



Evidence-based Series 1-9 Education and Information 2015

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

Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer

The Breast Cancer Disease Site Group

Report Date: July 6, 2010

Evidence-based Series 1-9 was put in the Education and Information Section in March 2015. The Breast Disease Site Group (DSG) made the decision that EBS 1-9 will not be updated as it has been replaced by EBS 1-21- Optimal Systematic Therapy for Early Female Breast Cancer that include the more recent literature. The recommendations in EBS 1-9 will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

EBS 1-9 is comprised of 3 sections
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Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review

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Evidence-based Series 1-9: Section 1

**Adjuvant Ovarian Ablation in the Treatment of Premenopausal
Women with Early Stage Invasive Breast Cancer:
Guideline Recommendations**

*A. Eisen, H. Messersmith, J. Franek, M. Trudeau,
and the Breast Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Breast Cancer Disease Site Group

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QUESTIONS

1. How does adjuvant ovarian ablation (OA) as systemic therapy improve clinically meaningful outcomes (disease-free survival, overall survival, quality of life and toxicity) when compared with and/or added to other systemic therapies, specifically chemotherapy and tamoxifen? As there are a number of ways that OA may be compared with or added to other systemic therapy, the following specific comparisons are addressed by this practice guideline:
 - a) OA alone versus no systemic therapy
 - b) OA plus chemotherapy versus chemotherapy alone
 - c) OA alone versus chemotherapy alone
 - d) OA alone versus tamoxifen alone
 - e) OA plus tamoxifen versus tamoxifen alone
 - f) OA plus tamoxifen and chemotherapy versus tamoxifen and chemotherapy
 - g) OA plus tamoxifen versus chemotherapy alone
 - h) OA plus tamoxifen versus no systemic therapy
 - i) OA plus tamoxifen and chemotherapy versus chemotherapy alone
2. What is the best way to ablate or suppress ovarian function: surgical oophorectomy, ovarian irradiation, or medical suppression?

TARGET POPULATION

Premenopausal women with hormone receptor-positive early-stage invasive breast cancer.

INTENDED USERS

Clinicians and others involved in the care of the target population.

RECOMMENDATIONS AND KEY EVIDENCE

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).

- A comprehensive individual patient data meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) (1) found a statistically significant benefit for OA versus no systemic therapy in terms of recurrence (ratio of annual recurrence rates 0.72; 95% confidence interval [CI], 0.64 to 0.82) and mortality (ratio of annual death rates 0.71; 95% CI, 0.62 to 0.83).
- In the EBCTCG meta-analysis (1), there was no significant benefit for the addition of OA to chemotherapy in terms of recurrence (ratio of annual event rates 0.92; 95% CI, 0.82 to 1.02) or mortality (ratio of annual death rates 1.01; 95% CI, 0.89 to 1.14).
- A meta-analysis of six randomized trials conducted for this guideline found no significant difference between OA and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-based chemotherapy in terms of disease-free (hazard ratio [HR], 0.96; 95% CI, 0.86 to 1.07) and overall survival (HR, 0.92; 95% CI, 0.78 to 1.09).
- In a meta-analysis by Cuzick et al (2), there was no significant benefit for the addition of luteinizing-hormone releasing hormone (LHRH) agonist to tamoxifen in terms of recurrence (HR, 0.85; 95% CI, 0.67 to 1.20) or death after recurrence (HR, 0.84; 95% CI, 0.59 to 1.19).
- The Cuzick et al (2) meta-analysis also found no significant benefit for the addition of LHRH agonist to the combination of tamoxifen and chemotherapy in terms of recurrence (-15.9% change in HR; 95% CI, -42.4% to 22.4%) and death after recurrence (-32.6% change in HR; 95% CI, -60.1% to 13.7%).
- One randomized trial (3) reported no significant difference between OA and tamoxifen in terms of time to recurrence (HR, 1.10; 95% CI, 0.81 to 1.49) and overall survival (HR, 1.16; 95% CI, 0.80 to 1.69).
- Six randomized trials (4-7) were identified that compared OA plus tamoxifen to tamoxifen alone. None of these trials reported a significant benefit for overall survival or other important outcome for the combination compared to tamoxifen alone.
- No evidence was identified that compared OA as systemic therapy to anthracycline and/or taxane-based chemotherapy regimens in current use, or to aromatase inhibitors.
- No evidence was identified that compared OA plus an aromatase inhibitor with other adjuvant treatments in premenopausal women.

Qualifying Statements

- The fundamental difficulty with the available data is that OA has not been compared with many systemic treatment options (anthracycline- and/or taxane-

based chemotherapy, aromatase inhibitors) currently in use today. Therefore, the role of OA is still not fully understood in the context of modern systemic therapy. Until such time as OA is studied in comparison to currently relevant systemic therapy options, the Breast Cancer Disease Site Group (DSG) recommends against its routine use, except in the cases described above.

- The above recommendation regarding the use of OA in patients who are candidates for, but otherwise will not receive systemic therapy, is based on the evidence from the EBCTCG meta-analysis from trials comparing OA to no systemic therapy. The Breast Cancer DSG recognizes however, that the patients who received no systemic therapy in the trials that were analyzed by the EBCTCG meta-analysis may be different from patients who would be covered by this recommendation. For example, patients who refuse systemic therapy today may be very different from patients who were randomized to no systemic therapy in trials conducted over a decade ago. The Breast Cancer DSG still concludes from the available evidence that OA is better than no systemic therapy, and that patients who are unwilling to undergo other forms of systemic therapy but who are willing to undergo OA (e.g., oophorectomy) might benefit from this therapy and it should be offered to them.
- The Cuzick et al (2) meta-analysis did report a significant benefit in terms of recurrence (-12.7% reduction in HR; 95% CI, -21.9 to -2.4; p=0.02) and death after recurrence (-15.1% reduction in HR; 95% CI, -26.7 to -1.8; p=0.04) with the addition of OA to any systemic therapy, defined as tamoxifen, chemotherapy, or chemotherapy plus tamoxifen. However, as the individual comparisons described above were not significant, and the chemotherapy regimens used in the analyzed trials were not the anthracycline- and/or taxane-based regimens in common use today, the interpretation of this result is unclear. Therefore, the Breast Cancer DSG did not consider this result conclusive or sufficient to alter the recommendation against the routine use of OA.
- None of the trials included in the meta-analyses were designed to test for equivalence or non-inferiority. However, the Breast Cancer DSG concludes that the available evidence does suggest that OA is non-inferior to CMF-based chemotherapy in terms of disease-free or overall survival (upper limit of the HR; 95% CI, 1.09). Therefore, in the specific case where patients are being considered for CMF-based chemotherapy, OA alone may be a reasonable alternative.

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.

- The mode of administration in nearly all of the available trials has been monthly administration.

Qualifying Statement

- 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.

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Evidence-based Series 1-9: Section 2

Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer: Evidentiary Base

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1. How does adjuvant ovarian ablation (OA) as systemic therapy improve clinically meaningful outcomes (disease-free survival (DFS), overall survival (OS), quality of life (QOL) and toxicity) when compared with and/or added to other systemic therapies, specifically chemotherapy and tamoxifen? As there are a number of ways that OA may be compared with or added to other systemic therapies; the following specific comparisons are addressed by this practice guideline:
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2. What is the best way to ablate or suppress ovarian function: surgical oophorectomy, ovarian irradiation, or medical suppression?

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in Canadian women (1). In 2008, an estimated 22,600 new cases and 5,400 deaths occurred as a result of the disease. Since 1993 breast cancer incidence rates have stabilized, while mortality rates have dropped (1). This decline in mortality, as well as a similar drop in disease recurrence, is in part due to the widespread development and use of adjuvant systemic chemotherapy.

OA (referring to surgical oophorectomy, ovarian irradiation, or chemical ovarian suppression) was the first systemic therapy used to treat breast cancer (2,3). In premenopausal women the ovaries are the primary source of estrogen, an important hormone involved in the process of breast oncogenesis. Therefore oophorectomy and pelvic irradiation were historically used to ablate the ovaries, effectively suppressing estrogen synthesis. More recently, luteinizing hormone-releasing hormone (LHRH) analogues have also been used to reduce circulating estrogens to postmenopausal levels.

It is hypothesized that one of the benefits of adjuvant chemotherapy in premenopausal women with hormone receptor-positive disease is the development of secondary amenorrhea. The incidence of amenorrhea depends on age and on the specific chemotherapy regimen used (4). Younger women, particularly those under 35 years, have a lower incidence of amenorrhea. Goldhirsch and others have shown that breast cancer patients in this age group with HR-positive disease paradoxically have a worse prognosis after treatment with chemotherapy alone than do those with hormone receptor-negative disease, presumably because of the absence of this additional hormonal benefit (5).

The precise role of OA in the treatment of early-stage invasive breast cancer is unclear, particularly in the context of systemic chemotherapy and other hormonal therapies. In this systematic review, nine specific questions about the value of OA in the treatment of breast cancer are considered. However, the most clinically relevant question today relates to the benefit of adding OA to systemic chemotherapy and tamoxifen, the latter reflecting the current standard of practice. Combined with the emergence of new data evaluating LHRH analogues, this lack of clarity led the Breast Cancer Disease Site Group (Breast Cancer DSG) to develop a practice guideline on adjuvant OA therapy for women with early-stage invasive breast cancer. This systematic review, and the evidence-based series (EBS) it is part of, is intended both to provide an overall summary of the evidence regarding adjuvant OA, and to address questions of practical clinical relevance as noted above. Other adjuvant systemic guidelines are being developed concurrently. The Breast Cancer DSG anticipates combining these reports at some point to form a comprehensive practice guideline on adjuvant systemic therapy for early-stage invasive disease.

METHODS

The EBS guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (6). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two methodologists (H. Messersmith and J. Franek).

This systematic review is a convenient and up-to-date source of the best available evidence on the use of adjuvant OA in early, operable breast cancer. The body of evidence in this review is primarily comprised of mature randomized controlled data from phase III trials. That evidence forms the basis of an EBS

developed by the Breast Cancer DSG. The systematic review and companion guideline recommendations are intended to promote evidence-based clinical practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Definition of Ovarian Ablation

OA, for the purpose of this review, refers to all methods of OA and suppression, including surgical oophorectomy, ovarian irradiation, and medical ovarian suppression by LHRH analogues unless stated otherwise.

Literature Search Strategy

MEDLINE (1966 to September 2009), EMBASE (1980 to September 2009), and the Cochrane Library (up to September 2009) databases were searched in their entirety within the dates indicated. A comprehensive search strategy was used that combined disease-specific (e.g., breast neoplasms), treatment-specific (e.g., OA, ovarian suppression, LHRH), and publication-type-specific (e.g., randomized controlled trial) search terms. The combined search strategy, available in Appendix A, was applied simultaneously to MEDLINE, EMBASE, and CENTRAL, and thus included all relevant subject and Emtree headings, text words, and publication types. The Cochrane Database of Systematic Reviews was searched using treatment-specific terms.

Online conference proceedings from the American Society of Clinical Oncology (ASCO) (<http://www.asco.org/>) and the San Antonio Breast Cancer Symposium (SABCS) (<http://www.sabcs.org/>) were also searched up to September 2009 for relevant abstracts or presentations using similar terms to those previously identified. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearing House (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines. Ongoing trials were identified through the U.S. National Institutes of Health databases at (<http://clinicaltrials.gov/>) and (<http://www.cancer.gov/>).

All relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were hand searched for additional trials.

Study Selection Criteria

Inclusion Criteria

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

- Adjuvant OA for women with early, operable breast cancer was evaluated by systematic review with or without meta-analysis, or phase III randomized controlled trial.
- Reported outcomes included DFS, OS, toxicity, or health-related QOL.
- Clinical trial results were reported in either full papers or abstracts.

Exclusion Criteria

Articles published in a language other than English were excluded due to lack of translation capabilities.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data was pooled using the Review Manager software (RevMan 4.1) provided by the

Cochrane Collaboration (Metaview® Update Software). Since hazard ratios (HRs), rather than number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (7), HRs were extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from reported confidence intervals (CIs). A random-effects model was used for all summary estimates because the assumption, necessary for fixed-effects modeling, of a common treatment effect to be measured was not supportable.

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

RESULTS

Literature Search Results

Thirty-four separate articles describing 22 different randomized controlled trials (8-40), two individual patient data meta-analyses (41,42), one trial-based meta-analysis (43), and three other systematic reviews were identified for inclusion (44-46). See Appendix B for flow diagram of search results.

Systematic Reviews and/or Meta-analyses

Four systematic reviews/meta-analyses were identified through literature searches. Two systematic reviews lacked meta-analyses and did not identify all trials relevant to this review and were thus excluded (44,45). A meta-analysis reported at the 2007 ASCO Annual Meeting was also excluded as it was reported in abstract form only, and thus individual trials could not be identified (43). Two additional meta-analyses were relevant for this review and are described below (41,42).

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published their fifth in a series of overviews of chemotherapy and hormonal therapy for early breast cancer (41). This overview included an individual patient data meta-analysis of randomized controlled trials initiated prior to 1995 of OA, by any method, versus no OA, either with or without chemotherapy in both arms. Only women younger than age 50 with estrogen receptor (ER)-positive or ER-unknown tumours were included in the analysis. Due to the depth and breadth of this meta-analysis, sufficient basis was provided to develop clinical recommendations for the addition of OA to no systemic therapy or to chemotherapy: comparisons a) and b). The authors of this systematic review found it superfluous to conduct analyses or further describe trials with regard to this comparison; therefore, such trials were excluded after the search was completed, even though they met the original inclusion criteria.

Cuzick et al. (42) report an individual, patient-level meta-analysis of randomized controlled trials initiated prior to 1995 of LHRH agonists alone or in combination with other systemic therapy and in comparison to various controls. A total of 9,022 premenopausal women with ER-positive and/or progesterone receptor (PgR)-positive tumours were included for analysis. In contrast to the EBCTCG meta-analysis, the meta-analysis by Cuzick et al. (42) excluded women with hormone receptor-unknown. Furthermore, women over the age of 50 were included.

The quality of the two included systematic reviews was evaluated using criteria derived from the AMSTAR tool (47). No major problems with quality were identified,

although neither review addressed individual trial quality either qualitatively or by a formal assessment tool.

A Cochrane systematic review, published in issue 4, 2008, of the Cochrane Library, assessed LHRH agonists as adjuvant therapy for early breast cancer (46). The review included 14 randomized controlled trials, all of which were included in this systematic review, except the Japan-Zoladex Breast Cancer Study Group (ZBCSG) trial (48), which is discussed below under the relevant sections. The Cochrane review also included one trial reported by Falkson et al. twice in abstract form at ASCO (1990 and 2001) that addressed the question of chemotherapy or chemotherapy plus OA (see above for a discussion of this question and why it is not discussed further). The Cochrane review did not combine the results of any of the 14 included studies in a meta-analysis, as that was judged not appropriate or not possible at the time of publication.

Randomized Controlled Trials

Twenty-two randomized controlled trials evaluating the use of adjuvant OA in early, operable breast cancer met the inclusion criteria (8-39). These trials were relevant for Questions c) through i). Trial patient and treatment characteristics are described in Table 2 and design and quality characteristics in Table 3. As noted above, trials that solely addressed Question 1 were excluded based on the post hoc determination that the EBCTCG overview provided an adequate basis to address that question.

Trial recruitment ranged from 1978 to 2001. Ten trials investigated the use of goserelin, either alone or in combination with other systemic therapies, in comparison to a control. Three trials evaluated oophorectomy, and one each evaluated ovarian irradiation, leuprorelin, and triptorelin. Four trials allowed OA in any form (e.g., surgical, irradiation, and LHRH suppression). Median follow-up ranged from 4.9 to 10.7 years. In six trials, patients received some form of chemotherapy that was not the object of treatment-arm comparison. This background chemotherapy was poorly defined and was often carried out according to local practice. When included as an object of treatment-arm comparison, chemotherapy was predominately cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Study entry criteria were not consistent across the trials, varying across such characteristics as hormone receptor status, patient age, nodal positivity status, and menopausal status. Only the four trials of the Zoladex in Pre-menopausal Patients (ZIPP) study (14) included postmenopausal women; however, the number of postmenopausal women was low (~6% total trial population).

Trial design and quality characteristics varied considerably (Table 3). Four trials did not meet original accrual targets due to slow accrual. Reported primary endpoints differed across trials, but actual disease event definitions were similar, thus allowing meta-analysis. The majority of trials reported intention-to-treat (ITT) analysis when analyzing primary efficacy endpoints, but methods of analysis were unreported in several trials. Three trials which reported ITT analysis appeared to exclude relevant patients post-randomization, counter to ITT principles. The definition of premenopausal status also differed considerably across trials.

Table 1. Patient and treatment characteristics of identified randomized controlled trials evaluating adjuvant OA.

Trial (Reference)	Sample Size ^a	Recruit Period	Arms	Median Follow-Up (yrs)	Other Chemotherapy	HR Status	Other Entry Criteria	Study addresses question...
ABCSG 05 (21,39)	1037	1990-1999	Gos (3 yrs) +Tam (5 yrs) CMF	5.0 for DFS 10.1 for RFS	None	ER+ and/or PgR+	Stage I or II, premeno	g
ABC(OAS) (8)	2144	1993-2000	OA ^b +Tam (5 yrs) Tam	5.9	According to local practice	Any	Stage I-IIIa, N0-1, M0, pre/perimeno	e
DBCG 89b (23)	762	1990-1998	Irradiation CMF	8.5 for DFS 10.5 for OS	None	ER+ and/or PgR+	N+ or Tum>5cm, premeno	c
ECOG 5188 (13)	1503	1989	CAF→Gos (5 yrs) +Tam (5 yrs) CAF→Gos (5 yrs) CAF	9.6	None	ER+ and/or PgR+	N+, premeno	i
FASG 06 (34)	331	1990-1998	Trip (3 yrs) +Tam (3 yrs) FEC-50	6.9	None	ER+ and/or PgR+	Age<50y, N+, premeno	g
GABG IV-A-93 (22)	771	1993-2001	Gos (2 yrs) CMF	4.9	None	ER+ and/or PR+	N-, premeno	c
GOCSI (29)	466	1991-1996	CMF→Gos (2 yrs)→Tam (2 yrs) CMF A→CMF→Gos (2 yrs)→Tam (2 yrs) A→CMF	6.0	None	Any	N+, premeno	i
GROCTA 02 (36)	244	1989-1997	OA+Tam (5 yrs) CMF	6.3	None	ER+	Pre/perimeno	g
IBCSG VIII (18)	1109	1990-1999	CMF→Gos (1.5 yrs) CMF Gos (1.5 yrs) Obs	7.0	None	Any	T1-3, N-, pre/perimeno	c
INT0142 (32,33)	345	1994-1997	OA+Tam (5 yrs) Tam (5 yrs)	5.0	None	ER+ and/or PgR+	Tum≤3cm, N-, premeno	e
Love et al (25)	709	1993-1999	Ooph+Tam (5 yrs) Obs.	7.0	None	Any	Tum≥2cm, stage II-IIIa, premeno	h
Nomura et al. (12,49)	1579	1978-1991	Ooph+Tam (2 yrs) Myt+C+Tam (2 yrs) Myt+C	8.2	None	ER+ or ER-	Stage I-IIIa but not M1 or N3, pre/postmeno	g
Roche et al. (37)	153	1983-1999	OA+Tam (2 yrs) FAC	7	None	ER+ and PgR+	N+, premeno	g
Salvadori et al. (38)	67	1989	Ooph CMF	6.3 7.0	None	ER+ and/or PgR+	N+, premeno	c
Scottish Trial A (30,31)	332	1980-1990	OA CMF	10.7	None	Any	T0-3, N0-2, M0, premeno	c

Trial (Reference)	Sample Size ^a	Recruit Period	Arms	Median Follow-Up (yrs)	Other Chemotherapy	HR Status	Other Entry Criteria	Study addresses question...
Söreide et al. (35)	320	1989-1994	Gos (2 yrs) Tam (2 yrs)	7.3	Perioperative chemo including V,C,5-FU,and M	Any	Age≤50 y, stage I-II, pN+	d
TABLE (27)	526	1995-1998	Leup (2 yrs) CMF	5.8	None	ER+ and/or PgR+ or ER/PgR unk	Stage II-IIIa, N+, premeno	C
ZEBRA (10)	1640	1990-1996	Gos (2 yrs) CMF	7.3	None	Any	Age≤50y, N+, stage II, pre/perimeno	C
ZIPP CRUK BCTG (14)	1191	1987-1999	Gos (2 yrs)+Tam (2 yrs) Gos (2 yrs) Tam (2 yrs) Obs	5.5	According to local practice	Any	Age<50y or premeno, stage I-II	e, f, i
ZIPP GIVIO (14)	382	1991-1996	Gos (2 yrs)+Tam (2 yrs) Gos (2 yrs) Tam (2 yrs) Obs	5.5	According to local practice	Any	Age<50y, stage I-III, any menopausal status	e, f, i
ZIPP STOCKHOLM (14)	926	1990-1997	Gos (2 yrs)+Tam (2 yrs) Gos (2 yrs) Tam (2 yrs) Obs	5.5	According to local practice	Any	Age<50y or premeno, stage I-II	e, f, i
ZIPP SE SWEDEN (14)	211	1989-1998	Gos (2 yrs)+Tam (2 yrs) Gos (2 yrs) Tam (2 yrs) Obs	5.5	According to local practice	Any	Age<50y, stage I-III, any menopausal status	e, i

Abbreviations: 5-FU, 5-fluorouracil; A, doxorubicin; ABC(OAS), Adjuvant Breast Cancer (Ovarian Ablation or Suppression); ABCSG, Austrian Breast and Colorectal Cancer Study Group; C, cyclophosphamide; CAF, cyclophosphamide, doxorubicin, and 5-fluorouracil; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; DBCG, Danish Breast Cancer Cooperative Group; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; ER+, estrogen receptor-positive; ER unk, estrogen receptor status unknown; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; FASG, French Adjuvant Study Group; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; GABG, German Adjuvant Breast Cancer Group; GOCSI, Gruppo Oncologico Centro-Sud-Isole; Gos, goserelin; GROCTA, Gruppo di Ricerca in Oncologia Clinica e Terapie Associate; IBCSG, International Breast Cancer Study Group; INT, intergroup; ITT, intent to treat; Leup, leuprorelin acetate; M, methotrexate; Myt, Mytomyacin C; NR, not reported; OA, ovarian ablation; Obs., observation; Ooph, oophorectomy; OS, overall survival; perimeno, perimenopausal; premeno, premenopausal; postmeno, postmenopausal; PgR+, progesterone receptor-positive; Pts, patients; TABLE, Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate; Trip, triptorelin; Tum, tumour; V, vincristine; y, years; ZEBRA, Zoladex Early Breast Cancer Research Association; ZIPP, Zoladex in Premenopausal Patients.

^aSample size includes total patient population available for analysis across all patient arms, including arms irrelevant to this review.

^bAll trials with treatment arms labelled "OA" achieved OA using more than one method of OA: surgery, irradiation or LHRH agonist.

Table 2. Study design and quality characteristics of identified randomized controlled trials evaluating adjuvant OA.

Trial (Reference)	n ^a	Primary Endpoints ^b	Required Sample Size, Expected Effect and Power	Achieved Sample Size?	ITT	Definition of Primary Endpoint Event	Definition of Postmenopausal
ABC(OAS) (8)	2144	Relapse-free survival, OS	492 events, 2000 pts for 5% diff in 5y OS (75-80%) at 5% α and 80% B.	Yes	Yes	Recurrence (local or distant) or death from BC w no known date of relapse.	Pre/perimenopausal if LMP<12mo.
ABCSG 05 (21,39)	1037	RFS, OS	Originally, 660 pts for 10% diff in 5y OS (65-75%) at 5% α and 10% B. Increased to 1050 pts due to large proportion of node-negative pts improving prognosis.	Yes	See note ^c	First relapse, local recurrence, cancer in the opposite breast, or death.	Ascertainable menses or LMP<12mo. In perimeno pts, FSH and LH w/ premeno levels.
DBCG 89b (23)	762	DFS, OS	750 pts for 5y DFS of 65% at 5% α and 80% B.	Yes	Yes	Locoregional recurrence, distant metastases, contralateral BC, or death.	LMP<2mo, LMP<12mo and FSH w/ premeno range, or age<50y w at least one ovary intact after hyst.
ECOG 5188 (13)	1503	DFS, TTR, OS	Originally, 960 pts. Increased to 1500 pts to increase statistical power. 1500 pts for 33.3% reduction in hazard rates of failure and death for gos added to CAF, and 40% reduction in failure and death hazard rates for tam added to gos+CAF at 2.5% α and 80% B.	Yes	Yes	Recurrence, new BC primary, or death.	LMP<4mo, LMP last 4-12mo w premono FSH levels, age<61y w previous ovary-sparing hyst and premeno FSH level, or previous HRT and age<56y w premeno FSH after cessation of therapy.
FASG 06 (34)	331	DFS, OS	553 pts for 10% diff in 5y DFS with 10% α and 80% B.	No	See note ^e	First relapse (local, regional and distant) or death. Contralateral BC was considered a new primary malignancy.	LMP<12mo and no previous hyst.
GABG IV-A-93 (22)	771	EFS, OS	Originally, 1060 pts for 7% diff in DFS at 5y over 80% DFS (80-87%) at 5% α and 80% B; equal to HR of 0.625 for gos vs. CMF. Recalculated to 770 pts for 140 events due to prolonged accrual.	Yes	Yes	Ipsilateral locoregional recurrence, contralateral BC, distant metastases, or secondary non-breast primaries, or death.	LMP<6mo or one of FSH<20 IU/L or LH>50 pg/mL.
GOCSI (29)	466	DFS, OS	940 pts for 8% abs diff in 3y DFS (70-78%) at 80% B.	No; halted due to slow accrual	Yes	Local recurrence, distant relapse, contralateral BC or death without relapse.	Regular occurrence of menses at the time of randomization. Premeno hormonal profile required for pts w \leq 6mo of amenorrhea and for pts w previous hyst.
GROCTA 02 (36)	244	DFS, OS	300 pts for 10-15% diff in 5y DFS at 5% α and 80% B.	No	Yes	Local recurrence, occurrence of regional and distant metastases, ipsilateral recurrence, contralateral BC, a second malignancy, or death.	Age<35y and still actively menstruating or LMP<12mo. Age<55y w previous hyst were premeno if FSH<50 IU/mL.

Trial (Reference)	n ^a	Primary Endpoints ^b	Required Sample Size, Expected Effect and Power	Achieved Sample Size?	ITT	Definition of Primary Endpoint Event	Definition of Postmenopausal
IBCSG VIII (18)	1109	DFS, OS	224 events for 72% 5y DFS w goserelin vs. 80% 5y DFS w CMF at 80% B for gos vs. CMF arm and 224 events for 8% diff in 5y DFS (80-88%) in CMF→gos vs. CMF arm.	Yes	Yes	Any recurrent disease (including ipsilateral BC), the appearance of a second primary cancer (including contralateral BC), or death.	One of the following: age>50y w LMP<12mo, age≤52y w LMP<3y, age ≤55y w hyst but no bilateral ooph, or biochemical evidence of continuing ovarian function.
INT0142 (32,33)	345	DFS, OS	1684 pts for 33% reduction in hazard for recurrence at 90% B and 33% reduction in hazard for death at 81% B.	No; halted due to slow accrual	NR	NR	NR
Love et al (25)	709	DFS, OS	700 pts for 10-12% increase in DFS from 50-55% in obs. arm, 82-94% power.	Yes	Yes	Recurrence or death.	LMP<12mo.
Nomura et al. (12,49)	1579	Relapse-free survival, OS	NR	NR	NR	Recurrence or death.	LMP<12mo or age <51y w at least one intact ovary remaining after hyst.
Roche et al. (37)	153	DFS, OS	NR	NR	NR	NR	NR
Salvadori et al. (38)	67	DFS, OS	NR	No; halted due to slow accrual	NR	NR	Actively menstruating or LMP<12mo.
Scottish Trial A (30,31)	332	EFS, OS	NR	NR	Yes	Recurrence (local, regional or distant) or death.	LMP<12mo or age<50y w at least one ovary intact following hyst.
Søreide et al. (35)	320	TTR, OS	320 pts for 15% abs diff in TTR (30-45%) at 90% B.	Yes	NR	Recurrence or death.	Age≤50y.
TABLE (27)	526	Relapse-free survival, OS	300 pts for max 10% diff in 2y RFS of 75% at 5% α and 80% B to test non-inferiority of leuprorelin to CMF.	Yes	See note ^d	Local or distant recurrence, second primary cancer, or death without relapse.	NR
ZEBRA (10)	1640	DFS, OS	688 events for 95% CI of equivalency HR of DFS and OS to be within 0.80-1.25 at 80% B. Non-inferiority if upper CI<1.25.	Yes	No	Tumour recurrence, a second primary cancer, or death.	Pre/perimenopausal. If in doubt, confirmed by FSH<30 IU/mL.
ZIPP CRUK BCTG (14)	1191	DFS, OS	Combined analysis of all four ZIPP trials: 2700 pts for abs diff in 5y OS of 5% (70-75%) at 83% B.	Yes	Yes	Recurrence (local or distant), second primary cancer or death.	LMP<6mo.
ZIPP GIVIO (14)	382	DFS, OS	Combined analysis of all four ZIPP trials: 2700 pts for abs diff in 5y OS of 5% (70-75%) at 83% B.	Yes	Yes	Recurrence (local or distant), second primary cancer or death.	LMP<6mo.
ZIPP STOCKHOLM (14)	926	DFS, OS	Combined analysis of all four ZIPP trials: 2700 pts for abs diff in 5y OS of 5% (70-75%) at 83% B.	Yes	Yes	Recurrence (local or distant), second primary cancer or death.	LMP<6mo.

Trial (Reference)	n ^a	Primary Endpoints ^b	Required Sample Size, Expected Effect and Power	Achieved Sample Size?	ITT	Definition of Primary Endpoint Event	Definition of Postmenopausal
ZIPP SE SWEDEN (14)	211	DFS, OS	Combined analysis of all four ZIPP trials: 2700 pts for abs diff in 5y OS of 5% (70-75%) at 83% B.	Yes	Yes	Recurrence (local or distant), second primary cancer or death.	LMP<6mo.

Abbreviations: ABC(OAS), Adjuvant Breast Cancer (Ovarian Ablation or Suppression); ABCSG, Austrian Breast and Colorectal Cancer Study Group; BC, breast cancer; DBCG, Danish Breast Cancer Cooperative Group; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FASG, French Adjuvant Study Group; FSH, follicle-stimulating hormone; GABG, German Adjuvant Breast Cancer Group; GOCSI, Gruppo Oncologico Centro-Sud-Isole; GROCTA, Gruppo di Ricerca in Oncologia Clinica e Terapie Associate; IBCSG, International Breast Cancer Study Group; HRT, hormone replacement therapy; INT, intergroup; Leup, leuprorelin acetate; LH, luteinizing hormone; LMP, last menstrual period; NR, not reported; Ooph, oophorectomy; OS, overall survival; perimeno, perimenopausal; premeno, premenopausal; postmeno, postmenopausal; Pts, patients; RFS, recurrence-free survival; RT, ovarian irradiation; TABLE, Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate; Trip, triptorelin; TTR, time to recurrence; Tum, tumour; V, vincristine; w, with; wi, without; y, years; ZEBRA, Zoladex Early Breast Cancer Research Association; ZIPP, Zoladex in Premenopausal Patients.

^aSample size includes total patient population available for analysis across all patient arms, including arms irrelevant to this review.

^bAs reported by trial authors.

^cAuthors claim ITT analysis, but excluded from the analysis randomized patients who did not fulfill eligibility criteria (33 pts) or who were deficient in relevant baseline information (32 pts).

^dAuthors report both PP and ITT analyses. Primary efficacy analyses were based on PP analysis. ITT analyses, however, excluded five patients in each treatment group who did not receive the allocated study medication.

(33 pts) or who were deficient in relevant baseline information (32 pts).

^eAuthors claim ITT analysis; however, one patient in each arm was excluded from analysis due to loss of follow-up.

The Austrian Breast and Colorectal Cancer Study Group (ABCSCG) 05 trial (21) randomized premenopausal women (n=1037) with hormone receptor-positive breast cancer to six cycles of CMF (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², and 5-fluorouracil 600 mg/m² on days 1 and 8, recycled on day 28), or goserelin (3.6 mg subcutaneously [s.c.] every 28 days for three years) plus tamoxifen (20 mg orally [p.o.] for five years). Updated 10-year efficacy and toxicity results were reported in abstract form (39).

The Adjuvant Breast Cancer Ovarian Ablation or Suppression (ABC(OAS)) trial (8) randomly assigned pre/perimenopausal women (n=2144) who were receiving prolonged tamoxifen treatment (20 mg/day for a minimum of five years) with or without chemotherapy (according to local practice) to OA (all forms; conducted according to centre policy and declared prior to randomization). Random assignment to treatment arms was permitted before chemotherapy or while chemotherapy was ongoing. Eighty percent of total patients (n=1717) received chemotherapy, with 73.1% of these patients (n=1256) receiving CMF and 21.7% (n=374) receiving anthracycline-based chemotherapy.

The Danish Breast Cancer Cooperative Group (DBCG) trial 89b (23) randomized premenopausal women (n=762) with node-positive and hormone receptor-positive breast cancer to either ovarian irradiation or nine cycles of CMF (cyclophosphamide 600 mg/m², methotrexate 50 mg/m², and 5-fluorouracil 600 mg/m² intravenously [i.v.] on days 1 of every third week). Some patients in the CMF arm who received anticancer radiotherapy also received one or two cycles of single-agent cyclophosphamide (850 mg/m²). CMF doses were adjusted according to white blood cell (WBC) and platelet counts. A separate publication reported on QOL (24).

The Eastern Cooperative Oncology Group (ECOG) E5188 trial (13) randomized premenopausal women (n=1503) with node-positive and hormone receptor-positive breast cancer to one of three arms: six cycles (each [q] 28 days) of CAF (cyclophosphamide at 100 mg/m²/day p.o. on day 1 through 14, and both doxorubicin at 30 mg/m² i.v. and 5-fluorouracil at 500 mg/m² i.v. on days 1 and 8), CAF followed by goserelin (3.6 mg s.c. q four weeks for five years beginning on cycle six, day 29 of CAF), or CAF plus goserelin plus tamoxifen (10 mg p.o. for five years beginning on cycle six, day 29 of CAF).

The French Adjuvant Study Group (FASG) trial 06 (34) randomized premenopausal women (n=331) with node-positive and HR-positive breast cancer to three years of triptorelin (3.75 mg intramuscularly [i.m.] monthly) plus tamoxifen (30 mg/day p.o.) or six cycles of FEC (5-fluorouracil 500 mg/m², epirubicin 50 mg/m² and cyclophosphamide 500 mg/m² i.v. q 21 days).

The German Adjuvant Breast Cancer Group (GABG) trial IV-A-93 (22) randomized premenopausal women (n=771) with node-negative, HR-positive breast cancer to goserelin (3.6 mg s.c. q 28 days for two years) or three cycles of CMF (cyclophosphamide 500 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m² i.v. on days 1 and 8 of a 28 day cycle).

The MAM-1 Gruppo Oncologico Centro-Sud-Isole (GOCSI) trial (29) used a factorial 2x2 design and randomized premenopausal women (n=466) with node-positive breast cancer to one of four arms: six cycles of CMF (cyclophosphamide 100 mg/m² p.o. on days 1 through 14, methotrexate 40 mg/m² and 5-fluorouracil 600 mg/m² i.v. on days 1 and 8 q four weeks), or four cycles of doxorubicin (75 mg/m² q 3 weeks) followed by six cycles of CMF, or six cycles of CMF followed by goserelin (3.6 mg s.c. q four weeks for two years) plus tamoxifen (20 mg p.o. for two years), or four cycles of

doxorubicin followed by six cycles of CMF followed by two years of goserelin plus tamoxifen.

The Italian Breast Cancer Adjuvant Study Group (GROCTA) trial 02 (36) randomized pre/perimenopausal women (n=244) with ER-positive breast cancer to six cycles of CMF (cyclophosphamide 100 mg/m² p.o. on days 1 to 14, methotrexate 40 mg/m² i.v. on days 1 and 8, and 5-fluorouracil 600 mg/m² i.v. on days 1 and 8) or tamoxifen (30 mg/day for five years) combined with OA (either surgical oophorectomy, ovarian irradiation, or medical suppression as determined locally). 70% of patients receiving OA (n=87) received goserelin, with 25% (n=31) receiving irradiation, and 5% (n=6) receiving surgery.

The International Breast Cancer Study Group (IBCSG) trial VIII (18) originally randomized premenopausal women (n=1109) with node-negative breast cancer to four arms: no adjuvant systemic therapy, six cycles (each q 28 days) of CMF (cyclophosphamide p.o. at 100 mg/m² on days 1-14, methotrexate i.v. at 40 mg/m² on days 1 and 8, and 5-fluorouracil i.v. at 500 mg/m² on days 1 and 8), goserelin (3.6 mg q 28 days for 24 months), or six cycles of CMF followed by 18 monthly implants of goserelin, with the first implant being given on day 28 of the sixth course of CMF. Trial recruitment began on March of 1990. Due to results from other trials, the no adjuvant systemic therapy arm was discontinued after recruiting 46 patients; results including this small cohort of patients were described in an older publication (19). The most recent publication describes comparisons only between the three active adjuvant therapy arms (18). A separate publication describes QOL and toxicity data (20).

Reported as an ASCO abstract (32) and presentation (33), the Intergroup (INT) trial 0142 randomized premenopausal women (n=345) with node-negative, hormone receptor-positive breast cancer to tamoxifen alone (20 mg/day p.o. daily for five years) or tamoxifen with OA (by surgical oophorectomy [42% of patients], irradiation [13%], or goserelin/leuprorelin acetate for five years [36%; dosage not reported]).

A randomized controlled trial by Love et al. (25,26) allocated premenopausal women (n=709) to surgical oophorectomy plus tamoxifen (20 mg p.o. daily for five years) or observation.

A randomized controlled trial conducted by Nomura et al. (12) involved a complex patient arrangement. Patients (n=1579) were originally separated based on ER and menopausal status. Relevant to this review, premenopausal women with ER-positive tumours were randomized to three arms: oophorectomy with tamoxifen (20 mg/day p.o. for two years), chemotherapy (0.06 mg/kg of body weight of mitomycin C i.v. followed by 100 mg/day cyclophosphamide p.o. three months on, three months off for four cycles in two years), or chemotherapy plus tamoxifen.

As reported in abstract form (37), a randomized controlled trial by Roche et al. compared premenopausal women (n=153) with node-positive and hormone receptor-positive breast cancer to six cycles of FAC (5-fluorouracil 500 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m² q 3 three weeks) or OA (surgical oophorectomy or ovarian irradiation) plus tamoxifen (30 mg for two years).

A randomized controlled trial by Salvadori et al. (38) randomized premenopausal women (n=67) with node-positive breast cancer to eight cycles of CMF (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², and 5-fluorouracil 600 mg/m² q three weeks) or surgical oophorectomy.

The Scottish Trial A (30,31) used a factorial 2x2 design and randomized premenopausal women (n=332) to OA (by surgical oophorectomy or irradiation) or CMF (cyclophosphamide 750 mg/m², methotrexate 50 mg/m² and 5-fluorouracil 500 mg/m² for eight cycles q three weeks) each with or without five years of prednisolone

(7.5 mg p.o daily from the date of OA or initiation of chemotherapy). The study began recruiting patients in 1980; however, as of 1984, the protocol was amended to six weekly cycles of CMF q three weeks.

A randomized trial by Söreide et al. (35) randomized premenopausal women (n=320) with node-positive and hormone receptor-positive breast cancer to two years of tamoxifen (20 mg p.o. daily) or two years of goserelin (3.6 mg s.c. q 28 days). All surgically treated patients less than 70 years of age (73% of all patients; n=235) received perioperative chemotherapy (vincristine 1 mg i.v., cyclophosphamide 400 mg/m², and 5-fluorouracil 500 mg/m², all given on day 0, and repeated on day 7 with cyclophosphamide replaced by methotrexate 50 mg).

The Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate (TABLE) trial (27,28) randomized premenopausal women (n=526) with hormone receptor-positive and node-positive breast cancer to LAD-3M (11.25 mg s.c. q three months for two years) or six cycles of CMF (cyclophosphamide 500 mg/m², methotrexate 40 mg/m², and 5-fluorouracil 600 mg/m² i.v. on days 1 and 8 q every 28 days).

The Zoladex Early Breast Cancer Research Association (ZEBRA) trial (9,10) randomized premenopausal women (n=1640) with node-positive breast cancer to goserelin (3.6 mg s.c. q 28 days for two years) to six cycles (q 28 days) of CMF (cyclophosphamide 500 mg/m² i.v. on days 1 and 8, or 100 mg/m² p.o. on days 1 to 14), methotrexate (40 mg/m² days 1 and 8), and 5-fluorouracil (600 mg/m² i.v. days 1 and 8). The trial was designed for equivalency and further predefined a non-inferiority margin if equivalency of goserelin to CMF was not supported. Separate publications describe QOL (11) and bone mineral density (BMD) (50) data.

The Zoladex in Pre-menopausal Patients (ZIPP) study (14) was a combination of four multicentre trials (CRUK BCTG, STOCKHOLM, GIVIO, and SE SWEDEN) that randomized premenopausal women (n=2710) into four arms: goserelin (3.6 mg s.c. q 28 days for two years), tamoxifen 20 or 40 mg p.o. daily for two years, goserelin plus tamoxifen for two years, or no further endocrine treatment in a 2x2 design. Patients also received background chemotherapy according to local practice. In the CRUK BCTG trial, 37% of patients (n=439) had chemotherapy (six cycles of CMF or a regimen of 5-fluorouracil, epirubicin, cyclophosphamide [5-FEC]) prior to randomization). In the STOCKHOLM trial, node-positive patients (50% of patients; n=459) received six cycles of CMF prior to randomization. In the GIVIO trial, 61% (n=232) had CMF prior to randomization. In the SE SWEDEN trial, 20% (n=43) had CMF prior to randomization. 61% of patients (n=860) in the CRUK BCTG and SE SWEDEN trials, originally randomized to the four patient arms, received elective tamoxifen, followed by randomization to goserelin or no goserelin because of data released on tamoxifen in younger patients. Three separate publications report on toxicity and adverse effects data from various trials of the ZIPP study (15-17). In this systematic review, the four ZIPP trials are counted separately in all totals, instead of being treated as a single trial. Additional long-term follow-up data for the ZIPP study (40) provided median 12-year follow-up on the 2706 women included in the analysis. The updated results are noted in the applicable sections.

Measures and Outcomes

Question 1: How does adjuvant ovarian ablation improve clinically meaningful outcomes.

The data from the identified meta-analyses and trials presented below is divided into subsections based on the particular comparison the data addresses:

a) Ovarian ablation alone versus no systemic therapy

b) Ovarian ablation plus chemotherapy versus chemotherapy alone

These two comparisons are addressed by evidence from the same source and are therefore presented together.

Results from the EBCTCG meta-analysis (41) regarding the addition of OA to no systemic therapy or to chemotherapy is shown in Table 3. An overall benefit for both recurrence and mortality was identified for the addition of OA alone to no systemic therapy or to chemotherapy (i.e., OA alone versus no systemic therapy AND OA plus chemotherapy vs. chemotherapy alone; Table 3, Row 1). However, no significant benefit was identified for the comparison of OA plus chemotherapy versus chemotherapy alone (Table 3, Row 5) when that comparison was analyzed separately. The EBCTCG meta-analysis seems to further suggest that the OS benefit for the addition of OA is driven primarily by non-chemical ablation, as the survival benefit for the addition of LHRH agonist was not significant (Table 3, Row 3).

Table 3. EBCTCG individual patient meta-analysis of trials of OA.

Comparison	Recurrence		Mortality	
	Total events/Total women	Ratio of annual event rates (95% CI)	Total deaths/Total women	Ratio of annual death rates (95% CI)
OA +/- ^A chemo vs. Nil +/- chemo	2775/49326	0.83 (0.76 to 0.90)	2045/7725	0.87 (0.79 to 0.96)
Non-chemical OA +/- chemo vs. Nil +/- chemo ^B	1725/33490	0.83 (0.74 to 0.92)	1491/4317	0.86 (0.77 to 0.97)
LHRH +/- chemo vs. Nil +/- chemo ^B	1050/15836	0.83 (0.73 to 0.95)	554/3408	0.89 (0.74 to 1.05)
OA vs. Nil ^C	1263/24962	0.72 (0.64 to 0.82)	948/3394	0.71 (0.62 to 0.83)
OA + chemo vs. Chemo ^C	1512/24364	0.92 (0.82 to 1.02)	1097/4331	1.01 (0.89 to 1.14)

Reference: (41)

Abbreviations: CI, confidence interval; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; LHRH, luteinizing hormone-releasing hormone agonist; nil, no systemic therapy.

NOTE: Confidence intervals and some ratios calculated from data provided and using methods described elsewhere (41).

^A Comparisons using the "+/-" terms refer to either both therapies plus X or both therapies minus X, e.g., OA +/- chemo vs. nil +/- chemo involves the following comparisons: OA vs. no systemic therapy or OA plus chemotherapy vs. chemotherapy.

^B Component analysis (i.e., data combine to form comparison in first row of table).

^C Component analysis (i.e., data combine to form comparison in first row of table).

As noted above and due to the depth and breadth of the EBCTCG meta-analysis, further trials examining the addition of OA were retrospectively excluded as sufficient evidence was available to develop recommendations. A meta-analysis by Cuzick et al. [41] conducted a similar analysis to that of the EBCTCG, but included only trials that used LHRH agonists to achieve ovarian suppression and had far fewer

subjects. The results from this analysis with regard to Question 1 are not reported here, because the data reported in row 3 of Table 3 are more comprehensive.

c) Ovarian ablation alone versus chemotherapy alone

Seven randomized trials compared OA alone to CMF chemotherapy: ZEBRA (9,10), IBCSG VIII International Breast Cancer Study Group (IBCSG) (18), GABG IV-A-93 (22), DBCG 89b (23), TABLE (27,28), the Scottish Trial A (30,31), and a trial by Salvadori et al. (38).

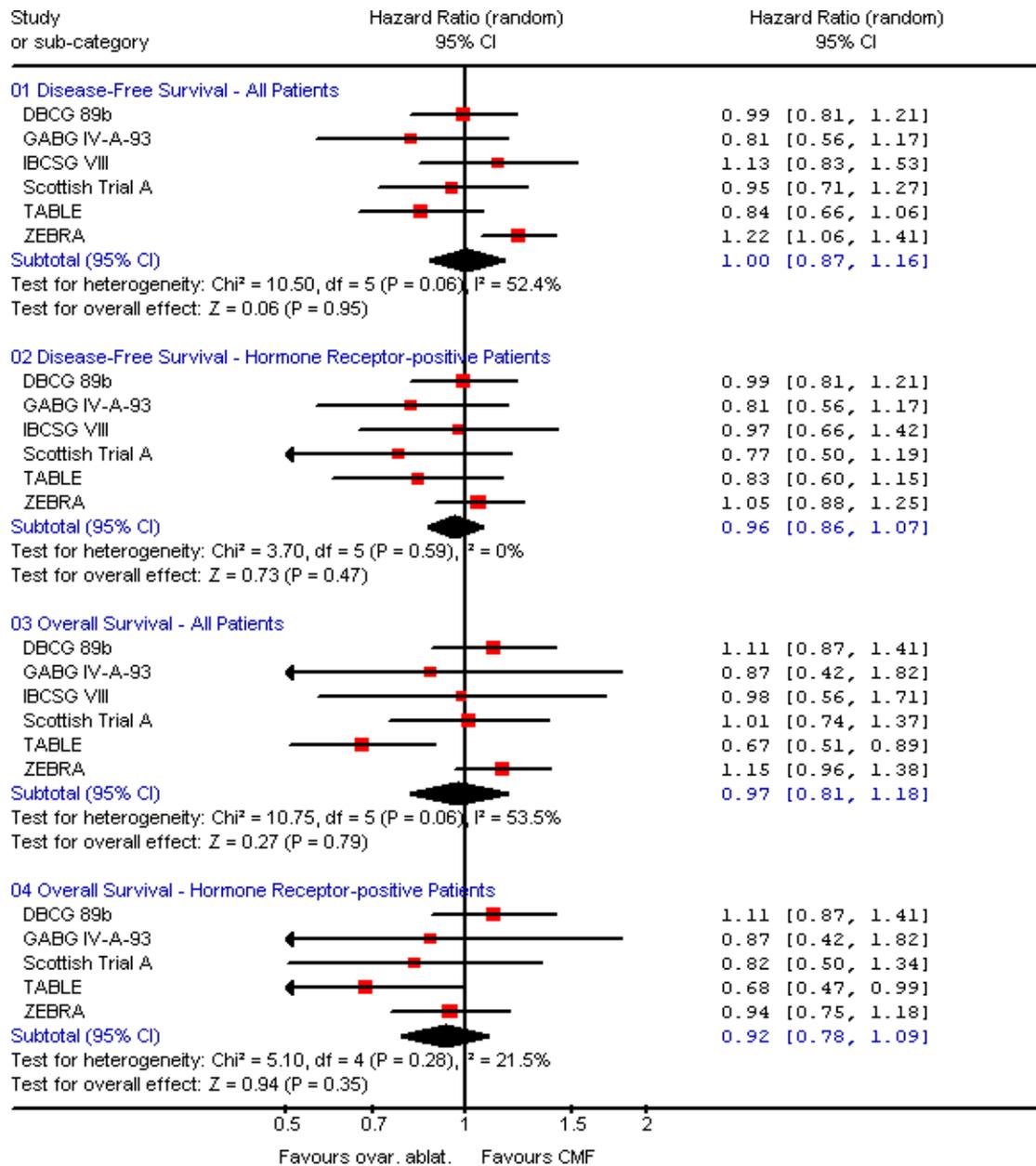
Summary statistics for DFS and OS shown in Figure 1 describe all included patients and patients with hormone receptor-positive cancers for those trials that reported relevant endpoints or provided sufficient information to derive them. Trials reported similar definitions of disease events, thus allowing for meta-analysis, except for the inclusion of second non-breast primary cancers (absent in two of six trials with clear reporting). A meta-analysis of these trials found no significant difference in DFS or OS between OA and CMF chemotherapy. Considerable statistical heterogeneity was present in the meta-analyses of DFS and OS for all patients. Statistical heterogeneity decreased when meta-analysis was conducted for patients with hormone receptor-positive cancers.

The trial by Salvadori et al. (38) did not report sufficient information to derive an appropriate HR, but did report significantly worse DFS (51% vs. 76%, $p=0.006$; 25% absolute difference at 7 years) but not OS (72% vs. 85%, $p=0.16$; 13% absolute difference at 7 years) at a median follow-up of seven years for OA compared to CMF. The ZEBRA trial also found significantly worse DFS (HR 1.83, 95% CI 1.33 to 2.52) and OS (HR, 1.64; 95% CI, 1.13 to 2.39) for OA compared to CMF in patients with ER-negative tumours in a retrospective subgroup analysis.

An individual patient-level meta-analysis by Cuzick et al. (42) investigated the comparison of LHRH agonists vs. CMF across four of the trials included in the meta-analysis above ($n=3184$ pts): the ZEBRA trial, IBCSG VIII, GABG IV-A-93, and TABLE. No significant benefit for LHRH versus CMF chemotherapy was found for recurrence (HR, 1.04; 95% CI 0.92 to 1.17; $p=0.52$) or for death after recurrence (HR, 0.93; 95% CI, 0.79 to 1.10; $p=0.40$).

Across the above trials, serious toxicity, particularly nausea, vomiting, and alopecia, was generally higher among patients receiving CMF chemotherapy, while common symptoms of estrogen suppression such as hot flashes and sweating were higher in patients receiving OA. Overall, both treatment modalities presented with mild toxicity. Several QOL substudies were reported: DBCG 89b (24), IBCSG VIII (20), and ZEBRA (11). All substudies had at least two years of follow-up and found significantly better reported QOL by multiple measures during the first six months of follow-up with OA compared to CMF chemotherapy. No significant differences were reported after six months. A protocolled BMD substudy of the ZEBRA trial (50) further found significantly greater loss of BMD in the with goserelin compared to CMF at two years following treatment initiation for lumbar spine (-10.5% vs. -6.5%, $p=0.0005$) and for femoral neck (-6.4% vs. -4.5%, $p=0.04$), although at three years, partial recovery of BMD was observed in goserelin patients.

Figure 1. Meta-analysis of disease-free and overall survival hazard ratios in trials of ovarian ablation versus CMF.



NOTE: Confidence intervals reported here may vary slightly (+/- 0.01) from those reported in respective references due to rounding error.

NOTE: The OS HRs from the IBCSG VIII and GABG IV-A-93 trials were derived from published survival curves and other reported data using Parmar methods (see Methods above).

Abbreviations: CI, confidence interval; CMF, cyclophosphamide, methotrexate, and fluorouracil; DBCG, Danish Breast Cancer Cooperative Group; GABG, German Adjuvant Breast Cancer Group; IBCSG, International Breast Cancer Study Group; TABLE, Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate; ZEBRA, Zoladex Early Breast Cancer Research Association.

References: DBCG 89b (23), GABG IV-A-93 (22), IBCSG VIII (18), Scottish Trial A (30,31), TABLE (27,28), ZEBRA (9,10).

d) Ovarian ablation alone versus tamoxifen alone

Only one trial directly compared OA to tamoxifen: the trial by Söreide et al. (35). The trial reported no significant difference for both TTR (time to recurrence; HR, 1.10; 95% CI, 0.81 to 1.49) and OS (HR, 1.16; 95% CI, 0.80 to 1.69) with goserelin alone compared to tamoxifen alone.

Although it did not directly compare OA with tamoxifen, the ZIPP update trial (ref) showed similar HRs for OA alone and tamoxifen alone when compared with no endocrine therapy. For OA, the HRs for event-free survival, OS, breast cancer recurrence, and breast cancer mortality were 0.67 (95% CI, 0.56 to 0.81), 0.71 (95% CI, 0.56 to 0.91), 0.66 (95% CI, 0.53 to 0.81), and 0.71 (95% CI, 0.55 to 0.92), respectively. For tamoxifen, the HRs were 0.71 (95% CI, 0.60 to 0.84), 0.74 (95% CI, 0.60 to 0.91), 0.69 (95% CI, 0.57 to 0.83), and 0.72 (95% CI, 0.58 to 0.90), respectively.

The Cochrane systematic review (46) identified one additional trial (48). The ZBCSG trial has been published only in Japanese and therefore was not identified by this review. No independent review of its results could be conducted by the authors. Sharma et al reported that it randomized patients to goserelin alone, goserelin plus tamoxifen, or tamoxifen, and that the goserelin plus tamoxifen group was closed early due to slow accrual. Sharma et al report that among 187 patients in the goserelin versus tamoxifen comparison, there was no statistically significant difference in recurrence-free survival (HR, 0.87; 95% CI, 0.47 to 1.63) or overall survival (HR, 2.10; 95% CI, 0.38 to 11.49).

e) Ovarian ablation plus tamoxifen versus tamoxifen alone

Six randomized trials examined the addition of OA to tamoxifen (i.e., OA plus tamoxifen versus tamoxifen alone), including INT0142 (32,33) and the ABC(OAS) (8). The four trials of the ZIPP study (14) had arms available for this comparison, but, because relevant data were not reported, it was not possible to calculate relevant endpoints from any of the data provided in the publications. However, a patient-level meta-analysis by Cuzick et al. (42) did examine all four trials of the ZIPP study and presented data for the above comparison. The meta-analysis (n=1013) found no significant difference for the addition of LHRH agonist to tamoxifen for recurrence (HR, 0.85; 95% CI, 0.67 to 1.20; p=0.20) or death after recurrence (HR, 0.84; 95% CI, 0.59 to 1.19; p=0.33).

The long-term follow-up results from the ZIPP study (40) showed the lack of benefit for the combination of OA and tamoxifen compared with tamoxifen alone continued at median 12 years: HRs for event-free survival, OS, recurrence, and breast cancer mortality were 0.92 (95% CI 0, 0.80 to 1.07), 0.90 (95% CI, 0.75 to 1.09), 0.91 (95% CI, 0.78 to 1.07), and 0.89 (95% CI, 0.73 to 1.09), respectively.

The INT0142 trial (32,33) reported no significant differences in either DFS (HR, 0.88; 95% CI, 0.48 to 1.61; p=0.67; 2.5% absolute difference at 5 years) or OS (HR, 0.65; 95% CI, 0.23 to 1.84; p=0.42; 2.4% absolute difference at 5 years) survival with the addition of OA to tamoxifen. The ABC(OAS) trial (8) also reported no significant differences in either relapse-free survival (unadjusted HR, 0.95; 95% CI, 0.81 to 1.12; p=0.56; adjusted HR, 0.98; 95% CI, 0.84 to 1.16; p=0.84; 0.9% absolute difference at 5 years; 95% CI -3.1 to 4.9) or OS (unadjusted HR, 0.94; 95%CI, 0.78 to 1.13; p=0.44; adjusted HR, 0.97; 95% CI, 0.81 to 1.17; p=0.79; 2.3% absolute difference at 5 years; 95% CI, -1.2 to 5.9) for all patients. In addition, no significant difference was reported for OS in patients with ER-positive tumours (HR, 0.84; 95% CI, 0.59 to 1.20) or ER-

negative tumours (HR, 1.12; 95% CI, 0.77 to 1.63) with p-values unreported. Additional subgroup analyses found no significant differences.

A meta-analysis conducted by the authors of this systematic review of these two trials (forest plot not shown), including only ER-positive patients from the ABC(OAS) trial and all patients from the INT0142 trial (ER-positive and/or PgR-positive), found no significant difference in OS (HR, 0.82; 95% CI, 0.58 to 1.14; $I^2=0$). Given the lack of reporting of the relevant outcomes, it was impossible to conduct a meta-analysis of all six relevant trials.

The INT0142 trial (32,33) indicated a significant increase in grade 3/4 hot flashes (16.1% vs. 4.7%; $p=0.0007$) for the addition of OA to tamoxifen. Health-related QOL, as measured by FACT (Functional Assessment of Cancer Therapy), menopausal symptoms, and sexual dysfunction were also significantly worse at one, two, and three years of follow-up with the addition of OA to tamoxifen. The ABC(OAS) trial (8) reported significant increases in night sweats ($p=0.005$), day sweats ($p<0.001$), and vaginal dryness ($p=0.001$) for the addition of OA. Accordingly, the ZIPP CRUK trial also reported greater incidence of hot flashes (44% vs. 17%) and sweating (5% vs. 1%) for the addition of OA to tamoxifen.

f) Ovarian ablation plus tamoxifen and chemotherapy versus tamoxifen and chemotherapy

A patient-level meta-analysis by Cuzick et al. (42) examined the addition of OA (LHRH agonist only) to tamoxifen plus chemotherapy (i.e., LHRH plus tamoxifen plus chemotherapy vs. tamoxifen plus chemotherapy). This meta-analysis was based on data from the ZIPP trials. The meta-analysis ($n=365$) found no significant difference for recurrence (-15.9% change in HR; 95% CI, -42.4 to 22.6; $p=0.37$) and death after recurrence (-32.6% change in HR; 95% CI, -60.1 to 13.7; $p=0.14$).

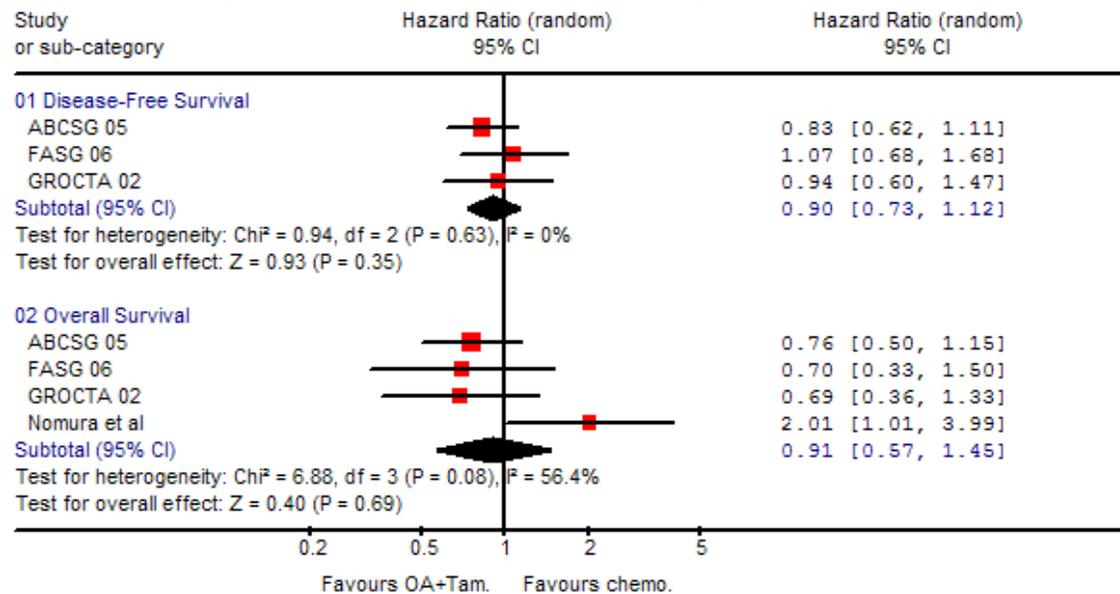
The follow-up report to the ZIPP study (40) did not include further data on this comparison.

g) Ovarian ablation plus tamoxifen versus chemotherapy alone

Five randomized trials compared OA plus tamoxifen to chemotherapy: ABCSG 05 (21,39), FASG 06 (34), GROCTA 02 (36), Nomura et al. (12), and Roche et al. (37). The type of chemotherapy differed considerably between trials, as outlined in Table 2.

Summary statistics for DFS and OS are shown in Figure 2 for those trials that reported relevant endpoints or provided sufficient information to derive them. All studies had similar definitions of disease events allowing for meta-analysis. Meta-analysis found no significant difference in DFS or OS between OA plus tamoxifen compared to chemotherapy. While there was no statistical heterogeneity for the meta-analysis of DFS, considerable statistical heterogeneity ($I^2=56.4\%$) was introduced by the trial by Nomura et al. (49) for the analysis of OS (see Discussion). When this trial was excluded from the analysis (forest plot not shown), the difference in OS in favour of OA plus tamoxifen approached statistical significance (HR, 0.73; 95% CI, 0.53 to 1.00; $p=0.05$) with no statistical heterogeneity ($I^2=0\%$).

Figure 2. Meta-analysis of disease-free and overall survival hazard ratios in trials of ovarian ablation plus tamoxifen versus chemotherapy.



NOTE: Confidence intervals reported here may vary slightly (+/- 0.01) from those reported in the references due to rounding error.

NOTE: The OS HRs from the trial by Nomura et al. (12,49) were derived from the published survival curves and reported data using the methods described by Parmar et al. (see Methods above). Insufficient data was provided to derive RFS data.

NOTE: The HRs for the ABCSG 05 trial are the inverse of the reported values, to reflect the appropriate comparison. OS HRs were derived from original publication (21), while RFS were provided from an abstract update; (39).

NOTE: The HRs reported from the FASG 06 trial (34) did not fall in the middle of their CIs when log-transformed, as would be expected. Therefore, the HRs from this trial and the widths of the CIs were taken as correct in order to calculate the log HR and its standard error as required by the meta-analysis. The reported values were as follows: adjusted DFS (HR 1.07, 95% CI 0.62 to 1.52) and adjusted OS (HR 0.70, 95% CI 0.25 to 1.15).

Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; chemo., chemotherapy; CI, confidence interval; FASG, French Adjuvant Study Group; GROCTA, Gruppo di Ricerca in Oncologia Clinica e Terapie Associate; OA, OA; Tam, tamoxifen.

References: ABCSG 05 (21,39), FASG 06 (34), GROCTA 02 (36), Nomura et al (12,49).

Absent from meta-analysis due to limited reporting, the trial by Roche et al. (37) reported a significant difference (p-value not reported) in seven year DFS between OA (surgical oophorectomy or ovarian irradiation) plus tamoxifen (82.8%; 95% CI, 71% to 90%) and FAC chemotherapy (55%; 95% CI, 43% to 56%), but also reported that after adjustment for the number of positive nodes, the difference was no longer significant. Roche et al. (37) also reported no significant difference in seven year OS (84% vs.74%; p-value not reported).

A meta-analysis by Cuzick et al. (42) reported individual patient-level data for the comparison of LHRH agonist plus tamoxifen versus chemotherapy across three of the trials described above: ABCSG 05, FASG 06, and GROCTA 02. The meta-analysis (n=1577) showed no significant difference for recurrence (HR, 0.90; 95% CI, 0.75 to 1.08; p=0.20) or death after recurrence (HR, 0.89; 95% CI, 0.69 to 1.15; p=0.37) between therapy arms.

Toxicity measures were similar to those reported by trials examining other comparisons. The ABCSG 05 trial (21) reported greater than 10% absolute difference between goserelin plus tamoxifen and CMF chemotherapy respectively for the following toxicities: hot flashes (91% vs. 54%), nausea (12% vs. 81%), alopecia (10% vs. 55%), stomatitis (4% vs. 23%), and diarrhea (3% vs. 15%). Treatment-induced

amenorrhoea occurred in all patients receiving goserelin plus tamoxifen (39). The FASG 06 trial (34) reported amenorrhoea in all patients receiving triptorelin plus tamoxifen vs. 64% in patients receiving FEC 50. An additional 32% of patients receiving FEC 50 experienced grade 3/4 nausea/vomiting, and 10% experienced grade 3 alopecia. Five patients on CMF in the GROCTA 02 trial (36) were hospitalized for adverse events vs. none receiving OA (all methods) plus tamoxifen. The overall proportion of adverse events, however, was similar (80% vs. 89%, OA plus tamoxifen vs. CMF). Leukopenia, thrombocytopenia, nausea/vomiting, and stomatitis were all significantly worse with CMF while hot flashes were significantly worse with endocrine therapy. In a preliminary report from the trial by Nomura et al (49), patients experienced less toxicity across multiple measures with oophorectomy plus tamoxifen vs. chemotherapy (mitomycin C plus cyclophosphamide) with the exception of hot flashes (45.3% vs. 5.7%).

h) Ovarian ablation plus tamoxifen versus no systemic therapy

Only the trial by Love et al. (25,26) examined OA plus tamoxifen compared with no systemic therapy. A significant improvement in both DFS and OS was observed for adjuvant oophorectomy plus tamoxifen in comparison to no systemic therapy (HR, 0.65; 95% CI, 0.51-0.82; $p=0.0003$ for DFS [13% absolute difference at 5 years; 95% CI, 7 to 21]; HR, 0.62; 95% CI, 0.48-0.80; $p=0.0002$ for OS [7% absolute difference at 5 years; 95% CI, 1 to 21]). This effect was more pronounced in patients with ER-positive breast cancer (ten-year DFS probability of 66% vs. 47%, and ten-year OS probability of 82% vs. 49%) in comparison to the whole population (ten-year DFS probability of 62% vs. 51%, and ten-year OS probability of 70% and 52%). No significant difference was identified in patients with ER-negative tumours ($p=0.46$ and 0.29 , DFS and OS respectively; HRs not reported).

While the ZIPP studies included arms that would address this question, no data have been yet reported. However, although it is not specifically stated, the patient-level meta-analysis by Cuzick et al. (42) provides patient-level data for the comparison of OA plus tamoxifen versus no systemic therapy that likely comes from the ZIPP studies. The meta-analysis ($n=407$) found significant improvement in both recurrence (-58.4% change in HR; 95% CI, -72.9% to -36.0%; $p<0.0001$) and death after recurrence (-46.6% change in HR; 95% CI, -70.5% to -3.4%, $p=0.04$) for patients receiving OA plus tamoxifen. It is unclear which trials were used to derive calculations.

i) Ovarian ablation plus tamoxifen and chemotherapy versus chemotherapy alone

Six trials examined the addition of OA plus tamoxifen to chemotherapy (i.e., OA plus tamoxifen plus chemotherapy vs. chemotherapy): ECOG 5188 trial (13), GOCSI (29), and four trials of the ZIPP study (14). While the ECOG 5188 trial did not report this comparison directly, a valid comparison was calculated from reported Kaplan-Meier curves using Parmar methods (see Methods above). All trials used goserelin to achieve ovarian suppression.

The type of chemotherapy differed across trials. Only the ECOG 5188 (CAF chemotherapy) (13) and GOCSI (CMF chemotherapy) (29) trials included chemotherapy as an object of treatment arm comparison (i.e., patients were randomized to chemotherapy), whereas patients in the ZIPP trials (14) received background chemotherapy according to local protocol (43% of all patients [$n=1173$] received CMF or FEC chemotherapy).

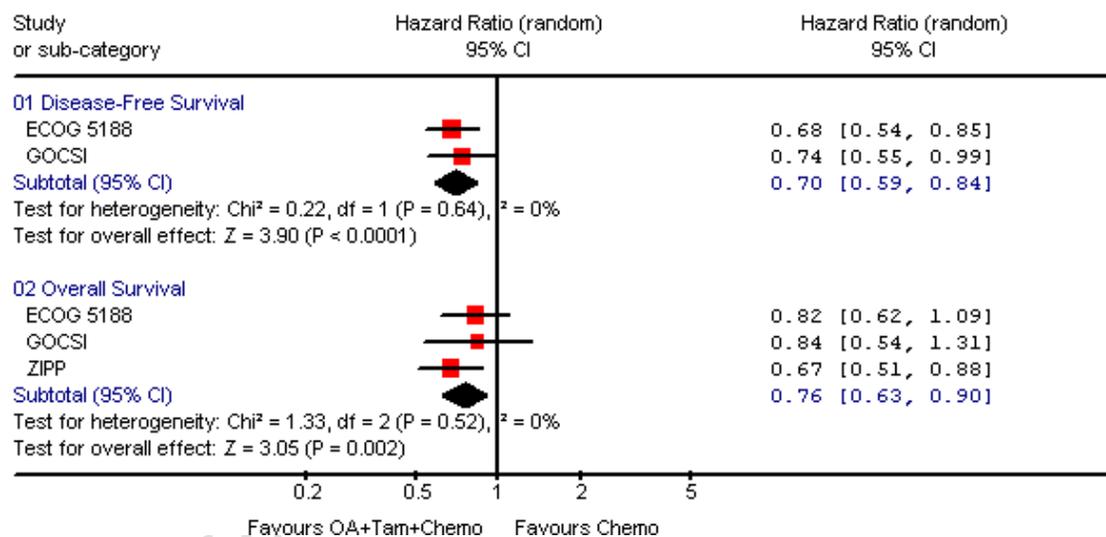
Summary statistics for DFS and OS are shown in Figure 3 for those trials that reported relevant endpoints or provided sufficient information to derive them. All

studies had similar definitions of disease events allowing for meta-analysis; however, the GOCSI trial did not include second primary cancers. Meta-analysis found significant improvement in DFS or OS with the addition of OA plus tamoxifen to chemotherapy. No statistical heterogeneity was noted.

An individual patient-level meta-analysis by Cuzick et al. (42) similarly examined the addition of LHRH plus tamoxifen to chemotherapy. Similar to the findings directly above, the meta-analysis (n=1210) found significant improvement for both recurrence (-26.7% change in HR; 95% CI, -38.7 to -12.3, p=0.001) and death after recurrence (-24.4% change in HR, 95% CI -39.0 to -6.4, p=0.01) with the addition of LHRH plus tamoxifen. It is unclear which trials were used to derive these calculations.

Data from the ZIPP study update (40) provided data for the comparison of OA plus tamoxifen compared with no endocrine therapy. The HRs for event-free survival, overall survival, breast cancer recurrence, and breast cancer mortality were 0.65 (95% CI, 0.55 to 0.78), 0.66 (95% CI, 0.54 to 0.83), 0.63 (95% CI, 0.52 to 0.76), and 0.64 (95% CI 0.51 to 0.81), respectively.

Figure 3. Meta-analysis of disease-free and overall survival hazard ratios in trials of ovarian ablation plus tamoxifen and chemotherapy versus chemotherapy alone.



NOTE: Confidence intervals reported here may vary slightly (+/- 0.01) from those reported in the references due to rounding error.

NOTE: The hazard ratios from the ECOG 5188 trial were derived from the published survival curves and reported data using the methods described by Parmar et al. (see Methods above).

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GOCSI, Gruppo Oncologico Centro-Sud-Isole; OA, OA; Tam, tamoxifen; ZIPP, Zoladex in Premenopausal Patients.

References: ECOG 5188 (13), GOCSI (29), Love et al (25), ZIPP (14).

The ECOG 5188 (13) trial reported similar toxicity between the arms. Grade 3/4 hot flashes and hypertension were respectively reported in 3.1% and 9.8% of patients who received additional goserelin plus tamoxifen vs. 0.4% and 2.4% in patients receiving CAF chemotherapy only. Grade 3/4 toxicities were similar between arms in the GOCSI trial (29). Data from the ZIPP CRUK study (14) indicated a higher proportion of hot flashes (44%) and weight gain (11%) for the addition of tamoxifen and goserelin in comparison to control (0% for both measures). A substudy of 89 patients in the ZIPP STOCKHOLM trial (17) found total body BMD significantly decreased from baseline to

24 months with the addition of goserelin and tamoxifen (p=0.02) but not with chemotherapy alone (p=0.76).

Two additional reports of detailed side effect measures (15,16) from the ZIPP study have been published. One report (15) focused on menopausal symptoms while the other (16) on the effect of therapy on sexuality. Both reports concluded that while goserelin, tamoxifen, and chemotherapy were associated with detrimental menopausal and sexual side effects, the effects of goserelin plus tamoxifen appeared to subside following the cessation of therapy.

The addition of ovarian ablation plus tamoxifen to no systemic therapy or to chemotherapy

A combined meta-analysis of trials was conducted to examine the broader comparison of the addition of OA plus tamoxifen to no systemic therapy or to chemotherapy (i.e., OA plus tamoxifen vs. no systemic therapy or OA plus tamoxifen plus chemotherapy vs. chemotherapy). The addition of the trial by Love et al. (25,26) to the meta-analysis in Figure 3 had virtually no effect on summary DFS and OS statistics (DFS HR, 0.68; 95% CI, 0.58 to 0.79; p<0.0001; I²=0; DFS OS, 0.74; 95% CI, 0.63 to 0.88; p=0.0004; I²=0).

Addition of ovarian ablation to any systemic therapy: additional data

The meta-analysis reported by Cuzick et al (42) included an analysis of the addition of OA to any systemic therapy, defined by Cuzick et al as tamoxifen, chemotherapy, or the combination of both. This analysis does not directly match any of the research questions addressed by this systematic review but is reported here because it is relevant. OA added to any systemic therapy, as defined by Cuzick et al, was associated with a significant benefit in terms of recurrence (-12.7% reduction in HR; 95% CI, -21.9 to -2.4; p=0.02) and death after recurrence (-15.1% reduction in HR; 95% CI, -26.7 to -1.8; p=0.04).

Question 2: What is the best way to ablate or suppress ovarian function: surgical oophorectomy, ovarian irradiation, or medical suppression?

No trials were identified that compared different forms of OA.

ONGOING TRIALS

The following ongoing trials were identified. All trials had unpublished data. Note that trials of OA versus observation, with or without chemotherapy, were not included, nor were trials where OA is being provided on all treatment arms.

Table 7. Ongoing or unreported phase III trials of ovarian ablation.

Protocol ID and NLM Identifier	First Published/Last Modified in Database	Trial Lead Organization	Projected Accrual	Trial Status	Arms
IBCSG-24-02 NCT00066690	30 July 2003 31 Oct 2008	IBCSG	3000	Active	Tam. Tam. + OA Exe. + OA
SCTN-BR9401 NCT00002580	1 Sep 1994 23 July 2008	SCTN	1000	Closed ^A	Tam. Tam. + CMF/AC Tam. + OA Tam. + CMF/AC + OA

Protocol ID and NLM Identifier	First Published/Last Modified in Database	Trial Lead Organization	Projected Accrual	Trial Status	Arms
NCT00002460	1 Nov 1999 23 July 2008	Cancer Research UK	1000	Closed	Observation Tam. Gos. Tam. + Gos.

Abbreviations: CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; Exe., exemestane; IBCSG, International Breast Cancer Study Group; OA, OA; SCTN, Scottish Cancer Therapy Network; Tam., tamoxifen

[^] Due to similarities in protocol ID's, this trial may be associated with the ABC(OAS) trial described above. However, it is assigned a separate NLM identifier from that assigned to the ABC(OAS) trial (NCT00002582).

DISCUSSION

Question 1: How does adjuvant ovarian ablation improve clinically meaningful outcomes?

In the discussion below, the data for each comparison will be discussed, followed by a discussion of the issues raised by the data as a whole.

a) Ovarian ablation alone versus no systemic therapy

b) Ovarian ablation plus chemotherapy versus chemotherapy alone

Results from the EBCTCG meta-analysis (41) confidently confirm that the addition of OA (all forms) to no systemic therapy (i.e., OA vs. no systemic therapy) offers significant benefit for both recurrence and mortality (Table 3, Row 4). Therefore, in premenopausal women with HR-positive breast cancer who cannot tolerate or who refuse chemotherapy, OA remains a viable treatment option.

The evidence, however, is not convincing for the addition of OA (all forms) to chemotherapy (i.e., OA + chemotherapy vs. chemotherapy). Neither the EBCTCG meta-analysis (41) nor the meta-analysis by Cuzick et al. (42) found significant benefit with the addition of OA to chemotherapy. It should be noted that the chemotherapy regimens used in the trials under meta-analysis would not be considered optimal today, and withholding tamoxifen from premenopausal women with HR-positive disease is not the current standard of practice; thus, the relevance of this finding and applicability to modern practice is debatable.

c) Ovarian ablation alone versus chemotherapy alone

The meta-analysis of the trials that compared OA to chemotherapy (Figure 1), as well as the patient-level meta-analysis by Cuzick et al. (42), indicate there is no significant difference between OA and CMF-based chemotherapy.

d) Ovarian ablation alone versus tamoxifen alone

The question still remains as to whether OA alone can be considered a true alternative to tamoxifen in patients who would otherwise be considered for tamoxifen alone, in the absence of chemotherapy. While the ZIPP study (14) included arms that addressed this question, data were not reported for this comparison. A randomized trial by Søreide et al. (35), on the other hand, did report on this comparison, finding no significant difference in either TTR or OS between goserelin and tamoxifen. However, the trial sample size was small, and thus it is possible that there was not enough power to identify a significant harm or benefit.

e) Ovarian ablation plus tamoxifen versus tamoxifen alone

The available evidence regarding the addition of OA to tamoxifen (i.e., OA plus tamoxifen vs. tamoxifen alone) argues against the addition of OA. When considering the identified evidence from six randomized trials, the meta-analysis of this evidence,

and a patient-level meta-analysis by Cuzick et al. (42) results indicate no significant difference for the addition of OA (all forms) to tamoxifen with respect to recurrence or survival. The addition of OA also resulted in a consistent increase in the incidence of hot flashes and sweating across trials.

f) Ovarian ablation plus tamoxifen and chemotherapy versus tamoxifen and chemotherapy

The issue of whether or not OA should be added to the combination of tamoxifen plus chemotherapy is perhaps the most relevant question to current practice addressed by this systematic review. Unfortunately, there is very limited evidence available that can be used to address it. While no individual trials reported data for this comparison, a patient-level meta-analysis of three ZIPP trials by Cuzick et al. (42) found no significant difference for the addition of LHRH to tamoxifen plus chemotherapy (the latter given according to local practice) for both recurrence or survival. See the section “Additional Discussion” below for further discussion of this issue. This question is currently being addressed in the actively accruing clinical trial IBCSG-24-02, which also includes the comparison to OA plus an aromatase inhibitor (exemestane).

g) Ovarian ablation plus tamoxifen versus chemotherapy alone

The evidence from five trials of OA (all forms) plus tamoxifen compared to chemotherapy alone, a meta-analysis of four of these trials (Figure 2), and the results of the patient-level meta-analysis by Cuzick et al (42), indicate that the combination of OA and tamoxifen is not significantly different from chemotherapy. However, there are several caveats to this evidence.

First the extracted HRs from the trial by Nomura et al. (12,49) show significantly worse OS for oophorectomy plus tamoxifen compared with mitomycin C plus cyclophosphamide chemotherapy (Figure 3). This is in marked contrast to all other trials, all of which reported a non-significant result with the HR favouring OA plus tamoxifen therapy (Figure 3). No reasons, methodological or otherwise, could be identified from trial reports to explain the discrepancy in the direction of treatment effect observed in the trial by Nomura et al. (12,49). When this trial was removed from our trial-based meta-analysis, the resulting OS HR was borderline significant ($p=0.05$) in favour of OA plus tamoxifen.

Second, only two of five identified trials for the comparison noted used an anthracycline-based chemotherapy regimen, and no trials used a taxane-based regimen. Thus, the relevance of this data to chemotherapy regimens in common use today is questionable.

Third, it is unclear whether this data is showing a benefit of OA or of tamoxifen. This is discussed further, below. Therefore, given the weaknesses in available evidence, OA plus tamoxifen cannot be considered an alternative to current adjuvant chemotherapy regimens.

h) Ovarian ablation plus tamoxifen versus no systemic therapy

The trial by Love et al. (25,26) and the patient-level meta-analysis by Cuzick et al. (42) both reported a significant benefit in terms of recurrence and survival for OA plus tamoxifen compared to no systemic therapy. However, it is still unclear whether the combination of OA and tamoxifen represents a viable alternative, as it is not clear what the source of the benefit might be; OA or tamoxifen. This is discussed further, below.

i) Ovarian ablation plus tamoxifen and chemotherapy versus chemotherapy alone

The results from the identified evidence from six randomized trials, the meta-analysis of this evidence (Figure 3), and a meta-analysis by Cuzick et al. (42) clearly indicate a recurrence and survival benefit for the addition of goserelin plus tamoxifen to older chemotherapy regimens (CAF and CMF). However, the source of this benefit is again unclear and that fact is discussed below. In addition, the chemotherapy regimens used across the trials in question are not particularly relevant to current practice. Therefore, the routine addition of both OA and tamoxifen, as opposed to tamoxifen alone, to chemotherapy regimens in typical use today is not supported by this data.

Additional Discussion

There is uncertainty regarding the degree of magnitude of additional benefit due to the addition of OA to other therapies. There is a general difficulty, as noted above, interpreting the data from trials where both OA and tamoxifen are on the experimental arm but not the control arm. This would include trials addressing comparisons g), h), and i). The difficulty is that, in these trials, it is unclear how much of any measured benefit is due to the OA as compared to tamoxifen. In fact, in light of the trials that address comparisons e) and f) (i.e., OA plus X vs. X) and comparison d) (OA vs. tamoxifen) it seems likely that the majority of the benefit seen in comparisons g), h), and i) was due to the tamoxifen. Therefore, none of this data can be considered to support the addition of OA to currently relevant systemic therapy options.

One result from the Cuzick et al. meta-analysis (42) is worthy of additional discussion, as it is directly relevant to clinical practice and does not fit neatly into any of the above questions. The meta-analysis did find a significant benefit for the addition of OA to any systemic therapy. That is, when the patients from all of the trials that compared OA plus tamoxifen versus tamoxifen, OA plus chemotherapy versus chemotherapy, and OA plus tamoxifen plus chemotherapy versus tamoxifen plus chemotherapy were combined, a significant difference in terms of recurrence and death after recurrence was identified.

It is difficult to know how to interpret this finding in light of the fact that the individual comparisons that were combined were not, in and of themselves, found to be significantly different. It is possible that there is a real, but small, benefit to the addition of OA, but whether this benefit is clinically relevant is not clear. The larger problem in interpreting this finding is that, as has been noted, the chemotherapy used in the trials analyzed by Cuzick et al. is simply not comparable to that used today. The ongoing trials identified above will likely definitively answer the question of whether OA should be added to tamoxifen or not, but as chemotherapy is not part of the randomization in any of those trials, the role of OA in addition to systemic therapy in general in today's clinical context is likely to remain unclear.

Unfortunately, none of the identified trials were designed as non-inferiority or equivalence trials. An overview of the magnitudes of effect reported in the trials identified here suggests that, while OA provides few statistically significant benefits, it seems possible that OA would be considered non-inferior to at least some of the alternatives that were studied. A specific example of this is the data from Figure 1 comparing OA alone to CMF-based chemotherapy. The 95% upper confidence limit of the OS HR is 1.09, which is within the range of what would have been considered a reasonable non-inferiority standard. At this time, the available data do not support

the routine use of OA, but the data do suggest a need for well-designed trials that study the question of non-inferiority or equivalence with regard to, and in the context of, currently relevant systemic treatment options (anthracycline and/or taxane based chemotherapy, aromatase inhibitors, or trastuzumab), instead of superiority.

Finally, all the meta-analyses reported in this review are composed of mostly small and somewhat disparate trials. Moreover, the multiple subset analyses of the patients in these analyses calls into question whether their conclusions can be considered definitive, in so far as it is possible that one large, well-conducted randomized trial could end up with a different conclusion (51). However, it seems unlikely at this point that such a definitive trial will ever be conducted for most of the comparisons described in this review. Therefore, the meta-analyses are the best available evidence, regardless of the difficulties inherent in interpreting them.

Question 2: What is the best way to ablate or suppress ovarian function: surgical oophorectomy, ovarian irradiation, or medical suppression?

The evidence of the EBCTCG meta-analysis suggests that the method of OA is not important in terms of recurrence or mortality. Moreover, in general across all identified trials, there does not appear to be any systematic variation in efficacy based on method of OA. Therefore, once the decision has been made to use OA as systemic therapy, the choice of actual method should be made on the basis of other factors, including patient preference and costs.

That being said, in the specific case of goserelin as OA, almost all of the included trials administered the drug as monthly injections. Therefore, in the absence of evidence to the contrary, monthly administration of goserelin should be considered the most reasonable option at this time.

CONCLUSIONS

Even though OA is the oldest form of systemic therapy for breast cancer (3), the appropriate use of this strategy is still not thoroughly understood. Based on the evidence identified in this systematic review, its role in current clinical practice seems limited to the following circumstances:

- OA is a reasonable option in patients who are candidates for systemic therapy but will otherwise not receive it; for example, in patients who refuse tamoxifen and/or chemotherapy.
- OA is a reasonable alternative in women who would otherwise receive CMF-based chemotherapy.

The available evidence does not provide a sufficient basis to recommend the routine addition of OA to other forms of systemic therapy (tamoxifen, chemotherapy, chemotherapy plus tamoxifen, or chemotherapy plus aromatase inhibitors), particularly when the additional toxicity is considered. The currently ongoing trials may provide such a basis when they are reported.

CONFLICT OF INTEREST

The authors wish to state they have no conflict(s) of interest at this time.

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For a complete list of the Breast Cancer Disease Site Group members, please visit the CCO website at <http://www.cancercare.on.ca/>

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Appendix A. Combined MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials search strategy.

1	clinical trial, phase III.pt.
2	clinical trial, phase IV.pt.
3	randomized controlled trial.pt.
4	clinical trials, phase III/ or clinical trials, phase IV/ or randomized controlled trials/
5	phase 3 clinical trial/ or phase 4 clinical trial/ or randomized controlled trial/
6	1 or 2 or 3 or 4 or 5
7	clinical trial.pt.
8	clinical trial, phase II.pt.
9	controlled clinical trial.pt.
10	clinical trials/ or clinical trials, phase II/ or controlled clinical trials/
11	phase 2 clinical trial/
12	(7 or 8 or 9 or 10 or 11) and randomized.tw.
13	meta-analysis/ or meta-analysis.pt. or meta-analysis.tw.
14	("Review Literature"/ or review.pt.) and systematic.tw.
15	"systematic review"/
16	14 or 15
17	guideline.pt. or practice guideline/
18	6 or 12 or 13 or 16 or 17
19	(comment or letter or editorial).pt.
20	18 not 19
21	exp Breast Neoplasms/ or exp Breast Cancer/ or exp Breast Tumor/
22	((breast or mammary) and (cancer or carcinoma or neoplasm% or tumor)).tw.
23	21 or 22
24	20 and 23
25	OVARECTOMY/
26	GONADORELIN/
27	GONADORELIN AGONIST/dt [Drug Therapy]
28	Antineoplastic Agents, Hormonal/ or Luteinizing Hormone/ or Triptorelin/ or Gonadotropin-Releasing Hormone/ or Buserelin/
29	(lhrh agonist or goserelin or leuprolide or buserelin or Triptorelin or lhrh analog).tw.
30	Goserelin/
31	OA.tw.
32	ovarian irradiation.tw.
33	ovarian suppression.tw.
34	(adjuvant or primary or early).mp.
35	(25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33) and 34
36	24 and 35

Codes: /, subject heading (MeSH in MEDLINE, Emtree in EMBASE); mp, many places (anywhere in complete database entry); pt, publication type; tw, text word (title, abstract)

Appendix B. Flow diagram of literature search results.

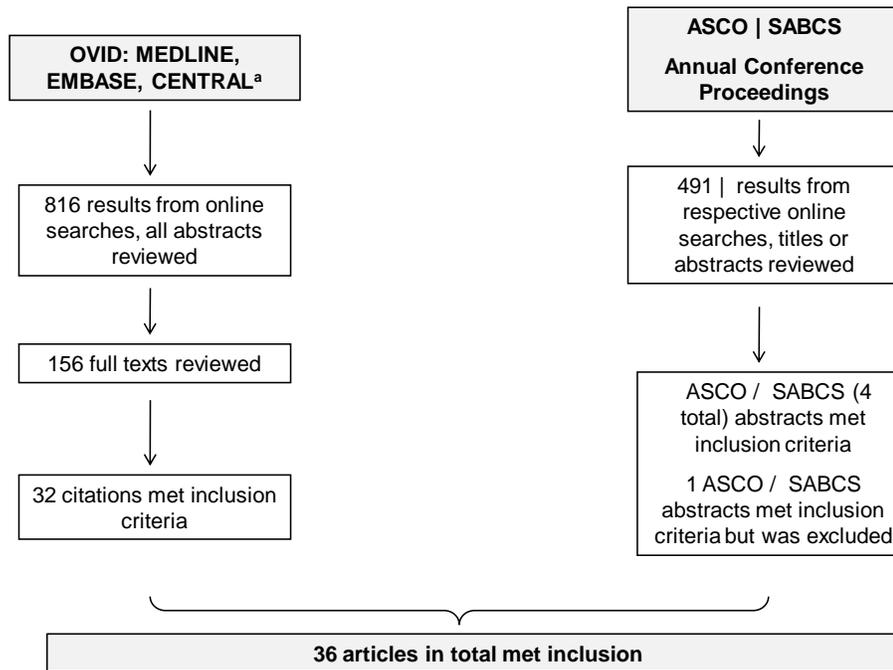


Figure 1. Flow diagram of literature results from search strategy, up to March, 2008.

Cochrane Library of Systematic Reviews did not yield any relevant results and thus was not included.

^a Online search strategy available in Appendix A.

Abbreviations: ASCO, American Society of Clinical Oncologists; CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medica; MEDLINE, Medical Literature Analysis and Retrieval System Online; SABCS, San Antonio Breast Cancer Symposium

Education à



Evidence-based Series 1-9: Section 3

Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer: EBS Development Methods and External Review Process

*A. Eisen, H. Messersmith, J. Franek, M. Trudeau,
and the Breast Cancer Disease Site Group*

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

Report Date: July 6, 2010

THE PROGRAM IN EVIDENCE-BASED CARE

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

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

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). 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.

The Evidence-Based Series

Each EBS is comprised of three 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 in Ontario 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: EBS Development Methods and External Review Process.* Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Breast Cancer DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on adjuvant OA in the treatment of women with early-stage invasive breast cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel (RAP), and the response of the authors to these issues, included:

- The RAP did not feel that the overall purpose of the guideline was clear; whether it was intended as an attempt to determine the actual utility of OA in the current treatment context, or whether it was intended more as an academic summary of the existing literature.

RESPONSE: The authors modified the Section 2 Introduction to address this concern, and make the overall purpose of the EBS clear.

- The RAP raised a concern regarding the evidence base supporting the recommendation that OA is a reasonable treatment option in women who were eligible for, but who would otherwise not receive, systemic therapy, raised as an issue. The generalizability of the data from trials of OA alone versus no systemic therapy to women who, for example, refuse systemic therapy in today's context, was questioned.

Response: The authors added an additional qualifying statement to Section 1 to address the generalizability of this data. While the authors agree that it is a concern, the authors still conclude that the evidence supports the conclusion that OA is better than nothing at all and have maintained the recommendation.

- The RAP asked the authors to discuss in more detail the limitations of the meta-analyses used in the review, especially the fact that they are based on a number of small and to some extent disparate trials.

Response: The authors added a discussion of this issue to Section 2.

- The RAP pointed out that, while many of the results reported in the review were non-significant, the magnitude of effect in many of the trials and analyses was in a range that suggested that the statistical power, and not the lack of benefit, was the reason for the lack of statistical significance.

Response: The authors added a discussion of the issue to Section 2. The authors agreed that this is a concern. The authors also felt that this concern was not sufficient to modify their recommendations against the routine use of OA.

- The RAP asked that the authors report absolute benefits where possible.

Response: The authors reviewed the identified trial reports and added additional absolute benefit data where it was available.

- The RAP raised a number of concerns regarding the organization of the research questions and recommendations, and expressed confusion over exactly which comparisons were being studied and how the recommendations were related to the questions.

Response: The authors modified the organization of the questions and the recommendations significantly in an effort to increase their clarity and to ensure that the most important message of the recommendations, that OA should not be used routinely, was stressed.

External Review by Ontario Clinicians

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 the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Breast DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Breast Cancer DSG.

<p>BOX 1: DRAFT RECOMMENDATIONS (approved for external review November 18, 2009)</p>
<p>OA should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy.</p>
<p>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 refuse other forms of systemic therapy).</p>
<ul style="list-style-type: none"> • A comprehensive individual patient data meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) (1) found a statistically significant benefit for OA versus no systemic therapy in terms of recurrence (ratio of annual recurrence rates 0.72; 95% confidence interval [CI], 0.64 to 0.82) and mortality (ratio of annual death rates 0.71; 95% CI, 0.62 to 0.83). • In the EBCTCG meta-analysis (1), there was no significant benefit for the addition of OA to chemotherapy in terms of recurrence (ratio of annual event rates 0.92; 95% CI, 0.82 to 1.02) or mortality (ratio of annual death

rates 1.01; 95% CI, 0.89 to 1.14).

- A meta-analysis of six randomized trials conducted for this guideline found no significant difference between OA and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-based chemotherapy in terms of disease-free (hazard ratio [HR], 0.96; 95% CI, 0.86 to 1.07) and overall survival (HR, 0.92; 95% CI, 0.78 to 1.09).
- In a meta-analysis by Cuzick et al (2), there was no significant benefit for the addition of luteinizing-hormone releasing hormone (LHRH) agonist to tamoxifen in terms of recurrence (HR, 0.85; 95% CI, 0.67 to 1.20) or death after recurrence (HR, 0.84; 95% CI, 0.59 to 1.19).
- The Cuzick et al (2) meta-analysis also found no significant benefit for the addition of LHRH agonist to the combination of tamoxifen and chemotherapy in terms of recurrence (-15.9% change in HR; 95% CI, -42.4% to 22.4%) and death after recurrence (-32.6% change in HR; 95% CI, -60.1% to 13.7%).
- One randomized trial (3) reported no significant difference between OA and tamoxifen in terms of time to recurrence (HR, 1.10; 95% CI, 0.81 to 1.49) and overall survival (HR, 1.16; 95% CI, 0.80 to 1.69).
- Six randomized trials (4-7) were identified that compared OA plus tamoxifen to tamoxifen alone. None of these trials reported a significant benefit for overall survival or other important outcome for the combination compared to tamoxifen alone.
- No evidence was identified that compared OA as systemic therapy to anthracycline and/or taxane-based chemotherapy regimens in current use, or to aromatase inhibitors.

Qualifying Statements

- The fundamental difficulty with the available data is that OA has not been compared with many systemic treatment options (anthracycline- and/or taxane-based chemotherapy, aromatase inhibitors) currently in use today. Therefore, the role of OA is still not fully understood in the context of modern systemic therapy. Until such time as OA is studied in comparison to currently relevant systemic therapy options, the Breast Cancer Disease Site Group (DSG) recommends against its routine use, except in the cases described above.
- The above recommendation regarding the use of OA in patients who are candidates for, but otherwise will not receive, systemic therapy, is based on the evidence from the EBCTCG meta-analysis from trials comparing OA to no systemic therapy. The Breast Cancer DSG recognizes, however, that the patients who received no systemic therapy in the trials that were analyzed by the EBCTCG meta-analysis may be different from patients who would be covered by this recommendation. For example, patients who refuse systemic therapy today may be very different from patients who were randomized to no systemic therapy in trials conducted over a decade ago. The Breast Cancer DSG still concludes from the available evidence that OA is better than no systemic therapy and that patients who are unwilling to undergo other forms of systemic therapy but who are willing to undergo OA (e.g., oophorectomy) might benefit from this therapy and should be offered it. The Cuzick et al (2) meta-analysis did report a significant benefit terms of recurrence (-12.7% reduction in HR; 95% CI, -21.9 to -2.4; p=0.02) and death after recurrence (-15.1% reduction in HR; 95% CI, -26.7 to -1.8; p=0.04) for the addition of OA to any systemic therapy, defined

as tamoxifen, chemotherapy, or chemotherapy plus tamoxifen. However, as the individual comparisons described above were all nonsignificant, and the chemotherapy regimens used in the analyzed trials were not the anthracycline- and/or taxane-based regimens in common use today, the interpretation of this result is unclear. Therefore, the Breast Cancer DSG did not consider this result conclusive or sufficient to alter the recommendation against the routine use of OA.

- None of the trials included in the meta-analysis were designed to test for equivalence or non-inferiority. However, the Breast Cancer DSG concludes that the available evidence does suggest that OA is non-inferior to CMF-based chemotherapy in terms of disease-free or overall survival (upper limit of the HR; 95% CI, 1.09). Therefore, in the specific case where patients are being considered for CMF-based chemotherapy, OA alone may be a reasonable alternative.

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.

- The mode of administration in nearly all of the available trials has been monthly administration.

Qualifying Statement

There is no available evidence on which to base a recommendation regarding which specific form of OA (surgical oophorectomy, ovarian irradiation, or medical castration) should be preferred.

Methods

Targeted Peer Review: During the guideline development process, seven targeted peer reviewers from across Canada considered to be clinical and/or methodological experts on the topic were identified by the authors. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three 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 December 15, 2009. The authors reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical and radiation oncologists and surgeons working in the field of breast and gynaecological cancer in Ontario were identified from the PEBC database and were contacted by email to inform them of the guideline and to solicit their feedback. 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. Participants 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). The notification email was sent on February 1, 2010. The consultation period ended on March 19, 2010. There were 34 respondents. The authors reviewed the results of the survey.

Results**Targeted Peer Review****Table 1. Responses to nine items on the targeted peer reviewer questionnaire.**

Question	Lowest Quality (1)	(2)	(3)	(4)	(5)	(6)	Highest Quality (7)
1. Rate the guideline development methods. <i>(Consider: The appropriate stakeholders were involved in the development of the guideline. The evidentiary base was developed systematically. Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs were made.)</i>					1	1	1
2. Rate the guideline presentation. <i>(Consider: The guideline is well organized. The recommendations were easy to find.)</i>					1	2	
3. Rate the guideline recommendations. <i>(Consider: The recommendations are clinically sound. The recommendations are appropriate for the intended patients.)</i>					1		2
4. Rate the completeness of reporting. <i>(Consider: The guideline development process was transparent and reproducible. How complete was the information to inform decision making?)</i>					1	1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?					1		2
6. What are the barriers or enablers to the implementation of this guideline report? Responses are compiled in the comments section below.							
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	(5)	(6)	Highest Quality (7)
7. Rate the overall quality of the guideline report.					1		2
	Strongly Disagree (1)	(2)	(3)	(4)	(5)		Strongly Agree (7)
8. I would make use of this guideline in my professional decisions.					1		2
9. I would recommend this guideline for use in practice.					1		2

Summary of Written Comments

- -One targeted reviewer suggested two studies (3, 4) that might have been erroneously omitted, however, one was included in the Cuzick meta-analysis (3), and the other was not a systematic review or RCT and thus did not meet the inclusion criteria (4).
- -It was suggested to have consistent terminology regarding chemical OA and use the term “ovarian suppression” rather than “castration.” This change was made.

- -Some layout changes to the document were proposed, but given the complexity of the material, the authors felt that such suggestions were based on personal preference and would not substantially improve the document.
- -At the suggestion of a reviewer, a clarifying sentence was added to the beginning of the Additional Discussion section to improve the readability.
- -It was suggested that the second recommendation referring to patients who refuse other forms of systemic therapy should be expanded to patients who cannot tolerate other forms of systemic therapy.
- -One reviewer proposed citing a study by Gnant et al (5) as part of the evidence on the topic of using AIs in rendering a premenopausal woman postmenopausal. However, the Gnant study contained OA in both study arms and did not meet inclusion criteria. A qualifying statement was added to indicate that no evidence was found comparing OA plus AIs with other adjuvant treatments in premenopausal women.
- -In response to a query about the use of OA in postmenopausal women, it was decided to add “premenopausal” to the title to explicitly indicate the scope of the document.

Professional Consultation

Table 2. Responses to three items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			2	17	15
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.		1	1	16	16
3. I would recommend this guideline for use in practice.		1	2	14	17

Summary of Written Comments

The comments generally indicated support for the recommendations, agreeing that the use of OA in modern breast cancer treatment is not straight forward and presents a challenge in current practice. Some reviewers noted that the guideline provides information on alternative treatment for patients who choose not to have chemotherapy.

Final DSG Deliberations

Members of the PEBC Breast Cancer DSG reviewed the external review feedback during a DSG meeting in June 2010. The changes made by the working group in response to the feedback were deemed acceptable and no further changes were suggested.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Breast Cancer DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

For a complete list of the Breast Cancer Disease Site Group members, please visit the CCO website at <http://www.cancercare.on.ca/>

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