixed AC→ XT vs AC→ T •DFS, HR=0.55, p=0.055 •OS, HR=0.38, p=0.04
Moebus, 2010 (208) Moebus,		Intense dose-dense ECP vs conventional EC→ P IDD: E→ P→ C: E (150 mg/m^2)	1284	High risk, N2+ (minimum 10 nodes removed),	58% N2 42% N3 30% pT1 55% pT2	48% premenopausal 72% ER+ 69% PR+	Radiation of the supra-clavicular, infraclavicular	• Median follow-up 62 mo: 5–y survival rate results, dose-dense vs conventional • DFS: 70% dose-dense vs 62% conventional, HR=0.72 (95% CI 0.59–0.87), p<0.001

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
2011 (209) [abstract]		q2w×3→ P (225 mg/m^2) q2w×3→ C (2500 mg/m^2) q2w×3 EC→ P: E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4 Filgrastim received every dose-dense cycle but not conventional; dose-dense pts also randomized to receive epoetin alfa		Stage II-IIIA	14% pT3	25% HER2+, 58% HER2−, 18% unknown	and parasternal lymph nodes, as well as radiation of the breast for BCS or chest wall for mastectomy recommended in all pts. HR+: 5 y tamoxifen; then 5 y letrozole if post-menopausal	• OS: 82% vs 77%, HR=0.76 (95% CI 0.59−0.97), p=0.029 • Dose-dense therapy associated with significantly more non-hematological and hematological adverse effects • Conclude dose-dense ECP less well tolerated but significantly improved survival Median follow-up 8 y, dose-dense vs conventional: • 8 pts vs 0 developed acute myeloid leukemia or myelodysplastic syndrome • Relapse : 231 pts vs 285 pts, HR=0.71 (95% CI 0.59−0.84), p<0.0001 • RFS: 62% vs 51% • OS: 71% vs 65%, HR=0.76 (95% CI 0.62−0.93), p=0.0086 • Results independent of hormone receptor, menopausal, HER2 expression status, and number of positive nodes
Bermejo, 2013 (136)	GEICAM 2003−10 2004−2007	ET→ X vs EC→ T ET (90/75 mg/m^2)q3w×4→ X (1250 mg/m^2 bid d1−14) q3w×4 EC (90/600 mg/m^2)q3w×4→ T (100 mg/m^2)q3w×4	1384	T1−3/N1−3 operable	66% N1, 25% N2, 9% N3	Stratified by site, menopausal status, number of nodes (1−3, 4−9, 9+), hormone receptor status	HER2+ pts excluded after first 803 pts recruited; 84% HR+, 11% HER2+	After median follow-up 6.6 y, survival rates at 5 y: •DFS: 82% EC→ X vs 86% EC→ T, HR=1.314 (1.042−1.657), p=0.0208 •OS not different: HR=1.113 (95% CI 0.809−1.531), p=0.511 EC→ X vs EC→ T : Neutropenia 10% vs 19%, hand-foot syndrome 20% vs 2%, diarrhea 11% vs 3%
Kelly, 2012 (210)	NCT00050167 2002−2008	P→ FEC vs TX→ FEC P→ FEC: P (80 mg/m^2) q1w×12→ F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×4 TX→ FEC: X (1500 mg/m^2; days 1−14) + T (75 mg/m^2) q3w×4→ FEC as above • Further stratified by timing of chemotherapy (preoperative, N=110 per group vs adjuvant,	601	Operable. High risk eligible for adjuvant therapy; include pN2a and pN3a, exclude pN2b, cN2, cN3, T4 (except limited T4 lesions, e.g.,	12% Stage I 47% Stage IIA 26% Stage IIB 10% Stage IIIA 4% Stage IIIB-C	45% premenopausal 71% ER+ 54% PR+ 6% HER2+ 25% TN excluded HER2+ after 2005	71% received adjuvant endocrine therapy, 72% received adjuvant RT	pCR: 19.8% TX vs 16.4% P, p=0.48 Median follow-up 50 mo, was 64 RFS events • RFS: 87.5% TX vs 90.7% P, p=0.51 • RFS, preoperative chemotherapy: 81.5% TX vs 85.5% P, p=0.65 • RFS, adjuvant chemotherapy: 90.9% TX vs 93.5% P, p=0.66 • OS: 92.2% XT vs 95% P, p=0.39 Hematological and non-hematological adverse effects were significantly higher in the XT arm Conclude no difference in efficacy; XT associated with higher GI, skin, neutropenic-

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		N=190 per group) • Stopped accrual at annual safety/efficacy review when 35 RFS observed (median follow-up 40 mo) and it was highly unlikely to find a difference among treatments		focal extension with negative margins). For preoperative portion must have clinically palpable disease in breast or axilla, exclude Stage I (T1N0).				related adverse effects
Hofmann, 2013 (211)	ADAPT HR+/HER2− Started 2012−	Neoadjuvant endocrine therapy (3 w; optional if N2/3 or RS ≥26) then randomize high-risk groups to Arm A or B chemotherapy (adjuvant or neoadjuvant), both with endocrine therapy as before Paclitaxel$_{175}$ q2w×4→ EC q2w×4 vs nab-paclitaxel$_{125}$ q1w×8→ EC q2w×4	4000 planned	HR+ HER2−		High risk=N2/3; or N0/1 with RS ≥26; or N0/1 with RS 12−25 and Ki-67 ≥10% post neoadjuvant endocrine therapy		Ongoing, started 2012
Hofmann, 2013 (211)	ADAPT Triple negative 2012 -	Neoadjuvant therapy (12 w): nab-paclitaxel + gemcitabine vs nab-paclitaxel + carboplatin	336 planned	Triple negative (HR− HER2−)				Ongoing, started 2012
Neoadjuvant								

Untch, 2011a (212)	PREPARE (prognosis)
	
	2002−2005
		Neoadjuvant
		EC→ P→ surgery (control) vs dd E→ dd P→ CMF→ surgery
		
		EC→ P→ surgery: E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4→ surgery
		
		E→ P→ CMF→ surgery: E (150 mg/m^2) q2w×3→ P (225 mg/m^2) q2w×3→ C (500 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3→ surgery
			714	T2+, included inflammatory	57% ypN0
					43% ypN+
					
					68% <4 cm
					32% ≥4 cm
					
					8% T4 (including inflammatory)
						68% HR+
						32% HR−
								• Estimated at 3−y EC→ P compared with dd E→ dd P→ CMF
								  • DFS 76% vs 79%, HR=1.14, p=0.37
								  • OS 88% vs 92%, HR=1.26, p=0.237
								• Estimated at 3 y, with vs without darbepoetin
								  • DFS 74% vs 80%, HR=1.31, p=0.061
								  • OS 88% vs 92%, HR=1.33, p=0.139
								• Pts with pCR vs without pCR
								  • DFS: 89% vs 75%, HR=2.27, p=0.001
								• Concluded neoadjuvant dose-intensified chemotherapy did not improve DFS, darbepoetin might have detrimental effect

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		Pts in both groups randomized to receive darbepoetin (DA) or none DA: 4.5 µg/kg body weight q2w starting with first dose E until 14 d after last dose of P, + 200mg oral iron (Fe^{2+}) daily dd pts received pegfilgrastim (6 mg SC on day 2 of cycles 1–6 (E_{dd}→ P_{dd}); primary prophylactic use of pegfilgrastim during CMF or in the EC→ T arm was not mandatory; filgrastim (5 µg/kg body weight daily) administered in cases of leucopenia for ≥3d, fever>38.5 C or infection and then pegfilgrastim administered prophylactically in remaining cycles						
Untch, 2011b (213)	PREPARE (pCR)	See previous entry in table (212)	733 714 treated	T2+, included inflammatory	50% cN0 38% cN+ 12% unknown 88% cT1–3 8% cT4 65% T <4 cm 30% T ≥4 cm	42% HR+ 20% HR– 38% missing 42% HER2, 0–1+ 39% HER2, 2+ 8% HER2, 3+ 10% missing	91% of pts had surgery after chemotherapy	• 13.2% of control and 18.7% of dose-dense group had pCR (p=0.043) • 10% control,17.4% dose-dense group had cCR • DA did not affect pCR, clinical response, or nodal response (p=0.972) • In TN subgroup, pCR 44.6% with dose-dense vs 30.4% control (p=0.12) • Both chemotherapy groups had had significant decrease in hemoglobin levels; no change in DA+ group • DA+ group had more thromboembolic events (6% vs 3%, p=0.055) • Hematological adverse effects generally mild, similar in all treatment groups • Grade 3–4 sensory neuropathy, neurological complaints, mucositis/stomatitis/proctitis were significantly higher in dose-dense group • Conclude: neoadjuvant dose-dense superior in terms of pCR, darbepoetin did not influence response

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results

Gianni, 2009 (195)	ECTO
	
	1996–2002
		Arm A: surgery→ A→ CMF vs
		Arm B: surgery→ AP→ CMF vs
		Arm C: AP→ CMF→ surgery (neoadjuvant)
		
		Arm A: A (75 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×4
		
		Arm B & C: A (60 mg/m^2) + P (200 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×4
			1355	T2–3, N0–1	54% N0
					46% N1–2
					
					80% ≤4 cm
					20% >4 cm
						68% HR+
						31% HR–
							RT after BCS; tamoxifen offered to all pts at start, only HR+ pts after July 2000	After follow-up 76 mo, report 7–y survival rates:
								• Arm B vs Arm A
								  • DFS: 76% vs 69%, HR=0.73 (95% CI 0.57–0.97), p=0.03
								  • OS: 85% vs 82%, HR=0.80 (95% CI 0.56–1.14), p=0.21
								• Arm B vs Arm C
								  • DFS: 76% vs 72%, HR=1.21 (95% CI 0.92–1.60), p=0.18
								  • OS: 85% vs 84%, HR=1.10 (95% CI 0.77–1.59), p=0.60
								• BCS: 63% arm C vs 34% arm A/B, p<0.001
								• Study not powered for OS

Zambetti, 2013 (196) [abstract]	ECTO	See previous entry in table	1335					10 y results, arm B (AP→ CMF) vs arm A • Freedom from progression (FFP): HR=0.77, p=0.045 • OS: HR=0.82, p=0.24 (no difference) Arm B vs Arm C (adjuvant vs neoadjuvant) • Freedom from progression: HR=0.79, p=0.07 Primary chemotherapy (arm C) allowed BCS in a significant percentage of pts
Kaufmann, 2010 (214) [abstract/ poster] Darb-Esfahani, 2009 (215)	GeparDuo NCT00793377 1999–2001	Preoperative dose-intensified AT×4 vs preoperative AC×4→ T×4 AT: T (50 mg/m^2) + A (75 mg/m^2) q2w×4 AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 GCSF administered with AT	913	T2–3, N0–2, M0	0.8% T1 84% T2 15% T3 60% N0 40% N+	28% ER–PR– 72% ER+ and/or PR+	All received tamoxifen	Preoperative AC→ T is superior for pCR 14.3% vs 7%, OR=2.22 (95% CI 1.41–3.49), p<0.001 Median follow-up 64.3 mo; 5–y DFS and OS reported • DFS: AC→ T 65% vs AT 69%; HR=1.11 (95% CI 0.884–1.40), p=0.36 • OS: 84% in both arms

Untch, 2009 (216)	AGO 1
	
	1998–2002
		Preoperative E+P vs intense dose-dense (IDD) E→ P
		
		E+P: E (90 mg/m^2) + P (175 mg/m^2) q3w×4
		IDD: E→ P: E (150 mg/m^2) q2w×3→ P (250 mg/m^2) q2w×3; all received filgrastim (5μg/kg) on days 3–10 of each cycle
			668	High risk:
				85% ≥3 cm;
				15% inflammatory
					34% N0
					54% N+
					12% unknown
					
					53% T2
					29% T3
					18% T4
						68% HR+
						49% <50 y old
							Tamoxifen (20 mg/d for 5 y) administered if HR+; RT for all BCS, PMRT where indicated	IDD vs conventional, median follow-up 55 mo
								• Improved pCR rate (18% vs 10%, p=0.008)
								• DFS: HR=0.71 (95% CI 0.54–0.92), p=0.011
								• OS: HR=0.83 (95% CI 0.69–0.99), p=0.041
								• Inflammatory cancers
								  • DFS: HR=1.10, p=0.739; OS: HR=1.25, p=0.544
								• Non-inflammatory cancers
								  • DFS: HR=0.65 (95% CI 0.48–0.88), p=0.005
								  • OS HR=0.77 (95% CI 0.63–0.95), p=0.013

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		All received 3 cycles of CMF after surgery; C (500 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) on days 1&8 q4w *after surgery*.						IDD associated with significantly more non-hematological adverse effects, anemia, and thrombocytopenia, but similar neutropenia and infection rates

Rastogi, 2008 (28)	NSABP B-27
	
	1995–2000
		Preoperative AC→ surgery vs preoperative AC→ T→ surgery vs preoperative AC→ surgery→ T
		
		AC→ surgery: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ surgery
		
		AC→ T→ surgery: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4→ surgery
		
		AC→ surgery→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ surgery→ T (100 mg/m^2)×4
			2344	T1c-3, N0–1; or T1–3, N1	70% N0
					30% N+
					
					14% T1
					58% T2
					28% T3
							RT after BCS, PMRT not allowed
							
							All groups:→ Tamoxifen (20mg/day) for 5 y initiated on first day of chemotherapy
								• After median follow-up 8.5 y, no statistically significant differences in DFS or OS
								  • DFS: group 2 vs 1: HR=0.92 (95% CI 0.78–1.08), p=0.29
								  • DFS: group 3 vs 1: HR=0.92 (95% CI 0.78–1.08), p=0.29
								  • OS: p=0.76 across all 3 arms
								• Addition of T did not significantly impact DFS (HR=0.93, 0.92, p=0.29) or OS (HR=0.93 and 0.97, p=0.46 and 0.76)
								• Preoperative AC→ T significantly increased clinical response (91% vs 86%, p<0.001), cCR (63% vs 40%, p<0.001), and pCR (26% vs 13%, p>0.001)compared to preoperative AC
								• Pts with pCR had significantly superior DFS and OS (8–y follow-up)
								  • DFS: HR=0.49, p<0.001, OS: HR=0.36, p<0.001

Mansi, 2010(201) Evans, 2005(217)	Anglo-Celtic (ACCOG) 1999–2002	Neoadjuvant AC vs AT AC: A (60 mg/m^2) + C (600 mg/m^2) q3w (6 cycles maximum) AT: A (50 mg/m^2) + T (75 mg/m^2) q3w (6 cycles maximum) 6% did not receive surgery after neoadjuvant chemotherapy	363	Large tumours (≥3cm), inflammatory, or LABC considered candidates for primary chemotherapy	Before chemotherapy: 77% operable 15% inflammatory 8% LABC Median 6 cm			pCR: 24% AC vs 21% A, p=0.61 cCR: 17% AC vs 20% AT, p=0.42 overall clinical response: 61% AC vs 70% AT, p=0.06 5–y survival rates • DFS: 54% AC vs 59% AT, p=0.20 • OS: 67% AC vs 72% AT, p=0.24
Lee, 2008 (156)	2002–2005	Neoadjuvant TX→ surgery→ AC vs Neoadjuvant AC→ surgery→ TX	204	N+, Stage II/III	Stage II/III 77% T1–2, 23% T3–4 69% N1, 31% N2–3	61% HR+ 34% HER2+ 47% HER2– 18% unknown	All received RT; tamoxifen or anastrozole if HR+	At median follow-up of 37 mo, no significant difference in DFS by treatment groups (p=0.932). Compared with AC, TX increased pCR in primary tumours (21% vs 10%, p=0.024) and clinical response (84% vs 65%, p=0.003). Fewer pts developed recurrence who achieved pCR in lymph node (LN); HR=0.189 (95% CI 0.044–0.815), p=0.025 in the multivariate analysis. TX was associated with less nausea and

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								vomiting, but more stomatitis, diarrhea, myalgia, and skin/nail changes than AC
Earl, 2014 (142)	Neo-tAnGo	Neoadjuvant: EC→ P vs P→ EC vs EC→ GP vs GP→ EC Effect of gemcitabine and role of sequence (EC→ P vs P→ EC) stratified by ER status, tumour size (50 mm cut-off), nodal status (N0/N+), inflammatory/locally advanced (yes/no)	831	Early invasive, >2 cm; no previous chemo, RT, endocrine therapy T4 eligible	80% T2, 20% T3 50% N+	67% ER+ 51% PR+ 25% inflammatory or LABC; 57% premenopausal, 6% peri-menopausal		Median follow-up 47 mo; first planned interim analysis found no significant difference in DFS or OS • DFS : EC→ P vs EC→ PG HR=1.13 (95% CI 0.88–1.46), p=0.34; P→ EC vs EC→ P HR=0.84 (95% CI 0.65–1.09), p=0.18 • OS: EC→ P vs EC→ PG HR=1.02 (95% CI 0.76–1.39), p=0.89; P→ EC vs EC→ P HR=0.82 (95% CI 0.60–1.11), p=0.19 • pCR greater with P→ EC than EC→ P (20% vs 15%, p=0.03); G did not increase pCR • pCR was correlated with significant improvement in DFS (p<0.001) and OS (p=0.0007)
Von Minckwitz, 2008, 2013 (218-221)	GeparTrio 2002–2005	TAC vs NX if poor response to TAC 2 cycles TAC then evaluated response; early responders randomized to 4 (N=704) or 6 (N=686) additional cycles TAC If no sonographic response (reduction in product of 2 largest perpendicular diameters was <50%) then randomized to 4 additional cycles TAC (N=321) or vinorelbine + capecitabine (NX; N=301); excluded those with disease progression	2012	Tumour ≥2 cm; at least one risk factor of age <36 y, <5 cm, ER–PR–, N+, undifferent-iated grade	61% T2, 19% T3, 12% T4a-c, 5% T4d; median 40 mm by palpation and 29 mm by sonography; 42% N0	LABC, inflammatory, N3 including or supraclav-icular nodes were assigned within a separate stratum		Median follow-up 62 mo • Early responders: DFS better for TAC×8 than TAC×6 (HR=0.78, 95% CI 0.62–0.97,p=0.026) • Early non-responders: DFS better for TAC→NX than TAC×6 (HR=0.59, 95% CI 0.49–0.82, p=0.001); • DFS for non-responders administered TAC→NX similar to early responders administered TAC×8 • Response-guided therapy (TAC×8 or TAC→NX) better than TAC×6 for DFS overall (HR=0.71, p<0.003) and for subgroups HR+ (luminal A, luminal B) but not HR– or TN pCR predicted improved DFS in TN, HER2+ (nonluminal) and luminal B (Her2–) • Adverse effects: NX had more hand-foot syndrome and sensory neuropathy but less hematological adverse effects, mucositis, infections, and nail changes • Post-treatment (after 2 cycles TAC) Ki-67 levels gave prognostic information for pts with HR+ cancer with residual disease after neoadjuvant chemotherapy (high Ki-67 had higher risk for relapse or death, p<0.0001)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Hofmann, 2013 (211)	ADAPT HR+/HER2−; ADAPT Triple negative 2012 −	See previously in this table (second-generation studies)						Ongoing, started 2012

Abbreviations: A, doxorubicin (Adriamycin); AC, doxorubicin + cyclophosphamide; ALND, axillary lymph node dissection; AT, doxorubicin + docetaxel; BCS, breast-conserving surgery; BCT, breast conserving therapy (BCS +RT); cCR, clinically complete response; CEF, cyclophosphamide + epirubicin + fluorouracil; CEX, cyclophosphamide + epirubicin + capecitabine; C, cyclophosphamide; CMF, cyclophosphamide + methotrexate + fluorouracil; dd, dose-dense; DDFS, distant disease-free survival rate; DFS, disease-free survival rate; E, epirubicin; EC, epirubicin + cyclophosphamide; EFS, event-free survival rate; EGFR, epidermal growth-factor receptor; ER, estrogen receptor; ET, epirubicin + docetaxel; F, 5−fluorouracil; FAC, fluorouracil + doxorubicin + cyclophosphamide; FEC, fluorouracil + epirubicin + cyclophosphamide; G, gemcitabine; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, Hormone receptor positive; HR−, hormone receptor negative; HRQoL, health-related quality of life; IDD, intensive dose-dense; IDFS, invasive disease-free survival rate; IHC, immunohistochemistry; LRR, locoregional recurrence; LVI, lymphovascular invasion; N0, no positive nodes; N+, positive nodes found; N1, 1−3 positive nodes; N2, 4−9 positive nodes; N3, 10+ positive nodes; nab-paclitaxel, nanoparticle albumin-bound-paclitaxel; NX, vinorelbine + capecitabine; OS, overall-survival rate; P, paclitaxel; pCR, pathologically complete response; PMRT, postmastectomy radiation therapy; PR, progesterone receptor; pts, patients; QoL, quality of life; RFS, recurrence-free survival rate; RR, relative risk; RT, radiation therapy; T, docetaxel (Taxotere); TAC, docetaxel + doxorubicin + cyclophosphamide; TN, triple negative (PR−,ER−, and HER2−); TOI, trial outcome index; TTR, time to recurrence; TX, docetaxel + capecitabine; X, capecitabine

*HER2, ER/PR, lymph node, risk, menopausal status

Intrinsic subtypes: luminal A=(ER+ and/or PR+) and not (HER2+ or Ki-67^{high}); luminal B=(ER+ and/or PR+) and either (HER2+ and/or Ki-67^{high}); HER2=HER2+ and ER−; triple negative (TN)=PR− and ER− and HER2−; basal=TN and either (EGFR+ or cytokeratins 5/6+)

4.2.3 Other Systemic Therapy Agents

a) Bevacizumab

The BEATRICE trial (227) studied the use of bevacizumab in patients with triple-negative operable breast cancer (95% hormone-receptor negative [HR−] and 5% hormone receptor low). Tumours were 36% T1, 59% T2, and 6% T3; 63% of patients were node negative, 25% N1, and 12% N2+. Patients were recruited between 2007 and 2010 and 2591 patients were randomized to receive chemotherapy alone or chemotherapy + bevacizumab (5 mg/kg weekly for 1 year). Chemotherapy was 36% anthracycline, 58% anthracycline-taxane, and 5% taxane. At median follow-up of 32 months, invasive disease-free survival (IDFS) events were reported in 14% of the bevacizumab group and 16% of the chemotherapy group (HR=0.88, 95% CI 0.72−1.07, p=0.18). Because survival rates were higher than expected in both groups, sample size and/or follow-up was not long enough for statistically significant results. Preliminary analysis after 200 deaths and median follow-up of 2.6 years found no difference in OS rates (HR=0.84, 95% CI 0.64−1.12, p=0.23), although prespecified analysis was to occur after 340 deaths or median follow-up of 5 years (whichever occurred first). Patients receiving bevacizumab had increased incidences of grade 3+ hypertension (12% vs 1%), severe cardiac events (1.5% vs 0.3%), and treatment discontinuation (20% vs 2%). Data suggests bevacizumab may have greater IDFS benefit in some subgroups, such as patients with node-negative cancer and those who did not receive anthracycline-taxane. It was concluded that bevacizumab cannot be currently recommended in unselected patients with triple-negative cancer. Longer follow-up is required.

The ARTemis trial (228,229) gave patients with early-stage HER2− breast cancer neoadjuvant docetaxel→FEC (T-FEC) chemotherapy with or without four cycles of bevacizumab. Patients were stratified by age (68% aged <50 years), ER status (33% ER−, 9% weakly ER+, 59% strongly ER+), tumour size (79% T2, T3−4), nodal involvement (52% node-positive, N+), and inflammatory/LABC (19% of patients). For the primary endpoint of pCR, bevacizumab + T→FEC was significantly better than T→FEC alone (pCR 22% vs 17%, p=0.03). pCR was higher in subgroups that were ER− (44% bevacizumab, 32% no bevacizumab) or weakly ER+ (52% bevacizumab, 26% no bevacizumab); there was low pCR in patients with strongly ER+ cancer (6% and 7% with or without bevacizumab). Accrual was from 2009 to 2013 and survival rate outcomes have not yet been reported.

b) Metformin

NCIC Trial MA.32 (230) is a study on metformin vs placebo for five years after standard adjuvant therapy in early-stage breast cancer (pT1cN0 and at least one of the following factors: grade 3, estrogen receptor (ER) and progesterone receptor (PR) negative, HER2+, lymphovascular invasion (LVI), Oncotype DX recurrence score (RS) >25, Ki-67 >14, pT2−3N0, pT1−3N1−3). Accrual closed in 2013 with 3649 patients and follow-up is ongoing (http://www.bcrfcure.org/researchers/pamela-j-goodwin)

c) Bisphosphonates

Several trials were located that were not included (or with insufficient follow-up) in the previous PEBC guideline (106). Several trials and meta-analyses were still ongoing at the time of the initial literature search for the current guideline. Of major importance is the pending

individual patient meta-analysis by the EBCTCG which has been presented as an abstract (231). Appendix D includes and a summary of other guidelines, meta-analysis, and systematic reviews (106,231-237) and a list of trials located during the literature search (238-268). Three trials included in other publications (269-273) did not meet our inclusion criteria. It was decided that bisphosphonates as a class of chemotherapy agents would not be included in the guideline, but would be the subject of a subsequent guideline.

d) Goserelin in Hormone Receptor-Negative Patients

The Prevention of Early Menopause Study (POEMS; SWOG S0230) (274,275) randomized patients with Stage I-IIIA HR− premenopausal breast cancer to standard cyclophosphamide-containing chemotherapy (mostly AC, many combined with taxane) with or without goserelin (3.6 mg monthly injections starting 1 week before the first chemotherapy). The primary endpoint was premature ovarian failure (POF) at two years, defined as amenorrhea for the prior six months and postmenopausal follicle-stimulating hormone (FSH), with secondary endpoints of survival rates and pregnancy. POF was 8% (goserelin arm) vs 22% (OR=0.30, p=0.03; adjusted logistic regression OR=0.36, p=0.08). Using a broader definition of POF as amenorrhea or elevated FSH, POF was 20% vs 45% (OR=0.29, p=0.006). There were 22 vs 13 pregnancies in the 5−year study period (21% vs 11%, OR=2.22, p=0.05), although among those trying to get pregnant the rates were 22/25 (88%) vs 12/18 (67%) (276). DFS and OS rates at four years were better in the goserelin arm (HR=0.49, p=0.04 and HR=0.43, p=0.05, respectively). The study authors considered the survival rate data to be exploratory. The study is limited as it closed early, had low enrolment (N=257), collected incomplete data (only 218 patients evaluable of which 62% had complete POF data), and has only been published as an abstract.

e) Vaccines

The literature search found studies evaluating the ability of the AE37 and E75 HER2 peptide vaccines to prevent disease recurrence in patients with node positive and high-risk node-negative breast cancer. The AE37 vaccine was evaluated in a randomized phase II trial involving 298 patients with any level of HER2 expression (IHC1−3+) (277). After standard care therapy, disease-free patients with either N+ or high-risk node negative (N0) cancer were randomized to AE37 + granulocyte-macrophage colony-stimulating factor (GM-CSF) or GM-CSF alone. Treatment was six monthly intradermal inoculations plus four boosters every six months. The relative reduction in recurrence (RRR) was 12% overall (HR=0.89, p=0.70), 40% in patients with HER2 non-overexpressing cancer (IHC 1/2+; HR=0.60, p=0.21), and 60% patients with triple-negative cancer (HR=0.40, p=0.12). The study concluded a phase III trial is justified.

The E75 vaccine was evaluated in phase I/II dose-escalation/schedule-optimization trials in patients with any degree of HER2 (IHC 1−3+) (278,279). Vaccine was administered in 4−6 monthly intradermal inoculations plus voluntary booster every six months to 108 patients and compared with 79 controls. Five-year DFS rates were 89.7% vs 80.3% (p=0.08). Due to the trial design some patients received a less-than-optimal vaccine dose. In optimally-dosed patients, DFS was 94.6% (p=0.05 vs control) compared with 87.1% in suboptimally-dosed patients. Among 21 patients who received a booster there was one recurrence (DFS=95.2%). Based on this data, a phase III trial evaluating E75 (NeuVax) started enrolment in 2011 (PRESENT: Prevention of Recurrence in Early-Stage, Node-Positive Breast Cancer with Low to

Intermediate HER2 Expressions with NeuVax™ Treatment; NCT01479244, see http://www.clinicaltrials.gov/show/NCT01479244).

4.3 HORMONAL THERAPY FOR HORMONE RECEPTOR-POSITIVE TUMOURS

The therapeutic manipulation of both endogenous estrogen levels and the interaction of estrogen with its receptor is a cornerstone of adjuvant therapy in female patients with hormone receptor positive breast cancer (HR+ = ER+ and/or PR+). In premenopausal patients the ovaries are the main source of hormone production; therefore, surgical removal, permanent inactivation by ovarian irradiation, or temporary ovarian suppression by administration of LHRH agonists (also called gonadotropin-releasing hormone [GnRH] agonists) have been used in treatment. Tamoxifen is a selective estrogen receptor modulator (SERM) that blocks the effect of estrogen in HR+ cancers. It has been found effective in both pre and postmenopausal patients. AIs prevent the action of aromatase in the synthesis of estrogen but are not effective in inhibiting the high levels of estrogen produced in the ovaries before menopause. After menopause the ovaries are no longer a significant source of estrogen production and AIs are then able to inhibit the lower level of estrogen production in other body tissues such as fat and muscle. Anastrozole and letrozole inactivate aromatase temporarily, whereas exemestane has permanent (irreversible) effect.

Menopausal status is an important factor in deciding on treatment. Some of the issues in determining menopausal status and appropriate treatment are discussed in the Danish guideline "Menopausal Status and Adjuvant Hormonal Therapy for Breast Cancer" (280).

There is evidence of benefit for ovarian ablation and/or suppression (OA/S) or tamoxifen in patients with HR+ cancer, as well as AIs in postmenopausal patients. There is less agreement in the value of using combinations of endocrine agents or endocrine agents with chemotherapy. Although OA/S should make premenopausal patients similar to postmenopausal patients, the use of AIs in those with induced menopause has been proposed but is not standard practice. The recent SOFT and TEXT trials (63,64,281-283) (see Section 4.3.3) investigated OA/S + AIs in premenopausal patients.

The accurate assessment of hormone receptor status is critical for the use of adjuvant hormonal therapy in breast cancer. This topic is discussed in Section 4.3.6.

4.3.1 Tamoxifen

The recent EBCTCG meta-analysis (5) is complete for studies comparing tamoxifen vs no tamoxifen and, therefore, is the basis for most of this evaluation. Duration of tamoxifen >5 years and delayed administration of tamoxifen are reported separately as additional or more recent data have been published.

a) Early Breast Cancer Trialists' Collaborative Group

The 2011 EBCTCG meta-analysis (5) included all trials worldwide on early breast cancer (excluding DCIS) that compared adjuvant tamoxifen vs no tamoxifen (unconfounded trials in which only the use of tamoxifen differed). The data for one to two years of adjuvant tamoxifen (N=33,000) was essentially unchanged since the previous report in 2005 (112). The 2011 report combined data for patients receiving tamoxifen for longer than two years. Most studies used 5 years tamoxifen, except for four trials at 3 years, one trial at 2 years then randomizing to either 3 more years of tamoxifen or stopping at 2 years, and two trials for 5

years then randomizing to stop or continue to 10 years. Ten-year recurrence rates are summarized in Table 4 (5) and corresponding survival rates are summarized in Table 5 (5).

Tamoxifen did not improve recurrence or survival rates in patients with ER poor (ER−) cancer. This is consistent with the EBCTCG 2008 analysis "Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer" (118), which concluded that tamoxifen had little effect on recurrence or death rates in female patients classified as ER-poor, and it did not significantly modify effects of polychemotherapy. Overall mortality rates were substantially reduced in patients with ER+ cancer (5). ER positivity at the level of ≥10 fmol/mg was enough to give a positive tamoxifen effect. Given the ER status, PR status was not significantly predictive of response. Chemotherapy and nodal status affected absolute risk but not the benefit from tamoxifen. Substantial and highly significant recurrence rate reduction and survival rate benefit were found in all subgroups: age (including those aged <45 years and presumed premenopausal), tumour grade and size, chemotherapy use and sequence with tamoxifen, and nodal status. Tumour differentiation and size (diameter) had no effect.

ER status was the only factor predictive of proportional reduction. The absolute risk reduction from tamoxifen depended on the absolute breast cancer risk. For patients with ER+ cancer there was more effect on ten-year breast cancer mortality rates with five years of tamoxifen compared with one or two years of tamoxifen. For patients with ER+ cancer who received five years of tamoxifen, 15−year recurrence rates were 33% vs 46.2% without tamoxifen, and breast cancer mortality rates were 23.9% vs 33.1%; thus, the benefit of tamoxifen persists after its use is discontinued.

Table 4. 10−year recurrence rates according to duration of tamoxifen, hormone receptor status and nodal status
Data from EBCTCG, 2011 (5)

Hormone receptor status, nodal status, and duration of tamoxifen	Number of women	10−year recurrence rate (tamoxifen vs none)
ER+, 1 y	3,482	44.5% vs 52.5%, p<0.00001
ER+, 2 y	10,999	36.2% vs 45%, p<0.00001
ER+, 5 y	10,645	25.9% vs 40.1%, p<0.00001
ER+PR+, 5 y	7,378	24.8% vs 37.7%, RR=0.63, p<0.00001
ER+PR poor, 5 y	2,310	28.6% vs 43.5%, RR=0.60, p<0.00001
ER poor, PR+	1,236	30.9% vs 32.5%, RR=0.90, p=0.35
ER poor, PR poor	4,748	29.0% vs 27.4%, RR=1.03, p=0.60
N0 ER+, 5 y, no chemotherapy	4,288	19.1% vs 34.8%, RR=0.57, p<0.00001
N+ ER+, 5 y, no chemotherapy	919	41.5% vs 57%, RR=0.63, p<0.00001
N0 ER+, 5 y, with chemotherapy	1,662	18.0% vs 24.6%, RR=0.74, p=0.005
N+ ER+, 5 y, with chemotherapy	3,772	36.1% vs 48.1%, RR=0.66, p<0.00001

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; N0, node negative, N+, node positive.

Table 5. 10−year risk of death (± recurrence) according to duration of tamoxifen use and ER status
Data from EBCTCG, 2011 (5)

Duration of tamoxifen use and ER status	Number of women	Any death, RR*	Death with recurrence, RR*	Women-years	Death without recurrence, RR* (% deaths/ woman-years)
1 y, ER+	3,482	54.6% vs 59.6%, RR=0.89, p=0.01	41.1% vs 48%, RR=0.84, p=0.001	29,241	1.6%/y vs 1.4%/y RR=1.09, p>0.1 (NS)
2 y, ER+	10,999	34.3% vs 38.1%, RR=0.83, p<0.00001	24.4% vs 29.5%, RR=0.80, p<0.00001	79,204	1.3%/y vs 1.3%/y RR=0.93, p>0.1 (NS)
≈ 5 y, ER+	10,645	33.4% vs 38.2%, RR=0.78, p<0.00001	21.7% vs 29.0%, RR=0.70, p<0.00001	105,966	1.1%/y vs 1.0%/y, RR=1.02, p>0.1 (NS)
1 y, ER poor	1,655	46.5% vs 49.9%, RR=0.83, p=0.02	40.7% vs 41.7%, RR=0.89, p>0.1 (NS)	12,738	0.7%/y vs 1.1%/y, RR=0.54, p=0.004
2 y, ER poor	6,448	36.4% vs 37.4%, RR=0.92, p=0.07	29.2% vs 30.5%, RR=0.94, p>0.1 (NS)	44,496	1.0%/y vs 1.0%/y, RR=0.85, p>0.1 (NS)
≈ 5 y, ER poor	6,880	25.7% vs 26.3%, RR=0.97, p>0.1 (NS)	20.9% vs 21.6%, RR=0.94, p>0.1 (NS)	53,889	0.6%/y vs 0.6%/y, RR=1.12, p>0.1 (NS)

Abbreviations: ER, estrogen receptor; NS, not significant

*RR=relative risk of death, tamoxifen use compared with control (no tamoxifen)

The earlier 2005 analysis (112) indicated that for ER+ disease only, five years tamoxifen reduced the annual breast cancer death rate by 31%, irrespective of use of chemotherapy, age, PR status, or other tumour characteristics. The 2011 update (5) found that tamoxifen reduced recurrence rates in patients with ER+ cancer by one-half in years 0−4 and by one-third in years 5−9. There was little effect after year 10. Over all time periods, the recurrence rate reduction averaged 39% (RR=0.61, p<0.00001 for any recurrence). Tamoxifen adverse effects were increased risk of uterine cancer (age >45 years) and increased risk of thromboembolic disease for those aged ≥55 years. There were 182 cases of uterine cancer (excluding cervical cancer) and 19 deaths, of which 137 cases and 18 deaths were in tamoxifen users vs 45 cases and 1 death in the controls. All deaths occurred in those aged >45 years; RR=2.5 for cases and 5.46 for deaths. Effects were small compared with the benefit on breast cancer or survival rates. The relative risk of death due to pulmonary embolus was 1.74 (2 vs 1 deaths aged <55 years, 14 vs 6 deaths aged ≥55 years).

b) Duration of Tamoxifen >5 years

The ATLAS (55) and aTTom (56,284) trials randomized 12,894 and 6,953 female patients with approximately five years of tamoxifen to another five years or stopping and found benefit of extended tamoxifen. These results contrast those from earlier smaller studies (NSABP B-14 and Scottish trials) which found no benefit of extending tamoxifen for more than five years (285-288).

The ATLAS trial (55) included 12,894 female patients and found that extending tamoxifen duration in ER+ female patients to 10 years further reduced the risk of breast cancer recurrence (617 vs 711 cases, -2.80% difference, p=0.002), breast cancer mortality (331 vs 397 deaths, p=0.01), and overall mortality (639 vs 722 deaths, -2.48% difference, p=0.01). The benefit for preventing recurrence was similar for the subgroups by menopausal status at study entry (premenopausal: HR=0.81, p=0.15; postmenopausal: HR=0.85, p=0.05), although premenopausal patients were only approximately 9% of the study and statistical significance was not reached likely because of the much smaller number of events in this group.

For all ER groups combined (ER+, ER−, or unknown) there was an increased incidence of pulmonary embolus (41 vs 21 cases, difference of 0.31%, RR=1.87, p=0.01), and endometrial cancer (116 vs 63, difference of 0.82%, RR=1.74, p=0.0002), although these did not result in a significant difference in mortality (10 vs 8 deaths, p=0.69 and 17 vs 11, p=0.29). There was an decrease in ischemic heart disease (127 vs 163 cases, -0.56% difference, p=0.02,) and lower rate of death due to heart attack or other vascular causes (excluding stroke or pulmonary embolism; 178 vs 205 deaths, difference -0.43%, p=0.10).

The aTTOM trial (published only as abstracts) (56,284) included 2755 ER+ and 4198 ER untested (estimated 80% ER+) also found that extending tamoxifen to 10 years compared with 5 years reduced recurrence rates (580 vs 672 events, p=0.003), breast cancer mortality rates (392 vs 443 deaths, p=0.05), and overall mortality rates (849 vs 910 deaths, p=0.1) with little effect on non-breast cancer mortality rates (457 vs 467 deaths, RR=0.94, 95% CI 0.82−1.07). There was an increase in endometrial cancer occurrence (102 vs 45 cases, RR=2.2, p<0.0001) and death (37 vs 20 deaths, 1.1% vs 0.6%, p=0.02). Combined results with the ATLAS trial gave enhanced statistical significance for extended tamoxifen benefit for recurrence (p<0.0001), breast cancer mortality (p=0.002), and OS (p=0.005).

The revised ASCO guideline (May 2014) on adjuvant endocrine therapy (289) recommends that tamoxifen be used for up to ten years. AIs for up to five years may be used instead of or subsequent to tamoxifen (two to five years) in postmenopausal patients (see 4.3.2 for more details). The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists report on Tamoxifen and Uterine Cancer (290) also indicated tamoxifen use may be extended to ten years. Patients should be informed of risk of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas; should report any abnormal vaginal symptoms; and postmenopausal patients should be monitored.

c) Delayed Adjuvant Tamoxifen

The TAM-02 trial (57) randomized patients treated with surgery, radiotherapy, and/or adjuvant chemotherapy but no hormone therapy at least two years earlier (mean 59 months) to tamoxifen for five years or no treatment. The ten-year results indicated that tamoxifen significantly improved OS and DFS rates in N+ and in HR+ (ER+ and/or PR+) tumours. Patients

with delay longer than five years had significantly improved DFS rates. An Italian study (58) randomized patients with at least two years delay after surgery (median 25 months) to receive either two years tamoxifen or follow-up alone. At median follow-up of 89 months, five-year results reported less contralateral breast cancer (4 vs 10 cases, p=0.11), and ER+ secondary breast cancers in the tamoxifen group (1 vs 10, p=0.005) but similar overall locoregional and distant relapses or metastasis and more ER− contralateral breast cancer. Approximately one-third of the patients were ER+, one-third were ER−, and one-third had unknown ER status. No significant differences were reported between these subgroups. The small size and the variability of the data limit the usefulness of this study. Although not definitive, these studies together with MA.17 (291-299) suggest that hormonal treatment may be beneficial for some patients even after a delay of several years.

d) Tamoxifen plus Octreotide

The NCIC CTG MA.14 trial (300) and the NSABP B-29 trial (NCT00002967; see https://clinicaltrials.gov/show/NCT00002967) studied whether there was a benefit to adding octreotide (SMS 201−995 PA LAR) to tamoxifen. A full publication of NSABP B29 results was not found, although Pritchard et al (300) indicated the trial was closed in 1999 because of excess gallbladder adverse effects. MA.14 included postmenopausal patients post-surgery, and randomized to five years tamoxifen + octreotide or tamoxifen alone. Assignment was stratified by adjuvant chemotherapy, nodal status, and ER/PR status. Because of symptomatic gallbladder disease and surgery, MA.14 was amended to reduce duration of octreotide to two years. At median follow-up of 7.9 years results were reported for event-free survival (EFS; HR=0.93, p=0.62), RFS (HR=0.84, p=0.31), and OS (HR=0.97, p=0.86). Cholecystectomy was required in 23% of patients receiving octreotide vs 1.4% without (p<0.001).

NSABP B-29 included only patients with node negative/HR+ cancer, whereas in the MA.14 trial 53% of patients had node negative cancer and 91% had HR+ cancer. These two trials were similar in design and a combined analysis was presented as an abstract (301). At a median 9.8 years for MA.14 (667 patients) and 6.8 years for B-29 (893 patients) DFS rates were 76% vs 80% for MA.14 (p=0.50) and 88% (both arms) for B-29 (p=0.59). Multivariate pooled HR was 0.98 (95% CI 0.81−1.20, p=0.84). It was concluded that octreotide does not significantly improve DFS rate.

e) Tamoxifen plus Radiotherapy

The British Association of Surgical Oncology (BASO) II trial (302) compared radiation therapy (RT), tamoxifen for five years, RT+ tamoxifen, or no adjuvant treatment after surgery in female patients with N0 tumours ≤2 cm without LVI. Tamoxifen and RT both reduced local recurrence rates compared to controls without either. The ten-year local recurrence-free rates were 93% tamoxifen (HR=0.35, p<0.001) and 93% radiotherapy (HR=0.36, p=0.001) compared with 83% with neither treatment. In comparison, there was only 2% recurrence in the group receiving RT + tamoxifen, which was significantly lower compared with either RT alone p=0.01 or tamoxifen alone p=0.006.

4.3.2 Aromatase Inhibitors

a) Aromatase Inhibitors vs Tamoxifen

At the time of the EBCTCG meta-analyses on AI vs tamoxifen (67), there was insufficient follow-up to evaluate long-term effects in most of the trials. This section summarizes the EBCTCG meta-analysis, 4 recent systematic review/guidelines, and 68 publications of 23 trials from the literature search (including studies updated or published since the EBCTCG meta-analysis). Results from the EBCTCG meta-analyses are provided in Table 6 and Table 7 (67,303), and the results of the literature search are provided in Table 8 (63,64,68,268,281-283,291-299,304-352). An update of the EBCTCG meta-analysis was presented at the ASCO 2014 annual meeting (303) and included 36,889 postmenopausal patients, compared to 18,871 in the 2010 publication (67). It may include some of the more recent studies summarized in Table 8, but is still limited to postmenopausal patients and a total of five years of endocrine therapy. Only an abstract has been published. Note that most of the studies in Table 8 were included in the PEBC #1–18 and ASCO guidelines (discussed subsequently) but the studies from the literature search provide more full publications (instead of abstracts) and longer-term follow-up.

The main types of studies conducted have been:

- AI vs tamoxifen as monotherapy
- Randomization at the start to two to three years of tamoxifen followed by a planned switch to an AI for a total of five years treatment vs tamoxifen for a total of five years
- Tamoxifen first for two to three years, followed by randomization of those patients without recurrence to either AI or tamoxifen for five years total treatment
- Five years of tamoxifen followed by randomization to AI or no further treatment
- Five years of AI vs tamoxifen (2–3 years) then AI for a total of five years
- AI + ovarian suppression vs tamoxifen in premenopausal patients (see Table 8 and Subsection 4.3.3)

<u>Clinical Practice Guidelines</u>

The PEBC/CCO Evidence-Based Series #1–18 (107) on AIs in postmenopausal patients with HR+ breast cancer included a systematic review covering until 2005 and was updated up to May 2007. This review was also published in *Cancer Treatment Reviews* (102). The American Society of Clinical Oncology (ASCO) guideline on endocrine therapy in HR+ breast cancer (353) is based on the evidence in the PEBC/CCO literature review plus a search of the published literature for the period May 2007–February 2009. A revised version released in May 2014 (289) included a review of trials published 2009 to June 2013.

The PEBC guideline recommends four approaches: a) tamoxifen (20 mg daily) for five years; b) anastrozole (1 mg daily) or letrozole (2.5 mg daily) for five years; c) tamoxifen 20 mg daily for two to three years, then switching to exemestane (25 mg daily) or anastrozole (1 mg daily) for a total of five years of endocrine therapy; d) five years tamoxifen followed by five years letrozole (2.5 mg daily). There was no data available to compare the strategies. The guideline recommended female patients receiving AIs be monitored for changes in bone mineral density. Data were mixed regarding cardiac outcomes and lipid profile changes. The ASCO guideline summarized relative adverse effects in greater detail.

ASCO (353) recommends that postmenopausal patients with HR+ breast cancer consider incorporating AI therapy at some point during adjuvant therapy, either upfront or sequentially after tamoxifen. Optimal timing and duration of endocrine therapy remains unresolved, although a key change in the 2014 revision (289) is to recommend tamoxifen for up to ten years rather than five years. Tamoxifen for 0–5 years followed by AI for up to 5 years is an alternative, provided postmenopausal status is confirmed before AI use. Tamoxifen and AIs are generally well tolerated but have specific adverse effects, including effects on bone, cardiovascular, and gynecological health. The profile of effects is different because tamoxifen is a selective ER modulator with mixed pro- and anti-estrogenic activities, whereas AIs achieve near complete estrogen deprivation in postmenopausal patients. AIs are associated with greater loss of bone mineral density and fractures, which may be mitigated with use of bisphosphonate therapy. AIs can cause a musculoskeletal/arthralgia syndrome characterized by bone and joint symptoms including pain, stiffness or achiness that is symmetric and not associated with other signs of rheumatological disorders. Data suggest AIs are associated with increased cardiovascular disease, possibly including ischemic cardiac disease, although differences are small. Some studies found an effect on lipid metabolism, including increased risk of hypercholesterolemia. It has been suggested that these unfavourable changes in lipid profile may be due more to the discontinuation of tamoxifen in the switching studies rather than a significant effect of the AI alone. Risk of venous thromboembolic events is higher with tamoxifen, with 1% to 2% greater risk of deep vein thrombosis. Tamoxifen is associated with an increased risk of uterine cancer (approximately 1% of patients), benign endometrial pathology (bleeding, polyps, hyperplasia), hysterectomy, and vaginal discharge. AIs seem less frequently associated with hot flashes. Results are inconsistent for vaginal dryness and loss of libido.

The Alberta Health Services guideline on AIs for early-stage HR+ breast cancer (354) is based on a literature search until October 2009. It recommends three strategies for postmenopausal patients with HR+ breast cancer: a) AI for five years, b) AI after two to three years of tamoxifen, or c) five years of tamoxifen then five years AI. During treatment with AIs, bone changes should be monitored, calcium and vitamin D supplements are recommended, and bisphosphonates are also recommended. AI therapy is contraindicated in pre or perimenopausal patients except in clinical trials. Postmenopausal is defined, based on NCCN criteria, as any of "(a) prior bilateral oophorectomy; (b) age ≥60 years; (c) age <60 years and amenorrheic for 12 months or more in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range; or (d) if taking tamoxifen or toremifene and age <60 years, then FSH and plasma estradiol levels in the postmenopausal ranges." Menopausal status cannot be assigned to patients who are receiving a LHRH agonist or antagonist. Amenorrhea is not a reliable indicator of menopausal status in patients who are premenopausal at the beginning of adjuvant chemotherapy, because ovarian function may still be intact or resume after chemotherapy. For these patients, oophorectomy or serial measurement of FSH and/or estradiol are needed to ensure postmenopausal status.

An expert panel (355) addressed the factors that should be considered in perimenopausal patients who may become eligible for AIs. There may be a case for use of AIs in perimenopausal patients at sufficiently high risk of recurrence, either upfront or after tamoxifen; however, there must be careful consideration of age, menstrual history, and effects of tamoxifen (which may make hormonal levels unreliable in determining ovarian

function). Treatment-naïve patients should start with tamoxifen if postmenopausal status cannot be confirmed by reliable serial hormone measurements. Serial monitoring may enable AI to be started. In the case of treatment-induced amenorrhea, a decision to start AI use requires baseline hormone levels consistent with postmenopausal status, and continuation of treatment requires periodic documentation of postmenopausal hormone levels.

Early Breast Cancer Trialists' Cancer Group Meta-Analysis

The EBCTCG meta-analysis (67) included patients with ER+ cancer in RCTs of AIs vs tamoxifen as monotherapy (Cohort 1) or after two to three years tamoxifen (Cohort 2) for a total of five years therapy (i.e., randomized to continue tamoxifen or to switch to an AI for an additional two to three years). It did not include trials of AI after five years of tamoxifen. The analysis included all trials started by year 2000 and was locked September 30, 2006, before the December 2008 San Antonio Breast Cancer Symposium; therefore, it did not include results presented at this conference. Data were not available from the ABCSG 12 trial and the switching arms for BIG 1–98 (IBCSG 18–98). ABCSG 12 started in 1999 and assigned 1803 premenopausal patients taking goserelin for ovarian suppression to either three years of anastrozole or three years of tamoxifen. BIG 1–98 started in 1998 and assigned 6193 female patients to either five years of letrozole, five years of tamoxifen, two years of tamoxifen followed by three years of letrozole, or two years of letrozole followed by three years of tamoxifen.

Cohort 1 (tamoxifen vs AI as monotherapy for five years) included 9856 patients from the ATAC and BIG 1–98 trials with a mean 5.8 years follow-up since the start of treatment. Results were calculated for AI therapy vs tamoxifen and are provided in Table 6. AIs resulted in better recurrence rates than tamoxifen, but there was no significant difference for mortality rates.

Cohort 2 included 9015 patients from four trials (German ABCG/Arimidex-Nolvadex, Intergroup Exemestane/BIG 02–97, Italian Tamoxifen Anastrozole [ITA], ABCSG 8) with a mean follow-up of 3.9 years calculated from the time of treatment divergence, that were reported at three and six years (approximately five and eight years after start of hormonal treatment). There was significant benefit of AIs for both recurrence and survival rates (see Table 7).

There was no apparent heterogeneity in proportional risk reduction with respect to age, nodal status, or grade. The overall conclusion was that AIs result in lower recurrence rates than tamoxifen. More follow-up for long-term survival information is required. Cause-specific mortality rates were not reported in this analysis. AIs achieved modest absolute improvements in breast cancer end points with significant reductions in recurrence rates in both cohorts. The absolute gain was greater in patients with poorer prognosis.

Comparisons A and B in the 2014 abstract (303) appear to correspond to Cohorts 1 and 2 and results are similar to the eight-year data in Tables 6 and 7. An additional comparison ("Comparison C") was made for five years of AI vs sequential tamoxifen then AI. They found recurrence benefit for continuous AI overall (RR=0.90, 95% CI 0.81–1.00) and in years 0–1 (RR=0.75, 95% CI 0.62–0.89) but not in years 2+. Five-year recurrence rates were 9.6% vs 10.7% (p=0.042) and breast cancer deaths were 6.2% vs 6.8% (p=0.097). For all groups combined there were fewer endometrial cancers (0.2% vs 0.6%, RR=0.37, 95% CI 0.27–0.51) but more fractures (8.1% vs 5.9%, RR=1.40, 95% CI 1.27–1.53) with AI than with tamoxifen.

Individual Studies and Comparison with Earlier Reviews/Meta-analyses

Table 8 summarizes characteristics and outcomes for individual studies of AIs vs tamoxifen identified in this review. Included are updates of most of the trials used in the EBCTCG meta-analysis and other guidelines summarized.

The EBCTCG meta-analysis of AI vs Tamoxifen monotherapy (Cohort 1) was based on ATAC and BIG 1−98 studies in postmenopausal patients and found benefit for recurrence but not survival. Longer-term follow-up of these studies, as summarized in Table 8, indicates significant DFS rate and recurrence rate benefits for anastrozole compared with tamoxifen in the ATAC trial for the full patient group and a larger effect in the subset of patients with HR+ cancer (84% of total). BIG 1−98 found an improvement in both DFS and OS rates for letrozole compared with tamoxifen. ATAC found more bone fractures with anastrozole during treatment but similar rates post-treatment. Anastrozole caused less endometrial abnormalities and other adverse effects. BIG 1−98 found more bone fractures in the letrozole group, whereas the HOBOE trial found this was counteracted by zoledronic acid. These studies did not find higher rates of cardiac events with AIs. Although the PEBC and Alberta guidelines gave no recommendation between AIs and tamoxifen, results of these two trials may help in the decision process.

The ABCSG-12, SOFT, and TEXT trials (see Table 8) studied a different patient group; namely, premenopausal patients receiving an AI + OA/S (goserelin in ABCSG-12, triptorelin in TEXT, triptorelin or ovarian surgery/irradiation in SOFT). These studies are also relevant to Subsection 4.3.3 on Ovarian Suppression. In the ABCSG-12 trial patients were randomized to three years anastrozole or tamoxifen, with secondary randomization to receive zoledronic acid or not. There were less serious adverse events with anastrozole. Overall there was no difference in DFS rates between anastrozole and tamoxifen, whereas tamoxifen resulted in significantly better OS. However, it was found zoledronic acid improved OS and DFS rates in both groups, and in the subgroup aged >40 years, but not in those aged ≤40 years. Both tamoxifen and anastrozole resulted in bone loss, with a greater adverse effect with anastrozole. This was prevented by concomitant zoledronic acid administration. Combined analysis of the SOFT and TEXT trials (63,64,282) found improved DFS rate with exemestane + OA/S compared with tamoxifen + OA/S but comparison with the tamoxifen-alone arm was not reported (follow-up is still ongoing).

Cohort 2 of the EBCTCG meta-analysis compared use of AIs following two to three years of tamoxifen vs continuation of tamoxifen. It included four trials with mean follow-up of 3.9 years from treatment divergence. AIs had significant benefit on recurrence and survival rates. Table 8 summarizes additional studies and longer follow-up that confirm the benefit of switching to AIs compared to continuing on tamoxifen. Most trials studied anastrozole, although the IES study also found OS and DFS benefit for switching to exemestane.

An additional issue not addressed in the previous analyses is whether there is benefit of more than five years treatment. MA.17 is the largest study; after five years tamoxifen patients received either five years letrozole or placebo. It found improved DFS rates overall as well as in N+ and N0 subgroups, and the age <60 years and age 60−69 years subgroups. Letrozole had significant benefit in OS for N+ but no effect in patients with node-negative cancer. A meta-analysis of four studies (published as an abstract) including MA.17 found AI therapy after five years tamoxifen had a 2.9% decrease in recurrence and 0.5% decrease in breast cancer mortality rates.

The summary of evidence from the available clinical practice guidelines, meta-analyses, and individual trials of tamoxifen and AIs in the adjuvant treatment of HR+ breast cancer suggests that the AIs are associated with a modest but significant improvement in clinical outcomes. The optimal sequence and duration of AI ± tamoxifen therapy is uncertain. It is also unknown how adjuvant regimens containing AIs compare to the strategy of tamoxifen for 10 years.

b) Comparison of Aromatase Inhibitors

Studies comparing AIs are provided in Table 9 (329,356-365). The MA.27 trial (359) found no difference in survival outcomes, but some difference in adverse effect profiles. The study concluded that exemestane is comparable to anastrozole. The FACE (361), DATA (364), and SOLE trials (365) are ongoing and do not have survival rate data yet. The TEAM Japan study (329) reported tamoxifen had a favourable effect on lipid profiles and may be preferred over exemestane and anastrozole (which both had no clinically significant effect on serum lipids) for patients at high risk of cardiovascular events such as hyperlipidemia. Further comparisons to tamoxifen are provided in the previous section (see Table 8). Two additional publications [abstracts only] provide an indirect comparison of anastrozole and letrozole from the BIG 1−98 and ATAC trials and conclude that letrozole may be more effective than anastrozole to reduce early distant recurrence and mortality rates at five years. This is based on trends (not statistically significant) and needs confirmation in ongoing trials. Taken together, these trials suggest that all AIs available in Ontario are active in this setting.

c) Aromatase Inhibitors plus Chemotherapy

The New Primary Endocrine-Therapy Origination Study (NEOS, N-SAS BC06) is a two-stage study that started recruitment in 2008 (366,367). This study is ongoing and will evaluate the need for adjuvant chemotherapy in addition to endocrine therapy in patients who respond to neoadjuvant letrozole. In the first phase neoadjuvant letrozole (2.5 mg/day) was administered for 24 to 28 weeks before surgery. Patients who did not progress (i.e., complete or partial response or stable disease) were then randomized to chemotherapy + letrozole (4.5−5 years) or letrozole alone. Recruitment of 850 patients (postmenopausal, N0, ER+, HER2−, >1.0 cm and ≤5.0 cm) was expected by May 2013.

Table 6. Recurrence and survival rates for aromatase inhibitors vs tamoxifen as monotherapy for five years: EBCTCG Cohort 1 or Comparison A.

Data from EBCTCG 2010 (67) and EBCTCG 2014 (303)

Time of outcome, source of data	Recurrence rate	Breast cancer mortality rate	Death without recurrence	Any death
At 5 y (Kaplan-Meier)	9.6% vs 12.6% p<0.0001	4.8% vs 5.9% p=0.1	4.4% vs 4.2% p=0.9	8.8% vs 9.6% p=0.3
At 8 y (Kaplan-Meier)	15.3% vs 19.2% p<0.0001	10.0% vs 10.5% p=0.1	9.1% vs 8.8% p=0.9	17.8% vs 18.0% p=0.3
From forest plots, ratio of annual event rates	11.8% vs 14.7% RR=0.769 p<0.00001	6.8% vs 7.5% RR=0.89 p>0.1 (NS)	5.8% vs 5.6% RR=1.01 p>0.1 (NS)	12.5% vs 13.1% RR=0.94 p>0.1 (NS)
2014 abstract	16.6% vs 19.6%, RR=0.84, p<0.0001 • Year 0–1: RR=0.66 • Year 2–4: RR=0.75 • Year 5+ RR=0.90	10.1% vs 11.4%, RR=0.86, p<0.014		

Table 7. Recurrence and survival rates for aromatase inhibitors following two to three years tamoxifen vs five years tamoxifen: EBCTCG Cohort 2 or Comparison B

Data from EBCTCG 2010 (67) and EBCTCG 2014 (303)

Time of outcome, source of data	Recurrence rate	Breast cancer mortality rate	Death without recurrence	Any death
At 3 y (5 y since diagnosis) (Kaplan-Meier)	5.0 vs 8.1% p<0.00001	1.7% vs 2.4% p=0.02	1.7% vs 2.1% p=0.1	3.3% vs 4.4% p=0.004
At 6 y (8 y since diagnosis) (Kaplan-Meier)	12.6% vs 16.0% p<0.00001	6.3% vs 7.9% p=0.02	5.0% vs 5.8% p=0.1	10.8% vs 13.0% p=0.004
From forest plots, ratio of annual event rates	7.9% vs 10.6% RR=0.711 p<0.00001	3.5% vs 4.5% RR=0.78 p=0.02	2.8% vs 3.3% RR=0.82 p=0.10	6.3% vs 7.8% RR=0.79 p=0.004
2014 Abstract	12.7% vs 14.7%, RR=0.87, p=0.0001 • During years 2–4: RR=0.56 • During year 5+: RR=0.97	6.1% vs 7.3%, RR=0.84, p=0.015		

Table 8. Studies comparing aromatase inhibitors to tamoxifen

(Studies from the literature search, including updates of some of the trials used in the EBCTCG meta-analysis)

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
PREMENOPAUSAL				
AI vs TAM as monotherapy: Premenopausal				
MA.17 (291-299) 1998–2003	See entries at end of this table		Subgroup was premenopausal at diagnosis but postmenopausal after TAM	

ABCSG-12 (304-308)
1999–2006
	ANA (3 y)+ GOS vs
	ANA (3 y) + GOS + zoledronic acid vs
	TAM (3 y) + GOS vs
	TAM (3 y)+ GOS + zoledronic acid
	
	ANA: 1 mg/d
	TAM: 20 mg/d
	GOS: 3.6 mg q4w
	Zoledronic acid: 4 mg every 6 m
		453
		450
		450
		450
			Premenopausal, ER+ and/or PR+, early-stage (Stage I-II)	**Effect of ANA vs TAM, 62 mo follow-up** (304,305):
				• ANA vs TAM
				  • DFS: HR=1.08 (95% CI 0.81–1.44, p=0.59)
				  • OS: HR=1.75 (1.08–2.83, p=0.02)
				• ANA ± zoledronic acid vs TAM ± zoledronic acid
				  • Subset with disease recurrence (N=185): relative risk of death HR=2.00 (1.23–3.24), p=0.005
				  • Subset with distant recurrence (N=100): relative risk of death HR=2.18 (1.23–3.86), p=0.009
				• No difference ANA vs TAM on DFS, worse OS with ANA (but not if zoledronic acid administered)).
				• ANA ± zoledronic acid had lower incidence of serious adverse events than TAM ± zoledronic acid (1% vs 7% endometrial hyperplasia, 1% vs 8% uterine polyp, 2% vs 4% uterine D&C, <1% vs 2% endometrial disorder)
				• ANA vs TAM had higher rate of non-serious adverse effects (33% vs 23% bone pain, 19% vs 8% arthralgia, 8% vs 2% muscle rigidity, 7% vs 3% arthropathy, 2% vs <1% joint stiffness)
				
				Effect of zoledronic acid, 62 mo follow-up (304,305):
				• ANA + zoledronic acid vs ANA
				  • DFS HR=0.68 (95% CI 0.45–1.02), p=0.061
				• TAM + zoledronic acid vs TAM
				  • DFS HR=0.67 (95% CI 0.44–1.03), p=0.067
				• ANA/TAM + zoledronic acid vs ANA/TAM
				  • DFS 92% vs 88%, HR=0.68, 95% CI 0.51–0.91,p=0.009
				  • DFS, age ≤40 y: HR=0.94 (95% CI 0.57–1.56), p=0.82
				  • DFS, age >40 y: HR=0.58 (95% CI 0.40–0.83), p=0.003
				  • OS HR=0.67 (95% CI 0.41–1.07, p=0.09)
				  • OS, age >40 y: HR=0.57, p=0.057
				• Addition of zoledronic acid to endocrine therapy improved DFS overall and for age >40 y but not <40 y
				• Zoledronic acid increased frequency of non-serious adverse effects (bone

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome

				pain, pyrexia, joint stiffness)
				
				Effect of zoledronic acid 76 mo follow-up (308):
				ANA/TAM + zoledronic acid vs ANA/TAM
				• DFS HR=0.73, p=0.021
				  • DFS, age ≤40 y: HR=0.91, p=0.707
				  • DFS, age >40 y: HR=0.66, p=0.013
				• OS: HR=0.59, p=0.042
				  • OS, age ≤40 y: HR=1.01, p=0.982
				  • OS, age >40 y: HR=0.51, p=0.018
				
				Effect of zoledronic acid 84 mo follow-up (306,307):
				ANA/TAM + zoledronic acid vs ANA/TAM
				• DFS: HR=0.72, p=0.014
				  • DFS, age ≤40 y: HR=0.87, p=0.527
				  • DFS, age >40 y: HR=0.66, p=0.013
				• OS: HR=0.63, p=0.049

ABCSG-12 bone mineral substudy (309)	(ANA or TAM) + GOS (3 y)+ vs (ANA or TAM) + GOS + zoledronic acid (3 y)	199 205		• Endocrine therapy alone (no zoledronic acid) caused significant loss of bone mineral density (BMD) at lumbar spine and trochanter (p<0.0001) at 36 mo • Without zoledronic acid, ANA caused greater BMD loss than TAM at 36 mo at lumbar spine (-13.6% vs -9.0%, p<0.0001) • 2 y after completion of treatment, pts without zoledronic acid still had decreased BMD compared with baseline, whereas pts with zoledronic acid had stable BMD at 36 mo and increased BMD at 60 mo compared with baseline • Conclude GOS + TAM/ANA causes significant bone loss, was prevented by concomitant zoledronic acid
SOFT IBCSG-24-02, NCT00066690 (63,64,281,282) 2003–2010 [See also (59,62) published after guideline completion, data not extracted]	TAM daily vs TAM + ovarian suppression* vs EXE + ovarian suppression Treatment continues 5 y *Ovarian suppression by one of triptorelin, surgical oophorectomy, or ovarian irradiation Pts stratified: prior adjuvant/neoadjuvant chemotherapy (yes vs no), number of positive axillary and/or internal mammary lymph nodes (0 vs 1 or more) and intended initial method of ovarian-function suppression (triptorelin vs	1021 1024 1021 Total: 3066	Premenopausal, ER+ and/or PR+, no inoperable LABC, prior or concurrent adjuvant trastuzumab allowed, neoadjuvant chemotherapy allowed if operable before neoadjuvant chemotherapy	TAM alone group data not expected until end of 2014 EXE + ovarian suppression vs TAM + ovarian suppression is presented as combined analysis of SOFT and TEXT (later in this table) per protocol amendment in 2011 to allow higher number of DFS events in a shorter time; otherwise estimated 13 additional years follow-up would be required

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
	oophorectomy vs ovarian irradiation)			
TEXT, NCT00066703 (63,64,282,283) 2003–2011	TAM + triptorelin vs EXE + triptorelin Treatment for 5 y Pts stratified by concurrent adjuvant chemotherapy, number of positive lymph nodes	2672	Inclusion criteria: ER+ and/or PR+ (at least 10% of tumour cells positive by IHC), premenopausal, no inoperable LABC or metastasis	EXE + ovarian suppression vs TAM + ovarian suppression is presented as combined analysis of SOFT and TEXT (see later in this table) per protocol amendment in 2011 to allow higher number of DFS events in a shorter time otherwise estimated 7 additional years follow-up would be required
Joint analysis of SOFT and TEXT trials (63,64,282)	See previous entry in table EXE + ovarian suppression vs TAM + ovarian suppression TAM alone group not reported	 2359 EXE 2358 TAM	Pts who received chemotherapy were more likely to be N+, T2+, HER2+, <age 39 y 42.5% no chemo 57.4% chemo 42.2% N+ 13% <1 cm 49% 1–2 cm 32% >2–5 cm 4% >5 cm 88% HER2–	Median follow-up 68 mo, 5–y survival rates, EXE vs TAM DFS: • Overall: 91.1% vs 87.3%, HR=0.72 (95% CI 0.60–0.85), p<0.001 • TEXT, no chemo:96.1% vs 93.0%, HR=0.54 (95% CI 0.32–0.92) • SOFT, no chemo: 95.8% vs 93.1%, HR=0.68 (95% CI 0.38–1–19) • TEXT, with chemo: 89.8% vs 84.6%, HR=0.69 (95% CI 0.53–0.90) • SOFT, with chemo: 84.3% vs 80.6%, HR=0.84 (95% CI 0.62–1.13) • N0: 95.1% vs 91.6%, HR=0.60 (95% CI 0.45–0.81) • N+: 85.6% vs 81.4%, HR=0.79 (95% CI 0.64–0.98) Breast cancer free: 92.8% vs 88.8%, HR=0.66 (95% CI 0.55–0.80), p<0.001 Distant recurrence free: 93.8% vs 92.0%, HR=0.78 (95% CI 0.62–0.97), p=0.02 OS: 95.9% vs 96.9%, HR=1.14 (95% CI 0.86–1.51), p=0.37 Targeted adverse effects, any grade (EXE vs TAM) • 98.3% of pts in both groups • Most common were hot flushes (91.7% vs 93.3%), depression (50.3% vs 50.1%), sweating (54.5% vs 59.0%), insomnia 58.2% vs 58.5%), and fatigue (61.3% vs 62.9%) • EXE group had more musculoskeletal symptoms (88.7% vs 76.0%), osteoporosis (38.6% vs 25.2%), vaginal dryness 52.4% vs 47.4%), decreased libido (45.0% vs 40.9%), and dyspareunia (30.5% vs 25.8%) • EXE group had less thrombosis/embolism (1.0% vs 2.2%), urinary incontinence (13.1% vs 17.8%), and sweating (54.5% vs 59.0%) Grade 3–4 adverse events • 30.6% EXE vs 29.4% suppression • EXE group had less thrombosis/embolism (0.8% vs 1.9%) but more musculoskeletal symptoms (11.0% vs 5.2%) Adverse effects (64): • Similar changes in global QoL indicators in both groups but different endocrine symptoms profile • TAM: more vaginal discharge (P<0.0001), more hot flushes with treatment difference persisting over time (each p<0.05; change from baseline improved

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
				over time for both groups) • EXE: more vaginal dryness and greater loss of sexual interest (p<0.0001), more bone/joint pain (p<0.0001)
HOBOE, NCT00412022 (268,310-312) 2004–2009	• TAM (20 mg daily for 5 y; switch for postmenopausal pts to LET allowed after 2 y) • LET (2.5 mg daily for 5 y) • LET + zoledronic acid (4 mg every 6 mo for 5 y) Triptorelin 3.75 mg IM q4w if premenopausal	≈500	Pre and post-menopausal, HR+, early breast cancer, chemotherapy allowed	Significantly distinct endocrine effects; positive effect of zoledronic acid on BMD largely counteracts damage produced by letrozole as compared with TAM; survival rate data not available yet
POSTMENOPAUSAL				
AI vs TAM as monotherapy: Postmenopausal				

ATAC (313,314)	ANA (1 mg/d for 5 y)
	TAM (20 mg/d for 5 y)
	ANA + TAM (5 y)
	
	The combination arm was discontinued after initial analysis because there was no benefit compared with TAM arm
		3125
		3116
		3125
			Postmenopausal, early-stage,
			84% HR+
				Median follow-up 120 mo
				• ANA vs TAM:
				  • DFS HR=0.91 (95% CI 0.83–0.99, p=0.04)
				  • Time to recurrence HR=0.84 (95% CI 0.75–0.93, p=0.001)
				  • Time to distant recurrence: HR=0.87 (95% CI 0.77–0.99, p=0.03)
				• ANA vs TAM, HR+ only:
				  • DFS HR=0.86 (95% CI 0.78–0.95, p=0.003)
				  • Recurrence: HR=0.79 (95% CI 0.70–0.89, p=0.0002)
				  • Distant recurrence HR=0.85 (95% CI 0.73–0.98, p=0.02)
				  • Mortality: HR=0.95 (95% CI 0.84–1.06, p=0.4)
				Fractures more frequent with ANA (451 vs 351, OR=1.33, p<0.0001)during treatment but similar post-treatment (110 vs 112); other adverse effects less with ANA; more lung and colorectal cancer (51 vs 34 and 66 vs 44) but less endometrial, melanoma and ovarian cancers (6 vs 24, 8 vs 19, and 17 vs 28)

ATAC endometrial subprotocol (315)	ANA (1 mg/d for 5 y) TAM (20 mg/d for 5 y)	44 41	Postmenopausal, early-stage	After 6-y follow-up, ANA vs TAM: • Endometrial abnormalities 12.4% vs 20.2%, OR=0.52 (95% CI 0.20–1.32, p=0.17, NS) • Time to first endometrial abnormality: HR=0.57 (95% CI 0.26–1.22, p=0.15, NS) • Fewer pts with ANA required medical intervention for endometrial abnormalities
BIG 1–98 (316-318) 1998–2003	LET (25 mg/d for 5 y) TAM (20 mg/d for 5 y) 619/2459 or 25.2% crossed over to LET after initial results presented in Jan 2005 Additional 2 arms reported (see later in this table: "Randomized at start,	2463 2459	Postmenopausal, early-stage, HR+ (ER+ and/or PR+), chemotherapy allowed	Median follow-up 8.7 y, LET vs TAM Intention to treat: • DFS: HR=0.86 (95% CI 0.78–0.96) • OS: HR=0.87 (95% CI 0.77–0.999) • DRFI: HR=0.86 (95% CI 0.74–0.998) • BCFI: 0.86 (95% CI 0.76–0.98) Using inverse probability of censoring weighted (IPCW) modelling (LET vs TAM): • DFS: HR=0.82 (95% CI 0.74–0.92) • OS: HR=0.79 (95% CI 0.69–0.90)

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
	at least one sequential arm with TAM and AI")			• DRFI: HR=0.79 (95% CI 0.68–0.92) • BCFI: HR=0.80 (95% CI 0.70–0.92) More bone fractures in LET group; grade 3–5 non-fracture adverse events (but not thromboembolic or cardiac) were higher in elderly pts in LET group Conclude LET compared with TAM significantly reduces death and recurrence rates in postmenopausal pts with HR+ breast cancer
BIG 1–98 (319)	See previous entry in table. Study of composite measure of prognostic risk using ER, PR, EGFR2 (HER2), Ki-67			5–y DFS, LET vs TAM using composite measure • Low risk group: 96% vs 94% • Medium risk: 90% vs 86% • High risk: 80% vs 69% Results for 2–3 y LET/TAM then switching were intermediate between these results
BIG 1–98 (320)	See previous entry in table. LET vs TAM Subgroups by cancer type: Invasive ductal (IDC) or lobular (ILC); Luminal A or B	2599 IDC; 324 ILC	IDC: 44% Luminal A, 36% Luminal B ILC: 59% luminal A, 22% luminal B	5–y survival rates, LET vs TAM: • DFS: IDC 88% vs 84%; ILC 89% vs 76% • DFS Luminal A: IDC 91% vs 89%; ILC 89% vs 78% • DFS Luminal B: IDC 85% vs 77%; ILC 89% vs 71% • OS: IDC 94% vs 92%; ILC 96% vs 86% • OS Luminal A: IDC 95% vs 95%; ILC 96% vs 90% • OS Luminal B: IDC 92% vs 89%, ILC 95% vs 76% TAM less effective in luminal B subtype of ILC
Randomized at start, at least one sequential arm with TAM and AI				
BIG 1–98, 1999–2003 (316)	LET (2 y)→ TAM (3 y) vs TAM (2 y)→ LET (3 y) (see previous entry in table for LET or TAM monotherapy) LET 25 mg/d TAM 20 mg/d	1540 1548	Postmenopausal, early, HR+	Median follow-up 8.0 y, LET, LET→ TAM, TAM→ LET, intention to treat, no significant differences • DFS: 78.6%, 77.8%, 77.3% • OS: 87.5%, 87.7%, 85.9% • DRFI: 89.9%, 88.7%, 88.1% • BCFI: 86.1%, 85.3%, 84.3% Sequential treatment does not improve outcome compared with LET alone, but may be useful strategies when considering individual patient's risk of recurrence and tolerability
BIG 1–98 (321)	See previous entry in table LET→ TAM vs TAM→ LET Subgroups by cancer type	2849 IDC; 363 ILC		8–y survival rate results, LET vs TAM-LET vs LET-TAM DFS: IDC 79% vs 79% vs 79%; ILC 85% vs 76% vs 75% OS: IDC 88% vs 86% vs 88%; ILC 90% vs 85% vs 89% All comparisons nonsignificant, but is a trend toward more benefit of LET in ILC
ABCSG-6 (322,323) 1990–1995	TAM (2 y) + aminoglutethimide → TAM (3 y) vs TAM (5 y) TAM 40 mg/d first 2 y, then 20 mg/d;	2021	Postmenopausal, ER+ and/or PR+, Stage I-II, pT1–2, 62% N0	Median follow-up 5.3 y DFS 83.6% vs 83.7%, p=0.89 OS 91.4% vs 91.2%, p=0.74 13.7% vs 5.2% (p=0.0001) failed to complete treatment because of adverse effects No difference in DFS or OS rates for subgroups of normal weight (p=0.70 for DFS, p=0.38 for OS) or for overweight + obese pts (p=0.79 for DFS, p=0.42 for OS)
ABCSG-8 (324,325)	TAM (2 y)→ ANA (3 y) vs	1865	Postmenopausal, ER+	Median follow-up 60 mo, TAM→ ANA vs TAM:

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
1996–2004	TAM (5 y)	1849	and/or PR+, no chemotherapy, operable G1 or G2 tumours, 75% N0, 75% T1	• RFS HR=0.80 (95% CI 0.63–1.01), p=0.064 • Distant RFS: HR=0.78 (95% CI 0.60–0.996), p=0.046 • DFS: HR=0.91 (95% CI 0.748–1.103), p=0.33 • DFS (censored for crossover): HR=0.87 (95% CI 0.717–1.064) • OS: HR=0.87 (95% CI 0.645–1.163), p=0.33 • OS (censored for crossover): HR=0.81 (95% CI 0.602–1.094) • More bone pain in TAM→ ANA arm (32.9% vs 29.3%), more uterine disorders in TAM arm (20.2% TAM vs 14.1% TAM→ ANA) Median follow-up 76.7 mo • DFS: HR=0.89 (95% CI 0.77–1.05), p=0.17 • OS: HR=0.82 (95% CI 0.66–1.01), p=0.06 • OS (censored for crossover); HR=0.79 (95% CI 0.64–0.98)
ABCSG-8, Ki-67 expression substudy (326)	See previous entry in table		Determined expression of Ki-67 by IHC	• Pts with high Ki-67 expression had shorter RFS and OS (HR=1.90 and HR=1.78 respectively). • Pts with medium or high ER levels had significant interaction between Ki-67 and endocrine treatment. • TAM→ ANA was superior to TAM in pts with low Ki-67 (DFS: adjusted HR=0.53, 95% CI 0.34–0.83, p=0.005) but not high Ki-67 (HR=1.18, 95% CI 0.66–1.89, p=0.68)

TEAM (68)
 	
2001–2006
	EXE (5 y) vs
	TAM (2.5–3 y) → EXE (2–2.5y); 5 y total
	
	EXE 25 mg/d
	TAM 20 mg/d
	
	Originally randomized to either EXE or TAM for 5 y, but modified trial after results of IES study
		4898
		4868
			Postmenopausal, ER+ and/or PR+, completed local treatment with curative intent, 95% N0–1, 94% T1–2; 36% chemotherapy	• TAM→ EXE vs EXE alone, 5–y results
				  • DFS: HR=0.97 (95% CI 0.88–1.08), p=0.60
				  • DFS (per protocol treatment): HR=0.93, p=0.22
				  • OS: HR=1.00 (95% CI 0.89–1.14), p>0.99
				• Sequential treatment associated with higher level of gynecological symptoms (20% vs 11%), venous thrombosis (2% vs 1%), endometrial abnormalities (4% vs<1%).
				• EXE alone caused higher adverse effects for musculoskeletal (50% vs 44%), hypertension (6% vs 5%), and hyperlipidemia (5% vs 3%)
				• Concluded no difference in DFS and OS but differences in adverse effect profile may play a role in treatment decisions

TEAM, PR expression substudy (327)	See previous entry in table	4598	Analysis according to PR poor and PR rich	No treatment by marker effect for PR was observed for EXE vs TAM, [PR rich HR=0.83 (95% CI 0.65–1.05), PR poor HR=0.85 (95% CI 0.61–1.19), p=0.88 for interaction]
TEAM, ER expression, Dutch & Belgium pts (328)	EXE (5 y) vs TAM (2.5–3 y) → EXE (2.5–2 y)	2603	82% IDC, 18% ILC; 235 ER poor (<Allred 7), 1789 ER-rich (≥7)	RFS rates, EXE vs TAM→ EXE • IDC: HR=0.83 (95% CI 0.67–1.03) • ILC: HR=0.69 (95% CI 0.45–1.06) • ER-rich: HR=0.71 (95% CI 0.56–0.89) • ER-poor: HR=2.33 (95% CI 1.32–4.11)

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
TEAM Japan: N SAS BC04 lipid substudy (329)	EXE (5 y) vs TAM (2.5–3 y) → EXE (2–2.5 y); 5 y total vs ANA (5 y) (1 mg/d)	52 52 50		Changes in lipid profiles with TAM were relatively favourable, whereas EXE and anastrozole had no clinically significant effect on serum lipids; TAM may be a treatment choice for pts at high risk of cardiovascular events such as hyperlipidemia
TEAM quality of life study, Dutch pts (330)	EXE (5 y) vs TAM (2.5–3 y) → EXE (2.5–2 y)	742		QoL questionnaires at 1 and 2 y after start of endocrine treatment. Less sexual enjoyment and more sexual function problems with EXE. More fatigue, dyspnea, insomnia, and arm symptoms with EXE. Most scales improved over time. Only clinically relevant and statistically significant difference was more insomnia in EXE pts
TEAM Japan: N SAS BC04 quality of life study (331)	EXE (5 y) vs TAM (2.5–3 y) → EXE (2–2.5 y); 5 y total vs ANA (5 y)	55 56 55		FACT-B scores increased and remained higher after TAM during the first year (p=0.045); FACT-B similar in EXE and ANA groups Endocrine subscale (ES) and CES-D (depression scales) similar in all groups; arthralgia and fatigue less frequent but vaginal discharge more frequent in TAM group; health-related QoL better with TAM
TEAM Japan: N SAS BC04 Bone substudy (332)	TAM vs EXE vs ANA	20 24 24		BMD higher at 2 y with TAM than EXE and ANA but insignificant intergroup difference (p=0.25 and p=0.075) Serum bone-specific alkaline phosphatase and urinary type I collagen cross-linked N-telopeptide were significantly lower in TAM pts (p<0.05) Conclude TAM may provide better bone protection
TEAM (333) meta-analysis of the US, German, Netherlands, and Belgium substudies	EXE (5 y) vs TAM (2.5–3 y) → EXE (2–2.5 y); 5 y total	200 212		• TAM: mean increase from baseline in lumbar spine BMD of 1.2% at 12 mo and 0.2% at 24 mo. • EXE: mean decrease from baseline of 2.6% after 12 mo and 3.5% after 24 mo (p=0.0001 at both time points). • Changes in BMD from baseline at the total hip were also significantly different between EXE and TAM (p<0.05 at both time points). Bone turnover markers decreased from baseline with TAM and increased with EXE.
TEAM gynecological ultrasound substudy (334)		143	Transvaginal ultrasound to assess endometrial thickness	EXE associated with significantly less endometrial thickening than TAM: no cases >10 mm with EXE vs 11 with TAM, p<0.00003 Time to endometrial thickness >5 mm or >10 mm was in favour of EXE (p<0.0001)
DBCG 89C (335)	TAM (6 mo)→ megestrol acetate (MA) (6 mo) vs TAM (1 y) vs TAM (2 y) TAM 30 mg/d, MA 160 mg/d	428 519 505	Postmenopausal, HR+ or unknown, high risk (N+ or T3)	Median follow-up >10 y, no difference in DFS or OS among the 3 arms
TAM; then randomized to AI or TAM (sequential)				
ITA (336,337) 1998–2002	TAM (2–3 y)→ ANA TAM (2–3 y)→ TAM 5 y total in both groups TAM 20 mg/d, ANA 1 mg/d	223 225	Postmenopausal, ER+, N+, no evidence of recurrent or metastatic disease; 47% T1, 50% T2+, 64% N1, 36% N2+	Median follow-up 64 mo, TAM→ ANA vs TAM • Event-free survival rate: HR=0.57 (95% CI 0.38–0.85), p=0.005 • RFS: HR=0.56 (95% CI 0.35–0.89), p=0.01 • OS: HR=0.56 (95% CI 0.28–1.15), p=0.1 • Adverse events ANA (94%) vs TAM (67%), p<0.001 • Serious adverse effects were similar (37 vs 40, p=0.7) except for gynecological

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
				changes (1.3% vs 8.4%) which were higher in the TAM group. • ANA greater rate of non-serious events: GI complaints (p=0.07), fatigue (p=0.045), lipid metabolism disorders (p=0.01), hyperglycemia (p=0.045), musculoskeletal disorders/bone fractures (p=0.2) • ANA lower rate of venous disorders (p=0.2)
ITA (338)	See previous entry in table	448		Median follow-up 128 mo, TAM→ ANA vs TAM EFS: HR=0.71 (95% CI 0.52–0.97), p=0.03 RFS: HR=0.64 (95% CI 0.44–0.94), p=0.023 OS: HR=0.79 (95% CI 0.52–1.21), p=0.3, study not powered enough for this endpoint Serious adverse effects: bone fracture same in both arms, gynecological problems less in TAM→ ANA arm (21 pts including 8 endometrial cancers vs 3 pts including 1 endometrial cancer, p<0.001),
ARNO 95 (339) 1996–2002	TAM (2 y)→ ANA (3 y) vs TAM (2 y)→ TAM (3 y)	489 490	Postmenopausal, ER+, early-stage; grade 1–3, pT1–3, pN0–2, no disease recurrence	Median follow-up 30.1 mo, calculated 3–y survival rates, TAM→ ANA vs TAM DFS: HR=0.66 (95% CI 0.44–1.00), p=0.049 OS: HR=0.53 (95% CI 0.28–0.99), p=0.045 Fewer serious adverse events with ANA (22.7% vs 30.8%), primarily due to more endometrial events on TAM; more musculoskeletal events with ANA (11.7% vs 4.9% arthralgia/bone pain and 2.9% vs 0.9% osteoporosis)

IES (340-342)
 	
1998–2003
	TAM (2–3 y) → EXE vs
	TAM (2–3 y) → TAM
	
	5 y total in both groups
		2352
		2372
			Postmenopausal, 85.8% ER+ (86%) or ER unknown (12%)
			disease free after 2–3 y of TAM
				TAM→ EXE vs TAM, outcomes at 8 y
				• OS: HR=0.86 (95% CI 0.74–0.99), p=0.04
				• DFS: HR=0.81 (95% CI 0.72–0.91), p<0.001
				• BCFS: HR=0.81 (95% CI 0.71–0.92), p=0.001
				  • On-treatment years 0–2.5: HR=0.60
				  • Post-treatment years 2.5–9: HR=0.94
				Fewer deaths reported for both breast cancer and intercurrent deaths following switch to EXE.
				Non-breast cancers higher in TAM group.
				
				• At median follow-up of 55.7 mo there was greater incidence of musculoskeletal adverse events in EXE group and higher incidence of serious gynecological adverse events (vaginal bleeding, endometrial hyperplasia, uterine polyps) on TAM.
				• At 91 mo, carpel tunnel syndrome in 2.8% EXE vs 0.6% TAM group (OR=5.23, p<0.0001) with most events during treatment phase; 46.7% vs 38.5% had musculoskeletal symptoms (OR=1.48, p<0.0001).
				• 8–y follow-up found smaller differences in rates of adverse events than in previous report

IES bone substudy (343)	Effect of endocrine treatment withdrawal on BMD, bone turnover markers and fracture rates	206		More fractures occurred during EXE treatment, similar rates after treatment withdrawal. Following treatment withdrawal, differences in BMD between the two groups partially reversed and the change from baseline was were similar in both groups by 2 y

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
IES endometrial substudy (344)	Sonographic uterine effects of EXE, primarily endometrial thickness >5 mm	183		2 y after randomization, proportion of pts with abnormal endometrial thickness significantly lower in EXE compared with TAM arm (36% vs 62%, p=0.004). Difference apparent within 6 mo of switching treatment and disappeared within 12 mo of treatment completion (30.8% vs 34.7%, p=0.67)
IES QoL substudy (345)	On-treatment and post-treatment QoL up to 60 mo assessed by questionnaire (FACT-B and endocrine symptom subscale)	582		Previously reported that the switch in treatment neither increased nor decreased endocrine symptoms from TAM and did not initiate significant reports of new ones. Vasomotor complaints high on treatment in both groups (>19%), vaginal discharge more frequent with TAM, libido did not recover to baseline post-treatment in either group. Both groups had gradual improvement in QoL and lessening of total endocrine symptoms post treatment compared with baseline.
NSAS BC-03 (346,347) (Japan) 2002–2005	TAM (1–4 y)→ ANA vs TAM (1–4 y)→ TAM 5 y total in both groups	347 349	Postmenopausal, ER+ and/or PR+; 79% <3 cm; 79% I-IIA, 14 IIB, 7% IIIA-B	Closed early after entry of ≈ 28% of planned pts Median follow-up 42 mo, ANA vs TAM DFS: HR=0.69 (95% CI 0.42–1.14), p=0.14 RFS: HR=0.54 (95% CI 0.29–1.02), p=0.06 QoL (FACTG-B, FACT-ES, FACT-G) were better on TAM than ANA (p=0.042, p=0.038, p=0.005), but no difference on CES-D (depression) scale
NSAS BC03 (348)	See previous entry in table. Follow-up of adverse effects from randomization to 36 m	696		Changes in hot flushes (p=0.001) and vaginal discharge (p<0.001) in favour of ANA; more arthralgia in ANA (p=0.00002) for first 12 mo then difference gradually decreased
TAM (approximately 5 y or more) then randomized to AI or placebo				
ATENA (349,350) 2001–2005	TAM (5–7 y)→ EXE (5 y) vs TAM (5–7 y)→ observation	211 200	Postmenopausal, operable breast cancer, 75% ER+ and/or PR+, 25% ER/PR unknown, Stage I-IIIA, absence of local or distant metastatic disease before randomization	Overall study closed early due to MA.17 trial, no survival rate results published Lipid Substudy, assessed at baseline, 6 or 12 mo and at 24 mo Total cholesterol and low-density lipoprotein increased over time in both arms, total cholesterol more pronounced for observation arm, high-density lipoprotein decreased significantly over time for EXE but not for observation arm, triglycerides decreased over time on both arms EXE lacks beneficial effect of TAM on lipids EXE does not alter lipid profile significantly compared with observational arm
ABCSG-6a (351) 1996 to ≈ 2001	TAM (5 y)→ ANA (3 y) TAM (5 y)→ none (3 y) Continuation of ABCSG-6 which randomized to TAM alone or TAM + aminoglutethimide for the first 2 y; both groups combined at 5 y, excluded those with recurrence or metastasis and then re-randomized to ANA or control TAM 40 mg/d first 2 y, then 20 mg/d; ANA 1 mg/d	386 466	Postmenopausal, ER+ and/or PR+, Stage I-II, 98% pT1–2, no recurrence or metastasis during TAM	Median follow-up 62.3 mo, ANA vs control • No statistically significant difference in OS rates between study arms (55 deaths [11.7%] for the no further treatment arm vs 40 deaths [10.3%] for the anastrozole arm; death from any cause HR=0.89 (95% CI 0.59 to 1.34), p=0.57 • Recurrence, HR=0.62 (95% CI 0.40–0.96), p=0.031 • Distant metastasis HR=0.53 (95% CI 0.29–0.96), p=0.034, advantage for ANA starting by 20 mo • Incidence of recurrence lower in pts initially receiving TAM + aminoglutethimide (HR=0.64, 95% CI 0.41–0.98, p=0.042); authors caution no conclusion should be made due to small number of pts in subgroups. • There was no significant difference in 5–y DFS for TAM ± aminoglutethimide • Serious adverse effects similar (7 events ANA vs 6 control) • Other adverse effects (grade 1) were more frequent in ANA group (hot flushes, asthenia, somnolence, allergy, cutaneous adverse effects, skin rash, hair loss, nausea, p<0.001), and it was concluded ANA was well tolerated

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
NSABP B-33 (292,352) 2001–2003	TAM (≈5 y) → EXE (5 y) TAM (≈5 y) → placebo (5 y) TAM 57–67 mo EXE 25 mg/d	783 779	Postmenopausal, ER+ and/or PR+, early-stage, T1–3N1M0 (61% T1, 52% N0), disease-free after 5 y TAM	Due to MA.17 results, unblinded in Oct 2003 and offered EXE to pts in placebo group Median follow-up 30 mo, EXE vs placebo at 4 y after randomization • DFS: 91% vs 89%, RR=0.68, p=0.07 • RFS: 96% vs 94%, RR=0.44, p=0.004 • OS: 98.0% vs 98.3%, RR=1.2 p=0.72 • In subset analysis, N+ pts did better on EXE (HR=0.50, p=0.01), but there was no effect (HR=1.13, p=0.74) for N0 pts • No difference in grade 4 adverse effects (1% each) • EXE group had more grade 3 adverse effects (9% vs 6%, p=0.03) • More fractures in EXE group (28 pts vs 20, p=0.33) QoL substudy: EXE had higher symptom severity on all 4 scales but no significant treatment effects in vasomotor (p=0.87), psychosocial (p=0.27), physical (p=0.13) or sexual (p=0.23) scales

NCIC CTG MA.17 (291,292)
 	
1998–2003
	TAM (≈5 y) → LET (5 y)
	TAM (≈5 y) → placebo (5 y)
	
	(TAM 4.5–6 y)
	
	5 y TAM then randomized to placebo or LET; after unblinding in 2003 (median 2.8 y), 66% of placebo group switched to LET (offered for 5 y) according to patient choice
		2583
		2587
		
		1579 placebo -LET
		
		804 placebo
			Postmenopausal at randomization (after TAM), ER+ and/or PR+ (97% positive, 2% unknown) 50% N0, 46% N+	Median follow-up 2.4 y, data received until August 2003. At first interim analysis the data safety monitoring committee recommended termination/unblinding due to a highly statistically significant effect of LET on DFS and a trend toward survival rate advantage in pts who received LET compared with placebo (291)
				• 75 vs 132 recurrences, HR=0.57 (95% CI 0.43–0.75), p=0.00008
				• 4–y DFS 93% vs 87%, p≤0.001
				• OS: 31 vs 42 deaths, HR=0.76 (95% CI 0.48–0.76), p=0.25
				• Effect of LET similar in N0 and N+ female pts
				• Low-grade hot flashes, arthritis, arthralgia, myalgia more frequent in LET; vaginal bleeding less frequent
				• 5.8% osteoporosis vs 4.5%, p=0.07
				
				Median follow-up 30 mo: Final analysis up to date of unblinding (Oct 9, 2003), (292)
				• DFS (4 y):94.4% vs 89.8%, HR=0.58 (95% CI 0.45–0.76), p<0.001
				  • DFS N+ subgroup: HR=0.61 (95% CI 0.45–0.84)
				  • DFS N0– subgroup: HR=0.45 (95% CI 0.27–0.73)
				• OS (4 y): 95.4% vs 95%, HR=0.82 (95% CI 0.57–1.19), p=0.3
				  • OS N+ subgroup: HR=0.61 (95% CI 0.38–0.98), p=0.04
				  • OS N0 subgroup: HR=1.52 (95% CI 0.76–3.06)

NCIC CTG MA.17 Intention- to-treat analysis (293)				Median follow-up 64 mo (database locked July 28, 2006): analysis based on original randomization, although 66% of placebo switched to LET
				• 4 y DFS 94.3% vs 91.4%, HR=0.68 (95% CI 0.55–0.83), p=0.0001
				  • DFS N+ subgroup: HR=0.74 (95% CI 0.58–0.94), p=0.01
				  • DFS N0 subgroup: HR=0.51 (95% CI 0.35–0.75), p=0.0005
				• 4 y OS 95.1% both groups: HR=0.98 (95% CI 0.78–1.22), p=0.853
				  • OS N+ subgroup: HR=0.84 (95% CI 0.63–1.12)
				  • OS N0 subgroup: HR=1.24 (95% CI 0.84–1.82)

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome

NCIC CTG MA.17
Analysis adjusted for crossover (294)
	Two approaches used to account for >60% of female pts on placebo crossing over to LET after the study was unblinded			Median follow-up 64 mo, LET vs placebo
				• Inverse probability of censoring weighted (IPCW) Cox model
				  • DFS: HR=0.52 (95% CI 0.45–0.61), p<0.001
				  • DDFS: HR=0.51 (95% CI 0.42–0.61), p<0.001
				  • OS: HR=0.61 (95% CI 0.52–0.71), p<0.001
				• Cox model with time-dependent covariates
				  • DFS: HR=0.58 (95% CI 0.47–0.71), p<0.001
				  • DDFS: HR=0.68 (95% CI 0.52–0.88), p=0.004
				  • OS: HR=0.76 (95% CI 0.60–0.96), p=0.02

NCIC CTG MA.17 according to ER/PR status (295)	• ER+PR+ • ER+PR− • ER−PR+ • ER−PR−	3809 636 200 8		LET vs placebo • DFS ER+PR+: HR=0.49 (95% CI 0.36–0.67) • DFS ER+PR−: HR=1.21 (95% CI 0.63–2.34) • DFS ER−PR+: HR=0.56 (95% CI 0.15–2.12) • OS ER+PR+: HR=0.58 (95% CI 0.37–0.90) • OS ER+PR−: HR=1.52 (95% CI 0.54–4.30) • OS ER−PR+: HR=2.16 (95% CI 0.22–20.77) Results suggest greater benefit for LET in ER+PR+ tumours. Because this is a subset analysis not measured centrally, the authors caution against using results for clinical decision making; this result contradicts other trials (IES, BIG 1–98, ATAC, ABCSG-8)

NCIC CTG MA.17
Subset by menopausal status at diagnosis (296)
	See previous entry in table
	
	Subdivided by menopausal status at diagnosis of breast cancer, whereas trial inclusion was based on being postmenopausal at time of randomization (after 5 y TAM)
		877
		premen
		opausal
			Postmenopausal after TAM	Extended LET vs placebo, 4–y outcomes
				• Premenopausal
				  • DFS 96.5% vs 86.8%, HR=0.26 (95% CI 0.13–0.55), p=0.0003
				  • OS 99.3% vs 96.8%, HR=0.43 (95% CI 0.08–2.22), p=0.31
				• Postmenopausal
				  • DFS 93.9% vs 90.5%, HR=0.67 (95% CI 0.51–0.89), p=0.006
				  • OS 94.6% vs 94.5%, HR=0.83 (95% CI 0.57–1.22), p=0.35
				
				Subgroups who switched from placebo to LET after unblinding vs stayed on placebo, 5–y outcome
				• Premenopausal:
				  • DFS 98.8% vs 90.5%, HR=0.39 (95% CI 0.14–1.09), p=0.07
				  • DDFS 99.6% vs 93.7%, HR=0.15 (95% CI 0.03–0.79), p=0.02
				  • OS 99.0% vs 98.2%, HR=0.51 (95% CI 0.06–4.11), p=0.53
				• Postmenopausal:
				  • DFS 97.0% vs 94.0%,HR=0.36 (95% CI 0.21–0.62), p=0.0003
				  • DDFS 98.1% vs 96.7%, HR=0.45 (95% CI 0.22–0.94), p=0.033
				  • OS 98.1% vs 93.0%, HR=0.28 (95% CI 0.15–0.49), p<0.0001

NCIC CTG MA.17 older female pts subset (297)	• Age <60 y • Age 60–69 y • Age ≥70 y	2152 1694 1323		At 4 y, LET vs placebo • DFS, age <60 y: HR=0.46, (95% CI 0.30–0.70), p=0.0004 • DFS, age 60–69 y: HR=0.68 (95% CI 0.44–1.04), p=0.078 • DFS, age ≥70 y: HR=0.67 (95% CI 0.41–1.11), p=0.12 • OS, age <60 y: HR=0.78, (95% CI 0.34–1.79), p=0.56

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
				• OS, age 60–69 y: HR=0.75 (95% CI 0.36–1.59), p=0.56 • OS, age ≥70 y: HR=0.82 (95% CI 0.50–1.35), p=0.44 No interaction between age and treatment, indicating similar effect of LET among all age groups No difference in adverse effects or QoL at 24 mo among LET and placebo-treated pts aged ≥70 y
NCIC CTG MA.17 late extended (298)	TAM (5 y)→ placebo (≈2 y) → LET (5 y) vs TAM (5 y)→ placebo (by patient choice)	1579 804	Pts who had large gap in treatment after initial 5 y TAM due to being randomized to placebo were offered LET	Median follow-up 5.3 y since initial randomization (2.8 y since unblinding); excludes those who died or relapsed before unblinding • DFS: HR=0.37 (95% CI 0.23–0.61), p<0.0001 • OS: 21 vs 36 deaths (1.3% vs 4.5%), HR=0.30 (95% CI 0.17–0.53), p<0.0001 LET group had more clinical fractures (5.2% vs 3.1%, p=0.02) and self-reported osteoporosis (5.3% v 1.6%; P<0.0001) Interpret that LET improves DFS even when substantial period of time since discontinuation of TAM (median 2.8 y in this study)
Meta-analysis of 4 studies: NCIC CTG MA.17; NSABP B33; ABCSG 6A; ATENA (299) [abstract only]	TAM (5 y)→ EXE, LET or ANA TAM (5 y)		See individual studies	Median follow-up 2.5 y AI therapy after 5 y TAM associated with absolute 2.9% decrease in breast cancer recurrence rate (43% relative decrease, p<0.00001), and absolute 0.5% decrease in breast cancer mortality rate (relative decrease 27%, p=0.11). Trend toward improved survival rate, may be underestimated due to cross-over after unblinding

Abbreviations: AI, aromatase inhibitor; ANA, anastrozole; BCFI, breast cancer-free interval; BCFS, breast cancer-free survival rate; BMD, bone-mineral density; DFS, disease-free survival rate; DDFS, distant disease-free survival rate; DRFI, distant recurrence-free survival rate; ER, estrogen receptor; EXE, exemestane; GOS, goserelin; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal cancer; IHC, immunohistochemistry; ILC, invasive lobular cancer; LET, letrozole; OR, odds ratio; OS, overall survival rate; pts, patients; PR, progesterone receptor; QoL, quality of life; RFS, recurrence (relapse)-free survival rate; TAM, tamoxifen; TDR, time to distant recurrence

Table 9. Studies comparing aromatase inhibitors (letrozole, anastrozole, exemestane) or their duration.

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
MA.27 (356-359) 2003–2008	EXE (25 mg/d) vs ANA (1 mg/d) for 5 y	7,576	Postmenopausal, HR+ 72% T1, 26% T2, 71% N0 31% had adjuvant chemotherapy, 4% trastuzumab for HER2+ since 2005	EFS rates at median follow-up 4.1 y, EXE vs ANA: • 91% vs 91.2%, HR=1.02 (95% CI 0.87–1.18), p=0.85 • N0, 93.2%, HR=1.04 (95% CI 0.85–1.27), p=0.73 • N+, 85.8%, HR=0.99 (95% CI 0.79–1.23), p=0.90 • Chemotherapy HR=1.02 (95% CI 0.80–1.29), p=0.89 • No chemotherapy HR=1.01(95% CI 0.84–1.23), p=0.89 OS 94.5% vs 94.1%, HR=0.93 (95% CI 0.77–1.13), p=0.46 DDFS 95.9% vs 95.7%, HR=0.95 (95% CI 0.76–1.18), p=0.64 Liver enzyme elevation, acne, androgenic changes occurred in ≈1–2% of pts and were significantly increased compared with ANA (p=0.04 to p<0.0001); hypertriglyceridemia occurred in 2% of EXE pts vs 3% of the ANA group (p=0.002), hypercholesterolemia in 15% vs 18% of pts (p=0.01), and osteoporosis in 31% vs 35% (p=0.001); vaginal bleeding was less common with EXE (1% vs 2%, p=0.04). Cardiovascular events were similar between the 2 arms, although atrial fibrillation was less common with ANA (2% vs 1%, p=002). Conclude EXE comparable to ANA, provides new option
MA.27B bone substudy (360) 2006–2008	See previous entry in table Group A: no osteoporosis at start (baseline T-score for BMD -2.0 or greater at the spine and hip) Group B: osteoporosis (T-score less than -2.0), administered bisphosphonate Both groups administered vitamin D and calcium daily	497 300 197	See previous entry in table, no bisphosphonates in 6 mo before registration in Group A	Group A (no bisphosphonate): BMD change, EXE vs ANA: • Bone loss at hip: 1 y: -0.62% vs -1.66%, p=0.01 • Bone loss at hip, 2 y: -1.93% vs -2.71(p=0.10) • Bone loss at L spine, 1 y: -0.59% vs -1.88% (p=0.32) • Bone loss at L spine, 2 y: -0.92% vs -2.39% (p=0.08) Group B: BMD increased in all groups despite EXE or ANA (effect of bisphosphonate + vitamin D + calcium) • BMD change, hip, 1 y: 0.61% vs 0.83% (p=0.23) • BMD change, hip, 2 y: 2.09% vs 0.00% (p=0.28) • BMD change, L spine, 1 y: 3.75% vs 2.60% (p=0.67) • BMD change, L spine, 2 y: 2.11% vs 3.72% (p=0.26)
TEAM Japan: N SAS BC04 lipid substudy (329)	EXE (5 y) vs TAM (2.5–3 y)→ EXE (2–2.5 y); 5 y total 5 y ANA	52 52 50		Changes in lipid profiles with tamoxifen were relatively favourable, whereas exemestane and anastrozole had no clinically significant effect on serum lipids; tamoxifen may be a treatment choice for pts at high risk of cardiovascular events such as hyperlipidemia
FACE (361)	Initial adjuvant treatment with ANA (1 mg/d) vs LET (2.5 mg/d) up to 5 y or until recurrence/relapse	4172	Postmenopausal, HR+, N+	Accrual complete March 2008, primary endpoint DFS at 5 y, secondary endpoint OS, TDR, safety No data yet available
Indirect comparison of ANA and	ANA (5 y) vs TAM		Postmenopausal,	Indirect statistical comparison (inverse probability censoring weighted

Trial and recruitment	Trial arms	# pts	Patient characteristics	Outcome
LET from the ATAC and BIG 1–98 trials [abstract] (362)	LET (5 y) vs TAM		early-stage, HR+	analysis): • OS for LET was HR=0.83 (95% CI 0.71–0.97), p<0.05 (median follow-up 74 mo) in BIG 1–98 • OS for ANA was HR= 0.97 (95% CI 0.85–1.12), p=0.70 (median follow-up 68 mo) in ATAC Indirect comparison: • DFS, HR=0.98 (95% CI 0.83–1.15) • Risk reduction for early distant recurrences between 2–2.5 y with LET (RR=0.75, 95% CI 0.52–1.07) over ANA • Trend for improved OS with LET, HR=0.86 (95% CI 0.70–1.05) • Authors conclude LET may be more effective than ANA to reduce early distant recurrence and mortality at 5 y but needs confirmation in ongoing trials
Comparison of benefit in ATAC and BIG-98 [abstract] (363)	See previous entry in table		See previous entry in table	Comparison using number needed to treat (NNT) analysis, number needed to treat with intervention to avoid one additional event, using time points of 2.5 y for ANA and 2 y for LET NNT, all recurrences, LET vs ANA: 75 vs 77 NNT, distant recurrence: 100 vs 300
DATA (364), NCT00301457	TAM (2–3 y) then randomized to 3 y vs 6 y ANA	1915	Postmenopausal (or chemotherapy-induced amenorrhea, CIA), HR+, already received 2 to 3 y of adjuvant tamoxifen, no signs of locoregional recurrences or distant metastases	Ongoing, enrolment complete 2014, see https://clinicaltrials.gov/ct2/show/record/NCT00301457
SOLE BIG 1–07 IBCSG 35–07 NCT00553410 (365)	4–6 y prior adjuvant endocrine therapy (selective estrogen receptor modulator and/or aromatase inhibitor) then randomized to 5 y continuous LET vs 5 y intermittent (daily for 9 months, then 3 month gap for years 1–4, 12 months for year 5)	4800 planned	Postmenopausal, post-surgery, disease-free, ER+, N+	Ongoing, recruitment complete, see http://clinicaltrials.gov/ct2/show/NCT00553410

Abbreviations: ANA, anastrozole; BCFI, breast cancer-free interval; BCFS, breast cancer-free survival rate; DFS, disease-free survival rate; BMD, bone-mineral density; DDFS, distant disease-free survival rate; DRFI, distant recurrence-free survival rate; EFS, event-free survival rate; ER+, estrogen-receptor positive; EXE, exemestane; GOS, goserelin; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; LET, letrozole; N+, lymph

node positive; NNT, number needed to treat; OS, overall survival rate; pts, patients; RFS, recurrence (relapse)-free survival; TAM, tamoxifen; TDR, time to distant recurrence

4.3.3 Ovarian Ablation (Surgical or Radiation) and Ovarian Suppression

a) Background

Ovarian ablation (OA) is the oldest form of systemic therapy for breast cancer (368,369). The term "ovarian ablation" is generally used to refer to surgical oophorectomy or ovarian irradiation, although sometimes ovarian suppression is included in the definition [e.g., the Cancer Care Ontario Guideline on Ovarian Ablation (101)]. Goserelin (Zoladex) is the most commonly used agent for ovarian suppression. Chemotherapy can partially interrupt ovarian estrogen production (permanently or temporarily), as indicated by chemotherapy-induced amenorrhea in a large portion of younger patients; however, it may have both cytotoxic and endocrine effects (370).

Ovarian ablation and/or suppression (OA/S) is a hormonal manoeuvre; thus it only benefits female patients with HR+ breast cancer. In addition, OA/S only has endocrine effects in premenopausal patients, and thus should only be considered as a therapeutic strategy in these female patients. Despite the large body of evidence regarding OA/S in early-stage breast cancer, its current role as a treatment strategy remains unclear.

b) Major Meta-analyses and Guidelines

A list of RCTs on OA/S in some of the most recent and comprehensive meta-analyses or systematic reviews is provided in Table 10 (41,61,63,64,101,112,119,265,282,304-307,309,371-408). For the EBCTCG meta-analysis (112), only those trials on OA/S are listed.

The data are complicated by the extremely large number of different comparisons made. Studies may use OA (by RT or surgery), ovarian suppression, or both. The comparisons may include no treatment, chemotherapy, or tamoxifen in either or both arms. In Table 10, data on comparisons without tamoxifen in either arm are given first. THE EBCTCG meta-analysis is the most complete comparison of OA vs none and of OA + chemotherapy vs chemotherapy, and these studies are not included in the other meta-analyses. The original studies were not obtained as these analyses are complete in the EBCTCG; thus, the details of hormone receptor status are not indicated in Table 10. For other categories, there are a few studies (e.g. SITAM-02) that appear to be unpublished and are only included in the EBCTCG report.

The main purposes of Table 10 are to highlight the treatment settings in which OA/S has been used and to indicate which studies have been included in the systematic reviews. Table 10 reveals that although some reviews cover certain subtopics comprehensively, no individual review/guideline covers them all. It is not possible to combine all the original trials into a new overall analysis, because the EBCTCG and LHRH studies used individual patient data to make additional comparisons and some of the studies are unpublished. Because of the individual patient data, these meta-analyses are considered the most useful and comprehensive for the areas that they cover, although they have some limitations. The various reviews or meta-analyses as well as new studies from the literature search are discussed in the following sections (4.3.3c–4.3.3h).

Table 10. Studies of ovarian ablation and/or ovarian suppression included in recent meta-analyses.

Category of treatment comparison and trial names	Treatment comparison	Hormone receptor status	EBCTCG meta-analysis (112,119)	LHRH meta-analysis (61)	PEBC #1–9 (101)*	Cochrane (371)	1–21 search
OA vs none							
Christie A	Irradiation vs control		Yes	No	No	No	No
Norwegian RH	Irradiation vs control		Yes	No	No	No	No
PMH Toronto	Irradiation vs control		Yes	No	No	No	No
Ontario CTRF (unpublished)	Irradiation vs control		Yes	No	No	No	No
CRFB Caen A	Irradiation vs control (<100 pts)		Yes	No	No	No	No
NSABP B-03	Oophorectomy vs control		Yes	No	No	No	No
Saskatchewan CF	Oophorectomy vs control		Yes	No	No	No	No
Bradford R1	Oophorectomy + selective radiotherapy vs selective radiotherapy (<100 pts)		Yes	No	No	No	No
Suppression vs none							
ZIPP (372); 1–21 search (373,374)	GOS vs none (≈ 62% received RT, 43% chemotherapy, according to local practice)	Any	(Yes)†	Yes	No	No	Yes
SITAM-02 (unpublished)	GOS vs none		(Yes)†	No	No	No	No
IBCSG VIII (41)	GOS vs none	Any	No	Yes	No	No	No
OA vs chemotherapy							
DBCG 89b (375); 1–21 search (376)	Irradiation vs CMF	HR+	No	No	Yes	No	Yes
Scottish Trial A (377,378)	OA (oophorectomy or irradiation) vs CMF	Any	No	No	Yes	No	No
Salvadori et al (379)	Oophorectomy vs CMF (<100 pts)	HR+	No	No	Yes	No	No
Suppression vs chemotherapy							
Zebra (380)	GOS vs CMF	Any	No	Yes	Yes	Yes	No
IBCSG VIII (41)	GOS vs CMF	Any	No	Yes	Yes	Yes	No
GABG IV-A-93 (381)	GOS vs CMF	HR+	No	Yes	Yes	Yes	No
TABLE (382,383)	Leuprorelin vs CMF	HR+ or unknown	No	Yes	Yes	Yes	No
Suppression + chemotherapy vs suppression							
IBCSG VIII (41)	CMF→ GOS vs GOS	Any, subgroup by ER status	No	No	No	Yes	No
OA + chemotherapy vs chemotherapy							
CAMS China (unpublished)	Ablation + CMF vs CMF (note: RT to ≈50%, CMF to ≈90%, tamoxifen to ≈70%) (384)		(Yes)‡	No	No	No	No
FNCLCC France	Chemotherapy→ ovarian irradiation/oophorectomy vs chemotherapy (≈ 60% receiving FAC or FEC, 35% CMF)		Yes	No	No	No	No
Toronto-Edmonton	Irradiation + CMF ± regional radiotherapy ± Bacillus Calmette-Guérin vs CMF ± Bacillus Calmette-Guérin		Yes	No	No	No	No
BCCA Vancouver	Ovarian irradiation + CMF vs CMF		Yes	No	No	No	No
IBCSG/Ludwig II	Oophorectomy then CMF vs CMF		Yes	No	No	No	No
Bradford RI	(Oophorectomy + methotrexate + triethylenephosphoramide) vs		Yes	No	No	No	No

Category of treatment comparison and trial names	Treatment comparison	Hormone receptor status	EBCTCG meta-analysis (112,119)	LHRH meta-analysis (61)	PEBC #1–9 (101)*	Cochrane (371)	1–21 search
	(methotrexate + triethylenephosphoramide) (<100 pts)						
SWOG 7827B	Oophorectomy + CMF+ vincristine vs CMF + vincristine		Yes	No	No	No	No
Suppression + chemotherapy vs chemotherapy							
Pretoria (385)	Buserelin + CMF vs CMF		Yes	No	No	Yes	No
FNCLCC France (386)	Triptorelin + chemotherapy vs chemotherapy	Any	Yes	Yes	No	No	No
ECOG E5188 (387)	CAF→ GOS vs CAF	HR+	Yes†	Yes	No	Yes	No
IBCSG VIII (41)	CFM→ GOS vs CMF	Any	No	Yes	No	Yes	No
GABG IV-B-93 (388)	GOS + CMF vs CMF GOS + EC/CMF vs EC/CMF	Any	No	Yes	No	Yes	No
SITAM-02	(GOS +CMF ± TAM) vs (CMF ± TAM) (<100 pts)		(Yes)†	No	No	No	No
Suppression vs TAM							
ZXBC1002 (ZBCSG Trial B) (Japan—Zoladex breast cancer study group trial-B) (389); as reported in (61)	GOS vs TAM	ER+	No	No	Yes	Yes	No
Soreide et al (390)	GOS vs TAM (perioperative chemotherapy including vincristine, cyclophosphamide, fluorouracil, and methotrexate)	Any	No	No	Yes	Yes	No
ZIPP (372); 1–21 search (373,374)	GOS vs TAM (≈ 62% received RT, 43% chemotherapy, according to local practice)	Any	(No)†	No	Yes	Yes	Yes
SITAM-02	GOS vs TAM		(No)†	No	No	No	No
OA/S + TAM vs none							
ZIPP (372); 1–21 search (373,374)	GOS + TAM vs none (≈62% received RT, 43% chemotherapy, according to local practice)	Any	(No)†	Yes	Yes	No	Yes
SITAM-02	GOS + TAM vs none		(No)†	No	No	No	
Love et al (391,392); 1–21 search (392)	Oophorectomy + TAM vs none	Any	No	No	Yes	No	Yes
OA/S + TAM vs TAM							
ZIPP (372); 1–21 search (373,374)	GOS + TAM vs TAM (≈ 62% received RT, 43% chemotherapy, according to local practice)	Any	(No)†	Yes	Yes	Yes	Yes
ZXBC1002 (ZBCSG Trial B) (Japan—Zoladex breast cancer study group trial-B) (389)	GOS + TAM vs TAM	ER+	No	Yes	No	No	No
SITAM-02	GOS + TAM vs TAM		(No)†	No	No	No	No
INT0142 (393,394) See also (65)**	OA (various) + TAM vs TAM	HR+	No	No	Yes	No	No
ABC (OAS) (395)	OA (various)+ TAM vs TAM (chemotherapy by local practice)	Any	No	No	Yes	No	No
SOFT (63,64,282) See also (59,62)**	TAM vs OA/S + TAM vs OA/S + EXE	HR+	No	No	No	No	Yes (on-going)

Category of treatment comparison and trial names	Treatment comparison	Hormone receptor status	EBCTCG meta-analysis (112,119)	LHRH meta-analysis (61)	PEBC #1–9 (101)*	Cochrane (371)	1–21 search
OA/S +TAM vs chemotherapy							
ABCSG 05 (396,397)	GOS + TAM vs CMF	HR+	No	Yes	Yes	Yes	No
FASG 06 (398)	Triptorelin + TAM vs FEC	HR+	No	Yes	Yes	Yes	No
GROCTA 02 (399)	OA/S (70% GOS, 25% irradiation, 5% surgery) + TAM vs CMF	ER+	No	Yes	Yes	No	No
Nomura et al (400,401)	Oophorectomy + TAM vs mitomycin C + C	ER+, ER– (separate analysis)	No	No	Yes	No	No
Roche et al (402)	OA (various) + TAM vs FAC	ER+PR+	No	No	Yes	No	No
Suppression +TAM + chemotherapy vs chemotherapy							
ECOG E5188 (387)	CAF→ GOS + TAM vs CAF	HR+	No§	Yes	Yes	Yes	No
GOCSI (MAM-1 GOCSI) (403)	CMF→ GOS + TAM vs CMF A→ CMF→ GOS + TAM vs A→ CMF	Any	No	Yes	Yes	Yes	No
SITAM-02	GOS +CMF ± TAM vs CMF ± TAM (<100 pts)		(No)†	No	No	No	No
Suppression +TAM +chemotherapy vs TAM + chemotherapy							
ZIPP (372); 1–21 search (373,374)	GOS + TAM vs TAM (≈ 62% received RT, 43% chemotherapy, according to local practice)	Any	(No)†	Yes	Yes	Yes	Yes
SITAM-02	GOS + CMF ± TAM vs CMF ± TAM (<100 pts)		(No)†	No	No	No	No
OA/S + TAM + chemotherapy vs OA/S + chemotherapy							
IBCSG 11–93; 1–21 search (404)	OA/S + TAM + AC or EC vs OA/S + TAM	HR+	No	No	No	No	Yes
ECOG E5188 (387)	CAF → GOS +TAM vs GOS +CAF	HR+	No§	No	No	Yes	No
SITAM-02	GOS + CMF ± TAM vs GOS +CMF (<100 pts)		(No)†	No	No	No	No
Suppression + AI vs suppression + TAM							
ABCSG-12 (265,304-307,309,405-407)	GOS + anastrozole vs GOS + TAM Both arms ± zoledronic acid	HR+	No	No	No	Yes	Yes
SOFT (63,64,282)	Tamoxifen vs OA/S + tamoxifen vs OA/S + exemestane	HR+	No	No	No	No	Yes
TEXT (63,64,282)	Triptorelin + tamoxifen vs Triptorelin + exemestane	HR+	No	No	No	No	Yes
Timing							
NCT00303524; 1–21 search (408)	GOS (q3 mo) + TAM vs GOS (q1mo) + TAM	ER+	No	No	No	No	Yes

Abbreviations: C, cyclophosphamide; CAF, cyclophosphamide + methotrexate + fluorouracil; CMF, cyclophosphamide + methotrexate + fluorouracil; EC, epirubicin + cyclophosphamide; ER+, estrogen receptor positive; F, 5–fluorouracil; FAC, fluorouracil + doxorubicin + cyclophosphamide; FEC, fluorouracil + epirubicin + cyclophosphamide; GOS, goserelin (Zoladex); HR+, hormone receptor positive; OA, ovarian ablation; OA/S, ovarian ablation and/or ovarian suppression; PR+, progesterone receptor positive; RT, radiation therapy; TAM, tamoxifen.

Note: Yes=study included; No=study not included; none=no chemotherapy/no endocrine therapy

*PEBC review relied on the EBCTCG meta-analysis and indirectly included studies of the EBCTCG meta-analysis (119).

† EBCTCG included the ZIPP and SITAM-02 studies, but ignored that TAM was used, and combined the groups ± TAM (≈62% received RT, 43% chemotherapy, according to local practice; this was not randomized chemotherapy trial, but chemotherapy was received for some and could be analyzed in individual patient data; Cochrane listed this in studies of LHRH + chemotherapy vs chemotherapy; LHRH + TAM + chemotherapy vs chemotherapy)

‡ EBCTCG included CAMS China study, although ≈70% received tamoxifen

§ EBCTCG included this study only under OA + chemotherapy vs chemotherapy.

**Published following completion of the review and guideline; data has not been extracted.

c) Early Breast Cancer Trialists' Collaborative Group

An individual patient data meta-analysis has been published by EBCTCG in 2005 (112). A summary of the meta-analysis is provided in Table 11. The EBCTCG included 7725 female patients aged <50 years with early breast cancer in six trials of either OA (N=4317) or ovarian suppression (LHRH inhibition=LHRHI, N=3408) compared with no adjuvant OA/S. Age <50 years was used as a surrogate for menopausal status. Chemotherapy was allowed if equivalent in both OA/S and controls. They included ER+ cancers and ER-unknown (63% of ablation ER untested, 26% of suppression ER untested) and subdivided results according to age <40 years or age 40–49 years. Overall, OA and suppression both significantly improved recurrence and survival rates compared with no treatment or any other treatment without OA or ovarian suppression. The overall recurrence rate at year 15 was 47.3% for OA/S vs 51.6% for control (p=0.00001). The breast cancer mortality rate at 15 years was 40.3% for OA/S vs 43.5% for control (p=0.004).

Subgroup analyses found the effect of OA/S was significant for patients without chemotherapy when both age groups were combined. The effect appeared smaller in studies in which chemotherapy was also administered, and was not significantly different than the control (chemotherapy alone), except for suppression in patients aged <40 years for which there was a statistically significant improvement in recurrence rates with ovarian suppression (RR=0.70, 95% CI 0.39–0.996). Because the overall effects were small and the subgroups had limited numbers of events (especially for mortality), caution should be used in interpreting subgroup data. One concern about this data is that less than half the patients on OA were confirmed to be HR+. The largest study on OA + chemotherapy (CAMS China) accounted for two-thirds of the patients in the meta-analysis, yet the EBCTCG meta-analysis on radiotherapy (384) indicated that approximately 70% of patients in the CAMS trial received tamoxifen and 50% received radiotherapy. No publication of the CAMS trial could be located.

Another observation not addressed in the report is that all the studies on ovarian suppression without chemotherapy compared goserelin ± tamoxifen vs none ± tamoxifen. The ZIPP trials and SITAM-02 actually consisted of four patient groups (control, tamoxifen, goserelin, and tamoxifen + goserelin), but the EBCTCG combined these into two groups, thereby ignoring the effect of tamoxifen. In the group of LHRH inhibitor + chemotherapy, the SITAM-02 study again included tamoxifen in some patients (GOS ± tamoxifen vs CMF ± tamoxifen). Removal of this study from the LHRH+ chemotherapy study analysis and recalculation of the risk without this trial indicates a greater effect of ovarian suppression. The ECOG E5188 study consisted of three groups (CAF, CAF + goserelin, CAF + goserelin + tamoxifen) (387), and it is unclear whether the EBCTCG analysis included the goserelin + tamoxifen group. The EBCTCG meta-analysis does not answer the question of whether or not LHRH adds to tamoxifen in patients treated with chemotherapy.

Table 11. Summary of EBCTCG 2005 meta-analysis on ovarian ablation and suppression

Data from EBCTCG 2005 (112)

	Ovarian ablation or suppression vs control					
Treatment	**Recurrence events/woman-years, rate ratio**			**Deaths/women, rate ratio**		
	Age <40 y	**Age 40–49 y**	**overall**	**Age <40 y**	**Age 40–49 y**	**overall**
OA, no chemotherapy	5.0% vs 6.5%, RR=0.70 (95% CI 0.30–1.10)	3.6% vs 5.2%, RR=0.67 (95% CI 0.45–0.87)	3.9% vs 5.4%, RR=0.68, p=0.00002	54.6% vs 58.5%, RR=0.71	45.2% vs 56.7%, RR=0.68	47.2% vs 57.1%, RR=0.68, p=0.00002
OA + chemotherapy	6.5% vs 6.6%, RR=0.96 (95% CI 0.73–1.19)	5.1% vs 5.5%, RR=0.90 (95% CI 0.74–1.06)	5.5% vs 5.8%, RR=0.94, p>0.1	32.2% vs 31.3%, RR=1.04	24.6% vs 25.1%, RR=0.98	27.1% vs 27.0%, RR=1.01, p>0.1
OA ± chemotherapy			4.7% vs 5.6%, RR=0.83 (95% CI 0.72–0.93), p=0.0005			33.3% vs 35.8%, RR=0.86, p=0.01
LHRH ± TAM vs control ±TAM	6.9% vs 8.2%, RR=0.79 (95% CI 0.45–1.14)	4.75% vs 6.2%, RR=0.77 (95% CI 0.56–0.97)	5.1% vs 6.6%, RR=0.77, p=0.003	14.3% vs 18.1%, RR=0.73	10.7% vs 13.7%, RR=0.79	11.5% vs 14.8%, RR=0.78, p=0.05
LHRH + chemotherapy	8.1% vs 11.9%, RR=0.70 (95% CI 0.39–0.996)	6.9% vs 6.5%, RR=1.08 (95% CI 0.84–1.32)	7.3 % vs 8.1%, RR=0.91, p>0.1	23.0% vs 29.1%, RR=0.80	20.2% vs 17.2%, RR=1.02	21.2% vs 21.3%, RR=1.02, p>0.1
LHRH + chemotherapy (excluding trial with TAM)			6.9% vs 7.9%, RR=0.88			
LHRH ± chemotherapy (4 trials)			6.0% vs 7.2%, RR=0.83 (95% CI 0.70–0.96), p=0.006			15.2% vs 17.3%, p>0.1
OA or LHRH, no chemotherapy	5.7 vs 7.3%, RR=0.75 (95% CI 0.49–1.01)	4.0% vs 5.6% RR=0.71 (95% CI 0.57–0.86)	[RR=0.72 (95% CI 0.64–0.82) from (101)]	29.9% vs 32.0%, RR=0.71	24.3% vs 29.9%, RR=0.71	[RR=0.71 (95% CI 0.62–0.83) from (101)]
OA or LHRH + chemotherapy	6.9% vs 8.0% RR=0.86 (95% CI 0.67–1.04)	5.5% vs 5.8% RR=0.95 (95% CI 0.82–1.09)	[RR=0.92, (95% CI 0.82–1.02) from (101)]	29.4% vs 30.6%, RR=0.96	23.3% vs 22.7%, RR=1.03	[RR=1.01 (95% CI 0.89–1.14) from (101)]

Abbreviations: LHRH, luteinizing hormone-releasing hormone; OA, ovarian ablation, TAM, tamoxifen

Table 12. Summary of LHRH-agonists in early breast cancer overview group results

Data from (61)

Therapy	Number of pts	Hazard ratio, LHRH vs control		% change in hazard ratios (95% CI) for recurrence	% change in hazard ratios (95% CI) for all deaths
		Recurrence	Death after recurrence		
LHRH vs no systemic	338	0.72 (95% CI 0.49–1.04), p=0.08	0.82 (95% CI 0.47–1.43), p=0.49	−28.4 (−50.5 to 3.5), p=0.08 −	−22.9 (−44.1 to 6.4), p=0.11
LHRH vs Chemotherapy	3184	1.04 (95% CI 0.92–1.17), p=0.52	0.93 (95% CI 0.79–1.10), p=0.40	3.9 (−7.7 to 17.0), p=0.52	−9.4 (−22.6 to 6.1), p=0.22
LHRH + chemotherapy vs chemotherapy	2376			−11.7 (−22.8 to 1.0), p=0.07 Age ≤40: −24.7%, p=0.01 Age >40: −5.1%, p=0.55	−11.5 (−24.8 to 4.2), p=0.14 Age ≤40: −27.5%, p=0.02 Age >40: −2.2%, p=0.83
LHRH + TAM vs no systemic	407			−58.4 (−72.9 to −36.0), p<0.0001	−49.4 (−70.8 to −12.2), p=0.02
LHRH +TAM vs TAM	1013	0.85 (95% CI 0.67–1.09), p=0.20	0.84 (95% CI 0.59–1.19), p=0.33	−14.5 (−32.7 to 8.6), p=0.20 Age ≤40: −32.0%, p=0.12 Age >40: −1.5%, p=0.91	−13.7 (−38.1 to 20.3), p=0.39 Age ≤40: −33.5%, p=0.22 Age >40: −0.3%, p=0.99
LHRH + TAM vs chemotherapy	1577	0.90 (95% CI 0.75–1.08), p=0.25	0.89 (95% CI 0.69–1.15), p=0.37	−10.1 (−25.0 to 7.8), p=0.25 Age ≤40: −19.8%, p=0.22 Age >40: −3.8%, p=0.72	−12.8 (−31.6 to 11.1), p=0.27 Age ≤40: −2.9%, p=0.90 Age >40: −13.6%, p=0.32
LHRH + TAM + chemotherapy vs chemotherapy	1210			−26.7 (−38.7 to −12.3), p=0.001	−19.8 (−34.6 to −1.7), p=0.03
LHRH + TAM +Chemotherapy vs TAM + chemotherapy	365			−15.9 (−42.4 to 22.6), p=0.37	−30.3 (−57.4 to 13.9), p=0.15
LHRH +(Chemotherapy ± TAM) vs chemotherapy ± TAM*	2741	0.88 (95% CI 0.77–0.99), p=0.04	0.85 (95% CI 0.73–0.99), p=0.04	−12.2 (−22.6 to −0.3), p=0.04	−13.6 (−26.0 to 0.9), p=0.07
LHRH + any systemic vs any systemic*	3754			−12.7 (−21.9 to −2.4), p=0.02 Age ≤40: −26.3%, p=0.002 Age >40: −3.3%, p=0.64	−13.6 (−24.9 to −0.6), p=0.04 Age ≤40: −28.2%, p=0.01 Age >40: −3.9%, p=0.66

Abbreviations: LHRH, luteinizing hormone-releasing hormone; TAM, tamoxifen

*Combination of other comparisons

d) LHRH-Agonists in Early Breast Cancer Overview

Another individual patient data meta-analysis was conducted by the LHRH-agonists in Early Breast Cancer Overview group in 2007 (61). The results of this meta-analysis are summarized in Table 12, and the included trials are indicated in Table 10. It involved 13 trials (16 trials considering the four ZIPP sites separately) in which premenopausal patients (N=11,906) received LHRH agonists (or more than half the patients received LHRH agonists if there were multiple methods of suppression in the trials). An important distinction is that this analysis focused on the 9,022 patients with HR+ cancer, of which 8,278 (91.8%) were ER+. They excluded patients with unknown receptor status, and reported briefly on patients that were HR− or ER/PR unknown. Of those patients receiving chemotherapy, 66% received CMF-based chemotherapy and 32% received anthracycline-based chemotherapy. Data was analyzed in several subgroups depending on chemotherapy and tamoxifen use. LHRH treatment was most commonly administered for two years, but 18 months and three- or five-year durations were also used. In addition to restricting the analysis to patients with HR+ cancer, when compared with the EBCTCG meta-analysis the LHRH-agonists' analysis included more studies with ovarian suppression, included more patients, and controlled for the use of tamoxifen. Although this meta-analysis is important, some of the comparisons are not relevant to modern practice.

LHRH improved recurrence and survival rates in several comparisons. The addition of LHRH + tamoxifen to no systemic treatment, and the addition of LHRH + tamoxifen to chemotherapy both gave significant improvement. It should be noted that these results do not provide direct evidence regarding the efficacy of LHRH alone because tamoxifen was not included in the control arm. The addition of LHRH to any systemic therapy (overall and aged ≤40 years subgroup but not the aged >40 years subgroup), and the addition of LHRH to chemotherapy ± tamoxifen also gave significant improvement. Addition of LHRH to tamoxifen did not have a significant improvement for the full age range of patients (change in hazard ratios for recurrence of −14.5%, p=0.20). For recurrence stratified by age there was no effect for patients aged >40 years (change in hazard ratio of − 1.5%, p=0.91), whereas for patients aged ≤40 years the effect was much larger (although still not statistically significant; change in hazard ratio of −32%, p=0.12).

LHRH vs no systemic treatment was almost significant (p=0.08 for recurrence and p=0.11 for all deaths), although it should be noted that this unexpected lack of significance may be due to the small number of patients (338 patients). When results were analyzed by age (≤40 or >40 years) there was a large effect of age for several comparisons. The addition of LHRH significantly improved recurrence rates for patients aged ≤40 years but not patients aged >40 years for the comparisons LHRH + chemotherapy vs chemotherapy, LHRH + (chemotherapy ± tamoxifen) vs chemotherapy ± tamoxifen, and LHRH added to any systemic therapy (note these last two are combinations of other comparisons). This finding is consistent with the EBCTCG analysis which found a significantly reduced recurrence with LHRH in those aged ≤40 years. When results were analyzed according to age in 5−year periods, the effect was greatest in those aged <35 years (HR=0.66) and aged 35−39 years (HR=0.77) but not in the older groups. Although these results indicate a benefit of LHRH in addition to chemotherapy (in the absence of tamoxifen use) for younger female patients, and possible benefit of the addition of LHRH to tamoxifen (in the absence of chemotherapy), they do not address the issue of adding LHRH to tamoxifen + chemotherapy.

In the group that was mostly HR− (ER−/poor plus PR−/poor/unknown), the addition of an LHRH agonist to other treatments did not generally affect the rates of death or recurrence. In contrast, LHRH agonist instead of chemotherapy resulted in significantly increased recurrence rate (p=0.001) and mortality rate (p=0.08), indicating that chemotherapy should be used instead of ovarian suppression for patients with HR− cancer.

e) PEBC Guideline #1−9: Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early-Stage Invasive Breast Cancer

This review and guideline (101) covers most of the literature, with a search up until September 2009. Included studies are indicated in Table 10. Recommendations are largely based on the individual patient data meta-analysis published by EBCTCG in 2005 (112) and by the LHRH-agonists in Early Breast Cancer Overview group (61). All forms of ovarian ablation or suppression are referred to as ovarian ablation.

The PEBC #1−9 recommendations were:

- OA should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy.
- OA alone is not recommended as an alternative to any other form of systemic therapy, except in the specific case of patients who are candidates for other forms of systemic therapy but who for some reason will not receive any other systemic therapy (e.g., patients who cannot tolerate other forms of systemic therapy or patients who choose no other form of systemic therapy).
- When chemical suppression using LHRH agonists is the chosen method of OA, in the opinion of the Breast Cancer DSG, monthly injection is the recommended mode of administration. This recommendation is based on the fact that the mode of administration in nearly all of the available trials has been monthly administration.
- There is no available evidence on which to base a recommendation regarding which specific form of OA (surgical oophorectomy, ovarian irradiation, or medical suppression) should be preferred.

This guideline relies on the EBCTCG meta-analysis for areas of OA (or suppression) vs none and OA (or suppression) + chemotherapy vs chemotherapy. The LHRH agonists meta-analysis was not used for these two questions, although it contains more trials, includes only patients with HR+ cancer for the main analyses, and separates out the effect of tamoxifen in the comparisons. There have been more recent updates of some of the trials since the PEBC #1−9 guideline.

f) Cochrane Collaboration (Goel et al), 2009. LHRH Agonists for Adjuvant Therapy of Early Breast Cancer in Premenopausal Women

The Cochrane review (371) included a literature search until February 2009 and gives a complete description of the trials and outcomes. The included trials are indicated in Table 10.

g) New Studies or Updates from the Current Literature Search

ABCSG-12, SOFT, and TEXT Trials

The ABCSG-12 (265,304-307,309,405-407), SOFT (IBCSG-24–02, NCT00066690) (63,64,282), and TEXT (NCT00066703) (63,64,282) trials are significant because they address the use of AIs together with ovarian suppression in premenopausal patients. Details and results of these trials are summarized in Table 8. The ABCSG-12 study compared goserelin + tamoxifen to goserelin + anastrozole in premenopausal patients with endocrine-responsive early breast cancer. It had a second randomization with or without zoledronic acid. Because all groups received goserelin, the contribution of ovarian suppression to other hormonal therapies could not be determined. Due to lower than expected events, the TEXT and SOFT trial results were combined to allow earlier reporting of the OA/S + exemestane vs OA/S + tamoxifen results. Other subgroups including comparisons to tamoxifen alone and comparisons with different means of OA/S have not been released. Exemestane +OA/S resulted in better DFS rates than tamoxifen + OA/S (91% vs 87%, p<0.001). Overall survival rates were similar in both groups (96%) and requires longer follow-up. The studies indicate higher survival rates with exemestane + OA/S in premenopausal patients.

Results of the comparison with the tamoxifen-alone arm in the SOFT trial (59,62) were only available subsequent to completion of this review and the corresponding guideline; results have not been included in Table 8 and the reader should consult the publications for additional details. There was a small benefit for the addition of ovarian suppression to tamoxifen (86.6% vs 84.7% DFS, p=0.10; p=0.03 after adjustment for prognostic factors). There was no difference in DFS (93.4% vs. 93.3%) or OS (99.2% vs. 99.8%) at 5 years in the subgroup of patients who had no prior chemotherapy (likely due to their having been assessed as having low risk of recurrence). Most recurrences and thus greater benefit was found in those who received chemotherapy. For patients who had received chemotherapy, the addition of ovarian suppression to tamoxifen resulted in significantly better overall survival [94.5% vs 90.9%, HR=0.64 (0.42-0.96)]. DFS and recurrence appeared to also be improved (80.7% vs 77.1% and 82.5% vs 78.9%, respectively), however these differences were not statistically significant. Rates of freedom from distant recurrence at 5 years in patients with prior chemotherapy were 83.6% tamoxifen, 84.8% tamoxifen plus ovarian suppression (HR=0.87, 95% CI 0.64-1.17), and 87.8% for exemestane plus ovarian suppression (HR=0.72, 95% CI 0.52-0.98). The benefit of ovarian function suppression plus exemestane was especially seen in the patient group under 35 years old (freedom from breast cancer 67.7% for tamoxifen, 78.9% for tamoxifen plus ovarian suppression, and 83.4% for exemestane plus ovarian suppression). Tamoxifen or exemestane plus ovarian function suppression was associated with more toxicity and adverse effect (endocrine symptom and sexual functioning) than for tamoxifen alone. There was a different profile of adverse effects for exemestane plus ovarian suppression (greater loss of sexual interest and arousal difficulties, vaginal dryness, bone pain) compared to tamoxifen plus ovarian suppression (more hot flushes and sweats). The INT-0142/E-3193 study(65) was also recently reported (after the current literature review). Tamoxifen was compared to tamoxifen plus ovarian suppression; the study and was terminated early due to slow accrual and is underpowered for survival endpoint. However, quality of life-and sexual function results showed more menopausal symptoms and sexual dysfunction and lower quality of life with addition of ovarian suppression. Effects on

quality of life need to be considered when choosing between tamoxifen, tamoxifen plus ovarian suppression, and exemestane plus ovarian suppression (59,62-65).

NCT00303524, Masuda et al (408)

Premenopausal Japanese patients with ER+ early breast cancer were randomized to subcutaneous depot injection of goserelin 10.8 mg every three months (N=86) vs 3.6 mg monthly (N=84). Both are sustained-release formulations containing a lactide/glycolide copolymer, but in different ratios (95:5 vs 1:1). The study reported area under the concentration-time curve (AUC) of estradiol (E2) over the first 24 weeks: 18.32 pg/mL·week (every 3 months) vs 18.95 pg/mL·week (monthly). The ratio was 0.974 (95% CI 0.80–1.19) indicating non-inferiority for goserelin every three months. From week 4 onward E2 serum concentrations were suppressed to postmenopausal levels (≤30 pg/mL) in 98.8% of patients across both treatment groups. Most patients experienced amenorrhea by week 8. Serum E2 and FSH remained suppressed throughout the study. No patient had menses after week 16. No clinically important differences in safety and tolerability were found.

International Breast Cancer Study Group Trial 11–93 (IBCSG 11–93) (404,409)

The study included premenopausal patients with endocrine-responsive (ER+ or PR+), node positive, early breast cancer (T1a,b,c, T2 or T3, pN1M0). It compared four cycles of chemotherapy added to OA/S + five years tamoxifen vs OA/S + tamoxifen without chemotherapy. Randomization of 174 patients occurred in the period May 1993—November 1998, but the trial closed before target accrual (N=760) due to low accrual rate. The method of ovarian function suppression was the choice of the participating centre: bilateral surgical oophorectomy, bilateral ovarian radiotherapy, or GnRH analogue 3.6 mg every 28 days for two years or until age 55 years (whichever was longer, median 2.0 years, range 0.07–12.6 years). Patients could switch the method of OA/S during the trial. Initially, distribution was 63% GnRH analogue, 26% oophorectomy, 11% irradiation; 30 patients initially on GnRH analogues switched (19 to oophorectomy, 11 radiation). Tamoxifen was administered at 20 mg daily until five years from randomization or until intolerance or relapse (median 5 years, range 0–9 years). Chemotherapy consisted of four courses of adjuvant anthracycline-cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 IV on day 1 for four 21–day courses).

At a median follow-up of 10 years there was no difference in DFS or OS rates between OA/S + tamoxifen + chemotherapy and OA/S +tamoxifen (DFS: HR=1.02, 95% CI 0.57–1.83, p=0.94; OS: HR=0.97, 95% CI 0.44–2.16, p=0.94). Because this study met <25% of its planned accrual, it may have been underpowered to draw firm conclusions. Adjuvant! Online predicted a 10–year relapse-free survival rate of 74.9% (73.1%-76.8%) for chemoendocrine therapy vs 64.4% (61.9%-67.2%) for endocrine therapy alone, compared with observed values of 74.9% (64.5–82.7) for chemoendocrine vs 76.4% (65.8%-84.0%) for endocrine therapy. This suggests Adjuvant! Online underestimates the effectiveness of endocrine therapy alone and therefore overestimates the added benefit of chemotherapy.

Zoladex in Premenopausal Patients (ZIPP) (373,374)

The ZIPP study includes patients aged <50 years with invasive, operable breast cancer in one breast and no signs of metastasis. The study description and some results were included in the other systematic reviews and meta-analyses. Long-term follow-up at a median of 12 years (373) is included for some subgroups in PEBC #1–9. The four groups were control (N=476), tamoxifen (N=879), goserelin (N=469), and tamoxifen + goserelin (N=882). The authors examined effects according to subgroups of age (<40 or ≥40 years), nodal status, ER status, previous adjuvant systemic chemotherapy (yes or no; 43% received chemotherapy and 62% radiotherapy), and stratified by trial centre (CRUK, GIVIO, SE Sweden, Stockholm). Some of the results are reproduced in Table 13. Goserelin, tamoxifen, and goserelin + tamoxifen all had similar effectiveness and were significantly better than none (control). It should be noted that the groups were not equal, because most patients who received chemotherapy were node positive and most without chemotherapy were negative. In this analysis there was no statistically significant benefit for giving both goserelin and tamoxifen compared with either agent alone.

Table 13. Hazard ratios in the ZIPP study

Survival outcomes for all patients and by subgroups	Goserelin vs none, hazard ratio (95% CI)	Goserelin + tamoxifen vs tamoxifen, hazard ratio (95% CI)
Overall survival	0.71 (0.56–0.91)	0.90 (0.74–1.09)
Event-free survival	0.67 (0.56–0.81)	0.92 (0.79–1.06)
• Age <40 y	0.89 (0.58–1.35)	0.86 (0.66–1.13)
• Age ≥40 y	0.65 (0.52–0.80)	0.95 (0.80–1.14)
• Node positive	0.58 (0.44–0.78)	0.82 (0.66–1.02)
• Node negative	0.84 (0.64–1.10)	1.01 (0.82–1.24)
• ER+	0.69 (0.53–0.91)	0.85 (0.70–1.05)
• ER–	0.75 (0.51–1.10)	1.05 (0.79–1.39)
• No prior chemotherapy	0.55 (0.42–0.73)	0.87 (0.71–1.06)
• Prior chemotherapy	0.83 (0.64–1.09)	1.00 (0.80–1.24)
• ER+, no chemotherapy	0.62 (0.43–0.90)	0.79 (0.60–1.03)
• ER+, chemotherapy	0.78 (0.53–1.15)	0.94 (0.69–1.28)

Sverrisdottir et al, 2011(374): Stockholm sub-study of ZIPP

Results for the Stockholm site of the study were reported for goserelin vs none, tamoxifen vs none, goserelin + tamoxifen vs none, and subgroups without tamoxifen. Randomization was stratified in three groups based on nodal status and use of other adjuvant therapies: node negative and no chemotherapy, 1–3 positive nodes and chemotherapy, 4+ positive nodes and chemotherapy + radiotherapy; stratification was not done in other centres of ZIPP. The time to first recurrence was better for goserelin vs no endocrine treatment (HR=0.68, 95% CI 0.52–0.89, p=0.005), tamoxifen vs no endocrine treatment, (HR=0.73, 95% CI 0.56–0.95, p=0.018), and goserelin + tamoxifen vs no endocrine treatment, (HR=0.76, 95% CI 0.59–0.98). In the highly ER+ group, goserelin was more effective than tamoxifen (HR=0.52, 95% CI 0.32–0.84, p=0.007 for goserelin vs none; HR=0.68, 95% CI 0.44–1.05, p=0.081 for tamoxifen vs none).

h) Summary of Conclusions for Each Class of Comparison from the Meta-analyses and Recent Data

For each category of comparison, the results of meta-analysis if available and/or results from the relevant studies if not included in the reported meta-analysis are provided so that an overall conclusion can be made. All of these data are summarized in Table 14 and conclusions appear after the table.

Table 14. Summary of comparisons of ovarian ablation or suppression for each category of study

(± chemotherapy, ± tamoxifen in either or both arms)

Endocrine therapy	Meta-analysis or guideline				
	EBCTCG 2005 meta-analysis (112)	**LHRH meta-analysis (61)**	**PEBC #1–9 (101)**	**Cochrane (371)**	**1–21 search**
Patient or study characteristics	Early, under 50 (subdivided by age <40 y, 40–49 y, ER+ or ER unknown), contribution of tamoxifen to outcome not considered	Early, premenopausal, focus on HR+ only (excluded hormone receptor unknown, HR– reported separately), LHRH agonists only, tamoxifen considered in analysis groups	Early, English only, combined OA and suppression; (relied on EBCTCG meta-analysis for OA/S vs none and OA/S + chemotherapy vs chemotherapy (did not include LHRH-meta-analysis or additional studies)	Early, premenopausal (defined as age <50 y), LHRH agonists only	
OA vs none	• Recurrence RR=0.68, p=0.00002 • Death RR=0.68, p=0.00002 • OA better age <40 y, 40–49 y, overall	N/A	Used EBCTCG analysis only, concluded overall benefit of OA/S, did not analyze OA and suppression separately	N/A	
Suppression vs none	•ZIPP, SITAM-02 trials, both studies confounded by TAM	• IBCSG VIII, ZIPP trials • Recurrence HR=0.72 (95% CI 0.49–1.04), p=0.08 • All deaths p=0.11 • Recurrence or death, p=0·01	See below	N/A	**ZIPP** follow-up (373) DFS HR=0.67 (95% CI 0.56–0.81); HR=0.55 (95% CI 0.42–0.73) without chemotherapy; TAM and GOS equivalent **Stockholm site of ZIPP (374)**: time to recurrence GOS vs none HR=0.68 (95% CI 0.52–0.89), p=0.005
• ***Suppression ± TAM vs none ±TAM (TAM not randomized)***	• ZIPP, SITAM-02 trials • Recurrence RR=0.77, p=0.003 • Death RR=0.78, p=0.05 • GOS ± TAM better than none ± TAM for both age groups, cannot distinguish between effect of GOS and TAM		Used EBCTCG analysis only, concluded overall benefit of OA/S did not analyze OA and suppression separately (except OA/S ± chemotherapy)		DFS HR=0.82 (95% CI 0.73–0.92), p=0.001; OS HR=0.83 (95% CI 0.71–0.96), p=0.013

Endocrine therapy	Meta-analysis or guideline				
	EBCTCG 2005 meta-analysis (112)	**LHRH meta-analysis (61)**	**PEBC #1–9 (101)**	**Cochrane (371)**	**1–21 search**
OA vs chemotherapy (CMF)	N/A	N/A	OA: DBCG 89b, Scottish A Suppression: ZEBRA, IBCSG VIII, GABG-IV-A93, TABLE trials Combined OA/S meta-analysis: • DFS HR=1.00 all pts, HR=0.96 HR+ • OS HR=0.97 all pts, HR=0.92 HR+ No significant difference; less statistical heterogeneity when pts with HR– cancer were excluded	N/A	DBCG 89b (376) see PEBC 1–9
Suppression vs chemotherapy	N/A	ZEBRA, IBCSG VIII, GABG-IV-A-93, TABLE trials Recurrence HR=1.04, p=0.52 All Death p=0.22 Suppression and chemotherapy may be equivalent in HR+ (but not HR–; see separate section and note following this table)		ZEBRA, IBCSG VIII, GABG-IV-A-93, TABLE trials ZEBRA, IBCSG VIII, TABLE found similar outcomes in ER+ for both groups but ER– and unknown had worse outcomes. Amenorrhea more common with LHRH than CMF and menses more likely to resume after end of LHRH than 36 mo after chemotherapy, LHRH better QoL during first 6 mo	
Suppression + chemotherapy vs suppression	N/A	N/A	N/A	IBCSG VIII (41), CMF +GOS vs GOS, (68% ER+): DFS overall 87% vs 79%, RR=0.71 (95% CI 0.52–0.99), p=0.04 due to strong effect in ER– pts; DFS ER–: 88% vs 73%, RR=0.49,(95% CI 0.28–0.87), p=0.01 ER+ DFS 86% vs 81%, RR=0.84 (95% CI 0.56–1.26), p=0.40 Stratified by age ER+ <40 y benefited from CMF + GOS compared with either alone (RR=0.34, p=0.02 vs GOS alone; RR=0.34, p=0.02 vs CMF alone, but no additional benefit for age >40 y	
OA + chemotherapy vs chemotherapy	• Largest study (CAMS China, 1984/3025=66% of all pts in meta-analysis) confounded by TAM • Recurrence RR=0.94 (RR≈0.87 without CAMS) • Death RR=1.01 (RR≈0.95 without CAMS)	N/A	Used EBCTCG analysis only; concluded no significant benefit for OA/S (did not analyze separately)	N/A	

Endocrine therapy	Meta-analysis or guideline				
	EBCTCG 2005 meta-analysis (112)	**LHRH meta-analysis (61)**	**PEBC #1–9 (101)**	**Cochrane (371)**	**1–21 search**
Suppression + chemotherapy vs chemotherapy	Pretoria, FNCLCC, ECOG (may have included TAM), SITAM-02 (confounded by TAM)	Trials without TAM: ECOG E5188, IBCSG VIII, ZIPP, GABG B93, FNCLCC Recurrence: All pts: p=0.07, age ≤40 y: p=0.01 age >40 y: p=0.55 All deaths All pts p=0.14, age ≤40 y: p=0.02 age >40 y: p=0.83	See below	• ECOG 5188: RFS 60% vs 57%, HR=0.93, p=0.22; OS 73% vs 70%, HR=0.88, p=0.14 • IBCSG VIII (CMF + GOS vs CMF): DFS overall RR=0.80 (95% CI 0.57–1.11, p=0.17); ER+ RR=0.80 (95% CI 0.54–1.19), p=0.26; ER– RR=0.75 (95% CI 0.40–1.39), p=0.35; ER+ age <40 y RR=0.34 (95% CI 0.14–0.87), p=0.02 • GAG-IV-B-93: RFS 71% vs 68%, HR=0.92 (95% CI 0.70–1.21), p=0.54; ER+ HR=0.77 (95% CI 0.47–1.24), p=0.27; ER– HR=1.01 (95% CI 0.72–1.42), p=0.97. • Pretoria: disease-free interval 6.8 y vs 6.2 y (NS)	
Suppression + chemotherapy ±TAM vs chemotherapy ± TAM * ***(TAM ignored in EBCTCG analysis)***	Pretoria, FNCLCC, ECOG, SITAM-02 Recurrence • RR=0.70 age <40 y • RR=1.08 age 40–49 y • overall RR=0.91 (NS) For death • RR=0.80 age <40 y • RR=1.02 age 40–49 y • Overall RR=1.02 Suppression + chemotherapy (± TAM) has benefit over chemotherapy alone for younger female pts	Trials above, plus ZIPP trials with TAM Recurrence •Age ≤40 y: HR=0.75, p=0.01 •Age >40 y: HR=0.96, p=0.63 •overall: HR=0.88, p=0.04 Death after Recurrence •Age ≤40 y: HR=0.72, p=0.01 •Age >40 y: HR=0.93, p=0.47 •Overall: HR=0.85, p=0.04 Any death p=0.07 Based on Forest plots, overall effect and differential age effect does not appear due to tamoxifen (see note)	**Used EBCTCG analysis only**; conclude no significant benefit for OA/S (did not analyze separately)		

Endocrine therapy	Meta-analysis or guideline				
	EBCTCG 2005 meta-analysis (112)	**LHRH meta-analysis (61)**	**PEBC #1–9 (101)**	**Cochrane (371)**	**1–21 search**
Suppression vs TAM	N/A	N/A	Soreide: OS HR=1.16 (95% CI 0.80–1.69) ZXBC1002: RFS HR=0.87 (95% CI 0.47–1.63), OS HR=2.10, (95% CI 0.38–11.49) ZIPP: OS HR=0.71 (95% CI 0.56–0.91); recurrence rate HR=0.66 (95% CI 0.53–0.81)	Soreide, at 88 mo no difference, recurrence rate RR=1.10 (95% CI 0.81–1.48), p=0.56 or death RR=1.16 (95% CI 0.80–1.69), p=0.42 ZBCSB: no significant difference RFS HR=0.87 (95% CI 0.47–1.63) or OS HR=2.10 (95% CI 0.38–11.49) ZIPP: of those with known hormone receptor status, only 68% were ER+; adverse effects 56% vs 41% but mostly by small numbers, only hot flushes (26% vs 17%) and weight gain (4% vs 7%) reported by >10 pts; survival rate data not reported	Stockholm site of ZIPP (374) In highly ER+, GOS more effective than TAM GOS vs none: HR=0.52 (95% CI 0.32–0.84), p=0.007 TAM vs none: HR=0.68 (95% CI 0.44–1.05, p=0.081
OA/S + TAM vs none	N/A	Suppression (ZIPP trials) Recurrence rate p<0.0001, all deaths p=0.02	Love: DFS HR=0.65 (95% CI 0.51–0.82), p=0.0003 OS HR=0.62 (95% CI 0.48–0.80), p=0.0002 Effect even larger when only HR+ analyzed) ZIPP (from LHRH meta-analysis)	N/A	Love et al (392), see PEBC 1–9 Stockholm site of ZIPP (374): Time to recurrence HR=0.76 (95% CI 0.59–0.98)

Endocrine therapy	Meta-analysis or guideline				
	EBCTCG 2005 meta-analysis (112)	**LHRH meta-analysis (61)**	**PEBC #1–9 (101)**	**Cochrane (371)**	**1–21 search**
OA/S + TAM vs TAM	N/A	Suppression (ZIPP, ZXBC1002 trials) Recurrence: Overall: HR=0.85, p=0.20 age ≤40 y: p=0.12 age >40 y: p=0.91 All deaths: Overall: p=0.39, age ≤40 y: p=0.22 age >40 y: p=0.99	Various methods of OA/S: INT0142 + ABC (HR+ only) meta-analysis: OS HR=0.82 (95% CI 0.58–1.14) ZIPP referred to LHRH meta-analysis; follow-up at 12 y still no significant benefit of GOS + TAM vs TAM (OS HR=0.90, 95% CI 0.75–1.09; recurrence rate HR=0.91, 95% CI 0.78–1.07) More QoL adverse effects with OA/S addition (menopausal symptoms, hot flashes, sexual dysfunction, vaginal dryness, and sweating)	Suppression: ZIPP Direct comparison not made, GOS vs none HR=0.80, p=0.002 and study noted effect was similar in those who received TAM	ZIPP follow-up (373,374) (see also PEBC 1–9); DFS median follow-up12 y: overall: HR=0.92 (95% CI 0.80–1.07); no chemotherapy: HR=0.87 (95% CI 0.71–1.06) ER+ HR=0.85 (95% CI 0.70–1.05) ER+ no chemotherapy: HR=0.79 (95% CI 0.60–1.03) Node +ve HR=0.82 (95% CI 0.66–1.02), small but nonsignificant improvement; effect greater in ER+ This will be addressed by the SOFT trial (see Table 8) but data are not yet available.
OA/S +TAM vs chemotherapy	N/A	Suppression: ABCSG 05, FASG 06, GROCTA 02 Recurrence: Overall HR=0.90 (95% CI 0.75–1.08), p=0.25; age ≤40 y, p=0.22; age >40 y, p=0.72 All deaths: Overall, p=0.27; age ≤40 y, p=0.90; age >40 y, p=0.32	Meta-analysis: ABCSG 05, FASG 06, GROCTA 02, Nomura; Roche not included in meta-analysis DFS: HR=0.90 OS: HR=0.91 Excluding Nomura due to statistical heterogeneity OS HR=0.73 (95% CI 0.53–1.00), p=0.05 Adverse effects: OS/A more hot flashes; chemotherapy more nausea, alopecia, stomatitis, diarrhea. GOS or triptorelin + TAM resulted in amenorrhea in all pts	ABCSG 05 (CMF), FASG 06 (FEC50) ABCSG 05: RFS 81% vs 76%, p=0.037; OS 92% vs 90%, p=0.195; more hot flushes and less nausea and alopecia FASG 06: RFS 76% vs 72%, p=0.13; OS 91% vs 88%, p=0.20; amenorrhea 100% vs 65%	

Endocrine therapy	Meta-analysis or guideline				
	EBCTCG 2005 meta-analysis (112)	**LHRH meta-analysis (61)**	**PEBC #1–9 (101)**	**Cochrane (371)**	**1–21 search**
Suppression +TAM +chemotherapy vs chemotherapy	N/A	ECOG E5188, GOCSI trials Recurrence p=0.001 All deaths p=0.03	Meta-analysis ECOG, GOCSI: DFS HR=0.79, p<0.0001; OS HR=0.76, p=0.002 GOS + TAM had greater hot flashes, hypertension (ECOG study), and weight gain; menopausal/sexual adverse effects subsided after cessation of therapy; BMD decrease with GOS/TAM but not with chemotherapy in substudy	ECOG, 5188, GOCSI ECOG: RFS 68% vs 57%, OS 76% vs 70% GOSCI: DFS 64% vs 53%, HR=0.74 (95% CI 0.56–0.99), p=0.04; OS 82% vs 80%, HR=0.84 (95% CI 0.54–1.32)	
Suppression +TAM +chemotherapy vs TAM + chemotherapy	(N/A)	ZIPP trials Recurrence p=0.37 All deaths p=0.15	Referred to LHRH meta-analysis for ZIPP trials	n./a	ZIPP (373) DFS HR=1.00 (95% CI 0.80–1.24)
OA/S + TAM +chemotherapy vs OA/S + chemotherapy	(N/A)	N/A	N/A	ECOG 5188 RFS 68% vs 60%, HR=0.73, p<0.01; OS 76% vs 73%, HR=0.91, p=0.21	IBCSG 11–93 (404) DFS: HR=1.02 (95% CI 0.57–1.83), p=0.94 OS: HR=0.97 (95% CI 0.44–2.16), p=0.94
OA/S+ AI vs OA/S + TAM	(N/A)	N/A	N/A	ABCSG-12: DFS did not differ, HR=1.10 (95% CI 0.78–2.53), p=0.59; RFS HR=1.11 (95% CI 0.80–1.56), p=0.53, OS HR=1.80 (95% CI 0.95–3.38), p=0.70 but based on small number of events; anastrozole group had significantly more arthralgia, bone pain, morning stiffness, whereas tamoxifen resulted in more thrombosis	ABCSG-12 (265,304-307,309,405-407), SOFT and TEXT trials (63,64,282) see section on AIs and Table 8
LHRH + any systemic vs any systemic		Recurrence Overall, p=0.02; age ≤49 y, p=0.002; age >40 y, p=0.64 Any death Overall, p=0.04; age ≤40 y, p=0.01; age >40 y, p=0.66	Quoted LHRH meta-analysis	N/A	

Endocrine therapy	Meta-analysis or guideline				
	EBCTCG 2005 meta-analysis (112)	**LHRH meta-analysis (61)**	**PEBC #1–9 (101)**	**Cochrane (371)**	**1–21 search**
Timing	N/A	N/A	N/A	N/A	NTC00303524 (408) GOS every 3 mo equivalent to every month (note different dose and formulation)
Hormone receptor negative, chemotherapy vs LHRH and other comparisons	N/A	Chemotherapy is better than LHRH, recurrence rate p=0.001; all deaths p=0.08. In general, adding LHRH to other systemic treatments did not affect rates of recurrence (p=0.23)or death (p=0.75)	N/A	n./a	

Abbreviations: BMD, bone mineral density; CMF, cyclophosphamide + methotrexate + fluorouracil; DFS, disease-free survival; ER, estrogen receptor; GOS, goserelin; HR+, hormone receptor positive; HR−, hormone receptor negative; LHRH, luteinizing hormone-releasing hormone; N+, node positive; N0, node negative, N/A, not applicable; OA, ovarian ablation; OA/S, ovarian ablation and/or ovarian suppression; OS, overall survival; QoL, quality of life; RFS, recurrence-free survival

*This is what is reported in EBCTCG and is a combination of separate comparisons in the LHRH-agonists meta-analysis
Note: The LHRH agonist's meta-analysis authors suggest LHRH agonists are equally effective as chemotherapy regimens used, and LHRH added to chemotherapy has additional benefit in female pts aged ≤40 y. In these pts, chemotherapy is less likely to induce permanent amenorrhea than in older pts. This may especially be the case with modern non-CMF-based chemotherapy for which permanent amenorrhea after treatment seems less common.

i) Conclusions from the ovarian ablation/suppression studies and meta-analyses

Hormone Receptor Negative
For female patients with HR− breast cancer, chemotherapy is superior to OA/S (41,61).

Hormone Receptor Positive
For female patients with HR+ breast cancer, OA/S has been compared with chemotherapy, tamoxifen and combinations of these therapies. Given the multiple treatment options, it is helpful to consider and summarize the results according to the following framework:

(1) OA/S alone vs no systemic therapy

OA and suppression are both better than no systemic treatment (61,112,373) for female patients with HR+ breast cancer. Thus, OA/S alone is a reasonable option in the specific case of patients who will not receive any other systemic therapy (e.g., patients who cannot tolerate other forms of systemic therapy or patients who choose no other form of systemic therapy).

(2) OA/S plus chemotherapy vs chemotherapy alone

The relevance of this comparison in modern practice is questionable, because the standard of care for these patients would generally also include tamoxifen. The available data suggest that there is benefit for added suppression for patients aged ≤40 years (41,61,371). In the EBCTCG meta-analysis, which included -patients with HR− cancer, the addition of OA to chemotherapy did not add any benefit (112). The LHRH agonists meta-analysis authors suggest LHRH agonists are equally effective as chemotherapy regimens used, and LHRH added to chemotherapy has additional benefit in female patients aged ≤40 years (61). In these female patients chemotherapy is less likely to induce permanent amenorrhea and may be more common with modern non-CMF-based chemotherapy for which permanent amenorrhea after treatment seems less common.

(3) OA/S alone vs chemotherapy alone

These studies compared the OA/S strategy to primarily CMF chemotherapy, thus the significance of these results to contemporary practice is limited. There was no significant difference between OA/S and CMF chemotherapy (61,101,371). The Cochrane review (371) found that amenorrhea was more common with LHRH than CMF, but menses were more likely to resume at the end of LHRH than 36 months after chemotherapy. This may be an important consideration in the treatment of young female patients with HR+ breast cancer.

(4) OA/S alone vs tamoxifen alone

The combined evidence suggests that there is no difference between these treatment options, except for ZIPP-Stockholm (374) which found a suppression benefit in those highly ER+. OA/S alone is a reasonable option for female patients who are not candidates for any other systemic therapy.

(5) OA/S plus tamoxifen vs tamoxifen alone

In the absence of chemotherapy, there is no evidence of overall benefit with the combination of OA/S + tamoxifen vs tamoxifen alone. There is some evidence that certain subgroups might benefit from this strategy. For example, there was a trend toward greater benefit in young female patients aged ≤40 years (recurrence rate p=0.12 for age ≤40 years vs p=0.91 for age >40 years) (61,373,374). The ZIPP follow-up (373,374) found greater effect in ER+ (HR=0.85, 95% CI 0.70−1.05) and in ER+ without chemotherapy (HR=0.79, 95% CI 0.60−1.03), but these results may not be generalizable if chemotherapy is administered. The ongoing SOFT trial (see Table 8) will also address this question.

(6) OA/S plus tamoxifen and chemotherapy vs tamoxifen and chemotherapy

This question is the most relevant to current practice. The results from a subset of a single study suggest no benefit from the addition of OA/S. Subgroup analysis of the ongoing SOFT trial (see Table 8) may address this.

(7) OA/S plus tamoxifen vs chemotherapy alone

The LHRH-agonists meta-analysis found no difference in outcome with these two strategies, although there was a trend toward benefit in female patients aged ≤40 years (p=0.22) vs those aged >40 years (p=0.72) (61). As expected, the adverse effects profiles of the treatments differed: OS/A caused more hot flashes; chemotherapy caused more nausea, alopecia, stomatitis, and diarrhea. Goserelin or triptorelin + tamoxifen resulted in amenorrhea in all patients (101).

(8) OA/S plus tamoxifen vs no systemic therapy

The combination of OA/S + tamoxifen decreased recurrence and improved survival rates when compared with no systemic therapy. However, as indicated in previously, whether or not OA/S provides benefit in addition to that from tamoxifen alone is unclear. Benefit may be higher in young patients (aged <40 years).

(9) OA/S plus tamoxifen and chemotherapy vs chemotherapy alone

The combination of OA/S + tamoxifen + chemotherapy is better than chemotherapy in all patients (61,101,371). In the ECOG E5188 trial (387), there was no consistent benefit to tamoxifen + (OA/S + chemotherapy) vs OA/S + chemotherapy. This trial did not have a chemotherapy + tamoxifen arm; thus, the significance of these results is difficult to interpret.

(10) OS/A plus tamoxifen vs OA/S plus aromatase inhibitors

The combined analysis of the TEXT and SOFT trials (see Table 8) indicated a DFS rate benefit for OA/S + exemestane over OA/S + tamoxifen in premenopausal patients. It is unclear how this compares to use of tamoxifen alone because results have not yet been reported.

(11) Other considerations:

Goserelin every three months was found to be equivalent to goserelin every month (408). The study used subcutaneous depot injection of goserelin 10.8 mg every three months vs 3.6 mg

monthly. Both were sustained-release formulations containing a lactide/glycolide copolymer, but in a different ratio (95:5 vs 1:1).

In the trials summarized in the previous subsections the optimal duration of LHRH was not addressed.

LHRH added to any systemic therapy was beneficial overall and in patients aged ≤40 years but not aged >40 years (61).

4.3.4 Endocrine Therapy plus Chemotherapy

The SWOG S1007 (410) is an ongoing trial of best endocrine therapy vs best endocrine therapy + chemotherapy started in 2011 in N1 ER+ HER2−patients with low RS (≤25). Planned accrual is 4000 patients and will be stratified by RS (10−13 vs 14−25), menopausal status, and axillary surgery (SLNB vs full dissection).

The Optima Prelim and Optima studies (Optimal Personalised Treatment of Early Breast Cancer using MultiParameter Analysis) (411) are ongoing trials evaluating whether chemotherapy + endocrine therapy is better than endocrine therapy alone for patients that have ER+ HER2− cancer with involved nodes (pN1−2). In the preliminary trial, patients are randomized to standard therapy (chemotherapy + endocrine therapy) or to chemotherapy alone with endocrine therapy added if there is high risk of recurrence based on results of the Oncotype DX test and other assays (Mammostrat, IHC4 and fluorescence IHC4, PAM50). The main trial will further assess the assays selected in the preliminary trial.

4.3.5 Endocrine Therapy plus Everolimus

Both the UNIRAD study (412) and the SWOG/NSABP s1207 study (413,414) are ongoing trials investigating adjuvant endocrine therapy + everolimus. The UNIRAD trial is randomizing patients (ER+, HER2−, pN+) who are disease-free after three years of adjuvant endocrine therapy to ongoing endocrine therapy with or without everolimus (10 mg/day) for a total adjuvant therapy of five years. The trial started in 2013 with planned enrolment of 1984 patients. The s1207 trial is randomizing patients (HR+; HER2−; high risk including either N0 T2+ and RS >25, N1 and RS >25, or N2+) to standard endocrine therapy plus one year everolimus (10 mg/day) vs standard endocrine therapy plus one year placebo. Targeted accrual is 3500 patients over 3.5 years with completion around 2020.

4.3.6 Assessment of Hormone Receptor Status

Although accurate hormonal receptor status is crucial in determining appropriate treatment, results have often been inaccurate and irreproducible. Thresholds for determining positivity also vary (e.g., ≥1%, ≥10%, any). As a result, Guideline Recommendations for Hormone Receptor Testing were prepared by CCO/PEBC based on a joint systematic review by American Society of Clinical Oncology/College of American Pathologists and CCO's Program in Evidence-Based Care (415-417). This guideline indicates that core biopsies may be used to assess ER and PR status before neoadjuvant therapy, but cautions that because these may be derived from only a small sample of a larger tumour in which normal ducts and lobules are frequently not present, and in view of the heterogeneity in tumour hormone receptor expression, it is preferable to test the tumour in the surgical excision specimen when adequate surgical specimens are available. The guideline also notes

that comparison of core biopsies vs standard surgical specimen in 18 studies found median concordance of 95% for ER (all studies >83%) and 88.5% for PR (all studies >69%).

Some studies have also indicated that ER and PR status may change during the course of treatment. Zhang et al (418) published a meta-analysis of nine studies comparing hormonal receptor status before and after neoadjuvant chemotherapy. ER status was changed in 14.6% (8.9% ER− →ER+, 5.6% ER+ →ER−), while PR status changed in 24.8% (7.3% PR− →PR+, 17.0% PR+ →PR−). This was a significant change in both ER (p=0.016) and PR status (p<0.001) compared with prechemotherapy status. The change with neoadjuvant chemotherapy was also greater than that found for controls (ER change 18% vs 12%, p=0.011; PR change 26% vs 17%, p=0.001). Possible limitations were heterogeneity among studies of antibody selection, cut-off values, and chemotherapy used. The large variation in distribution of ER+/ER−/PR+/PR− between the included studies also suggests the included trials were not equivalent in the patient populations studied. Most studies used an IHC cut-off value of ≥10%. It is not known whether using the IHC cut-off value of 1% as recommended in current CCO guidelines would have resulted in less variation. The literature search for this current guideline on systemic therapy in early breast cancer did not find any studies that evaluated whether response to endocrine therapy correlates better with hormone receptor status before or after chemotherapy.

Van de Ven et al (419) also conducted a systematic review of changes in ER, PR, or HER2 receptors after neoadjuvant therapy (with or without trastuzumab). Discordance was reported in 4 of 8 studies in 8% to 33% of patients. Studies that indicated ER/PR was stable were generally smaller. A switch to HER2− was reported in up to 43% of patients when neoadjuvant chemotherapy was combined with trastuzumab. Subsequent to these reviews, Lindstrom et al published another trial (420) of patients with relapse and found patients with breast cancer experience altered hormone receptor and HER2 status throughout tumour progression, possibly influenced by adjuvant therapies. Assessment of markers at relapse may improve management.

4.4 BIOLOGIC/TARGETED THERAPY FOR HER2+ TUMOURS

4.4.1 Search Results

a) Guidelines

NICE. Early and locally advanced breast cancer: diagnosis and treatment (97).
The NICE guideline includes evidence published until June 2008. The recommendations are as follows:

- Offer trastuzumab, administered at three-week intervals for one year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to female patients with HER2 positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable. Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to female patients who have any of the following:
    - A left ventricular ejection fraction (LVEF) of ≤55%
    - A history of documented congestive heart failure
    - High-risk uncontrolled arrhythmias

    - Angina pectoris requiring medication
    - Clinically significant valvular disease
    - Evidence of transmural infarction on electrocardiograph (ECG)
    - Poorly controlled hypertension.
- Repeat cardiac functional assessments every three months during trastuzumab treatment. If the LVEF drops by ≥10 percentage (ejection) points from baseline and to <50%, then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman.

PEBC #1−24: The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer (104).

Literature search was conducted up to May 2006, with a literature update until September 2009; the original recommendations were endorsed 2010. The recommendation is:

- Trastuzumab should be offered for one year to all patients with HER2+, N+ or N0, tumour >1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.

PEBC #1−17: The Role of HER2/neu in Systemic and Radiation Therapy for Women with Breast Cancer [archived] (86).

The original literature search was conducted up until December 2005, and the guideline was archived in 2011. Recommendations are as follows:

- Patients with HER2/neu-positive breast cancer should be considered for chemotherapy containing an anthracycline instead of CMF or melphalan and 5−fluorouracil (PF) chemotherapy.
- Although the current evidence does not support a definitive recommendation regarding tamoxifen therapy and HER2/neu status, the weight of the evidence, especially the Gruppo Universitario Napoletano (GUN) trial, suggests that the efficacy of tamoxifen may be greater in patients with HER2/neu-negative cancer than with HER2/neu-positive cancer. However, the evidence does not support a recommendation against tamoxifen therapy in patients with HER2/neu-positive cancer. Although it is possible that tamoxifen is more effective in patients with HER2/neu-negative cancer, there is still sufficient evidence that it is effective in patients with HER2/neu-positive cancer as well.

National Breast Cancer Centre (NBCC) (now Cancer Australia). Recommendations for use of Trastuzumab (Herceptin) for the treatment of HER2 positive breast cancer (421).

This guideline appears to contain evidence published up to 2006 and is less current than the NICE and PEBC guidelines. Recommendations are as follows:

- Patients should be informed of the potential adverse effects of trastuzumab and any uncertainties about long-term effects. Patients receiving trastuzumab should be reviewed regularly and monitored for adverse effects by clinicians familiar with the drug.
- Adjuvant trastuzumab should be offered with chemotherapy following surgery in patients with N+ or N0 tumours larger than 1 cm. Trastuzumab concurrently with an

anthracycline is not recommended because of risk of cardiotoxicity. Trastuzumab can be offered to patients who require radiotherapy, although long-term adverse effects are unknown.

b) ***Meta-analyses (mostly adjuvant trials)***

Moja et al/The Cochrane Collaboration, 2012 (79)

The authors concluded that trastuzumab-containing regimens improved OS (HR=0.66, p<0.00001) and DFS rates (HR=0.60, p<0.00001). Risk of congestive heart failure and LVEF decline were increased with trastuzumab (RR=5.11, p<0.00001 and RR=1.83, p=0.0008). Cardiotoxicity is often reversible if trastuzumab is stopped immediately on occurrence. There was no difference in hematological adverse effects. In patients at high risk of recurrence and without heart problems, trastuzumab benefit is much greater than the risk. The balance of risk to benefit in patients at low-risk of recurrence is less clear. Two small trials of trastuzumab administered for ≤6 months vs none (FinHer and Buzdar, N=273 patients total), found similar efficacy as in longer studies but less cardiotoxicity. In the shorter regimens they found a hazard ratio of 0.31 for DFS (p=0.04) and RR=0.89 (no difference) for decline in LVEF. Risk of congestive heart failure was lower (RR=0.5), but this was based on only three events. This meta-analysis excluded the docetaxel + carboplatin + trastuzumab (TCH) arm of BCIRG 006, which found less cardiotoxicity than with anthracyclines, and did not include the sequential arm of NCCTG N9831 because it had not yet been published.

Yin et al, 2011 (422)

This analysis also found better DFS, OS, locoregional recurrence, and distant recurrence rates (all p<0.001) when trastuzumab was added to adjuvant chemotherapy. They did not comment on cardiotoxicity, but found a higher incidence of central nervous system recurrence (p=0.01), which they suggested may be because of the prolonged survival of the trastuzumab patients.

c) Neoadjuvant Trials, Systematic Reviews, and Meta-analyses

Several recent systematic reviews on neoadjuvant trastuzumab have been published (423-427). Only the study by Buzdar et al focused on early breast cancer and was excluded from the current literature search because of the small number of patients. Most RCTs have reported pCR as the primary endpoint. However, despite these limitations, it should be mentioned that all the reviews concluded that trastuzumab + chemotherapy significantly increases pCR compared with chemotherapy alone in patients with HER2+ cancer (probability of pCR calculated as RR=1.85 and 2.07, p<0.001 in favour of trastuzumab in two of the meta-analyses). Buzdar et al (428) compared paclitaxel + trastuzumab (every three weeks for four cycles)→FEC + trastuzumab (every three weeks for four cycles) vs the same regimen without trastuzumab and found pCR rates of 65% vs 26%, and three-year DFS rates of 100% vs 85% (p=0.041).

d) Meta-analysis or Reviews of Cardiotoxic Effects

Chen et al, 2011 (429)

This meta-analysis of 11,882 patients in ten RCTs found LVEF decrease and congestive heart failure to be 7.5% and 1.9% among patients receiving trastuzumab. This was significantly higher compared to no trastuzumab (RR=2.13, p=0.003 and RR=4.19, p<0.00001). Congestive heart failure effect was found in both early and metastatic cancer. The effect was found in patients receiving anthracycline-based chemotherapy (RR=4.27, p<0.00001, almost all were early breast cancer) but uncertain for patients receiving non-anthracycline chemotherapy (3 small studies with 495 patients with metastatic breast cancer, RR=2.42, 95% CI 0.36−16.19, p=0.36). This study did not consider the non-anthracycline arm of BCIRG 006.

Costa et al, 2010 (430)

This publication reviewed the six major studies (NSABP B-31, NCCTG N9831, BCIRG 006, HERA, FinHer, PACS 04) with a focus on efficacy and cardiac safety. Cardiac events were 1.9% to 3.8% in anthracycline + trastuzumab arms and lowest with TCH (0.4%). While TCH has less cardiotoxicity and has better survival rates than the control, there is uncertainty as to whether it is as effective as AC → docetaxel + trastuzumab → trastuzumab. Most of the studies excluded patients who had pre-existing heart problems or who experienced cardiotoxicity during chemotherapy. FinHer administered trastuzumab for a shorter time (nine weeks) before anthracycline and found negligible cardiotoxicity, although the study was small and the results need confirmation. Several trials are ongoing to evaluate nine weeks vs one year of trastuzumab. For patients with risk factors for cardiac dysfunction or patients with low risk of recurrence, the review suggested AC→ taxane + trastuzumab is difficult to justify, and TCH or trastuzumab after completion of chemotherapy (as in the HERA trial) may be preferable.

e) Individual RCTs with trastuzumab

The literature search located updated data for six of seven studies in the PEBC guideline, and identified nine new studies and seven ongoing studies. Two studies on LABC/metastatic cancer and one study with <100 patients did not meet the inclusion criteria for the current guideline. Because the previous guidelines were based on limited studies, most of which now have updated results, Table 15 was prepared containing all the studies and the most recent results (69-72,80-85,87,92-96,211,431-457).

Table 15. HER2+ plus trastuzumab, lapatinib, and/or pertuzumab RCTs

Study	Trial arms	N	Characteristics	Outcome
Neoadjuvant trastuzumab, lapatinib, or pertuzumab				

NeoALTTO
BIG 01–06
EGF 106903
NCT00553358
(431,432)
2008–2010
	Oral lapatinib vs IV trastuzumab vs lapatinib + trastuzumab
	
	Anti-HER2 for 6 w → weekly paclitaxel + anti-HER2 for 12 w→ surgery→adjuvant FEC→ same anti-HER2 as previously for 52 w
		455	HER2+, >2 cm,	• Pathologically complete response (pCR) higher in lapatinib + trastuzumab group than trastuzumab alone (51.3% vs 29.5%, p=0.0001)
				• pCR similar (p=0.34) in lapatinib and trastuzumab groups
				• No major cardiac dysfunctions, grade 3 diarrhea and liver-enzyme alterations greater in lapatinib groups
				• Conclude dual inhibition might be a valid approach
				• Lapatinib arms had high rates of diarrhea (79%) and hepatic effects (41%)
				• Lapatinib + trastuzumab, lapatinib, trastuzumab arms:
				  • Grade 3 diarrhea 21.1%, 23.4%, 2.0%
				  • Grade 3/4 hepatic effects 10.6%, 18.1%, 7.4%
				  • Grade 3/4 neutropenia 8.5%, 15.6%, 2.6%
				  • Grade 3 skin disorders 6.6%, 6.5%, 2.7%
				• Secondary endpoints of DFS and OS rates not reported yet

ACOSOG Z1041 (433) (434)	Neoadjuvant chemotherapy • Arm A: FEC-75 ×4→ paclitaxel+ trastuzumab (q1w×12) • Arm B: paclitaxel + trastuzumab (q1w×12)→ FEC-75 + trastuzumab ×4	282	HER2+, operable	Ongoing; 282 enrolled, pCR 56% (95% CI 48–65) in sequential arm, vs 54.2% (95% CI 46-63) in concurrent arm, OR=0.90 (95% CI 0·55–1·49). The most common severe adverse effects were neutropenia (25.3% sequential vs 31.7% concurrent) and fatigue (4.3% vs 8.5%)
GeparQuinto GBG 44 (435,436)	Randomized to receive neoadjuvant trastuzumab or lapatinib: EC + trastuzumab (q3w×4)→ T + trastuzumab (q3w×4) vs EC + lapatinib→ T + lapatinib Pegfilgrastim administered with lapatinib as primary prophylaxis for febrile neutropenia and with trastuzumab as secondary prophylaxis	620	HER2+, ≥2 cm by palpation or ≥1 cm by sonography; cT1–4, 83% operable, 17% LABC, 31% CN0, 55% HR+	• 30.3% EC + trastuzumab→T + trastuzumab and 22.7% EC+ lapatinib→T + lapatinib group had pCR (OR=0.68, p=0.04) • Trastuzumab associated with more edema (39.1% vs 28.7%) and dyspnea (29.6% vs 21.4%) and less diarrhea and skin rash • Still ongoing, no long-term data
NeoSphere (437) NCT00545688	A. trastuzumab + docetaxel B. Pertuzumab + trastuzumab + docetaxel C. Pertuzumab + trastuzumab D. Pertuzumab + docetaxel All administered for 4 cycles neoadjuvant	417	HER2+; stratified by operable, locally advanced, and inflammatory, and by hormone receptor expression	B vs A, pCR 45.8% vs 29% D vs C, pCR 24.0% vs 16.8% Grade 3 neutropenia and leucopenia similar in Groups A, B, D; almost zero in group C Serious adverse events similar in A, B, D; lower in C Small study will not measure survival effects
JBCRG-10 (438,439) [abstract]	Neoadjuvant chemotherapy 1. FEC ×4 → TCH ×4 2. TCH ×4 → FEC ×4	180 planned	HER2+, T1C-3, N0–1, M0	FEC arms were discontinued after interim analysis and insufficient power for conclusions on preferable sequence; decrease in LVEF was significant for FEC→ TCH arm

Study	Trial arms	N	Characteristics	Outcome
	3. TCH ×6	103 actual		
ADAPT HER2+/HR+ (211)	Neoadjuvant therapy (12 w) T-DM1 vs T-DM1 + endocrine therapy vs trastuzumab + endocrine therapy	380 planned	HER2+ HR+	Ongoing
ADAPT HER2+/HR− (211)	Neoadjuvant therapy (12 w) Trastuzumab + pertuzumab vs trastuzumab + pertuzumab + paclitaxel	220 planned	HER2+ HR−	Ongoing
Trastuzumab for <1 y				
FinHer (94,95)	3 cycles docetaxel or vinorelbine • HER2+ secondary randomization to trastuzumab or not for 9 w administered together with docetaxel or vinorelbine FEC administered after docetaxel/vinorelbine ± trastuzumab was complete	232	1010 pts overall, 232 HER2+ N+ or high-risk N0 (tumour diameter >20 mm, and PR−)	Median follow-up 62 mo, DDFS and OS rates: • Docetaxel better than vinorelbine overall, DDFS HR=0.66, p=0.010; OS HR=0.70, p=0.086 • HER2+: trastuzumab better than chemotherapy alone, DDFS HR=0.65 (95% CI 0.38−1.12), p=0.12; OS HR=0.55, p=0.094 • HER2+, adjusted for nodal metastases: DDFS HR=0.57, p=0.047 • Docetaxel + trastuzumab + FEC better than docetaxel + FEC (DDFS HR=0.32, p=0.29; OS HR=0.42, p=0.14) and vinorelbine + trastuzumab + FEC (DDFS HR=0.31, p=0.20) • Trastuzumab group had less heart failure (0.9% vs 1.7%) and change in median LVEF (0% vs 4% decrease) • Subgroup with very high HER2 content (≥22−fold the median of HER2− cancers) did not benefit from trastuzumab (HR=1.23, p=0.75) whereas the rest of the HER2+ pts did (HR=0.52, p=0.05)
PHARE (92,93,440) NCT00381901 2006−2010	6 mo vs 12 mo trastuzumab	3382	HER2+, early, at least 4 cycles (neo)adjuvant chemotherapy; median 2 cm, 45% N+, 58% ER+, 88% RT, 58% trastuzumab, 73% anthracycline and taxane containing chemotherapy	• Median follow-up 42.5 mo • DFS HR=1.28 (1.05−1.56), non-inferiority of 6 mo vs 12 mo could not be demonstrated because the 95% CI crossed the prespecified non-inferiority margin of 1.15 • Results inconclusive but trend in favour of 12 mo overall; subgroup analysis not yet complete • Higher cardiotoxicity in 12 mo group (5.7% vs 1.9%)
E-2198 (96) NCT00003992 [abstract]	Arm A: Paclitaxel + trastuzumab (q3w×4)→ AC Arm B: same regimen + trastuzumab for 52 w	234	HER2+, Stage II	Median follow-up 64 mo DFS equivalent for arms B and A (73% vs 76%, p=0.55) Congestive heart failure rate same (Arm B, N=4; Arm A, N=3)
PERSEPHONE (441) [abstracts]	6 vs 12 mo trastuzumab Test for non-inferiority of 6 mo treatment	Planned 4000; 3080 to date	HER2+, early	Ongoing Recruitment expected to be completed late 2015 and first interim analysis mid-2016
Trastuzumab for 1 or 2 y				
HERA (81,442,443) BIG 1−01	Trastuzumab for 1 and 2 y (not reported) vs observation; all groups	3401	HER2+, early, 50% HR+, 33% N0 Inclusion criteria was N+ or N0 if	Median follow-up 48.4 mo, 4−y survival rate results, trastuzumab vs control

Study	Trial arms	N	Characteristics	Outcome
2001–2005	after standard neoadjuvant, adjuvant chemotherapy or both After 1 y, the control group was allowed to cross-over to trastuzumab and 52% did		>1 cm For N0: 60 pts <1 cm 33 pts 1 cm 510 pts >1 cm and <2 cm 484 pts ≥2 cm 566 pts HR– N0 533 pts HR+ N0 68% anthracyclines, 26% anthracycline + taxane 6% no anthracycline	Intention-to-treat analysis: • DFS: 78.6% vs 72.2%, HR=0.76 (95% CI 0.66–0.87), p<0.0001 • OS: 89.3% vs 87.7%, HR=0.85 (95% CI 0.70–1.04), p=0.11 Censored for crossover • DFS 78.6% vs 71.7%, HR=0.69, p<0.0001 • OS 89.3% vs 81.5%, HR=53 (95% CI 0.44–0.65), p<0.0001 Crossover pts vs control • Fewer DFS events: HR=0.68 (95% CI 0.51–0.90), p=0.0077 More grade 3–4 (14% vs 8%) and fatal adverse events (1% vs 0.5%) on trastuzumab than observation 3-y DFS (1 y trastuzumab vs observation): N0 (all sizes): 90.8% vs 84.9%, HR=0.59 (95% CI 0.39–0.91) N0 (1.1–2 cm): 91.3% vs 86.7%, HR=0.53 (95% CI 0.26–1.07) N+ (N1): 84.7% vs 75.9%, HR=0.61 (95% CI 0.43–0.87) N+ (N2+): 67.8% vs 62.2%, HR=0.64 (95% CI 0.49–0.83) HR– N0: 87.1% vs 86.5%, HR=0.68 (95% CI 0.40–1.16) HR+ N0: 94.8% vs 83.4%, HR=0.46 (95% CI 0.23–0.93) 2-y DFS (1 y trastuzumab vs observation) N0: HR=0.59 (95% CI 0.39–0.91) N1: HR=0.61 (95% CI 0.43–0.87) N2: HR=0.64 (95% CI 0.49–0.83) T1 (0–2 cm): HR=0.65 (95% CI 0.47–0.90) T2 (>2–5 cm): HR=0.55 (95% CI 0.43–0.71)
HERA (444)	See previous entry in table	5102	Included landmark analysis of 3105 pts (2 vs 1 y trastuzumab) disease-free 1 y after randomization to trastuzumab	Median follow-up 8 y • DFS: 23.6% in both 2–y and 1–y group, HR=0.99 (95% CI 0.85–1.14), p=0.86 • DFS: 1 y vs observation, HR=0.76 (95% CI 0.67–0.86), p<0.0001) • OS: 1 y vs observation, HR=0.76 (95% CI 0.65–0.88), p=0.0005 despite crossover of 52% of pts from observation to trastuzumab • More pts had grade 3–4 adverse events in the 2 y group than 1 y group (20.4% vs 16.3%) or observation (8.2%). Included neoplasms, infections; nervous system, vascular, cardiac, musculoskeletal, gastrointestinal disorders (no significance values stated for these) • Conclude 2 y trastuzumab is not more effective than 1 y; 1 y remains standard of care
HERA, BIG 1–01 (445)	See previous entry in table	5102		Median follow-up 8 y • Cardiac adverse events leading to discontinuation of trastuzumab 9.4% in 2–y arm and 5.2% in 1–y arm • 2 y vs 1 y vs observation: Severe congestive heart failure rate (0.8%, 0.8%, 0.0%) and confirmed significant LVEF decrease

Study	Trial arms	N	Characteristics	Outcome
				(7.2%, 4.1%, 0.9%) were significantly greater in both trastuzumab arms compared with controls • Acute recovery reached in 87.5% receiving 2–y trastuzumab and 81.2% of pts with 1–y trastuzumab
HERA (446)	See previous entry in table 1 y trastuzumab vs observation	3401		Competing risks analysis of cumulative incidence of first DFS events in the CNS vs other sites after median follow-up 4 y: CNS as first relapse 2% trastuzumab vs 2% control, p=0.55
Lapatinib (± trastuzumab) for 1 y				

TEACH (447-449)	Lapatinib (1500 mg) vs placebo daily for 12 m	3147	HER2+, previous adjuvant chemotherapy	Median follow-up 48 mo, lapatinib vs placebo:
				• DFS 87% vs 83%, HR=0.83 (95% CI 0.70–1.00), p=0.053
				• OS 94% vs 94%, HR=0.99 (95% CI 0.74–1.31), p=0.96
				• HR– pts: DFS 87% vs 80%, HR=0.68 (95% CI 0.52–0.89), p=0.006
				  • N0 subgroup: HR=0.57 (95% CI 0.35–0.92)
				  • N+ subgroup: HR=0.74 (95% CI 0.53–1.03)
				  • Premenopausal HR=0.59 (95% CI 0.37–0.94)
				• HR+ pts: DFS HR=0.98 (95% CI 0.77–1.25), p=0.89
				• Central review as HER2+ (79% of pts): DFS 87% lapatinib vs 83% placebo, HR=0.82 (95% CI 0.67–1.00), p=0.04
				• HER2– or borderline by central FISH testing: DFS 85% vs 81%, HR=0.94 (95% CI 0.56–1.57)
				More serious grade 3/4 adverse events with lapatinib than placebo (6% vs 5%): diarrhea 6% vs 0.6%, rash 5% vs 0.2%, hepatobiliary disorders 2% vs 0.1%
				Any adverse effect: diarrhea 61% vs 16% (p<0.0001), rash 59% vs 15% (p<0.0001), hepatobiliary disorders 8% vs 3% (p=0.21)

ALTTO BIG 2–06 NCCTG N063D (450,451) [abstract]	Lapatinib +trastuzumab (52 w) vs trastuzumab (12w)→ lapatinib (34 w after 6 w delay) vs lapatinib (52 w) vs trastuzumab (52 w) • N=4613 after chemotherapy • N=3337 concurrent with anthracycline→ taxane • N=431 concurrent with platinum-containing regimen	8381	Recruitment June 2007 to July 2011, L arm closed Aug 2011 for futility 40% N0, 57% HR+	Median follow-up 4.5 y, 4–y DFS Lapatinib + trastuzumab vs trastuzumab: 88% vs 86%, HR=0.84 (95% CI 0.70–1.02), p=0.048 Trastuzumab→ lapatinib vs trastuzumab: 87% vs 86%, HR=0.93 (95% CI 0.76–1.13), p=0.044 both not significant at author's cut-off of p=0.025 Diarrhea (75% vs 20%), rash (55% vs 20%), hepatobilliary adverse effects (23% vs 16%) were more frequent in lapatinib + trastuzumab vs trastuzumab Primary cardiac endpoints <1% in all arms Quality of life substudy (N=777): worse in all arms at 12 w but returned to baseline by end of treatment at 52 w Follow-up continues
Trastuzumab for 1 y				
NSABP B31 and NCCTG N9831 combined analysis	Doxorubicin + cyclophosphamide→ paclitaxel ± trastuzumab N9831 Arms A and C, NSABP B31 Groups	4045	See later in this table	Median follow-up 3.9 y, significant improvement favouring trastuzumab • DFS: HR=0.52 (95% CI 0.45–0.60), p<0.001

Study	Trial arms	N	Characteristics	Outcome
(69) 2000–2005	1 and 2, see later in this table			• OS: 39% reduction, HR=0.61 (95% CI 0.50–0.75), p<0.001 Analyzed by nodal status, significant only for N+ • 0 nodes: 4-y DFS 86.8% vs 89.6%, events HR=1.78 (95% CI 0.3–10.7) (not significant, only 33 events occurred) • 1–3: DFS 89.7% vs 80.6%, HR=0.58 (95% CI 0.40–0.82) • 4–9: DFS 83.5% vs 71.1%, HR=0.68 (95% CI 0.48–0.98) • 10+: DFS 73.7% vs 46.5%, HR=0.55 (95% CI 0.38–0.81) Effective for all tumour sizes 0–2 cm: DFS 90.9% vs 81.6%, HR=0.39 (95% CI 0.26–0.60) 2.1–5 cm: DFS 83.2 vs 70.3%, HR=0.72 (95% CI 0.55–0.94) >5 cm: DFS 78.2% vs 52%, HR=0.61 (95% CI 0.35–1.06) Effect was similar for all tumour grades, and both HR+ and HR–
NCCTG N9831 (70,82-85,87) 2000–2005	• Arm A: AC (q3w×4)→ paclitaxel (q1w×12) • Arm, B (sequential): AC→ paclitaxel→ trastuzumab (q1wx52) • Arm C (concurrent): AC→ paclitaxel + trastuzumab (q1w×12)→ trastuzumab (q1w×4) RT or hormonal therapy after completion of chemotherapy when indicated	3505	HER2+, operable, Stage I-III, N+ or high-risk N0 39% <2 cm 51% between 2.1–4.9 cm 8% ≥5 cm 13% N0 Initially only N+ disease; as of May 2, 2003, pts with high-risk N0 (>2 cm +HR+; or >1 cm and HR–)	•Median follow-up 6 y, 5–y results (87) • Arm B vs A: DFS 80.1% vs 71.8%, HR=0.69 (95% CI 0.57–0.85), p<0.001; OS: 89.3% vs 88.4%, HR=0.88 (95% CI 0.67–1.15), p=0.343 • Arm C vs B: DFS 84.4% vs 80.1%, HR=0.77 (95% CI 0.53–1.11) • Trend toward increase in DFS with C compared with B (concurrent vs sequential), but not significant because the p value (0.02) did not cross the prespecified O'Brien-Fleming boundary (0.00116) for the interim analysis • Cardiac events (congestive heart failure or cardiac death): 3–y cumulative incidence 0.3%, 2.8%, 3.3% in Arms A, B, C, respectively; cardiac function improved following trastuzumab discontinuation and cardiac medication (85) • ASCO/CAP guidelines for HER2 positivity identify less pts than US FDA guidelines (3.7% less by IHC, 1.3% by fluorescence in situ hybridization, 1.7% with both); improvement in DFS was similar using either definition (83) [Note the ASCO/CAP guideline has now been revised, see (76,77)] • Did not find association between MYC amplification and additional trastuzumab benefit (82) • Trastuzumab benefit seemed independent of HER2 centromere 17 ratio and chromosome 17 copy number (84) • Both HR+ and HR– pts benefit from trastuzumab (HR=0.42, p=0.005 and HR=0.60, p=0.0001) (84)
NSABP B-31 (69,452) 2000–2005	AC (q3w×4)→ paclitaxel (q3w×4 or q1w×12) vs AC→ paclitaxel + trastuzumab (P=q3w×4 or q1w×12; H=q1wx52)	2101	HER2+, operable, N+	See joint analysis with NCCTG N9831 previous entry in table Cardiac function assessment at 7–y follow-up • Cardiac events: 4.0% trastuzumab vs 1.3% control; RR=3.30 (95% CI 1.63–6.66), p<0.001 • One cardiac death in each arm

Study	Trial arms	N	Characteristics	Outcome
				• Most pts recovered LVEF in the normal range after stopping trastuzumab, although some decline from baseline often persists
BCIRG 006, UCLA-0102006 (71,72) 2001–2004	• [AC→ TH]: AC q3w×4 → T q3w×4, trastuzumab q1w during chemotherapy then q3w until 1 y • TCH: Docetaxel + carboplatin (q3w×6) + trastuzumab (q1w during chemotherapy then q3w until 1 y • AC→T: AC q3w×4 → T q3w×4	3222	HER2+, early T1–3, N0–1, M0; N+ or high risk N0 (N=922); for N0 (assessed by SLNB or at least 6 nodes resected) at least one risk factor of age ≤35 y, tumour >2 cm, HR–, histological and/or nuclear grade 2/3 29% N0, 38% N1, 23% N2, 10% N3 40% T1 (≤2 cm), 53% 2–5 cm	Median follow-up 65 mo • AC→ TH vs AC→ T • DFS: 84% vs 75%, HR=0.64, p<0.001 • N0: 93% vs 85%, HR=0.47 (95% CI 0.28–0.77), p=0.0028 • N+ : 80% vs 71%, HR=0.68 (95% CI 0.56–0.84), p=0.0003 • N+ (≥4 nodes): HR=0.66 (95% CI 0.51–0.86), p=0.0017 • Tumour size <1 cm: HR=0.36 (95% CI 0.14–0.93), p=0.034 • Tumour size <2 cm: HR=0.73 (95% CI 0.49–1.09) • Tumour size ≥2 cm: HR=0.62 (95% CI 0.50–0.76), p<0.0001 • OS: 92% vs 87%, HR=0.63, p<0.001 • N0: HR=0.38 (95% CI 0.17–0.87) • N+: HR=0.67 (95% CI 0.50–0.88) • Tumour size <2 cm: HR=0.49 (95% CI 0.27–0.91) • Tumour size ≥2 cm: HR=0.66 (95% CI 0.49–0.88) • TCH vs AC→ T • DFS: 81% vs 75%, HR=0.75, p=0.04 • N0: 90% vs 85%, HR=0.64 (95% CI 0.41–1.01), p=0.057 • N+: 78% vs 71%, HR=0.78 (95% CI 0.64–0.95), p=0.013 • N+ (≥4 nodes): HR=0.66 (95% CI 0.51–0.86), p=0.0016 • Tumour size <1 cm: HR=0.45 (95% CI 0.17–1.16), p=0.096 • Tumour size <2 cm: HR=1.11 (95% CI 0.73–1.69), p=0.64 • Tumour size ≥2 cm: HR=0.70 (95% CI 0.57–0.87), p=0.0009 • OS: 91% vs 87%, HR=0.77, p=0.04 • N0: HR=0.56 (95% CI 0.27–1.13) • N+: HR=0.81 (95% CI 0.62–1.05) • Tumour size <2 cm: HR=0.75 (95% CI 0.43–1.29) • Tumour size ≥2 cm: 0.77 (95% CI 0.58–1.02) • No significant difference in OS or DFS among trastuzumab regimens, but both superior to AC→T (AC→TH stronger effect in some subgroups) • Benefit in N0, N+, and high risk N+ (≥4 positive nodes) • Without TOP2A co-amplification: DFS benefit with trastuzumab even larger, but trastuzumab had no DFS benefit in TOP2A co-amplified (but TCH still better therapeutic index because of adverse effects profile) • Congestive heart failure and cardiac dysfunction higher in AC→T + trastuzumab than TCH (p<0.001) • 7 acute leukemia in AC-based regimens vs 1 in TCH group (but received anthracycline outside the study)
BCIRG 006 (453)	See previous entry in table	3222		Health-Related Quality of Life questionnaire, assessed at baseline

Study	Trial arms	N	Characteristics	Outcome
				(all groups similar), midpoint (cycle 4), end of chemotherapy, 12-mo follow-up: • Physical scale, global health, and systemic effects deteriorated for all groups but recovered by 12 mo • Repeated measurement analysis found significantly better physical, global health, and less systemic effects with TCH
FNCLCC PACS-04 (454)	FEC or epirubicin/docetaxel; HER2+ secondary randomization to trastuzumab for 1 y or observation	3010	3010 pts overall, N+; 528 in HER2+ subgroup	Median follow-up 47 mo 14% reduction in risk of relapse with trastuzumab, HR=0.86 (95% CI 0.61–1.22), p=0.41 3-y DFS: 81% vs 78%, HR=0.86 (95% CI 0.61–1.22) OS: 95% vs 96%, HR=1.27 (95% CI 0.68–2.38) Of trastuzumab group, 10% did not receive trastuzumab and 18% discontinued trastuzumab before 6 mo due to cardiac events or progressive disease
N-SAS BC 07 RESPECT (80)	Trastuzumab monotherapy for 1 y vs trastuzumab + chemotherapy	300 planned	HER2+, Age >70 y, Stage I, IIA, IIB, IIIA/M0	Protocol only
Trastuzumab in HER2 low pts (IHC 1+ or 2+)				
NSABP B-47 (455)	Chemotherapy ± 1 y of trastuzumab Chemotherapy by physician choice, either TC (q3w×6) or AC (q3w×4 or q2w×4)) plus paclitaxel (q1w×12)	3260 planned	HER2 IHC 1+ or 2+ scores but non-amplified by FISH N+ or high-risk N0	Ongoing 1416 enrolled Feb 2011–Jan 2013
Second agent (pertuzumab or neratinib) after trastuzumab				
ExteNET, NCT00878709 (456)	Neratinib for 1 y vs placebo	2842	HER2+, N+ pts who completed adjuvant trastuzumab within 1 y before randomization	No results released yet, recruitment completed 2012, see http://clinicaltrials.gov/show/NCT00878709
APHINITY BIG 4–11 NCT01358877 (457)	1 y trastuzumab + pertuzumab vs trastuzumab Chemotherapy is investigator's choice between anthracycline-taxane or taxane-platin containing regimens	4800	HER2+ with excision of tumour and adjuvant chemotherapy; either • N+ (pN1), • N0 and T>1cm, • or N0 and T 0.5–1 cm and one of grade 3, ER–/PR–, age <35 y Randomized 3–7 w after surgery	Ongoing Accrual complete August 2013 (458)

Abbreviations: AC; doxorubicin + cyclophosphamide; DDFS, distant disease-free survival; DFS, disease-free survival; EC, epirubicin + cyclophosphamide; ER, estrogen receptor; REC, fluorouracil + epirubicin + cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR-, hormone receptor negative; HR+, hormone receptor positive; LVEF, left ventricular ejection fraction; LABC, locally-advanced breast cancer; N+, node-positive; N0, node-negative; OS, overall survival; pCR, pathologically complete response; RT, radiation therapy; TCH, docetaxel + carboplatin + trastuzumab; T, docetaxel; T-DM1, trastuzumab emtansine; TH, docetaxel + trastuzumab.

4.4.2 Questions and Interpretation

For which patients is the benefit in preventing recurrence greater than the added risk of cardiotoxicity (risk-benefit profile)?

a) Is trastuzumab beneficial in small node negative tumours? (T <1 cm; T <2 cm and node negative?)

Most of the RCTs exclude patients with small node-negative cancers, so there is limited evidence to evaluate this question. HERA (73,81,442,443) had included N0 cases with small tumours: 60 cases <1cm, 33 cases of 1 cm, and 510 cases >1 and <2 cm. HERA found no difference in efficacy of trastuzumab between N+ and N0 tumours, and was effective in both 0–2 cm and 2–5 cm cases at two years; at three years the trastuzumab effect was similar in both all N0 and N0 subgrouped as 1.1–2 cm and ≥2 cm. BCIRG 006 (71,72) found benefit in both patients with N0 and N+ cancer and results are not further divided by tumour size for patients with N0 cancer alone. Trastuzumab was beneficial in <1 cm, <2 cm, ≥2 cm, but not 1–2 cm; inconsistency may be due to the small numbers in each category. N9831 (69,70,82-85,87) included 39% of tumours <2 cm, of which some were 1–2 cm and N0, but data were not reported separately for this later group.

Petrelli and Barni (78) summarized the studies on very early-stage pT1a/bN0M0 HER2+ breast cancer, including both RCTs and retrospective case series. They conclude these cancers have a higher rate of relapse and poorer survival rate than HER2– cancers of the same size/stage, and that biology/prognostic factors (proliferative index, hormone receptor status, etc.) should guide the choice of treatment more than the tumour size for small N0 tumours.

Exploratory analysis in the FinHer trial (94,95) found that a subgroup with very high HER2+ content did not benefit from trastuzumab.

b) What is the optimal duration of trastuzumab therapy?

HERA results (73,81,442,443) indicated that one year of trastuzumab is as good as two years and with less adverse effects. The small FinHer trial (94,95) found nine weeks of trastuzumab is more effective than the control, with no difference in cardiotoxicity or brain metastasis. E2198 (96) found no difference between twelve weeks and one year, although this is a small trial published only as an abstract. PHARE (91-93,440) was inconclusive whether six months is non-inferior to twelve months. There was a nonsignificant trend favouring 12 months. It is suggested that although the optimal duration is still unknown and one year is standard, lower cardiotoxicity may justify shorter duration for some patients and six months trastuzumab is better than none.

c) Should trastuzumab be administered concurrently with or sequentially after chemotherapy?

No adjuvant studies gave trastuzumab concurrently with anthracyclines. Most either gave anthracycline→ taxane→ trastuzumab, or anthracycline→ (taxane + trastuzumab). In the N9831 study trastuzumab was administered either concurrently or sequentially with taxanes, and there was a trend toward an increase in DFS rates for concurrent vs sequential, but this was not statistically significant. There are ongoing studies giving trastuzumab and anthracyclines concurrently in the neoadjuvant setting.

d) What is the most appropriate chemotherapy to be used in conjunction with trastuzumab?

Limited data are available because only BCIRG 006 (71,72) compared a non-anthracycline to anthracycline regimen. It found that TCH (docetaxel + carboplatin [q3w×6] + trastuzumab [52 weeks]) had less adverse effects than AC→T + trastuzumab (AC→TH), while both were superior for DFS and OS to AC→T alone. A direct comparison was not made between the two trastuzumab regimens; however, they were both compared with the same control AC→T. DFS rates for the three groups were 84% AC→TH, 81% TCH, and 75% AC→T. Rates of congestive heart failure and cardiac dysfunction were higher in AC→T + trastuzumab than for TCH ($p<0.001$). There were seven acute leukemia cases for the AC-based regimens vs one in the TCH group (received anthracycline outside the study). It is uncertain whether TCH is as effective as AC→TH; however, due to lower cardiotoxicity and leukemia it may be preferred for some patients. As suggested in the review by Costa et al (430), TCH may be preferred for those patients with risk factors for cardiac dysfunction.

e) HER2 status and taxane efficacy

Meta-analysis of 11,631 patients in six studies found taxanes superior to non-taxane-based regimens for DFS in both HER2+ and HER2− disease. There was no evidence of interaction between HER2 status and taxane efficacy (459).

5. CONFLICT OF INTEREST

The conflict of interest details are shown at the end of Section 3 and in Appendix A.

6. JOURNAL REFERENCE

The recommendations and systematic review of this EBS have been published in the journal Current Oncology in a supplement on breast cancer.

Eisen A, Fletcher GG, Gandhi S, Mates M, Freedman OC, Dent SF, et al. Optimal systemic therapy for early breast cancer in women: a clinical practice guideline. Curr Oncol. 2015;22(Suppl 1):S67-81. http://dx.doi.org/10.3747/co.22.2320.

Gandhi S, Fletcher GG, Eisen A, Mates M, Freedman OC, Dent SF, et al. Adjuvant chemotherapy for early female breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline. Curr Oncol. 2015;22(Suppl 1):S82-94. http://dx.doi.org/10.3747/co.22.2321.

Freedman OC, Fletcher GG, Gandhi S, Mates M, Dent SF, Trudeau ME, et al. Adjuvant endocrine therapy for early breast cancer: A systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline. Curr Oncol. 2015;22(Suppl 1):S95-113. http://dx.doi.org/10.3747/co.22.2326

Mates M, Fletcher GG, Freedman OC, Eisen A, Gandhi S, Trudeau ME, et al. Systemic targeted therapy for HER2-positive early female breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline. Curr Oncol. 2015;22(Suppl 1):S114-122. http://dx.doi.org/10.3747/co.22.2322.

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A complete list of the members of the Early Breast Cancer Systemic Therapy Consensus Panel and the Working Group, with their affiliations and conflict of interest information, is provided in Appendix A.

Evidence-Based Series 1−21: Section 3

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

Optimal Systemic Therapy for Early Female Breast Cancer:
Development Methods, Recommendations Development and External Review Process

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Orit Freedman, Susan Dent, Maureen Trudeau,
and members of the Early Breast Cancer Systemic Therapy Consensus Panel

Report Date: September 30, 2014

1. THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (108). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels consist of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (108,109). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS includes the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: Development Methods, Recommendations Development, and External Review Process*. Summarizes the EBS development process, including the recommendations development process and the results of the formal external review of the draft version of the EBS.

2. FORMATION OF GUIDELINE DEVELOPMENT/WORKING GROUP

The Breast Cancer DSG asked the PEBC to develop a guideline on Systemic Therapy for Early Female Breast Cancer. In consultation with the DSG, a Working Group was identified from the DSG membership. This Working Group consisted of six medical oncologists and one methodologist. The Early Breast Cancer Systemic Therapy Consensus Panel (see Consensus section and Appendix A), consisting of medical oncologists selected to represent all regions of Ontario, reviewed the evidence base and initial draft recommendations, and voted on the final recommendations. The members of the consensus panel also reviewed the draft document at the same time as the Report Approval Panel (RAP) review (see later in this section).

A consensus panel process was used due to the large amount of evidence and wide scope of the document, the current use of several chemotherapy regimens that do not have direct randomized controlled trial (RCT) comparisons and that may have differential benefits in specific subpopulations of patients, possible differences in practice patterns among different centres and regions of Ontario, and to identify gaps in evidence for certain practices. The consensus process was envisioned as a way to standardize practice, to raise awareness of some of the issues surrounding treatment decisions, and to reveal practices that are not according to best evidence.

3. RESEARCH QUESTION

What is the optimal adjuvant systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered?

4. GUIDELINE REVIEW

Almost all PEBC document projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as "the use and/or modification of (a) guideline(s) produced in one cultural

and organizational setting for application in a different context" (460). This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with *de novo* recommendations development.

The SAGE Directory of Cancer Guidelines (available at www.cancerview.ca) was searched in May 2012 for current versions of guidelines published 2008 or later. Most guidelines listed are evaluated using AGREE II, and no further appraisal of quality was undertaken for the current guideline on systemic therapy in early breast cancer. NICE (UK), SIGN (UK), ASCO (US), NCCN (US), National Health and Medical Research Council (Australia), and New Zealand Guidelines Group sites were searched in February 2012 for guidelines not yet indexed in SAGE. Guidelines were also located from a literature search on MEDLINE and EMBASE as indicated in Section 2. Relevant guidelines are summarized in the Section 2 (Evidentiary Base); however, none were considered up-to-date enough to be adapted or used as the sole literature base.

5. EVIDENTIARY BASE DEVELOPMENT

A literature search on MEDLINE and EMBASE was conducted for the period 2008 up to March 5, 2012, and updated May 12, 2014 as described in Section 2. The search was limited to RCTs, guidelines, systematic reviews, and meta-analyses. Information on trials published before 2008 was obtained from the guidelines, systematic reviews and meta-analyses. Additional targeted searches were conducted to locate further details of some of the studies. The evidence is summarized in Section 2.

6. INITIAL STATEMENTS/RECOMMENDATIONS

Using the evidentiary base in Section 2, the Working Group developed a set of initial consensus statements or recommendations. These initial recommendations were developed through a consideration of the aggregate evidence quality, the potential for bias in the evidence, and the likely benefits and harms. The initial recommendations were voted on by a consensus panel as described in the next subsection. The consensus panel was provided the evidence summary (Section 2) and the initial recommendations, but not the key evidence summaries or comments that appear following each recommendation in Section 1. Both initial and revised recommendations are provided in Appendix B. The exact wording of the final recommendations in Section 1 differ from those in the Appendix B because cross-referencing to tables in Section 2 or other evidence was removed from the recommendation boxes and placed with the qualifying statements and key evidence. In a few cases, the wording was edited for clarity but it is consistent with the intent of the recommendation as voted on.

7. CONSENSUS PANEL PROCESS

During the project planning stage it was decided that final recommendations would be decided on by consensus at a meeting, with participants being medical oncologists practicing in Ontario. All medical oncologists currently serving as members of the Breast Cancer DSG were invited. Additional medical oncologists with an interest in breast cancer were invited to ensure representation from all Cancer Treatment Centres and regions of Ontario. The initial list of people to invite was prepared by the Working Group chair (MT) in consultation with the Head of Medical Oncology or the Head of the Cancer Centre. Invitees who declined to participate were asked if they could recommend another medical oncologist from their institution/centre with an interest in breast cancer. The consensus panel members are listed in Appendix A and included the medical oncologists in the Working Group plus the additional medical oncologists who agreed to participate

The Working Group prepared 34 recommendation statements based on the evidence in the systematic review in Section 2. Because a systematic review was not conducted on patient and disease stratification factors, draft recommendations on these (R1–R7) were based on clinical practice guidelines, factors included or evaluated in clinical trials in our systematic review, and experience of the Working Group members.

A modified Delphi technique was used to try to reach consensus. The draft recommendations were circulated to all consensus group members and voted on before the consensus meeting using a 5–point scale (strongly disagree, disagree, undecided, agree, strongly agree). Consensus was defined as at least 80% agreement (agree or strongly agree) and with no responses of strongly disagree. Voting on the initial set of recommendations was coordinated using Survey Monkey (a third-party website), which allowed anonymous voting and feedback. Of those people receiving the online survey, 19 of 20 responded. Recommendations without consensus from the initial questionnaire were presented at a consensus meeting on November 23, 2012 and voted on by 16 participants after rewording (if required) and discussion. Some of the recommendations that met consensus but also had some responses of "disagree" were reviewed but not voted on again. No additional discussion was held at the consensus meeting for statements attaining consensus and all responses being undecided, agree, or strongly agree.

7.1 QUESTIONNAIRE AND RESULTS

The original questionnaire, statements added or modified at the consensus panel meeting, and a tabulation of responses are provided in Appendix B. In the online survey, 24 recommendations achieved consensus, whereas 10 recommendations did not attain consensus in their entirety (some recommendations contained multiple statements voted on separately). Of these ten statements, participants were able to attain consensus for at least part (i.e., at least one sub-statement or clause) for nine. Eight of the consensus statements had attained consensus with some disagreement and were discussed at the meeting but were not voted on again. The discussion has been incorporated into the comments, key evidence, and qualifying statements.

7.2 THE DELPHI TECHNIQUE

Consensus methods are a means of resolving conflicting scientific data. A consensus statement is often developed after a consensus conference where a comprehensive analysis by a panel of experts is undertaken to resolve a scientific or medical issue. Quantitative methods, such as meta-analyses, provide statistical overviews of the results of clinical trials and attempt to resolve inconsistencies in published studies. Consensus methods are concerned with deriving quantitative estimates through qualitative approaches.

Features of consensus methods include:

- Anonymity — to avoid dominance by panel members
- (Iteration — to allow individuals to change their opinions
- Controlled feedback — to demonstrate the distribution of the group's response
- Statistical group response — to express judgment using summary measures of the full group response (providing more information than just a consensus statement)

The Delphi technique is a well-established consensus technique in scientific and medical research. Through the use of sequential questionnaires and regular anonymous feedback, this technique allows for collection, grouping, sorting, and ranking of data through structured communication. The technique also allows for attaining consensus among a group of individuals without requiring face-to-face contact.

Questionnaires are distributed to participants and responses are summarized to develop additional questionnaires in an attempt to seek agreement, disagreement, and new insights from the same pool of participants. The process continues until no new opinions are raised.

A modified Delphi Technique was applied to this project through multiple phases:

- Phase 1 — An initial questionnaire was administered to a group of chosen specialists in Ontario.
- Phase 2 — The results of the initial questionnaire were summarized and were distributed at the consensus meeting. A brief presentation on some of the relevant issues was made by the Working Group. Following discussion the respondent group answered another questionnaire that only included the questions for which there had not been consensus before the meeting. Although some statements had achieved consensus on some of the clauses and therefore did not strictly require revote on all the clauses, it was decided that any statement not reaching consensus in its entirety would be voted on again in full.

7.3 STATEMENTS WITHOUT CONSENSUS

The following 10 consensus statements did not attain agreement on all clauses in initial voting; however, 9 of 10 statements did attain agreement on some clauses following the consensus meeting. The discussion at the consensus meeting is summarized. Percentages refer to the percentage of participants agreeing or strongly agreeing with the statement.

7.3.1 Patient Stratification

a) Disease Characteristics (Statement 1)

Although not useful in determining tamoxifen response, progesterone PR) status may have prognostic implications. Based on the EBCTCG meta-analysis (55), estrogen receptor (ER) status played a stronger role in determining response to tamoxifen, regardless of PR status. Caution was raised about the PR status in the studies of the EBCTCG meta-analysis because specimens were analyzed by older analytical methods which are not as standardized as ER analysis. Furthermore, the rarity of ER−PR+ breast cancer requires that pathological confirmation take place. As such, the analytical method is important and should be conducted according to CCO/ASCO guidelines. Within Ontario, there is still uncertainty regarding whether laboratories are using one methodology to ascertain ER or PR positivity. PR status may still have prognostic value even if it is not useful in determining tamoxifen response; however, the response of patients with ER−PR+ cancer to other endocrine agents besides tamoxifen was not covered in the EBCTCG meta-analysis. Much discussion was raised over the standardization of PR evaluation and whether PR status currently influences clinical practice. In the final vote consensus was reached.

Most disagreed with or were undecided about the relevance of Ki-67 and molecular subtype. With respect to Ki-67, some studies show a prognostic role; however, there is poor analytical reproducibility between various centres, as this test is not standardized. Molecular subtypes do influence prognosis and response to chemotherapy. Such response variation was detected in retrospective analysis but has not been studied in prospective trials. ER, PR, human epidermal growth factor receptor 2 (HER2) and grade provide the most prognostic and predictive information and there is currently little additional value of the intrinsic subtype. Consensus was not attained for the utilization of Ki-67 and molecular subtype as predictive or prognostic factors when deciding about adjuvant chemotherapy.

b) Risk Stratification Tools (Statement 2)

Most participants voted that Oncotype DX and Adjuvant! Online may be used as risk stratification tools to help determine the candidacy for systemic treatments, although 11.3% of participants initially disagreed with the usage of Adjuvant! Online and there was not consensus before the meeting. Additional discussion revealed that Adjuvant! Online, was more frequently used as a discussion tool to empower patients as opposed to facilitate physician decision-making. Limitations of this particular tool include lack of HER2 inclusivity. Furthermore, estimated risks are dependent on the comorbidities entered.

Prognostic information for Adjuvant! Online comes from SEER databases and validation studies (17,461). There is overall good correlation. Exceptions include a UK validation study (18) demonstrating patients did worse than predicted by Adjuvant! Online. This difference may relate to differences in the healthcare systems. There is good correlation between Adjuvant! Online and Oncotype DX in patients with mid-risk of recurrence, but poor correlation at the high and low ends.

Oncotype DX is not funded consistently across Canada. This 21−gene signature test, of which 16 genes are involved in proliferation and distant relapse, is of greatest use for ER+ N0 disease, but can be utilized ER+ N+ disease as well. It is a commercial RT-PCR test costing approximately $4100 (in 2012), and categorizes the risk of recurrence as low, intermediate, or high. High-risk results indicate a benefit from receiving chemotherapy and tamoxifen.

Conversely, the benefit of the addition of chemotherapy to tamoxifen among female patients with low-risk results is minimal (approximately 1% benefit) and therefore not indicated.

c) Tumour Characteristics (Statement 4)

For patients in which chemotherapy is assessed to be tolerated, adjuvant treatment should be considered if N+ (100%), ER− >5 mm (88.9%), HER2+ tumours (100%), and high-risk N0 tumours with T size >5 mm and another high-risk feature (88.9%). There was initial disagreement (non-consensus) on whether the Adjuvant! Online 10−year risk of death from breast cancer >10% (77.7%) should be included. Comments were made that value judgments may be being imposed. The threshold for improved benefit, particularly for tools such as Adjuvant! Online, may be different for physicians and patients. The group added an initial question on Adjuvant! Online with a 10−year risk of death of >15%. After the revote there was consensus for Adjuvant! Online at a cutoff of both 10% (14 agree, 1 strongly agree) and 15% (9 agree, 5 strongly agree), although agreement was stronger for 15% cut-off.

d) High-Risk Features for Node Negative Disease (Statement 5)

High-risk features for N− tumours include grade 3 histopathology (88.9%), triple negative receptor status (94.5%), and lymphovascular invasion positive (72.3%). One participant initially strongly disagreed with including intermediate or high recurrence score (RS) in the Oncotype DX tool, with an estimated distant relapse risk of ≥15% at 10 years (88.9%), although consensus was reached after discussion. Four participants had written in *HER2*+ as another factor to consider. HER2+ was included on the final vote, and consensus was reached.

e) Disease Characteristics that May Not Need Chemotherapy (Statement 6)

Patients with tumours <5mm, N0 and no other high-risk features (see R6) *may* not require adjuvant chemotherapy (100%). The majority indicated lymph node positive with micrometastases only (<2 mm) and no other high-risk feature may not need adjuvant chemotherapy; however, 25% disagreed or were undecided and consensus was not reached. Issues include a lack of data to determine whether chemotherapy is beneficial in addition to a lack of consensus over whether a micrometastasis itself is a high or low risk factor. Consensus was still not reached after the discussion.

Most of the literature addresses whether to proceed with a full axillary lymph node dissection (ALND). Although trials such as ACOSOG Z0011 (462) did not demonstrate a trend toward clinical benefit of ALND for patients with limited nodal disease, caution must be exercised to not generalize the results of such trials to all patient groups and treatment modalities.

f) Disease Characteristics for HER2 Negative, Hormone Positive Disease (Statement 7)

Among patients with HER2 negative, strongly ER and PR (>90%) disease, adjuvant chemotherapy may not be required for some patients. There was consensus for tumours <5 mm. The group added "A low recurrence score <18 on Onco*type* DX" and this reached consensus. Discussion was held regarding chemotherapy for patients with 1−3 positive lymph nodes or with lymphovascular invasion (LVI), but consensus was not reached. Lymph nodes with micrometastasis only (<2 mm) did not have consensus on the initial survey but reached

consensus after discussion. Macrometastasis to 1–3 lymph nodes did not reach consensus on either vote. Concerns were raised regarding using cut-off level categories (high, medium, low) for continuous data, because the physician bases this on a value judgment. Another problem is that studies evaluated multiple factors, not just single factors in isolation.

7.3.2 Adjuvant Chemotherapy

a) Anthracycline and Anthracycline-Taxane-Based Regimens (Statement 13)

Several chemotherapy regimens were considered acceptable. Consensus was not reached on the use of CEF in either vote, although the majority thought it can be used. CEF may have a role in a subgroup of patients with very high risk of recurrence and in good health who can tolerate it. In general, there are other regimens that are as effective and less toxic. FEC followed by weekly paclitaxel was not included in the initial questionnaire. It was discussed at the meeting and participants were asked to vote on this regimen. Four of 16 participants present did not vote; therefore, consensus was not attained. Of those voting, 11 agreed and 1 was undecided. Dose-dense AC followed by paclitaxel was another regimen suggested at the meeting, and consensus was reached.

7.3.3 Adjuvant Endocrine Therapy

a) ER Positive Patients (Statement 16)

Adjuvant endocrine therapy should be considered in all patients with ER+ cancer, defined by the ASCO/CAP guidelines as ER IHC staining ≥1%, taking into consideration overall disease risk, patient preference and potential adverse effects (94.4% agreed, 5.6% strongly disagreed). Discussion led to concerns about the term 'should' however, the operative phrase is 'should be considered' indicating that after consideration, no therapy may be indicated. "Overall disease risk" was added as an additional item to be considered, and consensus was reached on the final vote.

b) ER Negative, PR Positive Patients (Statement 17)

> "Evidence suggests that estrogen receptor negative (ER–) with progesterone receptor positive (PR+) tumours may not benefit from tamoxifen, as compared with ER + tumours (please see Table 4 in Evidence Summary). Nonetheless, adjuvant endocrine therapy should be offered to all estrogen receptor negative (ER–), but progesterone receptor positive (PR+) patients."
>
> Revised at consensus meeting to state "should be considered" instead of "should be offered":
> "Evidence suggests that patients with estrogen receptor negative (ER–), but progesterone receptor positive (PR+) tumours may not benefit from tamoxifen, as compared with patients with ER+ tumours (please see Table 4 in Evidence Summary). Nonetheless, adjuvant endocrine therapy <u>should be considered</u> in patients with estrogen receptor negative (ER–), but progesterone receptor positive (PR+) tumours"

Consensus was not obtained for the original or revised recommendation, although 12 of 19 and 11of 16, respectively, indicated agreement. The discussion centered on the risk-to-benefit ratio for patients. Some oncologists asserted that the risk of hormone treatment is

low and patients should be offered treatment with the caveat that their benefit would likely be minimal if any. Other oncologists emphasized that the evidence points to no benefit for these patients (118); therefore, treatment should not be offered. All participants agreed that this profile (ER−PR+) is rare, and pathology should be consulted to confirm this result. Discussion for Statement 1 is also relevant to this issue.

c) Endocrine Strategies in Postmenopausal Women (Statement 24)

Regarding the role of aromatase inhibitors (AIs) in postmenopausal patients, there was consensus that multiple strategies exist for acceptable use. These strategies include the use of AIs upfront for five years (instead of tamoxifen), or as a switch from tamoxifen after two to three years (for a total of five years of endocrine therapy), or as extended adjuvant therapy for at least five years (after five years of tamoxifen) are all acceptable strategies (100%). Participants disagreed (61.1%) or were undecided (27.8%) regarding the use of AIs for more than five years after completing five years of tamoxifen (i.e., > 10 years total endocrine therapy) due to lack of available literature supporting this practice. After discussion all participants either disagreed or were undecided.

7.4 CONSENSUS ATTAINED, WITH SOME DISAGREEMENT

The following eight statements attained consensus but there was some disagreement (no strong disagreement) in the pre-meeting survey. The Working Group considered it might be useful to discuss these statements to see if there was misinterpretation, problems with the wording, or additional issues for consideration. According to pre-established rules, because consensus had been achieved no change to the intent of a recommendation was allowed and a second vote on these statements did not occur. Issues raised have been included in the qualifying statements.

7.4.1 Patient Stratification

a) Patient Factors (Statement 3)

Patient factors, specifically age (94.4% agreement), menopausal status (94.4% agreement) and medical comorbidities (100% agreement) were believed to be considerations for systemic treatment selection. Regarding age, 5.6% of panelists disagreed with its consideration as a factor. Discussion revealed that advanced age in the absence of other comorbidities should not be a factor in determining treatment. Young age, in particular, may affect aggressiveness of cancer, response to treatment, desire to spare fertility and may be a surrogate for menopausal status. In the initial survey four respondents indicated that patient preferences should be considered.

7.4.2 Adjuvant Chemotherapy

a) Anthracycline-Taxane Containing Regimens (Statement 8)

In patients who can tolerate it, using an anthracycline-taxane containing regimen is considered the optimal strategy for adjuvant chemotherapy (94.4% agreed, 5.6% disagreed). Discussion was held around the NCIC MA.21 data (33), which demonstrates that CEF is statistically significantly better than AC→P q3w and that there is no statistically significant difference between EC→P and CEF. Given the increased adverse effects of CEF, the

increased number of visits compared with anthracycline-taxane regimens and the increased difficulty in administering granulocyte-colony stimulating factor (GCSF) during treatment, the consensus remains that anthracycline-taxane containing regimens are considered the optimal strategy for adjuvant chemotherapy.

7.4.3 Adjuvant Endocrine Therapy

a) Definitions of Menopause (Statement 15)

Menopausal status is an important factor to determine before selecting adjuvant hormonal therapy. The most reliable definitions include bilateral oophorectomy (100%) or at least 12 months of amenorrhea prior to initiation of chemotherapy or tamoxifen (94.4% agreed, 5.6% disagreed). Following discussion, consensus was achieved with the following qualifications. Most studies had age limits, such as age >50 years. As such, some participants use hormonal analysis, particularly high follicle-stimulating hormone (FSH) and low luteinizing hormone (LH) to confirm menopausal status. There was additional discussion about what is monitored and how frequently. Additional assessments such as hormonal status may be necessary in some patients (i.e., post hysterectomy). In female patients ≤60 years of age who experience amenorrhea secondary to chemotherapy or tamoxifen, defining menopause is difficult, and care must be taken when initiating an AI (100% agreement).

b) Duration of Therapy (Statement 18)

Duration of therapy with tamoxifen for five years was considered standard of care in premenopausal patients with ER+ tumours, regardless of chemotherapy use (94.4% agreed, 5.6% disagreed). Discussions emphasized that the potential for switching endocrine treatments must be considered because menopausal status must be regularly evaluated clinically after initiation of treatment. After the consensus meeting, new data became available. The ATLAS (55) and aTTOM trials (56,284) demonstrated that 10 years of therapy with tamoxifen is superior to 5 years. The recommendations were revised to reflect this and the consensus panel members were asked to approve the change.

c) Ovarian Ablation/Suppression in Premenopausal Women (Statement 20)

The benefit of ovarian ablation (OA) or suppression when administered in addition to other systemic treatments remains controversial. 83.3% of participants agreed that the addition of OA or suppression to tamoxifen in premenopausal patients is not standard of care; however, 16.7% of participants disagreed or were undecided given the existence of data that suggests a benefit in female patients aged <40 years. There was significant discussion and divergent opinions on this issue. Pending upcoming data, the addition of ovarian ablation or suppression to tamoxifen in premenopausal patients it is not standard of care.

A meta-analysis of LHRH agonists (61) suggests that subgroups such as young patients with ER+ cancer (aged <40 years) have additional benefit of LHRH added to tamoxifen, because the effect was stronger in this subgroup (aged ≤40 years: -32% change in hazard ratio for recurrence, p=0.12; age >40 years: -1.5% change, p=0.91). Although these data demonstrate a trend towards benefit, statistical significance was not achieved (p=0.12). The meta-analysis also found that LHRH agonists may be as effective as chemotherapy regimens used, and LHRH added to chemotherapy has an additional benefit in female patients aged ≤40 years. The EBCTCG data (112) found a statistically significant improvement in recurrence

rate with addition of ovarian suppression to chemotherapy for patients aged <40 years (RR=0.70, 95% CI 0.39–0.996) but did not address the issue of tamoxifen use. Both meta-analyses suggest greater benefit of LHRH agonists in young female patients but did not address adding LHRH to tamoxifen + chemotherapy.

d) Aromatase Inhibitors and Postmenopausal Women (Statement 23)

The optimal adjuvant endocrine therapy in this population should include an AI (94.4% agreed, 5.6% disagreed). "Optimal" was believed to be an inappropriate adjective selection, and this has been noted in the recommendation in Section 1. Tamoxifen is acceptable in low-risk patients with low risk of recurrence.

7.4.4 Adjuvant Targeted Therapy (HER2+)

a) Concurrent vs Sequential Trastuzumab (Statement 31)

The initiation of trastuzumab concurrently with a taxane is generally preferred (88.9% agreed, 5.6% undecided, 5.6% disagreed). Discussion was held around the evidence summary endorsing that no significant differences in survival rate outcome exists between concurrent vs sequential initiation. Re-examination of the data concluded that the NCCTG 9831 (69,87) trial did not show a statistically significant improvement in overall survival (OS). Given the evidentiary basis demonstrating disease-free survival (DFS) rate benefit and a lack of added adverse effects in clinical practice, concurrent trastuzumab with taxanes is supported.

b) TCH vs AC→TH regimens (Statement 32)

The combination of trastuzumab with taxotere and carboplatin (TCH) has been evaluated, and, given its decreased cardiotoxicity compared with ACTH, is recommended for patients at higher risk for cardiotoxicity (83.3% agreed, 11.1 disagreed, 5.6% undecided). Discussion was held around the statement that TCH was found to be equivalent to ACTH. Given that the BCIRG 006 trial (71,72) was not designed to demonstrate "equivalence", qualifying statements specifying the relative benefit of TCH to ACTH should be included.

7.5 SUMMARY

The overall consensus process reinforced that when high-quality evidence is available, agreement is easily attained. Areas in which there was disagreement or no consensus were specific areas in which there was limited evidence available or value judgments were necessary to interpret risk stratification.

The overall trend of the consensus process was to identify female patients in whom treatment should be offered. It was among these consensus statements that higher proportions of disagreement were identified. Regarding which specific treatment regimens should be offered, overall, there was a higher proportion of agreement.

For recommendations with second votes, there was a tendency to switch from strongly agree to agree, although this did not affect consensus.

8. INTERNAL REVIEW

Almost all PEBC documents undergo internal review. For this document, the consensus panel reviewed the document as part of the consensus recommendations-development process. Internal review was conducted by the RAP, and the Working Group was responsible for incorporating the feedback and required changes. RAP had to approve the document before it could be sent to External Review.

8.1 REPORT APPROVAL PANEL REVIEW AND APPROVAL

The purpose of the RAP review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline before Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

The RAP reviewed this document during September to October 2013. The RAP approved the document on October 16, 2013. Key issues raised by the Report Approval Panel are summarized below.

8.1.1 Section 1 Comments and Responses

1. **Section 1, Recommendation 2 and 4**

Make sure the language here about Adjuvant! Online aligns with CCO MONC-2. They were okay with Adjuvant! Online but it was a back up to Oncotype DX when the latter could not be used.

> **Response**: CCO MONC-2 is a summary from the Molecular Oncology Advisory Committee and says there is nothing better than Oncotype DX to approve Oncotype DX funding; however, Adjuvant! Online has broader applicability and has good correlation with Oncotype DX for some patient groups. MONC-2 is still in draft and was written for a different purpose.

2. Section 1, Recommendation 6

The wording of "may not need" in R6 and R7 is less consistent with the wording that is preferred as a recommendation statement. However, I appreciate this is tightly integrated into the methodology and can't be changed.

> **Response:** The group believes the wording is appropriate and was accepted by the consensus panel.

3. Section1, Recommendation 6/7 (Qualifying statements)
Given this is a MAY NOT recommendation (may being the operative word), do you want to state something to the effect that this becomes doctor-patient preference but the doctor needs to make sure the patient gets the information. Doctor cannot be a yes/no gateway?

Response: This is pertinent to all recommendations. The physician must ensure the patient is onboard with the recommendations. The group believed no statement is required for this specific recommendation.

4. Section 1, Recommendation 23 (originally Recommendation 22)
Given this, do you want to push it up to 10 years in the recommendation and then you have your * indicating this came post-consensus because the new data was presented/published?

Response: As external review also raised this point and the literature search was updated, 10 years was put in the recommendation and the consensus panel was notified.

5. Section 1, Recommendation 30
Do you want to strengthen this statement to reflect your statement underneath? Rather than say "generally not recommended" say "not recommended outside the context of a clinical trial due to potential for increased cardiotoxicity".

Response: There was a study at ASCO that found no increased adverse effects with limited number of cycles of FEC; in Europe, they do use concurrently. Neoadjuvant studies suggest it is okay to use concurrently so do not want to strengthen.

8.1.2 Section 2 Comments and Responses

6. There is no quality assessment of the evidence (guidelines, reviews, RCTs).

Response: Under Section 3.1, it was stated most guidelines had been evaluated by AGREE II by SAGE, and therefore no further assessment was made. The study selection criteria (Section 3.2) indicate only RCTs with at least 100 patients would be included. In response to the comments, further details of the types of evidence and assessment are provided in the literature search results (Section 4.1). A table has been added to the appendices summarizing the guidelines and AGREE II evaluation. Note that it is policy not to evaluate our own (PEBC) guidelines. Individual patient data meta-analyses by EBCTCG and LHRH-agonists group were considered to be the highest quality evidence, and these meta-analyses were relied on for several questions. Additional explanation of these studies and evidence quality was added. AMSTAR ratings of systematic reviews referred to in the Results or Discussion are now provided in a table in the Appendices. A summary of the quality assessment for individual RCTs (excluding those already in previous guidelines, systematic reviews, or meta-analyses) is also provided in the Appendices.

7. No overall statement of the yield of evidence. A summative statement about what makes up the evidence may help. Include an overall statement of the number and types of

studies considered in each section. What is the overall quality of the evidence and key issues for the reader?

8. Unclear how the various guidelines, meta-analyses, or reviews were used and how the new RCT data fits in. There is little discourse in the text about what the data says and what the bottom line is. Some tables are presented without any context or discussion. Are the conclusions consistent and is there still uncertainty? Include a concluding statement for each section.

   Response (7 and 8)
   The Results and Discussion have been edited to more clearly indicate the types of evidence included and how they fit together. Additional interpretation and conclusions have been added. A statement referring the reader to Section 1 for recommendations has been added at the start of the Results and Discussion.

9. There was concern with readability/accessibility of the document. Consider a paragraph on how to use the document, signposts, and contents/index for Sections 1 and 3.

   Response
   A table of contents has been added for all sections. Some introductory statements have been added.

9. EXTERNAL REVIEW BY ONTARIO CLINICIANS AND OTHER EXPERTS

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the draft document with recommendations modified as noted under Internal Review was circulated to external review participants for review and feedback.

The revised document was circulated to Consensus Panel members at the time of external review, as well as following completion of the external review process.

9.1 METHODS

9.1.1 Targeted Peer Review

During the guideline development process, five targeted peer reviewers from across Canada considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks before completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a

guideline. Written comments were invited. The questionnaire and draft document were sent out on March 24, 2014. Follow-up reminders were sent at two weeks and at four weeks. The Working Group reviewed the results of the survey.

9.1.2 Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals who are the intended users of the guideline. Breast DSG members not part of the Working Group or consensus panel, plus all other medical oncologists, surgical oncologists, and radiation oncologists in the PEBC database who had indicated breast cancer as an area of interest were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. The notification email was sent on March 24, 2014. The consultation period ended on May 2, 2014. The Working Group reviewed the results of the survey.

9.2 RESULTS

Several reviewers commented that the guideline is very detailed, comprehensive, well-organized, and well done. This is reflected in the ratings in the following sections. Concerns or suggestions for improvement along with the response of the authors are listed for both the targeted peer review and professional consultation.

9.2.1 Targeted Peer Review

a) Questionnaire

Three responses were received from four reviewers. Key results of the feedback survey are summarized in Table 16.

Table 16. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer ratings (N=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**				3	
2. **Rate the guideline presentation.**				2	1
3. **Rate the guideline recommendations.**			1	1	1
4. Rate the completeness of reporting.				2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				3	
7. Rate the overall quality of the guideline report.				2	1
	Strongly	(2)	Neutral	(4)	Strongly

	disagree (1)		(3)		agree (5)
8. I would make use of this guideline in my professional decisions.			2		1
9. I would recommend this guideline for use in practice.			2		1

6. What are the barriers or enablers to the implementation of this guideline report?

Publication of this guideline on the CCO website will ensure that it can be readily accessed by physicians treating this group of patients. Implementation of the guideline at practice level may be difficult to study. Assessing guideline adherence retrospectively may be the only way to determine efficacy of implementation.

b) Summary of Written Comments

The main points contained in the written comments and the guideline authors' responses are provided in Table 17.

Table 17. Targeted peer review comments and Working Group responses.

Comment	**Authors' response**
This guideline is already a bit dated as the literature search included publications up to March 2012.	Targeted searches were performed to locate full publications of data included as abstracts. The authors tried to keep up-to date with presentations at conferences. For these reasons the likelihood of being outdated is low. As a result of the comments the literature search was updated. Annotations that specific data was from publications after the literature search date were removed.
The order of factors in R4 and R5 is a bit dated and does not reflect current understanding of biology.	The factors were those developed by consensus and are in no particular order.
R6: should consider 'benefit' instead of 'need'	The authors agree and made the appropriate change.
<u>Chemotherapy (R8−14)</u>	
R13. The study comparing TC and AC suggested that TC was superior. Why is TC not a standard in R13.	A cross-reference to R14 that covers TC has been added.
R13. The emphasis on epirubicin-based regimens at the expense of other regimens may be increasingly difficult to justify. There is mounting evidence that the dose-escalation effect of epirubicin is now explained by a pharmacogenomic metabolic interaction (463). UGT2B7 "fast metabolzsers" of epirubicin have lower drug levels, less myelosuppression, and poorer long-term outcomes.	An additional bullet on epirubicin has been added. Data on UGT2B7 and pharmacogenomics (463,464) is exploratory molecular data that does not meet our inclusion criteria. The difference in the EBCTG meta-analysis was not statistically significant, although became greater with longer follow-up as indicated in the studies in Table 3. Benefit of adding a taxane was shown in individual studies such as PACS 01 which

The 2012 meta-analysis shows no significant benefit to adding taxanes if you reduce the number of anthracyline cycles. PACS 01 trial was stratified by age (cutpoint 50 years) and the superiority of FEC→T was observed only in older patients, and that the treatment interaction test by age was statistically significant. Consequently, FEC→T may well be undertreatment for i) female patients age <50 years, and ii) those female patients with UGT2B7 "fast metabolizer" genotypes.	had more patients and longer follow-up. This has been clarified. The PACS 01 authors (27) indicate subgroup analysis should be considered exploratory and underpowered. The difference between the two age groups was not statistically significant.
It would be great to address the use of AC→T every 3 w as there is evidence against this.	A sentence has been added to the qualifying statements.
<u>Hormone Receptor Positive</u>	
R18. Should be updated with the results of 10 years of tamoxifen and there should be more than an asterix for use of extended tamoxifen. I would suggest wording of R18 be reconsidered. Tamoxifen for 5 years has been standard in premen pts, but tamoxifen for 10 is reasonable option to consider given recent evidence.	The recommendation and key evidence sections have been updated to include the new evidence.
R20. ASCO will update the oophorectomy and tamoxifen and this maybe should be reconsidered if the results there are positive.	Section 1 (qualifying statements) and Section 2 were revised to note the TEXT and SOFT trials. Data on the tamoxifen alone arm is not yet reported.
R22/R23. I would say my personal preference would be for recommendation 22 and 23 to be reveresed.	These have been switched.
One of the areas of clinical conundrum is the use of tamoxifen for >5 years — in terms of the longevity of this guideline I think the recommendations/discussion may need to highlight this issue further.	The recommendations and discussion have been revised to include the aTTOM and ATLAS trial results and note that 10 years tamoxifen is recommended.
<u>HER2 (R 26–34)</u>	
R 31. It is concerning that the concurrent trastuzumab regimens are not more strongly favoured over the sequential trastuzumab regimens, given that the only randomized head to head comparison of concurrent vs sequence shows a clinically meaningful difference (4% DFS) in favour of concurrent administration.	This is a different interpretation of the strenth of evidence from NCCTG N9831. The differences are not statistically significant. We indicate that concurrent is generally preferred.
R29/32. The BETH study (SABCS 2013) did support TCH chemotherapy as highly effective systemic therapy with minimal cardiotoxicity. Furthermore, patients receiving TCH had a numerically higher	BETH is an abstract, and patients were randomized to bevacuzimab, not the chemotherapy administered. While TCH was effective it cannot be directly compared with the

DFS rate than those who received the anthracycline-taxane trastuzumab regimen.	anthryacycline. It appears similar to BCIRG 006 evidence (ie suggestive but not sufficient to make a strong recommendation in favour of TCH). No changes are required.
R29. The guideline implies TCH should be reserved for patients with cardiac risk factors — it is not included in the third bullet of R34. Why is neither BCIRG 006 regimen (TCH or AC→TH) mentioned here? Other guidelines administer TCH as a first tier regimen; e.g., NCCN gives two Preferred Options — AC-paclitaxelH and TCH. Sequential regimens (HERA) are given as "other options"	R29 indicates trastuzumab can be used with any accepted chemotherapy. BCIRG 006 does not mention radiotherapy so is not relevant to the R34 statement on radiotherapy. A sentence has been added to R31 and R32 deals with TCH.
<u>Other</u>	
Needs more discussion about what we know about biology and responsiveness	The authors felt this is outside the scope.
One consideration might be a qualifying statement somewhere about the applicability of the guideline recommendations to male breast cancer — although rare.	This is outside the scope.

9.2.2 Professional Consultation

a) Questionnaire

Twenty responses were received. Key results of the feedback survey are summarized in Table 18.

Table 18. Responses to items on the professional consultation survey.

General questions: Overall guideline assessment	Number of responses (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0 (0%)	0 (0%)	1 (5%)	7 (37%)	11 (58%)
	Strongly disagree (1)	(2)	(3)	(4)	Strongly agree (5)
2. I would make use of this guideline in my professional decisions.	1 (5%)	0 (0%)	2 (10%)	4 (20%)	13 (65%)
3. I would recommend this guideline for use in practice.	0 (0%)	0 (0%)	3 (15%)	4 (20%	13 (65%)

4. What are the barriers or enablers to the implementation of this guideline report?

Ease of navigation, structure, and table of contents make the document easy to use. Wide circulation is a strength. Barriers may be funding issues when patients vary from standard therapy, oncologists' personal biases, and keeping the document current.

b) Summary of Written Comments

The main points contained in the written comments and the guideline authors' responses are provided in Table 19.

Table 19. Professional consultation comments and Working Group responses.

Comments	Authors' Response
Patient/Disease Characteristics	
R1. Suggest adding perineural invasion and tumour histology (certain subtypes are less likely to metastasize e.g. papillary, colloid, acinar, tubular - if small and node -ve - and certain subtypes benefit less, if at all, from chemotherapy e.g. metaplastic cancers)	The list includes those factors for which consensus was reached. Other factors may be useful.
R1. (ER-/PR+ is more common than "1% of cases", likely 2–5%. There is a need to expand on the association between LVI and outcome.	Removed "1%". Decided the LVI discussion is okay as is.
R2. Adjuvant! Online can be adjusted for LVI and HER2 over expression/amplification using the "prognostic" function. Although the Adjuvant! Online mortality estimate is robust, the recurrence estimate over-estimates risk and morality should be used.	Users can enter prognostic factors and decide whether to use mortality or recurrence. Users need to be aware of how to use this tool fully and the website is provided in Recommendation 2. The authors decided further details are not required.
R2. Mammaprint should be included as it is a validated measure of prognosis. A comparison of Oncotype DX (assesses chemotherapy 'utility') and Adjuvant! Online (estimate absolute benefit) would be useful.	A reference to the MOAC guideline which compares molecular tests was added.
R3. Should include patient preference (quality of life, adverse effects) as a further factor.	This applies overall, and a statement has been added at the start of the recommendations.
R4. We really have no idea for whom chemotherapy "would be tolerated".	Changed to "likely to be tolerated".
R4. Where does T size >5mm come from? It seems inconsistent to use death data for Adjuvant! Online when we use distant relapse risk of ≥15% for Oncotype DX. Should there also be consideration of risk of relapse >x?	These factors were based on consensus.
R6. Should state 'likely would not benefit from'.	The wording "may not" is okay as is.
R7. The cut-off of ">90%" to define strong ER expression is without basis. The cut-off for Oncotype DX estimated 10-year risk of distant relapse <15% is without basis.	This is a reasonable estimate based on available data.
Chemotherapy (Rec 8–14)	
R8. There seems to be contradictory statements in Bullets 2 and 3 comparing adding taxane vs additional cycles of anthracycline. R8. I don't agree with the second bullet. In the PACS 01 study, FEC×3→ docetaxel×3 showed	The difference was not statistically significant in the EBCTG meta-analysis, although became greater with longer follow-up as indicated in the studies in Table 3. Benefit of adding a taxane was shown in individual studies such as PACS 01 which had more

superior survival to FEC×6 alone – It is important to note that the incremental benefit of using an anthracycline and/or adding a taxane depends on the absolute overall benefit of chemo in that particular patient.	patients and longer follow-up. This has been clarified.
R13. This list is not complete. AC×4, TC×4 and CMF are all reasonable regimens to use depending on the particular situation. MF (a very old regimen) is definitely better than no chemo for patients who insist they not develop alopecia.	A link to R14 has been added. Rationale is already provided in R14. CMF is listed in R12. The authors do not support routine use of MF.
<u>Endocrine Therapy/HR+ (Rec 15–25)</u>	
R16. There should be some guidance in regard to low risk endocrine sensitive breast cancer. With the increasing numbers of female patients of all ages being diagnosed with tiny, grade 1, ER/PR disease, it should be stated that some patients at low risk do not require adjuvant endocrine therapy and that the option of surgery alone is reasonable.	R16 indicates endocrine therapy "should be considered" and notes overall disease risk and adverse effects are factors to be taken into account.
R18. For ATLAS should also include the higher incidence of pulmonary embolus with extended tamoxifen, without an increase in PE-associated mortality.	This has been added.
R20. There is as yet no definitive data that ovarian suppression added to tamoxifen is beneficial. In postmenopausal patients (naturally or artificially) an adjuvant bisphosphonate (clodronate or zoledronic acid) improves survival. This is an argument for considering adding ovarian suppression, especially for patients at high risk of recurrence.	The TEXT and SOFT trials results have been added the qualifying statements and the results/discussion in Section 2. More definitive conclusions may be possible once the results for the tamoxifen alone arm are reported.
Adjuvant bisphosphonates are also a glaring omission from this guideline and, although I recognize that the definitive information didn't come out until after the "closing date" of the guideline, omission of this data renders this guideline outdated from the outset.	A list of trials on adjuvant treatment with bisphosphonates is included in Appendix D. This was not included in the consensus panel discussion and will be covered in a separate document. This is noted in Subsection 4.2.3c of Section 2.
R20, R21. The EBCTCG does provide a subgroup analysis for ovarian suppression and ablation which suggests benefit in premenopausal patients who have not had chemotherapy.	This is discussed in the qualifying statement and Section 2.
R20, R21. Has the data from the ABCSG been taken into account here?	ABCSG-12 compares tamoxifen vs anastrozole (both ± zoledronic acid) in premenopausal patients receiving goserelin, and found improved outcome for patients older than 40 y (but not age ≤40 y) when zoledronic acid was included (see Section 2). Because all groups received goserelin, no conclusion about whether it should be added is possible.

R22 & R23 are confusing, suggest reversing the order	This was done.
R23. I would add "unless contraindicated" to the end of the recommendation.	This is assumed for all recommendations, and does not need to be added explicitly.
R23. The working of the second bullet could be misinterpreted as it sounds like that tamoxifen and AI should be administered concurrently	Wording has been revised to clarify this is consecutive (not concurrent).
R24. As stated in the key evidence, upfront AI for 2 to 3 years followed by tamoxifen to complete 5 years is an equally valid option	The overall evidence supports superiority of AI over tamoxifen, and switching from tamoxifen to AI. Although the BIG 1−98 trial found no significant difference between letrozole→ tamoxifen and tamoxifen→ letrozole, this does not mean there is sufficient evidence to routinely switch patients to tamoxifen. However it is could be considered for patients for which tamoxifen adverse effects are preferred or specific subgroups (see last qualifying statement).
R24. I think there needs to be more nuance about extended adjuvant therapy with AI. In MA.17, differences in DFS rate only translated to OS difference in patients with node-positive cancer. Similar findings were also observed in the extended tamoxifen studies. There needs to be more discussion about patient selection for extended adjuvant therapy.	This is discussed in Section 2. In NSABP B-33 and MA.17, subgroups of patients with N+ cancer seem to benefit more from AIs than N0, but both studies were unblinded and allowed cross-over and this confounds the OS analysis. Qualifying statements were added to R22 and R24.
Some latest data on ATLAS/aTTOM were added after the preliminary data reported as key evidence, so needs to replace preliminary data so that people reading the key evidence will only see one interpretation of these studies re: 10 years tamoxifen.	The recommendation and key evidence were revised.
<u>Targeted Therapy/HER2+ (Rec 26−34)</u>	
R26. Guidelines for HER2 testing been changed. This needs to be updated	This was revised to include the criteria from the updated guideline
R28. The BCIRG006 included some patients with node negative tumours <1.0cm. The Qualifying statements should be updated with this in mind.	The qualifying statement is modified to refer to BCIRG 006 and HERA in R27.
R31. Trastuzumab should be administered concurrently with taxane whenever possible. There was a clear and significant DFS rate difference in favour of this.	The qualifying statement indicates concurrent use is generally preferred, although this is for practical reasons. The evidence is insufficient to make a recommendation on order based on survival. N9831 indicated the DFS rate difference was not significant and this has been clarified in Section 2.
R31. Is it worth specifying baseline MUGA requirements prior to initiation?	It was decided not to include this.
R33. It is difficult to understand this recommendation. If TCH is recommended as an anthracycline-free regimen with good clinical data to support it, why should TCycloH be recommended for the same setting with no supporting data?	It is indicated that it “may be used” and the rationale is provided, whereas TCH is “recommended” in R32.

Other	
Didn't notice any information regarding timing of adjuvant systemic therapy (optimal time from surgery to therapy).	There were no RCTs found that compared timing.

9.3 CONSENSUS PANEL

As a result of external review and the updated literature search, Recommendations 18 and 23 were revised to indicate the evidence supported use of tamoxifen up to ten years (instead of five years). The panel members approved this change.

9.4 CONCLUSION

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the authors and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

10. CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Early Breast Cancer Systemic Therapy Consensus Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

MT had responsibility as Head of Medical Oncology for donations from Roche and Amgen to the cancer program and fellowship funding from Eisai, Roche, Novartis, and Amgen. MT received grants or research support from Astellas, Medivation, and Novartis. SD is an principal investigator for the Aphinity trial; has received a speaking honorarium from Hoffman La Roche, Amgen, and Novartis; travel support from Celgene and Roche; and unrestricted educational grants from Roche, Pfizer, GSK, and Amgen. AE received a grant from Genomic Health and was an NCIC principal investigator for the OlympiA trial. SG received consulting fees as an advisory board participant and speaker at education rounds for Novartis. The other guideline authors declared they had no potential conflicts.

For the Consensus Panel, 10 members declared they had no conflicts of interest, and 4 (YM, VG, PB, BD) declared conflicts as indicated in Appendix A. The RAP reviewers declared they had no conflicts. Two of the targeted external reviewers declared no potential conflicts of interest. The third declared having been a principle investigator on four clinical trials and having managerial responsibility for an organization that received >$5000 funding from a company/corporation with a vested interest in an object of the study.

The COIs declared did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca

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Appendix A: Members of the Working Group and Early Breast Cancer Systemic Therapy Consensus Panel.

Participant	***Hospital/region***	***Conflicts declared***
Working Group, Content Experts (Medical Oncologists)		
Maureen Trudeau	Odette Cancer Centre (Sunnybrook), Toronto	Responsibility as Head of Medical Oncology for donations from Roche and Amgen to the cancer program and fellowship funding from Eisai, Roche, Novartis, and Amgen; grants or research support from Astellas, Medivation, and Novartis.
Andrea Eisen	Odette Cancer Centre (Sunnybrook), Toronto	Grant from Genomic Health for a pending research study; NCIC principal investigator for the OlympiA trial
Sonal Gandhi	Odette Cancer Centre (Sunnybrook), Toronto	Consulting fees as an advisory board participant and speaker at education rounds for Novartis
Susan Dent	The Ottawa Hospital Cancer Centre, Ottawa	Principal investigator for the Aphinity trial; speaking honorarium from Hoffman La Roche, Amgen, and Novartis; travel support from Celgene and Roche; and unrestricted educational grants from Roche, Pfizer, GSK, Amgen
Mihaela Mates*	Cancer Centre of South-Eastern Ontario, Kinston General, Kingston	None
Orit Freedman	Durham Regional Cancer Centre, Oshawa	None
Working Group, Research Coordinator/Methodologist *[did not vote on consensus statements]*		
Glenn Fletcher	PEBC, McMaster University	none
Early Breast Cancer Systemic Therapy Consensus Panel (Medical Oncologists)		
Phil Bedard *	Princess Margaret Hospital, Toronto	Grants from GSK, Roche, Novartis, Bristol Myers Squibb (clinical trials, site PI)
Nadia Califaretti	Grand River Regional Cancer Centre, Kitchener	none
Bindi Dhesy	Juravinski Hospital and Cancer Centre, Hamilton	Local PI of foretinib, NCIC co-chair for MAC.15 study of Oncotype DX; travel grant from Novartis
Dorie-Anna Dueck*	Northwestern Ontario Regional Cancer Centre, Thunder Bay	none
Katherine Enright	Peel Regional Cancer Centre, Mississauga	none
Vivian Glenns	North York	PI/grants for Marianne trials (MA17R)
Caroline Hamm	Windsor Regional Cancer Centre	none

Yolanda Madarnas	Cancer Centre of Southeastern Ontario/Kingston General Hospital; Department of Oncology, Queen's University, Kingston, ON.	Consulting (Roche) for case-based educational module development; PI at her institution for several multicentre trials
Yasmin Rahim	Southlake Regional Cancer Centre, Newmarket	none
Sara Rask	Royal Victoria Hospital, Barrie	none
Andrew Robinson	Kingston General Hospital (Health Sciences North, Sudbury at date of meeting)	none
Silvana Spadafora	Algoma District Cancer Program, Sault Ste Marie	none
Shailendra Verma *	The Ottawa Hospital Regional Cancer Centre, Ottawa	none
Jawaid Younus	London Regional Cancer Centre	none

*Unable to attend the consensus meeting. Dr Bedard attended part of the meeting but did not participate in the second vote following the discussion of the consensus statements.

Additional Attendees at the Consensus Meeting (Nonvoting)

George Browman	Chair, Cancer Guidelines Action Group
Louise Zitzelsberger	Program Director, Cancer Guidelines Action Group
Hans Messersmith	Assistant Director, PEBC
Sofia Torres	Medical Oncology Fellow, Sunnybrook
Shikha Thakral	Pharmacy Student, Sunnybrook
Jenna Fong	Project Coordinator, Disease Pathway Management, Cancer Care Ontario
Yvonne Rohlehr	Administrative Assistant, Medical Oncology, Sunnybrook

Appendix B: Statements/recommendations voted on by the Consensus Panel and results of the votes.

The initial vote was online and included 19 people. Except where indicated, the results refer to this vote. Revote refers to the second vote after discussion at the consensus conference and included 16 people. Wording was the same as for the initial vote except as noted (highlighted).

Patient Stratification

R1. The following disease characteristics (histopathologic parameters) are considered relevant when making a decision regarding adjuvant systemic therapies for breast cancer:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before to meeting	Consensus at meeting
Lymph node status	0	0	0	1	18	Yes	
Revote	0	0	0	2	14		Yes
T stage	0	0	1	6	12	Yes	
Revote	0	0	0	5	11		Yes
Estrogen receptor (ER) status	0	0	0	3	16	Yes	
Revote	0	0	0	4	12		Yes
Progesterone receptor (PR) status	1	1	4	6	7	No	
Revote	0	0	2	11	2		Yes
HER2 receptor status	0	0	0	2	17	Yes	
Revote	0	0	0	2	14		Yes
Tumour grade	0	0	0	8	11	Yes	
Revote	0	0	0	7	9		Yes
Presence of tumour lymphovascular invasion (LVI)	0	0	2	11	6	Yes	
Revote	0	0	0	14	2		Yes
Ki-67 (where available)	0	3	9	6	1	No	
Revote	1	6	9	2	1		No
Molecular subtype (luminal A, B, basaloid, HER2 enriched, etc.) (where available)	0	1	10	7	1	No	
Revote	0	3	7	5	1		No

R2. The following risk stratification tools may be used in determining patient candidacy for certain systemic therapies:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
Oncotype DX score (for hormone receptor positive, N0 or N1mic or ITC, and HER2 negative cancers)	0	0	1	10	8	Yes	
Revote	0	0	2	13	1		Yes
Adjuvant Online	1	1	1	11	5	No	
Revote	0	0	2	13	1		Yes
Other validated tool (specify)	0	0	7	2	0	No	N/A

Other: treatment guidelines (1), Mammaprint (1), uPA/PAI-1 (1)

R3. The following patient factors should be considered in making adjuvant systemic therapy decisions:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
Age	0	1	0	11	7	Yes
Menopausal status	0	0	1	8	10	Yes
Medical comorbidities (including validated tools used to measure health status)	0	0	0	10	9	Yes
Other (please specify below	0	0	4	2	3	No

Other: Patient preference/wishes/values (4), Functional Status (1), patient safety (1)

Adjuvant Chemotherapy

R4. In those patients in whom chemotherapy would be tolerated and is accepted to the patient, adjuvant chemotherapy should be considered for patients with the following tumour characteristics:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
Lymph node positive: one or more lymph nodes with a macro-metastatic deposit (>2 mm)	0	0	0	7	12	Yes	
Revote	0	0	0	9	7		Yes
ER negative tumours with T size >5mm	0	0	3	10	6	Yes	
Revote	0	0	0	10	5		Yes
HER2 positive tumours	0	0	0	4	14	Yes	
Revote	0	0	0	4	11		Yes
High-risk lymph node negative tumours with T size >5 mm and another high-risk feature (please see next question).	0	0	2	10	7	Yes	
Revote	0	0	0	9	5		Yes
Adjuvant Online 10-year risk of death from breast cancer >10%	1	1	2	9	6	No	
Revote	0	1	0	14	1		Yes
Adjuvant Online 10-year risk of death from breast cancer >15% [statement added at consensus meeting]	0	0	0	9	5	N/A	Yes

R5. When considering lymph node negative tumours with T>5mm, the following should be considered High-risk features (and thus considered candidates for chemotherapy):

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
Grade 3	0	2	0	10	7	Yes	
Revote	0	0	0	8	4		Yes
Triple receptor negative	0	0	1	6	12	Yes	
Revote	0	0	0	4	11		Yes
Lymphovascular invasion positive (LVI)	0	2	3	11	3	No	
Revote	0	0	0	14	2		Yes
Intermediate or High Recurrence Score in the Oncotype DX tool, with an estimated distant relapse risk of 15% or more at 10 years	1	0	1	14	3	No	
Revote	0	0	1	10	5		Yes
HER2+ [statement added at consensus meeting]	0	0	0	4	12	N/A	Yes
Other (please specify below)	0	0	2	5	2	No	N/A

Other: HER2 + (4), lymph node micromet (1), high recurrence score (1)

R6. Patients with the following disease characteristics may NOT need adjuvant chemotherapy:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
T <5mm, lymph node negative and no other high-risk features as above.	0	0	0	7	12	Yes	
Revote	0	0	0	6	10		Yes
Lymph node positive with micromets only (<2 mm), and no other high-risk feature as above.	0	1	6	3	9	No	
Revote	0	2	2	11	1		No

Comment: unless large primary, <40 year

R7. In considering HER2 negative, strongly ER and PR (e.g., >90%) positive breast cancer with the following additional characteristics, adjuvant chemotherapy may NOT be required:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
Lymph node positive with micromets (<2 mm) only.	0	1	5	9	4	No	
Revote	0	2	0	12	2		Yes
Lymph node positive with macromets (>2 mm), but only 1–3 nodes involved.	0	9	4	5	1	No	
Revote	1	2	3	9	1		No
T <5mm	0	0	1	9	9	Yes	
Revote	0	0	0	10	6		Yes
Lymphovascular invasion positive (LVI) [statement added at consensus meeting]	0	2	4	10	0	N/A	No
Low recurrence score <18 on Oncotype DX [statement added at consensus meeting]	0	0	1	7	6	N/A	Yes
Other (please specify below	0	0	2	0	1	No	N/A

Other: grade 1 (1), low risk Oncotype (1), recurrence score <16 (1)

R8. Aggregate data from several phase 3 clinical studies, as well as meta-analyses, have established the superiority of many anthracycline-taxane-based regimens compared to other chemotherapy (please see Table 2 and 3 in Evidence Summary). Therefore, in patients who can tolerate it, using an anthracycline-taxane containing regimen is considered the optimal strategy for adjuvant chemotherapy.

R9. Anthracyclines have been established to be superior to some non-anthracycline chemotherapy regimens (please see Table 2 in Evidence Summary.) Therefore, in patients in whom a taxane is contraindicated, an optimal dose anthracycline regimen (with more than doxorubicin 240 mg/m^2 or epirubicin 360 mg/m^2) is recommended.

R10. The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen does not improve DFS or OS and is more toxic (please see Table 3 in Evidence summary). As such, these combinations are not recommended for adjuvant chemotherapy.

R11. In patients over the age of 65, adjuvant capecitabine was found to be inferior to CMF (oral cyclophosphamide) and AC×4 (please see Table 1 in Evidence Summary). As such, capecitabine is not recommended as an adjuvant chemotherapy option.

R12. CMF chemotherapy has been found to be better than no chemotherapy in the adjuvant setting (please see Table 1 in Evidence Summary). In addition, CMF (oral cyclophosphamide) has been found to be equivalent to AC×4 (please see Table 2). Therefore, CMF (oral cyclophosphamide) is an acceptable chemotherapy regimen for patients in whom an anthracycline and taxane is contraindicated.

Question	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
R8	0	1	0	10	8	Yes
R9	0	0	0	10	8	Yes
R10	0	0	0	3	16	Yes
R11	0	0	0	2	17	Yes
R12	0	0	1	13	5	Yes

R13. Phase 3 clinical studies have shown improved outcomes from the adjuvant anthracycline and anthracycline-taxane-based regimens listed below (please see Table 2 and 3 In the Evidence Summary). As such, the following adjuvant chemotherapy regimens can be used for early breast cancer patients:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
FEC X 3ocetaxel×3 (superior to FEC×6)	0	0	0	5	14	Yes	
Revote	0	0	0	6	10		Yes
AC×4→ Docetaxel×4 (superior to AC×4)	0	1	1	5	12	Yes	
Revote	0	0	1	9	6		Yes
TAC×6 (superior to FAC×6)	0	0	0	10	9	Yes	
Revote	0	0	0	13	3		Yes
AC×4→ Paclitaxel given weekly	0	0	0	7	12	Yes	
Revote	0	0	0	11	5		Yes
CEF	0	2	4	10	3	No	
Revote	0	2	3	11	0		No
Dose-dense, dose-intense EC→ Paclitaxel	0	2	1	9	7	Yes	
Revote	0	0	3	11	0		Yes
Dose-dense AC→ Paclitaxel (q 2 weeks) [added at consensus meeting]	0	0	0	7	9	N/A	Yes
FEC→ weekly Paclitaxel [added at consensus meeting]	0	0	1	9	2	N/A	(No)*

*consensus not met as 4 people did not answer the question

R14. TC×4 has been found to be superior to AC×4 (please see Table 3 in Evidence summary). How it compares to an anthracycline-taxane regimen is currently unknown. Nonetheless, TC is an adjuvant regimen that can be used when an anthracycline is not preferred.

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
R14	0	0	0	14	5	Yes

Adjuvant Endocrine Therapy

R15. For the purpose of selecting adjuvant endocrine therapy, the most reliable definitions of menopause are:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
Bilateral oophorectomy	0	0	0	2	17	Yes
At least 12 months of amenorrhea prior to initiation of chemotherapy or tamoxifen	0	1	0	9	9	Yes
In female patients 60 years of age or younger, who experience amenorrhea secondary to chemotherapy or tamoxifen, defining menopause is difficult and care must be taken when initiating an aromatase inhibitor	0	0	0	4	15	Yes

R16. In considering all the compiled evidence (please see Section 4.3 in Evidence Summary), adjuvant endocrine therapy should be considered in all estrogen receptor positive patients, taking into consideration patient preference and potential toxicities.

R16, reworded at consensus meeting
Adjuvant endocrine therapy should be considered in all ER positive patients, defined by the ASCO/CAP guidelines as ER IHC staining >/=1%, taking into consideration overall disease risk, patient preference and potential toxicities (please see Section 4.3 in Evidence Summary).

R17. Evidence suggests that estrogen receptor negative (ER) with progesterone receptor positive (PR+) tumours may not benefit from tamoxifen, as compared to ER + tumours (please see Table 4 in Evidence Summary). Nonetheless, adjuvant endocrine therapy should be offered to all estrogen receptor negative (ER), but progesterone receptor positive (PR+) patients.

R17, reworded at consensus meeting
Evidence suggests that patients with estrogen receptor negative (ER−), but progesterone receptor positive (PR+) tumours may not benefit from tamoxifen, as compared to patients with ER+ tumours (please see Table 4 in Evidence Summary). Nonetheless, adjuvant endocrine therapy should be considered in patients with estrogen receptor negative (ER−), but progesterone receptor positive (PR+) tumours

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
R16	1	0	0	6	12	No	
R16, reworded at consensus meeting	0	1	0	5	10		Yes
R17	0	2	5	11	1	No	
R17, reworded at consensus meeting	0	2	3	10	1		No

R18. Tamoxifen for 5 years in premenopausal patients with estrogen receptor positive tumours, regardless of chemotherapy use, has been found to improve outcomes (please see Section 4.3.1 in Evidence Summary). As such, 5 years of tamoxifen is the standard of care in these patients.

R19. Based on compiled data, [please see Table 12 in Evidence Summary], premenopausal patients with estrogen receptor positive tumours, who ARE NOT candidates for any other systemic therapy (e.g., because they refuse), ovarian ablation or suppression is a reasonable treatment option.

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
R18	0	1	0	5	13	Yes
R19	0	0	0	11	8	Yes

R20. In premenopausal patients with estrogen receptor positive tumours, treated with or without chemotherapy, data suggests that the addition of ovarian ablation or suppression to 5 years of tamoxifen, offers no additional benefit over 5 years of tamoxifen [please see Tables 12 and 13 (Tables 11 and 12 in final version) in Evidence Summary]. Therefore, the addition of ovarian ablation or suppression to tamoxifen in premenopausal patients is NOT the standard of care.

R21. In premenopausal patients with estrogen receptor positive tumours, treated with or without chemotherapy, ovarian ablation or suppression plus 5 years of an aromatase inhibitor is NOT yet supported by any convincing data, and as such is NOT the standard of care.

R22. In considering the evidence [please see Tables 7–10 (Tables 6–9 in final version) in the Evidence Summary], the optimal adjuvant endocrine therapy for postmenopausal patients with estrogen receptor positive tumours should include an aromatase inhibitor.

R23. Based on clinical studies (please see Section 4.3 in Evidence Summary), postmenopausal patients with estrogen receptor positive tumours, treated with or without chemotherapy, 5 years of tamoxifen is an acceptable treatment.

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
R20	0	2	1	8	8	Yes
R21	0	0	1	9	9	Yes
R22	0	1	0	8	10	Yes
R23	0	0	0	13	6	Yes

R24. Several phase 3 clinical studies have evaluated the role of aromatase inhibitors in postmenopausal patients with estrogen receptor positive breast cancer [please see Tables 7– 9 (Tables 6–8 in final version)]. Based on this evidence, in these patients, treated with or without chemotherapy, the use of aromatase inhibitors upfront for five years (instead of tamoxifen), or as a switch from tamoxifen after 2–3 years (for a total of 5 years of endocrine therapy), or as extended adjuvant therapy for at least 5 years (after 5 years of tamoxifen) are all acceptable strategies:

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting	Consensus at meeting
Upfront for five years (instead of tamoxifen)	0	0	0	6	13	Yes	
Revote	0	0	0	7	9		Yes
As a switch after 2–3 years of tamoxifen (for a total of 5 years of endocrine therapy)	0	0	0	4	15	Yes	
Revote	0	0	0	7	9		Yes
As extended adjuvant therapy for 5 years, after completing 5 years of tamoxifen	0	0	0	7	11	Yes	
Revote	0	0	0	7	9		Yes
As extended adjuvant therapy for MORE than 5 years, after completing 5 years of tamoxifen	3	9	5	1	1	No	
Revote	4	8	4	0	0		No

R25. Evidence exists for the delayed initiation of both tamoxifen and aromatase inhibitors (please see Section 4.3 in Evidence Summary). Therefore, in patients with estrogen receptor positive tumours, who do not receive adjuvant endocrine therapy immediately after surgery or chemotherapy, delayed endocrine therapy (initiated at a mean of 2 years from diagnosis) is still clinically beneficial.

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
R25	0	0	2	13	4	Yes

Adjuvant Targeted Therapy (HER2 positive)

R26. HER2 positive breast cancer is defined as either IHC 3+, ISH ratio ≥2, or HER2 gene copies 6 or more per cell nucleus. Only patients with HER2 positive breast cancer should be offered adjuvant trastuzumab.

R27. Phase 3 clinical studies have demonstrated improved DFS and OS with the addition of trastuzumab to chemotherapy compared to chemotherapy alone in HER2 positive early breast cancer [please see Table 15 (Table 14 in final version) in Evidence Summary]. Therefore, trastuzumab plus chemotherapy is recommended for HER2+ patients with node positive breast cancer or node negative breast cancer >1 cm.

R28. There is little evidence for the benefit of trastuzumab in tumours <1cm (please see Section 4.4 in Evidence Summary). However, trastuzumab therapy can still be considered in these tumours as part of clinical studies, or evidence-building programs (such as the EBP currently available in Ontario).

R29. Trastuzumab can be given with any adjuvant chemotherapy regimen; most of the evidence exists for anthracycline-taxane-based regimens (for instance, ACT) [please see Table 15 (Table 14 in final version) in Evidence Summary].

R30. The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended due to the potential of increased cardiotoxicity.

R31. Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen; there appears to be no significant differences between these approaches in survival outcomes (please see Section 4.4.2 of Evidence Summary). However, initiating the trastuzumab concurrently with the taxane is still generally preferred.

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
R26	0	0	0	3	16	Yes
R27	0	0	0	3	16	Yes
R28	0	0	0	14	5	Yes
R29	0	0	0	12	7	Yes
R30	0	0	0	6	13	Yes
R31	0	1	1	11	6	Yes

R32. Evidence exists for trastuzumab in combination with taxotere and carboplatin (TCH), and this regimen was found to be equivalent to ACTH [please see Table 15 (Table 14 in final version) in Evidence Summary]. In addition, TCH is less cardiotoxic than ACTH, and as such is recommended for patients at higher risk for cardiotoxicity.

R33. Phase 3 evidence for the addition of trastuzumab to some chemotherapy regimens (such as TC-taxotere, cyclophosphamide) does not exist. However, these regimens may be in use and are reasonable options, particularly to mitigate cardiotoxicity in certain patients.

R34. Current evidence suggests that the optimal duration of adjuvant trastuzumab is one year (please see Section 4.4.2 in Evidence Summary); data for shorter durations of trastuzumab is evolving. Therefore, patients should be given one year total of adjuvant trastuzumab, with regular cardiac functional assessments during this period.

	1 Strongly disagree	2	3	4	5 Strongly agree	Consensus before meeting
R32	0	2	1	9	7	Yes
R33	0	0	2	12	5	Yes
R34	0	0	0	4	14	Yes

Appendix C: Literature search strategy, March 6, 2012.

Database: EMBASE <1996 to 2012 Week 09>, Ovid MEDLINE(R) without Revisions <1996 to February Week 4 2012>, Ovid MEDLINE(R) Daily Update <March 05, 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 05, 2012>

1. (exp Breast Neoplasms/ or exp breast tumour/ or exp breast cancer/ or breast cancer.mp. or breast neoplasm:.mp. or ((cancer: or neoplasm: or tumo?r: or carcinom:) and (breast or mammar:)).mp)

2. exp chemoradiotherapy/ or exp chemotherapy, adjuvant/ or exp neoadjuvant therapy/ or exp adjuvant therapy/ or exp cancer hormone therapy/ or exp cancer adjuvant therapy/ or exp cancer combination chemotherapy/ or exp aromatase inhibitors/ or exp antineoplastic agents/ or (adjuvant or neoadjuvant or chemotherapy or hormonotherapy).mp.

3. **(Anthracycline#** or doxorubicin or Adriamycin or epirubicin or Ellence or **Alkylating agent#** or cyclophosphamide or Cytoxan or Neosar or Fluorouracil or 5−fluorouracil or 5−FU or Adrucil or methotrexate or amethopterin or Mexate or Folex or Rheumatrex or gemcitabine or Gemzar or **Taxane#** or docetaxel or Taxotere or paclitaxel or Taxol or Abraxane or carboplatin or Paraplatin or cisplatin or Platinol or TAC, ACMF, ACT, ATC, CAF, FAC, CEF, CMF or **Anti-estrogens or Selective Estrogen Receptor Modulator: or SERM:** or **Endocrine Therapy** or tamoxifen or Nolvadex or Apo-Tamox or Tamofen or Tamone or **Aromatase Inhibitor#** or anastrozole or Arimidex or exemestane or Aromasin or letrozole or Femara or fulvestrant or Faslodex or **HER2 inhibitor:** or trastuzumab or Herceptin or lapatinib or Tykerb or **Antiangiogenesis:** or bevacizumab or Avastin or **Granulocyte colony stimulating factor** or GCSF or Pegfilgrastim or Neulasta or filgrastim or Neupogen or **Bisphosphonate:** or Pamidronate or Aredia or zoledronic acid or Zometa).mp

4. Ovariectomy/ or exp gonadotropin-releasing hormone/ or exp gonadorelin derivative/ or exp luteinizing hormone/ or (ovariectomy or (ovar: adj3 ablation) or (ovar: adj3 suppression) or (ovar: adj3 irradiation)).mp or (gnrh or gonadorelin or lhrh agonist or lhrn analog or leuprolide or buserelin or triptorelin or Lupron or goserelin or Zoladex or Trelstar).mp

5. exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp randomized controlled trials as topic/ or exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/ or exp clinical trials, phase II/ or exp clinical trials, phase III/ or exp clinical trials, phase IV/ or (randomized controlled trial or clinical trial, phase III or clinical trial, phase II).pt. or (random$ control$ trial? or rct or phase II or phase III or phase IV or phase 2 or phase 3 or phase 4).tw. or ((exp clinical trial/ or exp "clinical trial (topic)"/ or exp controlled study/ or clinical trial$.mp. or clinicaltrial$.mp.) and (random$.tw. or randomization/)) or (random$ adj3 trial$).mp. or randomization/ or "clinicaltrials.gov".mp

6. (meta-analysis.mp. or meta-analysis/ or meta-analysis.pt. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or (cochrane or medline or embase or cancerlit).ti. or (hand search or hand-search or manual search).ti. or practice guideline$.mp. or Practice Guideline/ or practice guideline.pt. or practice parameter:.tw)

1 and (2 or 3 or 4) and (5 or 6), limit to yr="2008 -Current", and duplicates removed
Result: 7380 publications after removing duplicates (6085 RCTs, 1295 systematic reviews and guidelines)

Appendix D: Bisphosphonates and other bone agents.

Bisphosphonates as chemotherapeutic agents were within the scope of the literature search but due to timing of the consensus meeting were not included in the documents circulated and approved by the consensus panel. Table A1 compares the studies included in the guidelines located, as well as the current literature search. A brief summary of the guidelines and systematic reviews/meta-analyses is provided.

Early Breast Cancer Trialists' Collaborating Group (EBCTCG). Effects of Bisphosphonate Treatment on Recurrence and Cause-Specific Mortality in Women with Early Breast Cancer: A Meta-Analysis of Individual Patient Data from Randomised Trials. (231)

- This was presented as an abstract at the San Antonio conference in December 2013
- Individual patient meta-analysis of 17,751 female patients from 41 randomized trials comparing bisphosphonates to placebo/control
- Primary outcomes of time to recurrence, time to first distant recurrence, breast cancer mortality rate
- Subgroup comparisons by type of bisphosphonate, duration and schedule of treatment, menopausal status, age, ER status, concomitant chemotherapy, site of distant recurrence. Most comparisons not yet reported.
- No improvement on bone or other recurrence rates or premenopausal patients
- The largest effect was on bone recurrence rate (overall: rate ratio 0.79, p=0.002; postmenopausal: rate ratio 0.65, p=0.00001; premenopausal: no improvement, RR=1.00, p=0.97)
- Postmenopausal: improvement in breast cancer mortality (RR=0.83, p=0.004), breast cancer recurrence (RR=0.86, p=0.002), bone recurrence rates (RR=0.65, p=0.00001),
- Postmenopausal: other distant recurrence (not bone) (RR=0.93, p=0.26)

Cancer Australia. Recommendations for Use of Bisphosphonates in Early Breast Cancer. (232)

- Search January 2007–August 2010 + Cochrane review 2005 and 2007 update; included 13 RCTs
- Concluded that bisphosphonates (clodronate, risedronate, zoledronic acid) do not significantly affect OS or recurrence rates (based on systematic review by Cancer Australia (465), plus AZURE trial) or bone or visceral metastases (based on Cochrane review, Diel, Kristensen, ABCSG-12 studies)
- Based on ABCSG-12, zoledronic acid is associated with longer DFS and RFS in female patients undergoing ovarian suppression in combination with endocrine therapy
- In postmenopausal patients, upfront addition of intravenous zoledronic acid to AIs compared with delayed treatment improved DFS rate and reduced bone mineral density loss, but may have increased adverse effects

PEBC. Use of Bisphosphonates in Women with Breast Cancer. (106)

- Search 2002, updated to 2004, new search to March 2011 but guideline not updated

- Guideline with systematic review/meta-analyses

The Cochrane Collaboration. Bisphosphonates and Other Bone Agents for Breast Cancer (Review). (233)

- Search to 2011 Apr 30.
- 34 RCTs (early, advanced, metastatic)
- 12 studies in 10,124 pts with early breast cancer
- Bone metastases, bisphosphonate vs none: RR=0.94 (95% CI 0.82–1.07), p=0.36
- Bone metastases, early bisphosphonates vs delayed treatment, RR=0.73 (95% CI 0.40–1.33), p=0.31
- Insufficient evidence, although several large studies have completed accrual and are awaiting results

Mauri et al. Does Adjuvant Bisphosphonate in Early Breast Cancer Modify the Natural Course of the Disease? A Meta-Analysis of Randomized Controlled Trials. (234)

- Search until January 2009
- 13 trials, 6886 pts
- Any bisphosphonate vs none
    - OS: OR=0.71 (95% CI 0.48–1.04), p=0.08
    - Bone metastasis: OR=0.92 (95% CI 0.77–1.11), p=0.41
    - Overall recurrence: OR=0.84, (95% CI 0.60–1.18), p=0.32
    - Distant relapse OR=0.90 (95% CI 0.67–1.19), p=0.45
- Zoledronic acid subgroup:
    - Recurrence OR=0.68 (95% CI 0.48–0.95), p=0.03
    - Death OR=0.64 (95% CI 0.39–1.06)
    - Bone metastasis OR=0.66 (95% CI 0.38–1.15)
    - Nonsignificant trend toward better outcome

Valachis et al. Lack of Evidence for Fracture Prevention in Early Breast Cancer Bisphosphonate Trials: A Meta-Analysis. (235)

- Search until January 2009
- 21 trials, 14 trials with fracture data, 7461 pts
- Fracture rate OR=0.99, p=0.92

Valachis et al. Adjuvant Therapy with Zoledronic Acid in Primary Breast Cancer: A Systematic Review and Meta-Analysis. [Abstract (236), full publication after date of literature search (237)]

- Search until December 2011
- 15 studies
- OS: HR=0.81 (95% CI 0.70–0.94), p=0.007
- DFS: HR=0.86 (95% CI 0.70–1.06), p=0.15

- Locoregional recurrence: OR=0.81 (95% CI 0.50−1.30), p=0.38
- Bone metastasis, OR=0.94 (95% CI 0.64−1.37), p=0.74
- Fracture rate: OR=0.78 (95% CI 0.63−0.96), p=0.02
- Osteonecrosis of the jaw: 0.52% with zoledronic acid vs none in control arms

Assessment

Based on the summary of guidelines and reviews and the comparison of included studies in Table A1, the Cochrane Collaboration review, and Cancer Australia review, and the review by Valachis et al are most complete. The NSABP-34 trial and updates of ABCSG-12, AZURE, and E-ZO-FAST trials would need to be included. The EBCTCG meta-analysis is the most important summary to consider and preparation of a guideline on this topic will await the EBCTCG meta-analysis publication.

Table A1. RCTs in literature search and recent guidelines evaluating survival or recurrence rate effects of bisphosphonates.

Study	# pts	Bisphosphonate	Design	PEBC (106)	Cochrane (233)	Australia (232)	1-21 search	Notes
Diel ,1998, 2008 (238,239)	302	Oral clodronate	vs control	Y (1998, 2000) [2008 in DART]	Y	Y	Y	T1-4, N0-2 with positive immunocytochemical detection of tumour cells in bone marrow; systemic according to guidelines
Saarto, 2001,2004 (240,241)	299	Oral clodronate	vs control	Y (2001)	y	Y	Y (242) (bone effects)	Operable, N+, T1-3, N1-2, M0
Powles, 2002, 2006 (243,244)	1069	Oral clodronate	vs control	Y (2002)	Y	Y	Y (245) (bone effects)	Operable, pre + postmenopausal,
NSABP-34 (246) NCT00009945	3323	Oral clodronate	vs control	N	No results yet	N	Y (246)	Stage I-III (246)
Kristensen, 2008 (247)	953	Oral pamidronate	vs control	[DART]	Y	Y	Y	Premenopausal, N0, T1-2; Premenopausal, HR-,N+ or T3+; Postmenopausal, HR-, N+ or T3+
AZURE, BIG 01-04 (250) abstract, (248)	3360	zoledronate	vs control	N	Y	Y	Y (248-253)	Resected Stage II or III, systemic therapy ± ZOL
E-ZO-FAST (254,255)	527	zoledronate	vs delayed	N	abstract	abstract	2012 (256)	Early, resectable, Stage I,II,IIIA, HR+, adjuvant letrozole for 5 y
Z-FAST (257,258)	602	zoledronate	vs delayed	[DART 2007]	Y	Y	Y (259)	Postmenopausal, early resectable Stage I,II,IIIA, HR+, on letrozole for 5 y
ZO-FAST (255,260)	1064	zoledronate	vs delayed	[DART]	Y	Y	Y (261,262)	Postmenopausal, early resectable Stage I,II or IIIA, HR+, letrozole for 5 y
Hershman, 2008, 2010 (263,264)	103	zoledronate	vs control	N	Y	Y	Y	Premenopausal, early, adjuvant chemo
ABCSG-12 (265)	1803	zoledronate	vs control	[DART, 2008]	Y	Y	Y, (265,304)	Premenopausal, Stage I or II, ≤10 nodes; 75% T1, 66% N0 Monthly goserelin + either TAM or ANA with or without ZOL
GAIN	2640	ibandronate for 2 y	vs control	N	N	N	(266)	ETC ± ibandronate; EC-TX ± ibandronate
D-CARE	4509	denosumab	vs placebo	N	N	N	(267)	Stage II or III, ongoing trial
HOBOE	Ongoing	zoledronic acid	See note	N	N	N	(268)	Tamoxifen vs letrozole vs letrozole + zoledronic acid
Aft, 2010 (269)	120	zoledronate		[DART]	Y	N	Excluded: LABC (269,270)	Stage II-III (>T2 and/or N1)
Tevaarwerk, 2007 (271,272)	68	zoledronate		N	Y	N	Excluded: <100 pts	Postmenopausal, Stage II/III
REBBeCa (273)		Risedronate	vs control	N	N	y	Excluded: <100 pts	Newly postmenopausal (<8 y); weekly for 2 y

Appendix E: Guidelines evaluated by AGREE II [4].

Guideline	Domain 1, Scope and Purpose	Domain 2, Stakeholder Involvement	Domain 3, Rigor	Domain 4, Clarity Presentation	Domain 5, Applicability	Domain 6, Editorial Independence
Burstein et al (ASCO) **(353)**. Update on adjuvant endocrine therapy for female patients with hormone receptor-positive breast cancer	66.7%	50.0%	54.2%	66.7%	39.6%	54.2%
Alberta **(354)**. Aromatase inhibitors as adjuvant therapy in postmenopausal patients with early-stage hormone receptor positive breast cancer	72.2%	19.4%	44.8%	69.4%	10.4%	33.3%
NICE **(97)**. Early and locally advanced breast cancer: diagnosis and treatment	83.3%	88.9%	85.4%	91.7%	70.8%	87.5%
National Breast Cancer Centre (Cancer Australia) **(421)**. Recommendations for use of Trastuzumab (Herceptin) for the treatment of HER2 positive breast cancer	55.6%	52.8%	46.9%	91.7%	6.3%	8.3%

[4] Assessment was performed by SAGE and is reproduced from the Guidelines Resource Centre at www.cancerview.ca

Appendix F: Literature reviews evaluated by AMSTAR (120)

Review	A priori design	Duplicate selection/ extraction	Comprehensive literature search	Used grey literature	List of excluded studies	Characteristics of include studies	Assessed quality of studies	Used quality appropriately	Pooled or combined results appropriately	Publication bias assessed	Conflict of interest, funding sources*
Gines (224)	?	No	MEDLINE only	Yes	No	Yes	No	NA	Yes	No	No RCTs, Yes overall
Goel (371)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No RCTs, Yes overall
Moja (79)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	?	No RCTs, Yes overall
Yin (422)	?	Yes	MEDLINE + supplementary	Yes	No	Yes	No	NA	Yes	Yes	No RCTs, Yes overall
Chen (429)	?	2 for data	Yes	Yes	No	Yes	No	NA	Yes	Yes	No RCTs, Yes overall
Costa (430)	Not systematic review	?	N/A	N/A	N/A	Yes	No	NA	Yes	No	No RCTs, Yes overall
EBCTCG (1,5,112,118, 119)	Yes	? verification with RCT authors	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Used published + non-published data	No RCTs, None or ? overall
LHRH-agonists (Cuzick) (61)	?	? verification with RCT authors	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No RCTs, Yes overall

Note: Choices for each question are: Yes, No, ?=cannot answer, N/A=not applicable

*Conflict of interest: none of the reviews commented on conflicts within individual RCTs, all the reviews indicated a statement about conflicts of interest for the review authors (other than EBCTCG which included a statement in some of the EBCTCG publications)

Appendix G: Quality assessment of new studies (studies not reported in previous guidelines or meta-analyses)

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
ABCSG-07 (123)	Randomized	NA	Yes	NR	NR	NA	NR	NR	No
CALGB 49907 (40,124)	Randomized	No	Yes (except tumour size)	Partial	Non-inferiority study, HR>0.8046 required; futility and non-inferiority bounds	NR	Yes	NR	Yes, unlikely to be inferior
DBCG 89D (127)	Minimization method	NR	Yes	Partial	80% power to detect a 1.20 hazard ratio for CMF vs CEF, preplanned sample size 1500	Yes	Yes	Yes	Yes due to EBCTCG results
FinXX, NCT00114816 (39)	Permuted blocks	Open-labelled	Yes	Partial	Assumed RFS would improve from 83.0% to 88.5% (HR= 0.65). 1,500 pts and 210 events were required to achieve 80% power assuming a3%annual dropout rate, α=028 (two-sided)	Yes	Yes	NR	No
N-SAS BC 01 (137)	Minimization method	NR	Yes	Partial	HR=0.77–1.30 for recurrence UFT vs CMF acceptable for non-inferiority. To maintain an *a* error of 0.05 and a *B* error of 0.20, the required size was 1300 pts (370 events). Interim results (not enough events yet)	No	Yes	NR	Yes, slow enrolment as AC introduced; longer follow-up needed
tAnGo (141,203)	Randomized	NR	Yes	NR	Anticipated 550 DFS events at the preplanned primary endpoint efficacy analysis at 30 minimum follow-up	NR	NR	NR	Interim analysis, follow-up ongoing
Schneeweiss (144)	Randomized	Open label	Yes	Yes	Primary endpoint of pCR Not powered for statistical comparisons between treatment groups.	NR	Yes	NR	Median DFS currently not mature
Kimura (36)	Dynamic allocation, minimization	NR	Yes	partial	Expected and clinically significant 5–y DFS rate of CEF was set to 72.5–75%, estimated necessary number of events (recurrence or death) after a mean 6–y follow-up was 140 for CMF pts and 100–110 for CEF pts, which required 350 pts for each treatment group (total of 700 pts)	Yes	Yes	NR	Yes, 294 pts
Lee (156)	Stratified block randomization	NR	Most	Partial	Primary objective to compare pCR; sample size of 209 pts was required to detect a 15% difference in pCR rate (from 15% to 30%) with 80% power at the 5% significance level, allowing for a withdrawal rate of up to 10%	Yes	Yes	NR	No

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
POCOB, EORTC 10902; (153)	Central randomization stratified	NA	Yes	No	The trial was designed to detect a 10% survival rate difference at 5 y (from 75% to 85%) with 80% power, for which 102 events were needed.	Yes	NR	NR	No
PREPARE (212,213)	Randomized	Open label	NR	Yes	The sample size of 720 pts chosen to provide 80% power to detect an improvement in DFS at 3 y from the standard therapy with a DFS of 70% to a DFS of 80% in pts receiving dose-dense chemotherapy. This equals a hazard ratio of 1.4 with a type I error of alpha 5% using a one-sided test	Yes	Yes	NR	No
GeparDuo, NCT00793377 (214,215)	Randomized	Open	Yes	No	Sample size calculation was based on pCR as primary endpoint	NR	NR	NR	No
HE 10/00 (176,177)	Stratified randomization balanced by centre	NR	Yes	NR	For a two-sided test at the 5% level of significance and power of 80%, the number of pts required to detect a difference between the two treatment arms within 5% (62.5%) to the baseline rate of 80% in DFS at the 3–y time point was 1040 pts. Taking into consideration a 5% withdrawal, 1100 pts (550 per group) needed to enter the study.	Yes	Yes	NR	No, Interim analysis, follow-up is ongoing
Anglo-Celtic (ACCOG) (201)	Randomized	NR	Yes	Yes	The sample size was determined as 350 pts to provide 90% power at the (one sided) 5% significance level of detecting an improvement in the clinical overall response rate from 70 to 84% (a relative improvement of 20%) with the combination of AD. The study has 80% power for detecting a 15% difference in DFS and a 14% difference in OS.	Yes	Yes	NR	No
Loesch (202)	Randomized, stratified	Open label	Yes	Yes	Assumed DFS duration followed exponential distribution, 25% decrease of annual hazard rate from9%per year, accrual time estimated to be18 mo, with 3 y as follow-up time. With a two-sided significance level of p=0.05, and with a desired power of 90% to detect such 25% difference, the accrual rate was evaluated to be approximately 100 pts per month. Therefore, the total sample size was calculated to be 1,810	Yes	Yes	Yes	No

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
NSABP B30, NCT00003782 (44-46)	Randomized, stratified	NR	Yes	Partial (drugs)	Designed to detect a 25% reduction in OS rate between the concurrent-ACT group and the sequential-ACT group (two-sided superiority test, 80% power), and to test equivalence between doxorubicin-docetaxel vs concurrent ACT and doxorubicin-docetaxel vs sequential ACT (non-inferiority analysis, 90% power). 3 planned interim analyses.	Yes	Yes	Yes	No
tAnGo (141,203)	Randomized	NR	Yes	NR	Anticipated 550 DFS events at the preplanned primary endpoint efficacy analysis at 30m minimum follow-up	NR	NR	NR	Interim analysis, follow-up ongoing
FinXX, NCT 0114816 (39)	Permuted blocks	Open-labelled	Yes	Partial	Assumed RFS would improve from 83.0% to 88.5% (hazard ratio [HR], 0.65. 1,500 pts and 210 events required to achieve 80% power assuming a3% annual dropout rate, when α=0.028 (two-sided)	Yes	Yes	NR	No
N-SAS-BC02 (205,206)	Randomized centrally, minimization method	NR	Yes, except age	NR	NR	NR	NR	NR	Interim analysis
NSABP B-38 (38,48)	Stratified then randomized, biased-coin minimization algorithm	NR	Yes	Partial	Designed to detect a 25% reduction in the DFS event rate with dd AC→ PG compared with both TAC and dd AC→ P (90% power at a one-sided level of 0.025), final analysis when the minimum number of DFS events in both pairs of the groups reached 613.	Yes	Yes	Yes	No
US Oncology 1062, USON 01062 (133,134)	Randomized	NR	Yes	NR	Failed to meet its primary endpoint of DFS, 304 events at 5 y vs 518 expected	NR	NR	NR	No, but lower than expected event rate at 5 y
Moebus (208,209)	Randomized, stratified	NR	Yes	Yes	1,154 evaluable pts had to be recruited and observed for a median period of 5 y to achieve 80% power to identify an improvement from60%to67%in EFS after 5 y at 5% significance (one sided).	Yes	Yes	NR	No
NCT00050167 (210)	Randomized centrally, moving block scheme	NR	Yes	Partial	77 RFS events were necessary to have 80% power to detect an increase in RFS from85% to92%. Annual safety and efficacy reviews at	Yes	Yes	NR	No, accrual stopped as unlikely to find

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
					35 events indicated the probability the trial would conclude in favour of neither treatment was 99.3%.				difference
NSABP B-14 (285,288)	Stratified then randomized	Yes	Yes	No	Assumed an annual DFS failure rate of 5.0% for pts discontinuing tamoxifen. To detect a 40% reduction in this rate for those pts continuing on tamoxifen with power of at least 0.85 and allowing for a 5% probability of falsely concluding that continued tamoxifen is superior, needed 115 events. Projected this analysis to occur approximately 8 y after the start of the second randomization, which began in April 1987. The early stopping criterion ($2\alpha \leq 0.00346$) was not satisfied (observed p=0.015). It was apparent; however, that the study could not conclude in favour of 10 y of tamoxifen	Yes	Yes	NR	Terminated based on interim findings indicating that a benefit for continuing tamoxifen would not be realized
Scottish trials (286,287)	Central randomization, stratified	NR	Yes	NR	NR	Yes	Yes	Yes	No
ATLAS (55,466,467)	Central computer using minimization	NR	Yes	Partial	The protocol stated that 20,000 pts would need to be randomized in ATLAS and the other trials of tamoxifen duration to detect reliably an absolute difference of 2%–3% in mortality rate. Entry to ATLAS was halted in 2005 (with 12,894 pts, including 6846 with ER+ disease) because the MA.17 trial found benefit from continued endocrine treatment after 5 y of tamoxifen	Yes, No (varies for sub-groups)	Yes	Yes	Yes
aTTom (56,468)	Randomized	NR	NR	NR	NR	NR	Yes	NR	No
TAM-02 (57)	Central randomized by phone, stratified	NR	Yes (except less ER+ in TAM group; 87% vs 95%)	NR	NR ER status known only in 55% of pts	Yes	Yes	Yes (no loss)	No
Italian (Veronesi) (58)	Randomized; stratified by time from local treatment	NR	Yes	NR	The sample size (197 pts per arm, plus 10% allowance) was based on the assumption of a 30% decrease in the number of events occurring at a rate of 5% annually in the 10 y following randomization. 433pts randomized	Yes	Yes	NR	No

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
					(TAM 217, follow-up 216)				
Finnish Breast Cancer Group (469)	Central randomized by phone; random digits method	Open	Yes	NR	The trial was powered based on an assumption of an equivalent efficacy between the two treatment arms, reached planned accrual	Yes	NR	NR	No, follow-up continuing
IBCSG 12−93 & IBCSG 14−93 (470,471)	Randomized, stratified by ER status and local therapy	NR	Yes	No	Target 760 pts for Trial 14−93 and 1140 for Trial 12−93, which provided a 90% power to detect a 25% increased risk of failure with toremifene compared with tamoxifen using a one-sided a=0.05 statistical test. Because toremifene was not available in all IBCSG countries and recruitment to Trial 12−93 was lower than expected, a total of 1035 pts were actually recruited for the toremifene vs tamoxifen comparison in both trials. With the consequent decrease in statistical power, 95% confidence intervals (CIs) for the risk ratios (RRs) (toremifene vs tamoxifen) rather than p-values were used to provide interpretation of the results.	Yes	Yes	NR	14−93 No 12−93 ? (interim analysis before all events reached)
HOBOE, NCT00412022 (268,310-312)	Central randomization using minimization	NR	Yes (NR but stratified in randomization)	Partial (drugs)	NR Survival data not reported	Yes (for bone effects)	Yes	NR	Ongoing
DBCG 89C (335)	Central randomization	Open label	Yes	NR	The preplanned sample size was 1 500 pts in 5 y, with an additional 5−y follow-up. Assuming a 5−y DFS rate in the control group of 50%, the study was designed to detect a 20% improvement in DFS with a power of 90%. Recruited 1 615 pts nationwide. An interim analysis at that time found that TAM/MA could not gain superiority compared with TAM1, and in addition more adverse effects were reported on megestrol acetate than on Tamoxifen. Pts already on treatment in the sequential arm were continued on or changed to Tamoxifen for a total treatment time of 1 y. This caused a relatively larger number of protocol violations in the TAM/MA arm. The	Some (see other column)	Yes	Reported there was no loss for OS	No (see other columns)

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
					study was extended and continued to randomize between TAM1 and TAM2 until December 31, 1996 when the results of the Swedish 2 y vs 5 y Tamoxifen trial was published. Pts on treatment were advised to continue Tamoxifen for 5 y. This means that the intention to treat analysis of the study extension was highly biased and the primary analysis of efficacy in this part of the study was therefore performed on both an ITT (N=1 795) and a per-protocol population (N=1 304).				
ATENA (349,350)	Randomized	Open label	Yes	Yes (partial)	NR Survival data not yet available	NR	NR	NR	Yes, poor recruitment due to MA.17 results
MA.27 (356-359)	Randomized, dynamic minimization	Open label	Yes	Partial	Originally looked for an improvement in 5-y EFS from 78.2%on anastrozole to 81.8% on exemestane, with a planned accrual of 6,830 pts and a factorial design with or without celecoxib. Accrual was reduced to 5,800 pts when celecoxib was removed. In both instances, the trial had 90% power. The sample size was revised again when 68-m outcomes in the ATAC trial18 found an estimated 5-y EFS rate on anastrozole of 86.5%. 6,840 pts and 630 events were needed for final analysis.	Yes	Yes	Yes	No
FACE (361)	Randomized	NR	NR	NR	NR Accrual complete, survival rate data not yet available	NR	NR	NR	No, ongoing
NCT00303524 Masuda (408)	Randomized	Open label	Yes	Yes	Calculated for estradiol suppression (not for secondary endpoint including survival). With 76 pts per group, this study had 80% power to establish non-inferiority at the 2.5% (one-sided) significance level, with the limit of non-inferiority defined as 1.25	Yes	Yes	NR	No
IBCSG 11-93 (404,409)	Randomized	NR	Yes	No	The planned sample size was 760 pts to provide an 80% power to detect a 10% difference in 5-y DFS. Included 174 pts.	NR	Yes	NR	Yes, due to low accrual rate

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
NeoSphere, NCT00545688 (437)	Central randomization using adaptive randomization method, stratified	Open label	Yes	Yes	Planned sample size of 400 pts to provide ≈ 80% power to detect an absolute difference in pCR of 15% between groups. *a* level set at a 20% level as was phase 2 proof of concept study. Survival not reported.	Yes	Yes	NR	No
NeoALTTO, BIG 01−06, EGF 106903, NCT00553358 (431)	stratified, permuted blocks randomization	Open label but assessor masked	Yes, except tumour size	Yes	We planned to enrol 450 pts to detect a difference in pCR rate from 25% in the trastuzumab group to 42% in either of the experimental groups, with 80% power and p=0·025 two-sided significance level. Survival was secondary endpoint, not reported.	Yes	Yes	NR	No
GeparQuinto, GBG 44 (435,436)	Central randomization, dynamic allocation with minimization, stratified	Pathol-ogists only	Yes	Yes	NR Survival not reported yet.	Yes	Yes	NR	No
PHARE, NCT00381901 (92,93,440)	Central randomization, stratification minimization,	Open label	Yes	No	The non-inferiority hazard ratio margin of 1·15 was derived from an estimated absolute difference in 2−y DFS rate of 2%, 1040 events, 7000 pts. Originally planned for 2−y accrual and analysis at 4 y. Based on HERA, changed to 4−y accrual and analysis at 8 y, with a reduced sample size of 3400. In May, 2010, the independent data monitoring committee recommended interruption of recruitment (4 y, N=3384) without cross-over and to analyze the data when a 2−y minimum follow-up was attained for all pts	Yew	Yes	NR	Yes (see other column)
ACOSOG Z1041 (434) (433)	Central randomization, biased coin minimization algorithm, stratified	No	Yes	No	256 female pts needed for a 90% chance to detect a difference of more than 20% for pCR assuming that the proportion of pts who would achieve a pCR in the sequential group was no more than 25% and with a two-sided *a* of 0·05. Survival data ongoing; will be reported later.	Yes	Yes	NR	No, survival rate monitoring ongoing
JBCRG-10 (438) (439) [abstracts]	Randomized	NR	Yes	NR	NR After unplanned interim analysis,	NR	NR	NR	Yes, see other column

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
					anthracycline (FEC) arms discontinued as no additional pCR benefit and one death, continued TCH only				
N-SAS BC 07, RESPECT (80)	Central randomization, stratified	NR	NA (recruitment ongoing)	No	The primary endpoint (DFS) will require 120 events in total, given a power of 80% and a threshold hazard ratio of 1.69. Giving that the 3−y DFS probability in the study population is 68% and assuming that the survival time follows the exponential distribution, a total of 260 pts will be necessary for 3 y of follow-up after 4 y of registration to assess the 120 events. Therefore, the target number of registration was determined to be 300	NA	NA	NA	Study ongoing
TACT2 (129,131) [abstract]	Randomized	NR	NR	NR	X can be declared non-inferior to CMF is the upper 95.78% CI for TTR hazard ratio is less than 1.24 based on excluding a reduction in 5 year TTR from 86% to 83%	Per protocol population	No	No	No
Ohno (132)	Randomized	NR	Yes	Yes	434 assessable patients required to achieve 80% power for detection an increase in pCR rate. No calculation for survival outcomes. Enrolment was 504 patients.	Yes	Yes	Yes	No
OOTR N003 (143) [abstract]	Randomized	NR	NR	NR	NR; likely underpowered for survival as pCR was primary outcome	NR	Yes	No	NR
Neo-tAnGo (142)	Randomized, central, stratified by minimization for age (≤50, > 50), ER status, size (≤5 cm, > 5 cm), nodal status, inflammatory or LABC	NR	Yes	Partial	Power calculations assumed pCR would be 20%; allowed absolute difference in pCR in excess of 10% to be detected at the 5% significance level with 85% power. Aimed for 200 patients in each group (800 total). Actual accrual 831. No mention of calculations for survival outcomes.	Yes	Yes	No loss	No
PACS (159) [abstract]	Randomized	NR	Yes		Powered to detect a 6% difference in favour of 6 cycles.	Yes	No	No	No
GEICAM/2003-02 (172)	Randomized, central, stratified by institution, menopausal status,	NR	Yes	Yes	Designed to have overall statistical power of 80% to detect a 5% an increase in DFS at 5 years from an estimated 80% to 85%. Required 1812 evaluable patients; 1925	Yes	Yes	Yes	No

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
	nodal status diagnostic method (SLN or ALND), HR status				enrolled.				
SWOG S0221 (154)	Randomized	NR	Yes`	NR	Powered to find DFS HR≤0.82 for weekly vs every 2 weeks; AC randomization halted for futility and continued paclitaxel arm. Accrual halted at 3294, analyzed at 487 events, which crossed the futility boundary	NR	NR	NR	See statistical power.
Monsoura University (185)	Randomized, permuted block design, stratified by age, HR, stage of disease	NR	Yes	NR		NR	Yes	NR	No
CALGB 40101 (197,198)	Randomized, permuted block design, stratified by menopausal status, HR status, (HER2 status after Oct 2005)	NR	Yes	No	Designed with 89% power to test non-inferiority of T with AC (RFS HR=1.3) with target accrual of 4646 and 567 RFS events. With enrollment of 3171 patients the 6-cycle arm was closed and randomization was restricted to other arms (4 cycles AC or T). Permanently closed due to slow accrual with 3871 patients, which was short of 4646 planned. 437 RFS events observed.	Yes	No	No	See statistical power.
GeparTrio (218-221)	Randomized	NR	Yes	Yes	NR	Yes	Yes	No	No
BEATRICE (227)	Randomized with block randomization, stratified by nodal status, chemotherapy type, HR status, type of surgery	NR	Yes	Yes	Sample size calculated to detect HR of 0.75 at 80% power for IDFS, required 388 events and 1140 patients in each group; OS pre-specified at 340 deaths or 5 years median follow-up a with 75% power to detect HR=0.75. Actual accrual 2591 patients, 393 IDFS events, 200 deaths (needs longer follow-up for OS)	Yes	Yes		No
AE37 vaccine (472,473)	Randomized	Single-blinded	Yes	NR	NR, but was Phase II trial	Yes	NR	NR	NR
POEMS-SWOG S0230 (274)	Randomized	NR	NR	No	Less than targeted patient accrual; 38% had missing data, results considered exploratory		Yes	Incomplete follow-up (missing data)	Yes

Study or author	Reported allocation sequence	Blinding	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawals described	Reported loss to follow-up	Terminated early
MA.14 and NSABP B-29; (301) [results in table for MA.14]	Randomized, using minimization, stratified by adjuvant chemo, nodal status, ER/PR status	NR	Yes	Partial	Needed 248 events to detect Tam/Tam-Oct hazard ratio of 1.5 with improvement of 8.2% in EFS with 90% power; modified to detect same effect with 80% power and 191 events; planned enrollment 650; actual 667 enrolled and 220 events	Yes	Yes	Yes	Octreotide reduced to 2 years due to gallbladder toxicity
TEXT and SOFT (63,64,282)	Randomized, internet-based system using permuted blocks, stratified by nodal status and intended use of adjuvant chemo; also by intended method of ovarian suppression in SOFT if in suppression group	NR	Yes	Partial	Both trials met enrolment goals; original plan was to compare DFS in each trial separately; patients had lower-risk characteristics than expected so trials were combined and protocol amended. Estimated with 436 events would be 84% power to detect HR=0.75; was 514 events at analysis.	Yes	Yes	Yes	No
TEACH (447-449)	Randomized, computer-generated sequence and stratified (HR status, nodal status, time since diagnosis and chemo)	Yes, investigators, clinicians, patients	Yes	Yes	Need 3000 women and 463 DFS events for 80-% power to detect 23% reduction in DFS (HR=0.769); 3161 enrolled, 474 events	Yes	Yes	Yes	No
ALTTO / BIG 2-06 / NCCTG N063D (450,451) Abstract only	Randomized	NR	Yes	NR	850 DFS events in L+T vs T comparison would provide 80% power to detect HR of 0.80; 555 DFS events observed and follow-up is ongoing	NR	NR	NR	Lapatinib arm closed for futility, follow-up for rest continues

NR=not reported; NA=not applicable