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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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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.

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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 high-risk 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 not benefit from adjuvant chemotherapy:**

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

R7. **Adjuvant chemotherapy may not 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, *or***
- **T <5mm, *or***
- **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 <u>not</u> 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 not 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 <u>not</u> 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 $pT_{1a/b}N_0M_0$ 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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