Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background Bisphosphonates have profound effects on bone physiology, and could modify the process of metastasis. We undertook collaborative meta-analyses to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer.

Methods We sought individual patient data from all unconfounded trials in early breast cancer that randomised between bisphosphonate and control. Primary outcomes were recurrence, distant recurrence, and breast cancer mortality. Primary subgroup investigations were site of first distant recurrence (bone or other), menopausal status (postmenopausal [combining natural and artificial] or not), and bisphosphonate class (aminobisphosphonate [eg, zoledronic acid, ibandronate, pamidronate] or other [ie, clodronate]). Intention-to-treat log-rank methods yielded bisphosphonate versus control first-event rate ratios (RRs).

Findings We received data on 18 766 women (18 206 [97%] in trials of 2–5 years of bisphosphonate) with median follow-up 5·6 woman-years, 3453 first recurrences, and 2106 subsequent deaths. Overall, the reductions in recurrence (RR 0·94, 95% CI 0·87–1·01; 2p=0·08), distant recurrence (0·92, 0·85–0·99; 2p=0·03), and breast cancer mortality (0·91, 0·83–0·99; 2p=0·04) were of only borderline significance, but the reduction in bone recurrence was more definite (0·83, 0·73–0·94; 2p=0·004). Among premenopausal women, treatment had no apparent effect on any outcome, but among 11 767 postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002), distant recurrence (0·82, 0·74–0·92; 2p=0·0003), bone recurrence (0·72, 0·60–0·86; 2p=0·0002), and breast cancer mortality (0·82, 0·73–0·93; 2p=0·002). Even for bone recurrence, however, the heterogeneity of benefit was barely significant by menopausal status (2p=0·06 for trend with menopausal status) or age (2p=0·03), and it was non-significant by bisphosphonate class, treatment schedule, oestrogen receptor status, nodes, tumour grade, or concomitant chemotherapy. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR 0·85, 95% CI 0·75–0·97; 2p=0·02).

Interpretation Adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival, but there is definite benefit only in women who were postmenopausal when treatment began.

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*Full list of members available at http://www.ctsu.ox.ac.uk/research/meta-trials/ebctcg/ebctcg-page

Correspondence to: EBCTCG Secretariat, Clinical Trial Service Unit, Nuffield Department of Population Health, Richard Doll Building, Oxford OX3 7LF, UK
bc.overview@ctsu.ox.ac.uk

Introduction

Circulating tumour cells can be attracted to surfaces within the bone where they can displace haemopoietic stem cells and bind to the osteoblastic niche.[1] These disseminated malignant cells can remain quiescent for years. Then, for reasons that are not well understood, they can exit this dormant state, start to proliferate, and establish macrometastases in the bone or elsewhere.[2,3] Bisphosphonates have profound effects on osteoclasts, and affect T-cell function, so could also be effective as adjuvant treatments, particularly in preventing or delaying bone recurrence.[4–6] For this reason, and because bisphosphonates can be added to the aromatase inhibitor treatment of postmenopausal breast cancer to restrict adverse skeletal effects of oestrogen deprivation, reliable evidence is needed about the effects of bisphosphonates on breast cancer outcomes.

Improvements in bone-metastasis-free survival, disease-free survival, and overall survival in women with early breast cancer have been reported in some adjuvant trials of oral clodronate[7,8] or of intravenous zoledronic acid.[9,10] However, in other trials of adjuvant bisphosphonates no significant benefits were seen in analyses that included all randomised patients, although both planned and exploratory subset analyses suggested benefits either in postmenopausal women[11] or in older women.[12,13] This led to the hypothesis[11–13] that treatment is of benefit only in patients with low concentrations of reproductive hormones (ie, those who are postmenopausal or undergoing ovarian suppression therapy).[14–16]

To help clarify whether adjuvant bisphosphonates reduce the risk of bone and other metastases, and whether menopausal status affects efficacy, we undertook collaborative

meta-analyses of all unconfounded randomised trials that compared breast cancer outcomes in those allocated adjuvant bisphosphonate versus those who were not.

Methods

Identification of studies and collection of data

The methods of identifying trials, seeking collaboration, data collection, collation, checking, and presentation are as in previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reports.[17–19] Trials were eligible if they began before 2008 and randomly assigned women between a bisphosphonate of any type, dose, and schedule versus a control group (open label or placebo) with no bisphosphonate, all other treatments being similar in both groups. Information was sought during 2012–14 for each individual patient on date of randomisation, allocated treatment, age, menopausal status, tumour diameter, grade, spread to locoregional lymph nodes, HER2 and oestrogen and progesterone receptor (ER/PR) status, dates and sites of any breast cancer recurrence, other second primary cancer, bone fracture, and the date and cause of death.

The main definitions and analysis methods are those used in previous EBCTCG reports,[17–19] but with some amendments that reflect the potential effect of bisphosphonates on bone metastases (appendix).

See Online for appendix

For the **CTSU policy on data sharing** see http://www.ctsu.ox.ac.uk/research/data-access-policies/data-access-and-sharing-policy/view

Outcomes

The pre-defined coprimary endpoints were any recurrence of breast cancer (distant, locoregional, or new primary in the contralateral breast); distant recurrence, ignoring any previous locoregional or contralateral recurrence; and breast cancer mortality (estimated by log-rank subtraction, as in previous EBCTCG reports[18,19]).

Secondary outcomes were all-cause mortality; death without recurrence; bone recurrence as the first distant recurrence (with or without concurrent other recurrence); other first (extraskeletal) distant recurrence (with all analyses of distant recurrence ignoring any previous locoregional or contralateral recurrence); locoregional recurrence as first event (ipsilateral breast, chest wall, or locoregional lymph nodes); contralateral new primary breast cancer as first event; and any bone fractures.

Statistical analyses

Time-to-event analyses were stratified by age, ER status, nodal status, and trial. Within each stratum, they compared all those allocated bisphosphonate versus all those allocated control, regardless of treatment compliance (yielding intention-to-treat analyses). Log-rank statistics were used to assess the effects (bisphosphonate *vs* control) on various outcomes, and, for each, to estimate first-event rate ratios (RRs) and their CIs. We did statistical analyses using EBCTCG in-house Fortran programs.

Pre-specified primary subgroup investigations were of site of first distant recurrence (bone, other), menopausal status (premenopausal, perimenopausal, postmenopausal [natural or induced, either potentially reversibly, using luteinising hormone-releasing hormone analogues, or permanently by oophorectomy] or, if menopausal status was unavailable, years of age, grouped as <45, 45–54, ≥55 years), and class of bisphosphonate (aminobisphosphonate [zoledronic acid, ibandronate, pamidronate, risedronate, alendronate], other [clodronate]). Exploratory investigations were undertaken of potential interactions between treatment efficacy and ER status, nodal status, histological grade, use or not of adjuvant chemotherapy, and follow-up period. If appropriate, tests comparing effects in different subgroups were for trend rather than heterogeneity.

We pre-specified that comparisons of treatment efficacy within subgroups would exclude local and contralateral recurrence if the prior hypothesis that bisphosphonates would reduce distant but not local or contralateral recurrence was established from analyses of the overall results in all randomised patients. As bone recurrence was the only type of recurrence significantly reduced by bisphosphonates we used this instead as the primary endpoint for subgroup comparisons, but the appendix includes subgroup analyses for any distant recurrence. Because the ABCSG-12[9] and AZURE[11,14] trials had helped generate the hypothesis of the relevance of menopausal status to the effects of treatment, we provide sensitivity analyses of this hypothesis that treated these trials as hypothesis-generating, with the remaining trials hypothesis-testing. The policy on data sharing from this study is available online.

	Studies identified		Studies with data received			
	Trials (n)	Patients (n)	Trials (n)	Patients (n)	%*	Years†
Up to 1 year of treatment						
<1 year clodronate	2	120	1	72	60%	0·5
<1 year aminobisphosphonate	2	208	1	40	19%	0·1
1 year aminobisphosphonate	7	1088	3	448	41%	1·0
Total for ≤1 year of treatment	11	1416	5	560	40%	0·9
2–5 years of treatment						
2 years clodronate	4	3978	3	3912	98%	2·0
3–5 years clodronate	1	1069	1	1069	100%	3·0
2 years aminobisphosphonate	10	3654	8	3514	96%	2·0
3–5 years aminobisphosphonate	12	11 910‡	9	9711	82%‡	4·5
Total for 2–5 years of treatment	27	20 611‡	21	18 206	88%‡	3·5
Any clodronate regimen	7	5167	5	5053	98%	2·6
Any aminobisphosphonate§	31	16 860‡	21	13 713	81%‡	3·8
Total, all regimens	38	22 027‡	26	18 766	85%‡	3·4

*Number of patients with data received as a percentage of all randomised patients in identified studies. †Mean scheduled treatment duration (weighted in proportion to numbers of patients with data received). ‡Includes two trials (2116 patients) still in progress; excluding these, the total with data received is 94%. §The aminobisphosphonates in these trials were zoledronic acid (9290 patients with data received, 1582 recurrences [46% of all recurrences]), ibandronate (3072 patients, 380 recurrences [11%]), pamidronate (953 patients, 473 recurrences [14%]), risedronate (398 patients, 13 recurrences [0·4%]), and alendronate (no trials with data received); the only non-aminobisphosphonate in these trials was clodronate (5053 patients, 1005 [29%] recurrences).

Table: **Numbers of unconfounded randomised trials of an adjuvant bisphosphonate identified, and numbers with data received, by duration and type of bisphosphonate treatment**

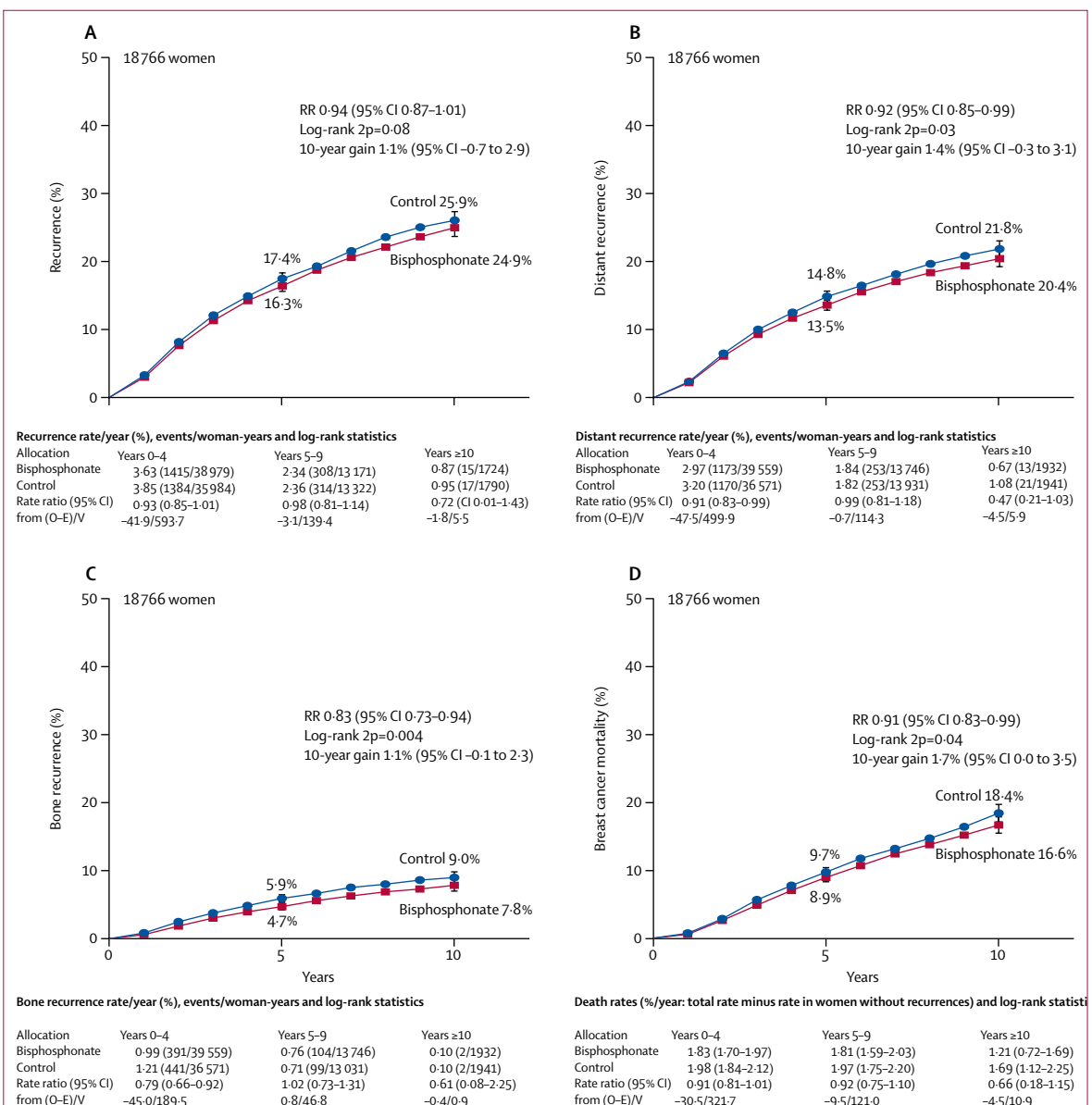
Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The writing committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Individual patient datasets were provided for 26 trials with 18766 participants, 97% of all 19291 women in the 32 completed trials that recorded recurrence data (table, appendix). In four other trials (620 women) recurrence was not recorded, and from the two ongoing trials (2116 women) outcome data cannot yet be provided. Mean scheduled treatment duration was 3·4 years; 18206 (97%) of 18766 participants were in trials of 2–5 years of treatment. Median follow-up was 5·6 woman-years (IQR 3·7–8·0). 3453 women had a recurrence, after which 2106 died.

Recurrence rates were slightly lower with than without bisphosphonates, but this was not significant in analyses that included all 18766 women (RR 0·94, 95% CI 0·87–1·01; 2p=0·08; figure 1). However, there was a borderline significant reduction in the risk of distant recurrence, ignoring any previous local or contralateral



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	3·63 (1415/38979)	2·34 (308/13171)	0·87 (15/1724)
Control	3·85 (1384/35984)	2·36 (314/13322)	0·95 (17/1790)
Rate ratio (95% CI)	0·93 (0·85–1·01)	0·98 (0·81–1·14)	0·72 (CI 0·01–1·43)
from (O–E)/V	−41·9/593·7	−3·1/139·4	−1·8/5·5

Distant recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	2·97 (1173/39559)	1·84 (253/13746)	0·67 (13/1932)
Control	3·20 (1170/36571)	1·82 (253/13931)	1·08 (21/1941)
Rate ratio (95% CI)	0·91 (0·83–0·99)	0·99 (0·81–1·18)	0·47 (0·21–1·03)
from (O–E)/V	−47·5/499·9	−0·7/114·3	−4·5/5·9

Bone recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	0·99 (391/39559)	0·76 (104/13746)	0·10 (2/1932)
Control	1·21 (441/36571)	0·71 (99/13031)	0·10 (2/1941)
Rate ratio (95% CI)	0·79 (0·66–0·92)	1·02 (0·73–1·31)	0·61 (0·08–2·25)
from (O–E)/V	−45·0/189·5	0·8/46·8	−0·4/0·9

Death rates (%/year: total rate minus rate in women without recurrences) and log-rank statisti

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·83 (1·70–1·97)	1·81 (1·59–2·03)	1·21 (0·72–1·69)
Control	1·98 (1·84–2·12)	1·97 (1·75–2·20)	1·69 (1·12–2·25)
Rate ratio (95% CI)	0·91 (0·81–1·01)	0·92 (0·75–1·10)	0·66 (0·18–1·15)
from (O–E)/V	−30·5/321·7	−9·5/121·0	−4·5/10·9

Figure 1: **Recurrence by site and breast cancer mortality in 24 trials of bisphosphonate versus no bisphosphonate (control)**
Kaplan-Meier graphs showing effects of treatment allocation on 10-year outcomes in all 18766 patients. (A) Any recurrence. (B) Distant recurrence. (C) Bone recurrence. (D) Breast cancer mortality. O–E=observed minus expected. V=variance of O–E. RR=rate ratio (exp[(O–E)/V]). Error bars are SE.

Category	Events/women		Bisphosphonate events		Ratio of annual event rates bisphosphonate : control	Rate ratio (CI)
	Allocated bisphosphonate	Allocated control	Log-rank O–E	Variance of O–E		
(a) Age, years (trend χ^2_1=4·9; 2p=0·03)						
<45	164/2475 (6·6%)	151/2141 (7·1%)	–0·3	71·3		1·00 (0·79–1·26)
45–54	152/3532 (4·3%)	173/3224 (5·4%)	–14·2	74·3		0·83 (0·61–1·11)
55–69	168/3314 (5·1%)	196/3022 (6·5%)	–25·1	84·4		0·74 (0·56–0·98)
≥70	13/531 (2·4%)	22/521 (4·2%)	–5·1	7·1		0·49 (0·19–1·29)
Age unknown	0/4 (0·0%)	0/2 (0·0%)				
(b) Menopausal status (trend χ^2_1=3·5; 2p=0·06)						
Premenopausal	217/3296 (6·6%)	212/2875 (7·4%)	–7·9	96·4		0·92 (0·71–1·20)
Perimenopausal	28/461 (6·1%)	19/367 (5·2%)	2·0	8·8		
Postmenopausal	252/6099 (4·1%)	311/5668 (5·5%)	–42·1	128·0		0·72 (0·57–0·90)
(c) ER status (χ^2_1=0·6; 2p=0·4)						
ER negative	107/1964 (5·4%)	135/1684 (8·0%)	–15·7	56·4		0·76 (0·54–1·07)
ER unknown	42/637 (6·6%)	47/690 (6·8%)	1·2	20·9		1·06 (0·60–1·86)
ER positive	348/7255 (4·8%)	360/6536 (5·5%)	–26·9	169·1		0·85 (0·70–1·04)
(d) Nodal status (trend χ^2_1=0·5; 2p=0·5)						
N0/N–	70/2638 (2·7%)	68/2631 (2·6%)	0·6	32·3		1·02 (0·72–1·44)
N1–3	225/4323 (5·2%)	231/3352 (6·9%)	–24·0	104·1		0·79 (0·62–1·02)
N4+	160/1205 (13·3%)	183/1190 (15·4%)	–14·3	76·1		0·83 (0·62–1·11)
N other/unknown	42/1690 (2·5%)	60/1737 (3·5%)	–6·9	24·6		0·76 (0·45–1·27)
(e) Tumour grade (trend χ^2_1=0·4; 2p=0·5)						
Well differentiated	24/877 (2·7%)	26/793 (3·3%)	–1·6	10·9		
Moderately differentiated	196/3667 (5·3%)	203/3249 (6·2%)	–11·7	94·4		0·88 (0·68–1·15)
Poorly differentiated	156/2801 (5·6%)	174/2326 (7·5%)	–17·6	76·8		0·80 (0·59–1·07)
Grade unknown	121/2511 (4·8%)	139/2542 (5·5%)	–4·4	61·4		0·93 (0·67–1·29)
(f) Bisphosphonate type (χ^2_4=0·3; 2p=0·6)						
Clodronate	139/2514 (5·5%)	165/2539 (6·5%)	–16·7	67·5		0·78 (0·57–1·07)
Aminobisphosphonate	358/7342 (4·9%)	377/6371 (5·9%)	–27·9	169·7		0·85 (0·70–1·03)
(g) Bisphosphonate (χ^2_4=5·9; 2p=0·21)						
Clodronate	139/2514 (5·5%)	165/2539 (6·5%)	–16·7	67·5		0·78 (0·57–1·07)
Zoledronic acid	200/4642 (4·3%)	250/4648 (5·4%)	–24·1	108·7		0·80 (0·63–1·03)
Pamidronate	80/460 (17·4%)	76/493 (15·4%)	5·1	33·1		1·17 (0·83–1·64)
Ibandronate	78/2040 (3·8%)	49/1032 (4·7%)	–8·0	27·3		0·75 (0·46–1·22)
Risedronate	0/200 (0·0%)	2/198 (1·0%)	–0·9	0·5		
Alendronate	(no data)					
(h) Bisphosphonate dose (χ^2_1=0·4; 2p=0·5)						
More intensive	434/7040 (6·2%)	457/6089 (7·5%)	–34·5	201·7		0·84 (0·70–1·01)
Low intensity	63/2816 (2·2%)	85/2821 (3·0%)	–10·1	35·5		0·75 (0·49–1·16)
(i) Bisphosphonate duration (trend χ^2_1=0·2; 2p=0·7)						
<1 year	4/277 (1·4%)	4/283 (1·4%)	0·8	1·7		
2 years	169/3081 (5·5%)	154/2091 (7·4%)	–18·5	68·6		0·76 (0·56–1·04)
>2 years	324/6498 (5·0%)	384/6536 (5·9%)	–26·9	166·9		0·85 (0·70–1·04)
(j) Chemotherapy (χ^2_1=0·3; 2p=0·6)						
Absence	39/1616 (2·4%)	53/1616 (3·3%)	–6·3	21·0		0·74 (0·48–1·14)
Presence	458/8240 (5·6%)	489/7294 (6·7%)	–38·3	216·2		0·84 (0·70–1·00)
(k) Follow-up period, years (trend χ^2_1=2·5; 2p=0·11)						
0–1	173/9856 (1·8%)	204/8910 (2·3%)	–25·0	85·0		0·75 (0·56–0·99)
2–4	218/8445 (2·6%)	237/7609 (3·1%)	–20·0	104·6		0·83 (0·64–1·06)
5–9	104/5711 (1·8%)	99/5614 (1·8%)	0·8	46·8		1·02 (0·73–1·31)
≥10	2/706 (0·3%)	2/758 (0·3%)	–0·4	0·9		
Total	**497/9856 (5·0%)**	**542/8910 (6·1%)**	**–44·6**	**237·1**		**0·829 (0·730–0·941)**
						2p=0·004

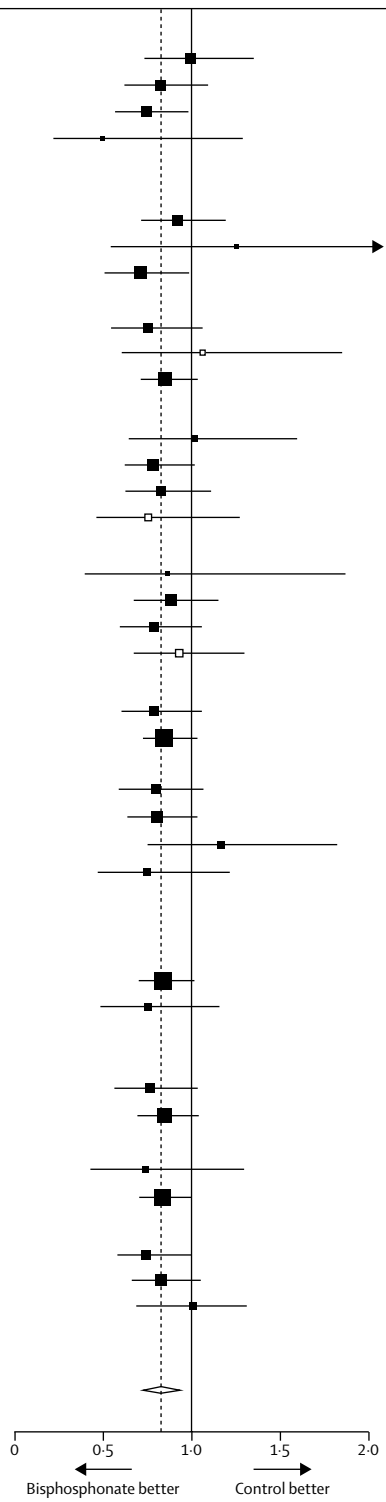


Figure 2: **Multiple subgroup analyses of effects on bone recurrence in trials of bisphosphonate versus no bisphosphonate (control)**
Results are plotted as black squares with horizontal lines that denote 99% rather than 95% CIs to allow for multiple hypothesis testing. Total is plotted as a white diamond that denotes 95% CI. ER=oestrogen receptor. O–E=observed minus expected.

breast recurrence (10-year risk 20·4% bisphosphonate *vs* 21·8% control; RR 0·92, 95% CI 0·85–0·99; 2p=0·03; figure 1), whereas there was no significant effect on the incidence of local recurrence as first event (RR 1·10, 0·94–1·28; 2p=0·25; appendix) or of contralateral breast cancer as first event (RR 0·96, 0·74–1·25; 2p=0·79). The greater efficacy of bisphosphonates in preventing distant recurrence than in preventing other (local or contralateral) breast cancer recurrence was significant (test for interaction 2p=0·01).

The effect on distant recurrence was mainly because of a reduction in bone recurrence (10-year risk 7·8% *vs* 9·0%; RR 0·83, 95% CI 0·73–0·94; 2p=0·004; figure 1). There was significantly (p=0·04) greater effect on bone recurrence than on other first distant recurrence (RR 0·98, 95% CI 0·89–1·08; 2p=0·69; appendix), although this apparent lack of efficacy could be partly because delay of bone recurrence with bisphosphonate in a woman who would otherwise have had both bone and other distant recurrence allowed the other recurrence to be the first event.

Breast cancer mortality was borderline significantly lower in patients allocated bisphosphonate than control (10-year risk 16·6% *vs* 18·4%; RR 0·91, 95% CI 0·83–0·99; 2p=0·04; figure 1), and all-cause mortality was similarly reduced (10-year risk 20·8% *vs* 22·3%; RR 0·92, 0·85–1·00; 2p=0·06; appendix). Of 2607 deaths from any cause, 501 (19%) were in recurrence-free women; this non-breast cancer mortality appeared to be unaffected by the treatment allocation (RR 0·99, 95% CI 0·82–1·19; 2p=0·91).

We did many subgroup analyses to investigate the effects of bisphosphonates on any recurrence, distant recurrence, bone recurrence, and breast cancer mortality (appendix). In the overall analyses, among all 18766 women, the clearest evidence of effect of bisphosphonates was, as anticipated, on bone recurrence, so the most informative subgroup analyses should relate to this endpoint (figure 2). The efficacy of bisphosphonates in reducing bone recurrence appeared to be greater in older women (2p=0·03 for trend with age in treatment effect) or, similarly, in postmenopausal women (2p=0·06 for trend with menopausal status). As menopausal status and age are closely correlated, we cannot determine reliably which is more relevant (appendix). Among the 4616 women younger than 45 years, bone recurrence appeared to be unaffected by the treatment allocation (RR 1·00, 95% CI 0·79–1·26; 2p=0·97), but among the 7388 women 55 years or older there was a highly significant treatment effect (RR 0·72, 0·59–0·88; 2p=0·002). Sensitivity analyses of the possible relevance of age and menopausal status that omitted the hypothesis-generating ABCSG-12[9] and AZURE[11,14] studies still showed significant (2p=0·004) benefit only in postmenopausal women (appendix). As was the case for bone recurrence, the reductions in any distant recurrence with bisphosphonate were also significantly greater in older women (2p=0·003 for trend with age) and postmenopausal women (2p=0·01).

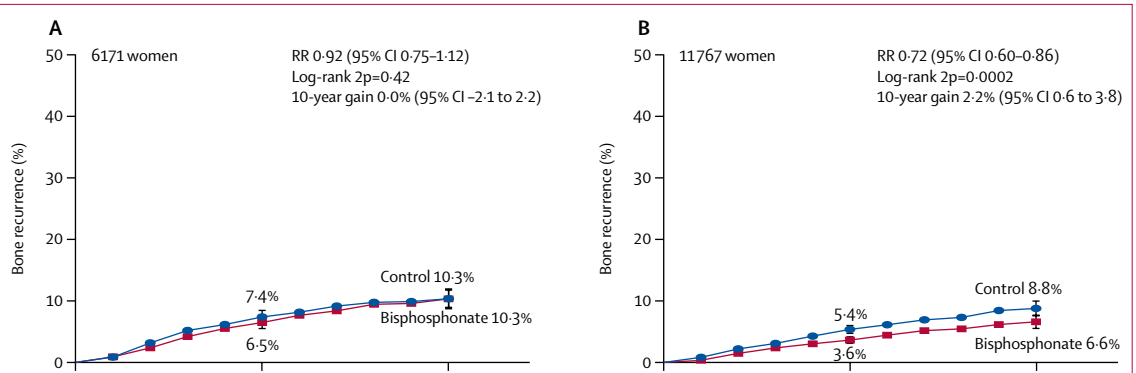
None of the other subgroup analyses of bone recurrence in figure 2 revealed any significant evidence of heterogeneity of benefit by tumour type (or for other breast cancer outcomes; appendix). Although the benefit appeared somewhat larger in ER-negative than ER-positive disease and in node-positive than node-negative tumours, this apparent heterogeneity of treatment effect did not approach significance and could be a chance finding.

Likewise, there was no significant heterogeneity between the apparent effects on bone recurrence of the different bisphosphonate regimens tested in these trials. For this outcome, the benefits of the non-aminobisphosphonate (clodronate, n=5053) and of the two most widely tested aminobisphosphonates (zoledronic acid, n=9290, and ibandronate, n=3072) appeared similar, but there was no apparent benefit in the smaller oral pamidronate group (n=953).

For bone recurrence, the benefits appeared to be similar in trials of low-intensity anti-osteoporosis schedules (eg, 6-monthly intravenous zoledronic acid) and in trials of more intensive schedules such as those approved for use in metastatic bone disease (eg, monthly zoledronic acid, daily oral ibandronate, or daily oral clodronate). Likewise, the average effect appeared similar in trials that tested different durations of treatment (trials of 2 years bisphosphonate *vs* none: RR 0·76, 95% CI 0·60–0·97; 2p=0·026; trials of 3–5 years bisphosphonate *vs* none: RR 0·85, 0·73–0·99; 2p=0·037; figure 2), and in the presence or absence of chemotherapy. There were significant reductions in bone recurrence during years 0–1 and years 2–4 after randomisation but there appeared to be no further reduction thereafter. Again, though, this decrease in treatment effect over time was not significant (trend 2p=0·11), perhaps because there is thus far only limited follow-up after the first 5 years.

The 10-year disease outcomes for premenopausal and postmenopausal women separately are summarised in figure 3 and the appendix. In premenopausal women, treatment appeared to have little effect on bone metastases or breast cancer mortality, whereas in postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002; appendix), distant recurrence (RR 0·82, 0·74–0·92; 2p=0·0003; appendix), bone recurrence (RR 0·72, 0·60–0·86; 2p=0·0002), and breast cancer mortality (RR 0·82, 0·73–0·93; 2p=0·002). In both menopausal subgroups, rates of first distant recurrence at sites other than bone appeared to be unaffected by treatment. In the postmenopausal subgroup, for bone recurrence the absolute gain from treatment was 2·2% (95% CI 0·6–3·8) (10-year risks 6·6% *vs* 8·8%; RR 0·72, 95% CI 0·60–0·86; 2p=0·0002), whereas for breast cancer mortality the absolute gain was 3·3% (95% CI 0·8–5·7) (10-year risks 14·7% *vs* 18·0%; RR 0·82, 0·73–0·93; 2p=0·002).

To enhance statistical power, the multiple subgroup analyses of bone recurrence (figure 2) and the corresponding analyses of other outcomes (appendix) can



Bone recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·35 (169/12 510)	1·00 (47/4710)	0·07 (1/1390)
Control	1·54 (175/11 390)	0·69 (36/5196)	0·07 (1/1424)
Rate ratio (95% CI)	0·86 (0·66–1·07)	1·24 (0·73–1·74)	0·37 (0·02–2·33)
from (O–E)/V	−11·4/77·4	3·9/18·5	−0·4/0·4

Bone recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	0·78 (197/25 220)	0·67 (55/8157)	0·0 (0/513)
Control	1·06 (251/23 642)	0·76 (60/7870)	0·0 (0/484)
Rate ratio (95% CI)	0·68 (0·52–0·84)	0·90 (0·54–1·26)	
from (O–E)/V	−39·3/101·2	−2·8/26·8	

Recurrence outside bone rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	2·64 (330/12 510)	1·25 (59/4710)	0·43 (6/1390)
Control	2·41 (275/11 390)	1·14 (59/5196)	0·77 (11/1424)
Rate ratio (95% CI)	1·12 (0·93–1·30)	1·03 (0·64–1·42)	0·37 (0·13–1·08)
from (O–E)/V	14·2/128·4	0·7/26·1	−3·0/3·1

Recurrence outside bone rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·67 (420/25 220)	1·04 (85/8157)	0·78 (4/513)
Control	1·98 (427/23 642)	1·17 (92/7870)	1·65 (8/484)
Rate ratio (95% CI)	0·90 (0·77–1·04)	0·89 (0·60–1·19)	0·38 (0·09–1·34)
from (O–E)/V	−18·4/182·4	−4·5/39·7	−1·7/1·8

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	2·43 (2·16–2·69)	2·26 (1·84–2·67)	1·13 (0·58–1·68)
Control	2·50 (2·22–2·79)	2·03 (1·65–2·40)	1·29 (0·71–1·88)
Rate ratio (95% CI)	0·97 (0·81–1·14)	1·10 (0·81–1·40)	0·71 (0·34–1·50)
from (O–E)/V	−3·3/130·6	5·0/50·0	−2·3/6·9

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·56 (1·41–1·72)	1·57 (1·30–1·84)	1·30 (0·34–2·26)
Control	1·74 (1·58–1·91)	2·04 (1·74–2·35)	2·73 (1·30–4·16)
Rate ratio (95% CI)	0·86 (0·72–0·99)	0·76 (0·55–0·97)	0·52 (0·18–1·44)
from (O–E)/V	−27·1/174·9	−18·0/65·0	−2·4/3·6

***Figure 3*: Main outcomes in premenopausal (excluding perimenopausal) and in postmenopausal women in trials of bisphosphonate versus no bisphosphonate (control)**

Kaplan-Meier graphs showing the effects of treatment allocation on 10-year breast cancer outcomes. (A) Premenopausal and (B) postmenopausal bone recurrence. (C) Premenopausal and (D) postmenopausal distant recurrence outside the bone. (E) Premenopausal and (F) postmenopausal breast cancer mortality. O-E=observed minus expected. V=variance of O–E. RR=rate ratio (exp[{O–E}/V]). Error bars are SE.

all be restricted to postmenopausal women (appendix). In postmenopausal women, there was significant (p=0·01) heterogeneity between agents in the reductions in bone recurrence, explained by the apparent lack of benefit from pamidronate. The clodronate results did appear somewhat more promising than the aminobisphosphonate results but this difference was not significant for distant recurrence or for bone recurrence, and was of only borderline significance for breast cancer mortality, even though the reduction in postmenopausal breast cancer mortality was significant with clodronate but not with the aggregate of all aminobisphosphonate regimens.

Information on fractures was available from only 13 341 (71%) of 18 766 women. Among them, 422 (6·3%) of 6649 bisphosphonate-allocated patients had a fracture reported, as against 487 (7·3%) of 6692 control patients (RR 0·85, 95% CI 0·75–0·97; 2p=0·02; appendix), and the 5-year fracture risk was reduced from 6·3% to 5·1%, with little effect in years 0–1 and most of the gain in years 2–4. After year 5 there appeared to be little further gain, but in both groups the absolute rates after year 5 were lower than in years 0–4, perhaps reflecting incomplete ascertainment.

Discussion

Taking all women together, regardless of menopausal status, this collaborative meta-analysis of individual patient data from 18 766 women randomised in trials of adjuvant bisphosphonates found a highly significant reduction only in bone recurrence, and not in other breast cancer outcomes. Subgroup analyses suggested benefit just in postmenopausal women, among whom there were highly significant reductions not only in bone recurrence but also in any distant recurrence (bone or other), breast cancer mortality, and overall mortality.

Neither in the overall results nor in the results just among postmenopausal women, however, was there any significant effect on distant recurrence at extra-osseous sites, on locoregional recurrence, or on the incidence of contralateral breast cancer. The lack of effect on new contralateral breast cancers is consistent with findings of the large FIT and HORIZON-PFT fracture prevention trials,[20] but contrasts with reports from epidemiological studies that breast cancer incidence is reduced in postmenopausal women taking bisphosphonates for osteoporosis.[21,22] Thus, the randomised evidence provides no support for the use of bisphosphonates as a breast cancer chemoprevention strategy.

Though the statistical significance of the apparent interaction between menopausal status and treatment efficacy is not extreme, greater benefit for postmenopausal women had been hypothesised to explain the apparent discordance between the ABCSG-12[9] and AZURE[11,14] trial results. Sensitivity analyses that excluded these two hypothesis-generating datasets only marginally weakened the evidence of an interaction with menopausal status, and the benefit was still significant in the remaining postmenopausal women.

Moreover, there is some preclinical evidence that reproductive hormones can inhibit bisphosphonate efficacy against cancer cells in the bone. The effects of zoledronic acid (100 μg/kg weekly) on the growth of disseminated MDA-231 breast cancer cells in bone were compared in ovariectomised mice (modelling the postmenopausal setting) and in sham-operated mice (modelling the premenopausal setting). Zoledronic acid decreased the number of detectable tumours in bone only in the ovariectomised animals.[23] Likewise, in a prostate cancer mouse model the ability of disseminated tumour cells in the bone to form detectable tumours was inhibited by zoledronic acid only in castrated mice, not in sham-operated mice.[24]

The effects on bone recurrence emphasise the potential importance of host microenvironment factors to metastasis. Further studies are needed to clarify why menopausal status should importantly affect the response to bisphosphonates. The complex interactions between reproductive hormones, tumour biology, bone cell function, and bone marrow stem cells could well change as patients progress from the premenopausal setting, where oestradiol and inhibin are of major importance in bones, to the postmenopausal setting, where activin and other members of the TGF-β superfamily become the main regulators of bone cell metabolism.[25] A clearer understanding of some of the other mechanisms involved in the development of bone metastasis is now emerging, although how these relate to menopausal status and reproductive hormones remains unknown.[26]

Other than the apparent effect of menopausal status or, similarly, age on treatment efficacy, the proportional reductions in bone recurrence and breast cancer mortality with treatment did not depend significantly on other patient or clinicopathological primary tumour characteristics, including ER status, axillary lymph node involvement, and tumour grade. Similar reductions were seen in the presence and absence of chemotherapy, suggesting that the benefits of bisphosphonates are approximately additive to those of chemotherapy, and vice versa.

As subgroup analyses can yield erratic results, it is difficult to determine from them whether different bisphosphonate regimens have different effects. The endpoint that should yield the most reliable subgroup analyses is bone recurrence. Both for all women and for postmenopausal women, subgroup analyses of bone recurrence suggested similar effects of oral clodronate and of the aggregate of all aminobisphosphonate regimens (mainly intravenous zoledronic acid). Likewise, they suggested no significant heterogeneity in efficacy between the different aminobisphosphonates, though no benefit was seen with oral pamidronate (which could be real, as oral pamidronate is poorly absorbed, has little effect on bone resorption biomarkers or the underlying metastatic bone disease, and failed to show efficacy in myeloma[27,28]). Numbers were insufficient to assess the efficacy of the standard treatments for osteoporosis, oral

risedronate or alendronate, as therapy for early breast cancer. Subgroup analyses based instead on breast cancer mortality suggested a greater effect with clodronate than with aminobisphosphonates. However, as the two drugs appeared to have similar effects on bone recurrence, their apparently different effects on breast cancer mortality could be a chance finding.

Much more reliable comparisons of different bisphosphonate regimens will emerge from ongoing trials that compare them directly. The SWOG0307 trial (NCT00127205) comparing clodronate versus zoledronic acid versus ibandronate in 5400 patients has completed recruitment and addresses the choice of agent; the SUCCESS trial (NCT02181101) comparing 5 years versus 2 years of zoledronic acid in 3800 patients has also completed recruitment and addresses duration. Similarly, results from two ongoing trials (HOBOE-premenopausal [NCT00412022] and TEAM-IIb [ISRCTN17633610]), plus longer follow-up of the trials included in this meta-analysis, will eventually provide better evidence on any effect of bisphosphonates in premenopausal women, and will provide more stable estimates of the 10-year outcomes in postmenopausal women.

Consistent with the known effects on bone mineral density and quality, the use of adjuvant bisphosphonates was associated with a small reduction in fracture incidence. Although not highly significant, it can be accepted as real because of evidence of fracture reduction in other types of patient. There was no apparent effect of adjuvant bisphosphonates on non-breast cancer mortality. Major adverse events with bisphosphonates are uncommon, but can include impaired renal function and osteonecrosis of the jaw. From the data provided, we were unable to assess the incidence of osteonecrosis of the jaw, but previous reports suggest it ranges from under 1% with clodronate, ibandronate, or 6-monthly zoledronic acid[12,13,29] to about 2% with more intensive zoledronic acid schedules.[30]

These trials have shown that some years of adjuvant bisphosphonate treatment can reduce breast cancer recurrence rates in bone and improve breast cancer survival, but have provided clear evidence of benefit only in women who are postmenopausal (natural or induced) at the time bisphosphonates are started. The use of bisphosphonates in breast cancer is mainly to reduce bone loss and risk of fracture in postmenopausal women with ER-positive disease treated with aromatase inhibitors. Our results show that such bisphosphonate treatment can, in addition, provide oncological benefit, and suggest that adjuvant bisphosphonates should be considered in a broader range of postmenopausal women.

Contributors

Analyses were planned by R Coleman, R Gray, T Powles, A Paterson, M Gnant, J Bergh, K I Pritchard, J Bliss, and D Cameron, and undertaken by R Bradley, R Gray, H Pan, and R Peto in Oxford. R Coleman, R Gray, T Powles, and A Paterson drafted the report and revised it with advice from all writing committee members. The EBCTCG secretariat (R Bradley, J Burrett, M Clarke, C Davies, F Duane, V Evans, L Gettins, J Godwin, R Gray, H Liu, P McGale, E MacKinnon, T McHugh, S James, P Morris, H Pan, R Peto, S Read, C Taylor, Y Wang, Z Wang) identified trials, obtained datasets, and had full access to them.

Writing committee

R Coleman (Sheffield Cancer Research Centre, Weston Park Hospital, University of Sheffield, UK); T Powles (Royal Marsden Hospital, Sutton, Surrey, UK); A Paterson (Tom Baker Cancer Centre and University of Calgary, Calgary, Alberta, Canada); M Gnant (Department of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Austrian Breast & Colorectal Cancer Study Group, Vienna, Austria); S Anderson (Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA); I Diel (Center for Gynecological Oncology, Mannheim, Germany); J Gralow (University of Washington School of Medicine, Seattle, WA, USA); G von Minckwitz (German Breast Group, Neu-Isenburg, Germany); V Moebus (Klinikum Frankfurt Höchst, Frankfurt, Germany); J Bergh (Karolinska Institutet and University Hospital, Stockholm, Sweden); K I Pritchard (Sunnybrook Odette Cancer Centre and University of Toronto, Toronto, Canada); J Bliss (ICR-CTSU, Division of Clinical Studies, The Institute of Cancer Research, London, UK); D Cameron (Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK); V Evans (Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK); H Pan (Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK); R Peto (Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK); R Bradley (Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK); R Gray (Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK).

Groups contributing data to the adjuvant bisphosphonates meta-analyses

Austrian Breast Cancer Study Group, Vienna, Austria (R Bartsch, P Dubsky, C Fesl, H Fohler, M Gnant, R Greil, R Jakesz, A Lang, G Luschin-Ebengreuth, C Marth, B Mlineritsch, H Samonigg, C F Singer, G G Steger, H Stöger); British Columbia Cancer Agency, Vancouver, Canada (I Olivotto, J Ragaz); Danish Breast Cancer Cooperative Group, Copenhagen, Denmark (P Christiansen, B Ejlertsen, M Ewertz, M-B Jensen, S Møller, H T Mouridsen); German Adjuvant Breast Group, Frankfurt, Germany (W Eiermann, J Hilfrich, W Jonat, M Kaufmann, R Kreienberg, M Schumacher); German Breast Group, Neu-Isenburg, Germany (J U Blohmer, S D Costa, H Eidtmann, B Gerber, C Jackisch, S Loibl, G von Minckwitz); Hellenic Breast Surgeons Society, Greece (U Dafni, C Markopoulos); Helsinki University, Finland (C Blomqvist, T Saarto); Korean Cancer Study Group, Seoul, South Korea (J-H Ahn, K H Jung); Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy (F Perrone); National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA, USA (S Anderson, G Bass, A Brown [deceased], J Bryant [deceased], J Costantino, J Dignam, B Fisher, C Geyer, E P Mamounas, S Paik, C Redmond, S Swain, L Wickerham, N Wolmark); North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN, USA (E Perez, JN Ingle, V J Suman); ProBONE study group, Marburg, Germany (P Hadji); Royal Marsden Hospital, London and Sutton, UK (R A'Hern, M Dowsett, A Makris, M Parton, K Pennert, T J Powles, I E Smith, J R Yarnold); SABRE trial group (international) (G Clack, C Van Poznak); Tel Aviv Sourasky Medical Center, Israel (T Safra); University of Leeds, UK (R Bell, D Cameron, RE Coleman, D Dodwell, S Hinsley, H C Marshall); University of Saarland, Germany (E Solomayer, T Fehm); University of Sheffield, UK (R E Coleman, J Lester, M C Winter, J M Horsman); Washington University, St Louis, Missouri, USA (R Aft); Z-FAST, ZO-FAST & E-ZO-FAST study groups (international) (A M Brufsky, R Coleman, H A Llombart on behalf of Novartis Pharmaceuticals).

EBCTCG steering committee

J Bergh (co-chair), K Pritchard (co-chair), K Albain, S Anderson, R Arriagada, W Barlow, E Bergsten-Nordström, J Bliss, F Boccardo, R Bradley*, M Buyse, D Cameron, M Clarke*, A Coates, R Coleman, C Correa, J Costantino, J Cuzick, N Davidson, C Davies*, A Di Leo, M Dowsett, M Ewertz, J Forbes, R Gelber, C Geyer, L Gianni, M Gnant, A Goldhirsch, R Gray*, D Hayes, C Hill, J Ingle, W Janni, E MacKinnon*, M Martín, P McGale*, L Norton, Y Ohashi, S Paik, H Pan*, E Perez, R Peto*, M Piccart, L Pierce, V Raina, P Ravdin, J Robertson, E Rutgers, J Sparano, S Swain, C Taylor*, G Viale, G von Minckwitz, X Wang, T Whelan, N Wilcken, E Winer, N Wolmark, W Wood. *Secretariat.

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