Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial

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Summary

Background Analysis of the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) at 48 months' follow-up showed that addition of zoledronic acid to adjuvant endocrine therapy significantly improved disease-free survival. We have now assessed long-term clinical efficacy including disease-free survival and disease outcomes in patients receiving anastrozole or tamoxifen with or without zoledronic acid.

Methods ABSCG-12 is a randomised, controlled, open-label, two-by-two factorial, multicentre trial in 1803 premenopausal women with endocrine-receptor-positive early-stage (stage I–II) breast cancer receiving goserelin (3·6 mg every 28 days), comparing the efficacy and safety of anastrozole (1 mg per day) or tamoxifen (20 mg per day) with or without zoledronic acid (4 mg every 6 months) for 3 years. Randomisation (1:1:1:1 ratio) was computerised and based on the Pocock and Simon minimisation method to balance the four treatment arms across eight prognostic variables (age, neoadjuvant chemotherapy, pathological tumour stage; lymph-node involvement, type of surgery or locoregional therapy, complete axillary dissection, intraoperative radiation therapy, and geographical region). Treatment allocation was not masked. The primary endpoint was disease-free survival (defined as disease recurrence or death) and analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00295646; follow-up is ongoing.

Findings At a median follow-up of 62 months (range 0–114·4 months), more than 2 years after treatment completion, 186 disease-free survival events had been reported (53 events in 450 patients on tamoxifen alone, 57 in 453 patients on anastrozole alone, 36 in 450 patients on tamoxifen plus zoledronic acid, and 40 in 450 patients on anastrozole plus zoledronic acid). Zoledronic acid reduced risk of disease-free survival events overall (HR 0·68, 95% CI 0·51–0·91; p=0·009), although the difference was not significant in the tamoxifen (HR 0·67, 95% CI 0·44–1·03; p=0·067) and anastrozole arms (HR 0·68, 95% CI 0·45–1·02; p=0·061) assessed separately. Zoledronic acid did not significantly affect risk of death (30 deaths with zoledronic acid *vs* 43 deaths without; HR 0·67, 95% CI 0·41–1·07; p=0·09). There was no difference in disease-free survival between patients on tamoxifen alone versus anastrozole alone (HR 1·08, 95% CI 0·81–1·44; p=0·591), but overall survival was worse with anastrozole than with tamoxifen (46 *vs* 27 deaths; HR 1·75, 95% CI 1·08–2·83; p=0·02). Treatments were generally well tolerated, with no reports of renal failure or osteonecrosis of the jaw. Bone pain was reported in 601 patients (33%; 349 patients on zoledronic acid *vs* 252 not on the drug), fatigue in 361 (20%; 192 *vs* 169), headache in 280 (16%; 147 *vs* 133), and arthralgia in 266 (15%; 145 *vs* 121).

Interpretation Addition of zoledronic acid improved disease-free survival in the patients taking anastrozole or tamoxifen. There was no difference in disease-free survival between patients receiving anastrozole and tamoxifen overall, but those on anastrozole alone had inferior overall survival. These data show persistent benefits with zoledronic acid and support its addition to adjuvant endocrine therapy in premenopausal patients with early-stage breast cancer.

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Introduction

Historically, treatment for early-stage breast cancer has focused on direct targeting of cancer cells. However, increasing evidence suggests that modification of the microenvironment surrounding cancer cells can have potent anticancer effects.[1] Bisphosphonates have shown anticancer potential in various cancer types in preclinical and clinical studies,[2] and there is growing awareness that combination of tumour-targeted therapy with treatments that affect the cancer-cell environment, such as bisphosphonates, can improve anticancer response and long-term outcomes.

Although bisphosphonates are a bone-targeted treatment, their anticancer activity might not be limited to bone. For example, at 36 months' follow-up in the Zometa-Femara Adjuvant Synergy Trial (ZO-FAST) study in postmenopausal women with early breast cancer (N=1065), addition of zoledronic acid to adjuvant endocrine therapy reduced the relative risk of disease-free survival events (hazard ratio [HR] 0·59, 95% CI

0·36–0·96; p=0·0314),[3] and continued to reduce the risk at 48 months' follow-up (HR 0·59, 0·38–0·92; p=0·0175).[4] In this trial, adjuvant zoledronic acid reduced disease recurrence in bone and non-bone sites. In the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial (N=3360) in women with early (stage II or III) breast cancer,[5] although there were no statistically significant improvements in disease-free survival (HR 0·98, 95% CI 0·85–1·13; p=0·79) or survival (HR 0·85, 0·72–1·01; p=0·07) in the overall population, a tapered dosing regimen of zoledronic acid significantly reduced the risk of disease-free survival events (HR 0·76, 0·60–0·98; p<0·05) and the risk of death (HR 0·71, 0·54–0·94; p=0·017) in patients who were postmenopausal for longer than 5 years before study entry (n=1041; n=1101 when patients older than 60 years were included). Moreover, other subset analyses from the AZURE trial[6] showed that addition of monthly zoledronic acid to neoadjuvant chemotherapy significantly reduced residual invasive tumour size by 44% (15·5 *vs* 27·4 mm, respectively; p=0·006), improved the rate of pathological complete response, and reduced the need for mastectomy (n=205 for neoadjuvant subset). Further evidence from three recent retrospective database analyses (total N=164718)[7–9] suggests that oral bisphosphonates might prevent breast cancer in healthy postmenopausal women receiving treatment for osteoporosis. Taken together, these data suggest that bisphosphonate anticancer effects might be beneficial early in the disease course.

In the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12), the event-driven primary endpoint for comparisons of zoledronic acid versus no zoledronic acid and tamoxifen versus anastrozole was first reported after a median follow-up of 48 months (range 0–101·8).[10] However, because patients in this trial have a good prognosis, there was an insufficient number of events to assess definitively the effects of individual treatments on overall survival or to examine benefits in informative patient subgroups. For example, there was a non-significant difference in overall survival favouring patients receiving tamoxifen versus patients receiving anastrozole,[10] which is counter to previous reports of superior oestrogen depletion in premenopausal women[11] and a significant increase in disease-free survival in postmenopausal patients with breast cancer treated with aromatase inhibitors versus tamoxifen.[12–14]

Now, after a median follow-up of 62 months (range 0–114·4; longer than 2 years after completion of therapy based on a median treatment duration of 35·9 months in this study) in ABCSG-12, 49 (186 *vs* 137; 36%) more patients have had disease-free survival events and there have been 31 (73 *vs* 42; 74%) more deaths on study than were reported at 48 months' follow-up.[10] We undertook an analysis at 62 months' follow-up to clarify previously unanswered questions about disease-free and overall survival outcomes in ABCSG-12 and to provide additional information about tolerability and persistent benefits of zoledronic acid combined with endocrine therapy in these patients.

Methods

Trial design and patients

The trial design was described previously.[10] Briefly, ABCSG-12 is a randomised, phase 3 trial in premenopausal

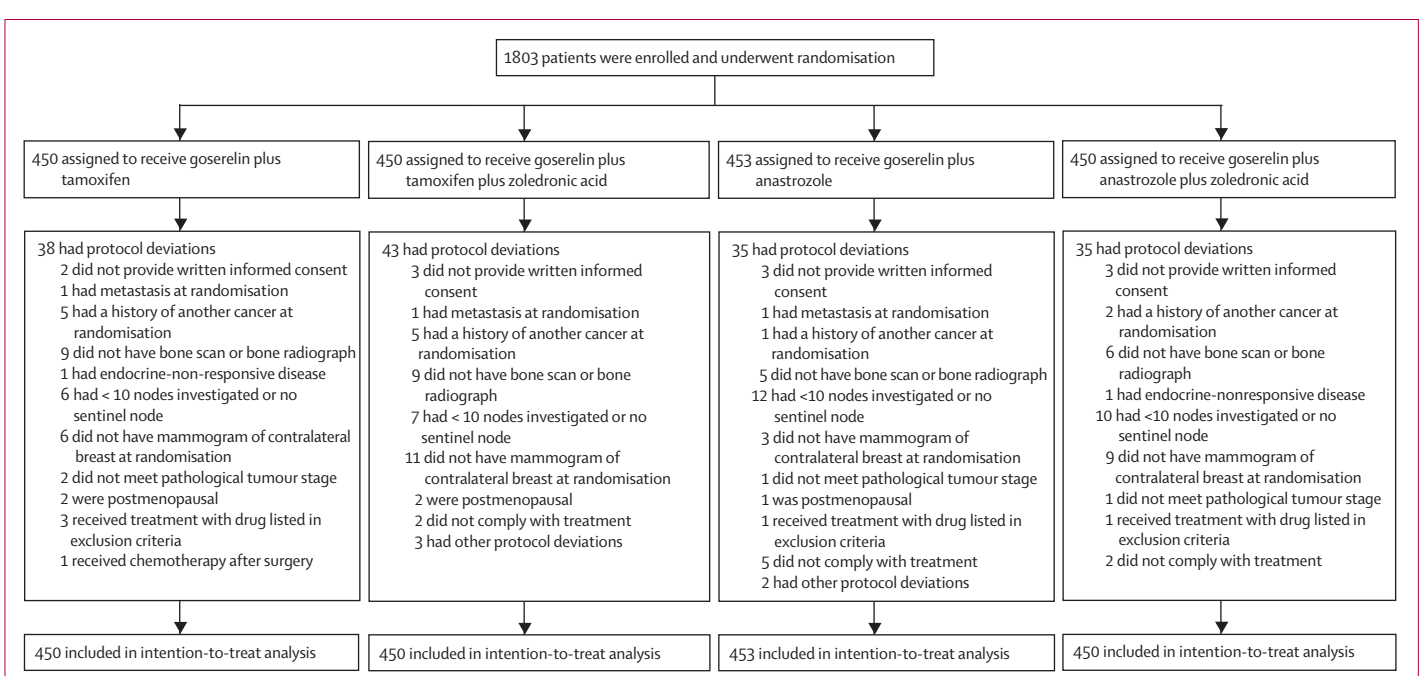

Figure 1: **Trial profile**

women with stage I or II oestrogen-receptor-positive and/or progesterone-receptor-positive breast cancer. Patients' premenopausal status was defined by a clinically estimated regular menstrual cycle or a last menstrual cycle occurring not more than 1 year before study entry. In women with indeterminate menstrual status (eg, posthysterectomy), serum concentrations of follicle-stimulating hormone and luteinising hormone were used to establish premenopausal status. Patients were enrolled between 1999 and 2006, had fewer than ten positive lymph nodes, and were scheduled to receive standard therapy with goserelin. Preoperative chemotherapy was allowed, and postoperative radiotherapy was administered according to institutional guidelines. Exclusion criteria were T1a (except yT1a), T4d, and yT4 tumours; a history of other neoplasms; preoperative radiotherapy; pregnancy, lactation, or both; and contraindications for study drugs. No patients received adjuvant chemotherapy.

This study was undertaken in compliance with the Declaration of Helsinki, and the protocol, informed consent form, and other patient-related materials were reviewed and approved by an institutional review board and independent ethics committee at each study centre. All patients provided informed consent.

Randomisation and masking

The ABCSG used a computer-generated adaptive randomisation method to assign treatment groups via an automated telephone service. Patients were randomly assigned (in a 1:1:1:1 ratio on the basis of Pocock and Simon's minimisation method for a two-by-two factorial design[15]) to goserelin (AstraZeneca Austria GmbH, Vienna, Austria; 3·6 mg subcutaneously every 28 days) plus either tamoxifen (AstraZeneca Austria GmbH, Vienna, Austria; 20 mg per day orally) or anastrozole (AstraZeneca Austria GmbH, Vienna, Austria; 1 mg per day orally) with or without zoledronic acid (Novartis International AG, Basel, Switzerland; 4 mg intravenously every 6 months) for 3 years. For the treatment centres in Germany, study drugs were provided by the respective affiliates in Germany. Randomisation lists were provided by a computer program at the randomisation centre at the University of Vienna Surgical Department (Vienna, Austria). At the individual sites, eligibility of patients was confirmed with a predefined randomisation checklist. After a phone call by the investigator to the randomisation centre, patients were randomly assigned to the four treatment arms by the computer program. The four treatment arms were balanced for eight important prognostic variables: age (19–34 years *vs* ≥35 years), neoadjuvant chemotherapy (no *vs* yes with complete response *vs* yes without complete response), pathological tumour stage (pT1 *vs* pT2 *vs* pT3), lymph-node involvement (0 *vs* 1–3 *vs* 4–9), type of surgery and radiation treatment, complete axillary dissection (yes *vs* no), intraoperative radiation (yes *vs* no), and geographical region (ten regions [nine in Austria, one in Germany]). In this open-label trial, no investigators, staff at participating centres, or patients were masked to treatment group; however, individuals analysing disease recurrence from laboratory results were masked to treatment group. All events underwent double central medical review with masked source data, and only histopathology reports or appropriate imaging were regarded as acceptable for confirmation of disease recurrence.

	Tamoxifen alone (N=450)	Tamoxifen and zoledronic acid (N=450)	Anastrozole alone (N=453)	Anastrozole and zoledronic acid (N=450)
Age				
Median (years)	45 (27–56)	45 (27–54)	44 (25–58)	44 (28–56)
≤40 years	101 (22%)	84 (19%)	112 (25%)	116 (26%)
>40 years	349 (78%)	366 (81%)	341 (75%)	334 (74%)
Cancer stage				
T1	341 (76%)	339 (75%)	352 (78%)	343 (76%)
≥T2	98 (22%)	97 (22%)	93 (21%)	98 (22%)
Missing	11 (2%)	14 (3%)	8 (2%)	9 (2%)
Nodal status				
Negative	305 (68%)	298 (66%)	304 (67%)	304 (68%)
Positive	134 (30%)	138 (31%)	141 (31%)	137 (30%)
Missing	11 (2%)	14 (3%)	8 (2%)	9 (2%)
Histological grading				
1–2	346 (77%)	347 (77%)	347 (77%)	341 (76%)
3	85 (19%)	85 (19%)	89 (20%)	93 (21%)
Missing	19 (4%)	18 (4%)	17 (4%)	16 (4%)
Oestrogen receptor*				
Negative	16 (4%)	20 (4%)	14 (3%)	17 (4%)
+	50 (11%)	62 (14%)	54 (12%)	57 (13%)
++	169 (38%)	151 (34%)	170 (38%)	155 (34%)
+++	204 (45%)	203 (45%)	207 (46%)	212 (47%)
Missing	11 (2%)	14 (3%)	8 (2%)	9 (2%)
Progesterone receptor*				
Negative	40 (9%)	32 (7%)	35 (8%)	36 (8%)
+	54 (12%)	66 (15%)	59 (13%)	59 (13%)
++	160 (36%)	142 (32%)	149 (33%)	131 (29%)
+++	185 (41%)	196 (44%)	201 (44%)	215 (48%)
Missing	11 (2%)	14 (3%)	9 (2%)	9 (2%)
Preoperative chemotherapy				
No	379 (84%)	382 (85%)	389 (86%)	386 (86%)
Yes	25 (6%)	23 (5%)	23 (5%)	26 (6%)
Missing	46 (10%)	45 (10%)	41 (9%)	38 (8%)

Data are median (range) or n (%). All patients received goserelin. *Reiner score for staining: +, 10–50%; ++, 51–80%; and +++, 81–100%.

***Table 1*: Patient demographics and baseline disease characteristics (intention-to-treat population)**

Procedures

The primary endpoint was disease-free survival, defined as time from randomisation to the first occurrence of any of the following: a local or regional recurrence, contralateral breast cancer, distant metastasis, second primary carcinoma, and death from any cause. Secondary

	Tamoxifen (N=900)	Anastrozole (N=903)	No zoledronic acid (N=903)	Zoledronic acid (N=900)	Total (N=1803)
Total disease-free survival events	89	97	110	76	186†
Locoregional recurrence	22	23‡	30‡	15	45‡
Distant recurrence	44	56‡	56‡	44	100‡
Bone metastases	22	31	32	21	53
Contralateral breast cancer	10	4§	8	6	14
Secondary malignancy	12	15¶	16¶	11	27¶
Total deaths	27	46	43	30	73
Death without previous recurrence	1	1¶	2¶	0	2¶

Data are number of patients. *Only the first event per patient is shown in this table. †Total disease-free survival events include 113 patients who had disease recurrence and 73 who died. ‡One patient with locoregional and distant recurrence documented at the same time. §At re-evaluation, five breast cancers that were initially reported[10] as contralateral were reclassified as ductal carcinoma in situ because invasion was not proven; there were two new contralateral breast cancer events. ¶One patient with secondary malignancy and death documented at the same time.

Table 2*: Events by treatment group (intention-to-treat population)

endpoints included recurrence-free survival (including all disease-free survival events apart from death) from randomisation, overall survival from randomisation, and bone mineral density. Bone metastasis-free survival was an exploratory endpoint. Results from the bone mineral density substudy have been reported previously.[16,17] Included in this analysis are disease-free survival, overall survival, and safety outcomes.

Safety was assessed throughout the study by monitoring of the frequency of adverse events and changes in laboratory values. Renal function was evaluated every 3 months during administration of study treatments. Because adverse events in our trial were not classified according to Common Terminology Criteria for Adverse Events, we are unable to provide specific grades for toxic effects; adverse events were graded as intermediate or strong. Assessment of severity reflected qualitative assessment of the extent or intensity of an adverse event as determined by the investigator or patient, rather than clinical importance. Serious adverse events were defined as any lethal or life-threatening adverse events; events that resulted in permanent damage, inpatient hospitalisation, or extended inpatient treatment; or events that placed the patient at risk or that necessitated medical or surgical intervention. Patients' compliance with therapy was assessed with special prescription record cards. The tear-off sections of study drug labels were affixed to these cards and signed and dated by the dispensing physician or delegate. Patients were requested to confirm intake of oral drugs every 4 weeks. Administration of zoledronic acid (if applicable) was documented in patients' medical records. Corresponding case report form entries were monitored appropriately.

Statistical analysis

The primary analysis was triggered by the occurrence of 124 disease-free survival events, and 13 additional events occurred during data preparation (total of 137 disease-free survival events for the primary analysis). The preplanned, event-driven analysis in this report was scheduled for a timepoint at which 50% more disease-free survival events were projected to have occurred on the basis of the protocol-defined event rate required to trigger the primary analysis; this report actually includes 36% more events than were included in the primary analysis, because the primary analysis included 137 events. All prospective analyses were done in the intention-to-treat (ITT) population.

Disease-free and overall survival were compared between treatments using Cox's proportional hazards regression model.[15] For analyses based on the entire ITT population, Cox's model was stratified by endocrine therapy for comparison between zoledronic acid and no zoledronic acid, and by zoledronic acid for comparison between anastrozole and tamoxifen. Protocol-defined stratification factors included age 35 years or less and age older than 35 years, preoperative chemotherapy, tumour stage, nodal status, type of surgery, and complete axillary dissection. However, because fewer patients than expected fell into the age 35 years or younger category (only 6% of patients), in the statistical analysis plan we preplanned to expand the lower boundary to age 40 years or less (23% of all patients). Between the four treatment arms, there were no significant differences in the proportions of patients in the age categories (χ^2 test for zoledronic acid *vs* no zoledronic acid, p=0·49). The proportional hazard assumption was confirmed for the interaction of time to event with the respective therapy variables. Additionally, all results were quantified with HRs, associated 95% CIs, and p values according to the log-rank test, and Kaplan-Meier plots were provided for selected comparisons.

Each of the two tests related to the primary endpoint, disease-free survival (zoledronic acid *vs* no zoledronic acid, and anastrozole *vs* tamoxifen), was done with a two-sided significance level of 0·025 according to a Bonferroni adjustment to account for multiple comparisons. Analyses of subgroups were undertaken in an exploratory manner and adverse events were analysed with a two-sided significance level of 0·05.

Although events after the first relapse were not part of the original protocol, to elucidate differences in overall survival between the tamoxifen and anastrozole groups, a retrospective data collection process was started. In an effort to obtain data about treatment after relapse and secondary events, all centres were invited to collect these data. Particularly, we reviewed how many patients from the anastrozole arm received aromatase inhibitors during the first three lines in the temporal sequence of different therapies after relapse compared with those from the tamoxifen arm. Overall survival after first relapse and after first distant relapse was compared between anastrozole and tamoxifen with Cox's proportional hazards regression model. SAS (version 9.2) was used for all analyses.

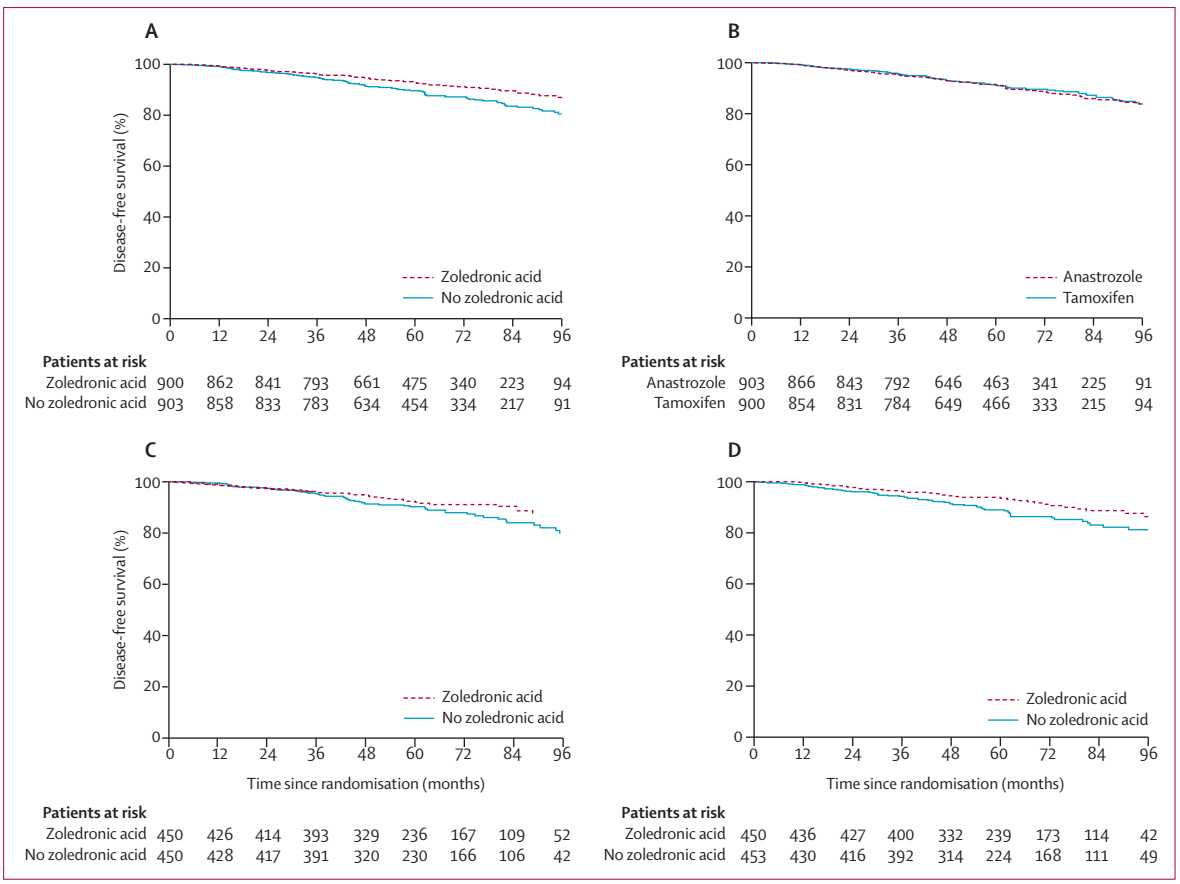

***Figure 2*: Kaplan-Meier estimates of disease-free survival**
The primary endpoint of disease-free survival is shown for women with breast cancer who received adjuvant endocrine therapy, by zoledronic acid versus no zoledronic acid (A) and tamoxifen versus anastrozole (B). Analyses of disease-free survival were also done for zoledronic acid versus no zoledronic acid in women receiving tamoxifen (C) or anastrozole (D).

Because of adaptations to evolving study progress and rigorous additional data review to comply with US Food and Drug Administration regulatory procedures for product registration, some safety data might slightly differ by comparison with the results reported previously after a median follow-up of 48 months (webappendix pp 2–8).[3] Particularly, the categories for adverse events and serious adverse events have changed, and we now present Medical Dictionary for Regulatory Activities (MedDRA)-coded preferred terms (version 10.1).[18]

This trial is registered, number NCT00295646.

Role of the funding source

The authors and the ABCSG scientific board (webappendix p 1) were responsible for the design and coordination of the trial and maintained sole responsibility for collection, management, monitoring, and analysis of the data. Data were collected by physicians, study nurses, and other study-centre staff and were processed at the central ABCSG data centre. All authors reviewed the report. The corresponding author (MG) and the ABCSG-12 statistician (CF) had full access to all data and share responsibility for integrity of the data and the accuracy and completeness of the data analyses. MG had final responsibility to submit for publication. Novartis provided zoledronic acid and AstraZeneca provided anastrozole and tamoxifen, but neither company was involved in data collection or analysis.

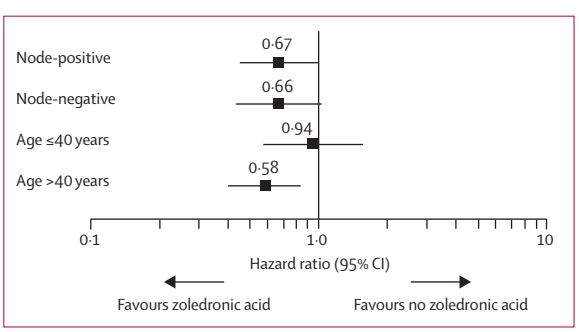

***Figure 3*: Forest plot estimates of disease-free survival**
The primary endpoint of disease-free survival is shown for women with breast cancer who received adjuvant endocrine therapy, by zoledronic acid versus no zoledronic acid, in subgroups of women with node-positive or node-negative breast cancer, and for age 40 years and younger or older than 40 years.

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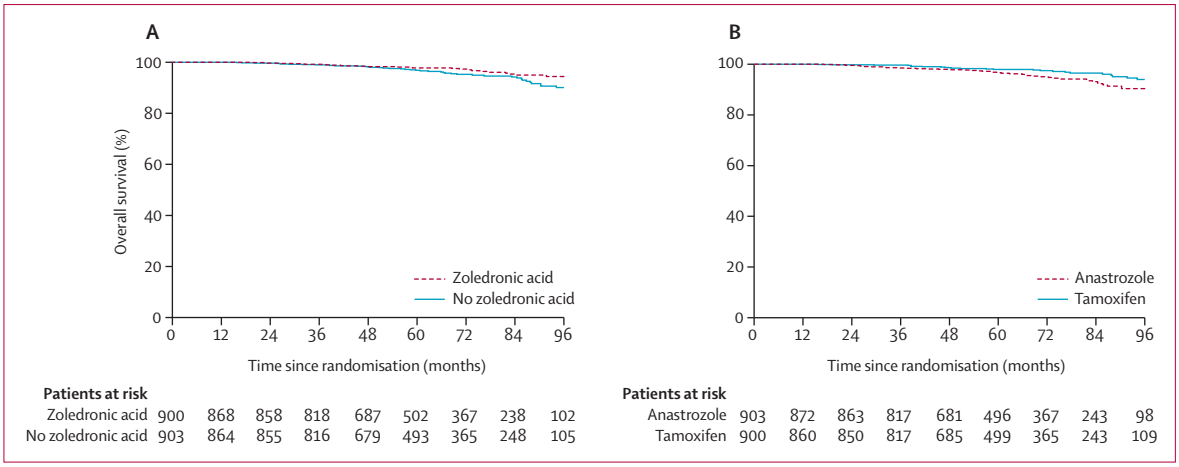

Figure 4: **Kaplan-Meier estimates of overall survival**
The secondary endpoint of overall survival is shown for women with breast cancer who received adjuvant endocrine therapy, by zoledronic acid versus no zoledronic acid (A), and tamoxifen versus anastrozole (B).

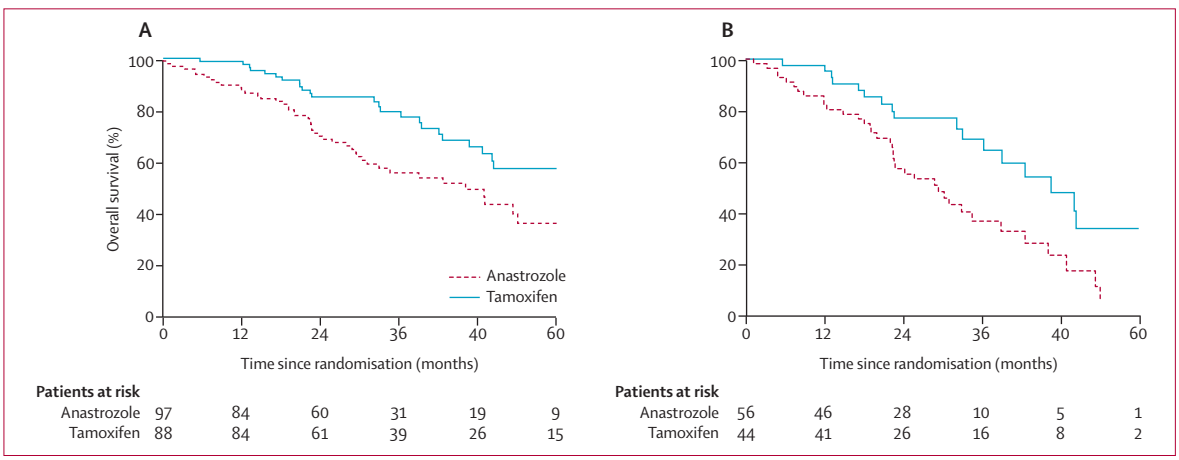

Figure 5: **Kaplan-Meier estimates of survival after disease recurrence**
The secondary endpoint of overall survival is shown for women with breast cancer who received adjuvant endocrine therapy after first disease recurrence (A) and after first distant metastasis (B).

Results

1803 patients were randomly assigned to treatment groups in the ABCSG-12 trial (figure 1), including 1375 (76%) with T1-stage cancer, and 550 (31%) with node-positive cancer. Median age at randomisation was 45 years (range 25–58 years), and all tumours were endocrine-responsive (oestrogen-receptor-positive, progesterone-receptor-positive, or both). Disease and demographic characteristics were well balanced between groups (table 1). The first patient was enrolled on June 17, 1999, and the last patient on May 17, 2006. The database for this analysis was locked on May 18, 2010. Information about treatment and secondary events occurring after the primary endpoint was obtained for 182 (98%) of 186 patients. Among these were 11 patients who received only supportive care after disease relapse. Compliance with study drugs was high during the 3-year treatment phase of ABCSG-12. Patient compliance with endocrine therapy was confirmed in 4362 (89%) of 4884 visits for anastrozole alone, 4769 (98%) of 4886 visits for anastrozole plus zoledronic acid, 4492 (93%) of 4823 visits for tamoxifen alone, and 4450 (93%) of 4778 visits for tamoxifen plus zoledronic acid, and compliance with zoledronic acid therapy was confirmed in 4448 (93%) of 4778 visits in the tamoxifen group and 4768 (98%) of 4886 visits in the anastrozole group.

186 disease-free survival events have been reported to date, including 73 deaths, 45 locoregional relapses, 100 distant relapses (53 in bone), 14 contralateral breast cancer, and 27 new primary tumours outside of the breast (only first event per patient is included; table 2). At a median follow-up of 62 months (range 0–114·4 months), there was no significant interaction between endocrine therapy and zoledronic acid (p=0·978; webappendix p 9). Addition of zoledronic

acid to adjuvant endocrine therapy significantly improved disease-free survival versus endocrine therapy alone (92% *vs* 88%, respectively; log-rank p=0·008). This 4% absolute difference in disease-free survival corresponded to a significant reduction in the relative risk of events for patients receiving zoledronic acid versus those not taking this drug, stratified by endocrine therapy (76 *vs* 110 events; HR 0·68, 95% CI 0·51–0·91; Cox p=0·009, log-rank p=0·008; figure 2A). Disease-free survival did not differ significantly between the tamoxifen and anastrozole groups (anastrozole, 97 events *vs* tamoxifen, 89 events; HR 1·08, 95% CI 0·81–1·44; Cox p=0·591, log-rank p=0·608; figure 2B). In patients who received either tamoxifen or anastrozole, the zoledronic acid-mediated reduction in the risk of disease-free survival events was similar, but not statistically significant (for tamoxifen, 36 events with zoledronic acid *vs* 53 without, HR 0·67, 95% CI 0·44–1·03, p=0·067; for anastrozole, 40 events with zoledronic acid *vs* 57 without, HR 0·68, 0·45–1·02, p=0·061; figures 2C and 2D).

Zoledronic acid reduced the relative risk of disease-free survival events to a similar extent in both node-positive (HR 0·67, 95% CI 0·45–0·99) and node-negative disease (HR 0·66, 95% CI 0·43–1·03; figure 3). Fewer patients receiving zoledronic acid had distant disease recurrence at bone and non-bone sites (44 *vs* 56 events), including locoregional recurrence (15 *vs* 30 events) and contralateral breast cancer (six *vs* eight events; table 2). In a preplanned subset analysis by patient age at study entry, a treatment-by-covariate interaction based on age 40 years or younger versus older than 40 years did not reveal significant heterogeneity (p=0·121). However, in patients who were 40 years or younger at baseline (n=413), zoledronic acid did not significantly reduce the relative risk of disease-free survival events (HR 0·94, 95% CI 0·57–1·56; figure 3), whereas in patients who were older than 40 years at study entry (n=1390) the risk reduction with addition of zoledronic acid was significant (HR 0·58, 95% CI 0·40–0·83; figure 3).

30 deaths (3% of 900 patients) occurred in the zoledronic acid group compared with 43 deaths (5% of 903 patients) in the no zoledronic acid group (table 2); risk of death did not differ significantly between these groups (HR 0·67, 95% CI 0·41–1·07; Cox p=0·09; figure 4A). Overall survival also did not differ significantly between treatment groups in patients with node-positive (HR 0·62, 95% CI 0·34–1·15) and node-negative disease (HR 0·70, 95% CI 0·33–1·52). Patients who received anastrozole had a significantly increased relative risk of death compared with those treated with tamoxifen (46 *vs* 27 deaths; HR 1·75, 95% CI 1·08–2·83; Cox p=0·02; figure 4B).

In a retrospective subset analysis in patients with disease recurrence (n=185), the relative risk of death was significantly higher in the anastrozole group (ie, anastrozole only and anastrozole plus zoledronic acid patients) compared with the tamoxifen group (ie, patients taking tamoxifen only and tamoxifen plus zoledronic acid; 46 *vs* 26 deaths; HR 2·00, 95% CI 1·23–3·24; Cox p=0·005, log-rank p=0·006; figure 5A). Similarly, in patients who had distant disease recurrence (n=100; webappendix p 9), the relative risk of death was significantly higher in the anastrozole group compared with the tamoxifen group (37 *vs* 18 deaths; HR 2·18, 95% CI 1·23–3·86; Cox p=0·009, log-rank p=0·008; figure 5B). Overall, among patients who received anticancer treatments after disease recurrence, 49 (61%) of 80 patients in the tamoxifen group received aromatase inhibitors, whereas only 37 (41%) of 91 patients in the anastrozole group received this treatment. No other noteworthy differences in postrelapse treatment were identified (webappendix pp 9–10).

The combination of zoledronic acid with adjuvant endocrine therapy was generally well tolerated during active therapy (36 months) and has not resulted in any long-term safety concerns at 62 months' follow-up. Adverse events reported thus far are consistent with the known safety profiles for each of the agents administered. The most frequent adverse events occurring in 10% or more of patients in any group were bone pain, fatigue, headache, arthralgia, sleep disorder, and pyrexia. Patients in the

	Tamoxifen (N=450)	Tamoxifen plus zoledronic acid (N=450)	Anastrozole (n=453)	Anastrozole plus zoledronic acid (n=450)	p value*
Adverse event†					
Bone pain	102 (23%)	147 (33%)	150 (33%)	202 (45%)	<0·0001
Fatigue	72 (16%)	89 (20%)	97 (21%)	103 (23%)	0·06
Headache	63 (14%)	60 (13%)	70 (15%)	87 (19%)	0·07
Arthralgia	35 (8%)	42 (9%)	86 (19%)	103 (23%)	<0·0001
Sleep disorder	47 (10%)	50 (11%)	53 (12%)	55 (12%)	0·85
Nausea	23 (5%)	26 (6%)	32 (7%)	53 (12%)	0·0009
Pyrexia	9 (2%)	37 (8%)	12 (3%)	48 (11%)	<0·0001
Ocular discomfort	31 (7%)	24 (5%)	19 (4%)	30 (7%)	0·26
Muscle rigidity	11 (2%)	15 (3%)	36 (8%)	38 (8%)	<0·0001
Arthropathy	14 (3%)	15 (3%)	33 (7%)	35 (8%)	0·0008
Pain in limb	18 (4%)	23 (5%)	22 (5%)	34 (8%)	0·12
Depression	24 (5%)	21 (5%)	29 (6%)	17 (4%)	0·33
Lymphoedema	28 (6%)	22 (5%)	23 (5%)	16 (4%)	0·33
Hypertension	14 (3%)	18 (4%)	19 (4%)	26 (6%)	0·28
Peripheral oedema	22 (5%)	21 (5%)	12 (3%)	13 (3%)	0·16
Back pain	18 (4%)	13 (3%)	13 (3%)	17 (4%)	0·69
Musculoskeletal pain	15 (3%)	13 (3%)	13 (3%)	19 (4%)	0·67
Hot flush	13 (3%)	18 (4%)	13 (3%)	11 (2%)	0·59
Diarrhoea	11 (2%)	16 (4%)	12 (3%)	13 (3%)	0·80
Breast pain	15 (3%)	13 (3%)	12 (3%)	8 (2%)	0·50
Scar pain	11 (2%)	12 (3%)	7 (2%)	11 (2%)	0·66
Joint stiffness	2 (<1%)	3 (1%)	7 (2%)	26 (6%)	<0·0001
Dizziness	9 (2%)	11 (2%)	4 (1%)	13 (3%)	0·14
Paraesthesia	7 (2%)	7 (2%)	11 (2%)	11 (2%)	0·61
Alopecia	6 (1%)	10 (2%)	7 (2%)	11 (2%)	0·58

(Continues on next page)

	Tamoxifen (N=450)	Tamoxifen plus zoledronic acid (N=450)	Anastrozole (n=453)	Anastrozole plus zoledronic acid (n=450)	p value*
(Continued from previous page)					
Serious adverse event†					
Endometrial hyperplasia	27 (6%)	33 (7%)	9 (2%)	3 (1%)	<0·0001
Uterine polyp	29 (6%)	35 (8%)	1 (<1%)	3 (1%)	0·0001
Uterine dilation and curettage	18 (4%)	18 (4%)	7 (2%)	8 (2%)	0·03
Fracture	8 (2%)	4 (1%)	7 (2%)	6 (1%)	0·73
Endometrial disorder	7 (2%)	11 (2%)	1 (<1%)	2 (<1%)	0·0046
Erysipelas	8 (2%)	5 (1%)	3 (1%)	3 (1%)	0·32
Uterine leiomyoma	5 (1%)	8 (2%)	2 (<1%)	4 (1%)	0·26
Breast reconstruction	4 (1%)	2 (<1%)	2 (<1%)	5 (1%)	0·59
Cholelithiasis	5 (1%)	4 (1%)	3 (1%)	1 (<1%)	0·43
Postmenopausal haemorrhage	6 (1%)	4 (1%)	3 (1%)	0	0·08
Metrorrhagia	3 (1%)	2 (<1%)	3 (1%)	3 (1%)	1·00
Breast calcifications	1 (<1%)	2 (<1%)	3 (1%)	4 (1%)	0·65
Carpal tunnel syndrome	1 (<1%)	1 (<1%)	4 (1%)	4 (1%)	0·34
Meniscus lesion	1 (<1%)	3 (1%)	2 (<1%)	4 (1%)	0·57
Vaginal bleeding	3 (1%)	4 (1%)	1 (<1%)	2 (<1%)	0·50
Menorrhagia	1 (<1%)	4 (1%)	3 (1%)	1 (<1%)	0·45
Ovarian cyst	2 (<1%)	4 (1%)	0	3 (1%)	0·18
Bilateral salpingo-oophorectomy	1 (<1%)	1 (<1%)	5 (1%)	2 (<1%)	0·34
Cervical dysplasia	2 (<1%)	3 (1%)	0	3 (1%)	0·32
Hypertension	3 (1%)	1 (<1%)	1 (<1%)	3 (1%)	0·60
Hysterosalpingo-oophorectomy	2 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	0·69
Mastectomy	5 (1%)	1 (<1%)	0	1 (<1%)	0·05
Vaginal haemorrhage	3 (1%)	3 (1%)	1 (<1%)	0	0·28
Recurrent breast cancer	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	1·00
Breast mass	1 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	0·71
Deep vein thrombosis	1 (<1%)	5 (1%)	0	0	0·01

Data are n (%).*p values are for a four-group comparison (Fisher's exact test). †MedDRA-coded preferred terms (all preferred terms referring to fractures are submitted under the term "Fractures").

Table 3: **The most frequent adverse events and serious adverse events on treatment**

anastrozole groups had a higher incidence of bone pain and arthralgia than did patients in the tamoxifen groups. Patients in the zoledronic acid groups had a higher incidence of bone pain, arthralgia, and pyrexia compared with the no zoledronic acid groups. Overall, there was no significant difference in the incidence of serious adverse events, apart from that the incidences of endometrial hyperplasia, endometrial disorders, and uterine polyps were higher in patients who received tamoxifen than in those who received anastrozole ($p<0·01$ for each; table 3). Additionally, there were no reports of renal toxic effects or osteonecrosis of the jaw after 62 months' follow-up.

Discussion

The primary endpoint of the ABCSG-12 trial, using a two-by-two factorial design, was to compare disease-free survival for zoledronic acid versus no zoledronic acid and tamoxifen versus anastrozole in premenopausal women receiving adjuvant ovarian suppression for early breast cancer. With longer follow-up and substantially more events than in our earlier report, our new analyses confirmed previous findings and showed that the the benefits of zoledronic acid extend for 2 years after treatment completion. The addition of zoledronic acid to adjuvant endocrine therapy provided a sustained and durable disease-free survival benefit compared with endocrine therapy alone, probably because anticancer benefit occurred early in the disease, when distant relapse risk was greatest (ie, 2–3 years).[19] Previous studies[20–22] of oral clodronate have suggested a potential for improved disease-free survival with bisphosphonates (panel).[20–27] However, a meta-analysis[28] of these and other trials of clodronate in combination with adjuvant therapies did not identify any significant improvement in overall survival, bone-metastasis-free survival, or metastasis-free survival.

The hypothesis first proposed by Stephen Paget in 1889 suggests that bone provides a fertile "soil" for growth of the cancer "seed."[29] Indeed, disseminated tumour cells often can be isolated from the bone marrow of patients with breast cancer treated with curative intent, and levels of these cells have been associated with an increased risk of disease recurrence.[30] The seeding of distant future disease recurrence by disseminated tumour cells could result from their ability to lie dormant in the bone marrow, a haemopoietic stem-cell niche that seems to protect them from chemotherapy cytotoxicity.[31,32] Results from ABCSG-12 and several additional adjuvant trials showing extended disease-free survival with zoledronic acid are consistent with the idea that zoledronic acid modifies the microenvironment surrounding cancer cells ("soil"), making it less conducive to cancer-cell survival and seeding of disease recurrence. However, because zoledronic acid has a wide range of anticancer activities and preferentially targets bone, it might be especially effective in reduction of disseminated tumour cells. Although several phase 2 studies have shown the ability of zoledronic acid to reduce disseminated tumour cells in women with breast cancer,[33–36] whether this mechanism is responsible for the improved disease-free survival seen in clinical trials of zoledronic acid is unclear.[3] Similar to disease recurrence outcomes in ABCSG-12, women who received zoledronic acid (4 mg every 6 months) in the ZO-FAST study[3] had reduced disease recurrence events at all sites, including bone and non-bone sites, in analyses of secondary endpoints. However, the smaller sister trials (Z-FAST, N=602, and E-ZO-FAST, N=527) have not shown similar significant disease-free survival benefits.[4]

Further insight into the effects of zoledronic acid on the disease course in early-stage breast cancer has been provided by the second interim analysis of the AZURE trial.[5] In the overall AZURE trial population (N=3360), there was no disease-free survival benefit with zoledronic

acid, and no benefit in the premenopausal subset (who received mostly chemotherapy).[5] These results are, on the surface, contrary to those of ABCSG-12. However, reductions in disease recurrence led to significant disease-free and overall survival improvements in AZURE in women who had been postmenopausal for longer than 5 years at study entry (n=1041) and, on the basis of the interpretation that zoledronic acid might be most effective in a low-oestrogenic environment, these results are scientifically consistent with ABCSG-12 subgroup data showing that the disease-free survival benefit with zoledronic acid seems to be driven by the subgroup of patients who were older than 40 years of age. Although all patients in ABCSG-12 received ovarian function suppression plus endocrine therapy, those who were older than 40 years at baseline might have achieved more complete oestrogen deprivation. This assertion is supported in part by case reports showing that only very young premenopausal patients with breast cancer have become pregnant or resumed menses while receiving ovarian function suppression with a luteinising-hormone-releasing hormone analogue,[37,38] suggesting that oestrogen concentration might not be completely suppressed. This idea is also in keeping with the lower incidence of chemotherapy-induced amenorrhoea in women younger than 40 years (61%) versus those older than 40 years (97%), and illustrates the important effect of age on ovarian function during cancer therapy.[1,39] Taken together, data from adjuvant trials (ABCSG-12, ZO-FAST, and AZURE) suggest that the anticancer activity of zoledronic acid might be increased by age-dependent or oestrogen-dependent changes to the bone microenvironment. This explanation is one possibility, and reflects an attempt to reconcile results from very different patient populations. Furthermore, several issues clearly still need to be resolved before wider application of zoledronic acid in the adjuvant setting can be recommended.

Initially, there was some speculation that the effect of zoledronic acid on disease-free survival in ABCSG-12 might be more pronounced in the patients treated with anastrozole because of potential synergy between the two compounds. However, now, with longer follow-up in this analysis, the benefit of zoledronic acid has been shown to be independent of the type of endocrine therapy used and is consistent with an additive benefit.

Further evidence for the anticancer activity of zoledronic acid comes from a phase 3 trial in patients with newly diagnosed multiple myeloma (Myeloma IX; N=1960).[40] In this trial, addition of zoledronic acid to antimyeloma therapy significantly extended survival by 5·5 months (50·0 *vs* 44·5 months; p=0·04) and reduced the risk of disease progression (HR 0·88, 95% CI 0·88–0·98; p=0·018) versus clodronate plus antimyeloma therapy. A trial in patients with bone metastases from advanced lung cancer (N=144) showed increased survival (578 *vs* 374 days; p<0·001) and time to disease progression (265 *vs* 150 days; p<0·001) in patients receiving zoledronic acid.

***Panel*: Research in context**

Systematic review

We searched PubMed for relevant clinical trials using the keywords "premenopausal", "breast cancer", "endocrine-responsive", "bisphosphonate", hormone receptor positive", "ovarian suppression", "adjuvant", and "survival". The combination of suppression of ovarian function (with gonadotropin-releasing-hormone analogues) and tamoxifen in premenopausal women with hormone-receptor-positive breast cancer has been shown to be at least as effective as established cytotoxic chemotherapy regimens and is better tolerated than chemotherapy.[23–26] Previous studies[20–22] in patients with early-stage breast cancer suggested that adjuvant bisphosphonate therapy could improve disease-free survival. Austrian Breast and Colorectal Cancer Study Group trial-12 is the first trial to compare the efficacy of adjuvant endocrine therapy plus zoledronic acid with endocrine therapy alone in premenopausal women with hormone-receptor-positive, early-stage breast cancer.

Interpretation

This study shows that addition of zoledronic acid (4 mg every 6 months) for 3 years in premenopausal women receiving ovarian function suppression with goserelin plus adjuvant endocrine therapy for low-or-moderate-risk, hormone-receptor-positive, early-stage breast cancer significantly improves disease-free survival. Therefore, we suggest that zoledronic acid therapy be considered in women with breast cancer who meet the inclusion criteria for this trial. This recommendation is consistent with European Society for Medical Oncology clinical practice guidelines for primary breast cancer,[27] which suggest that zoledronic acid therapy might be appropriate for prevention of bone loss and reduction of the risk of breast cancer recurrence in premenopausal women receiving endocrine therapy and in postmenopausal women receiving aromatase inhibitors.

Similarly, patients with bone metastases from bladder cancer (N=40) had significantly better 1-year survival with zoledronic acid versus placebo (36·3% *vs* 0%, respectively; p=0·004).[41,42] Taken together, a wealth of preclinical and clinical trial data support the anticancer activity of zoledronic acid on both the "seed" and the "soil," and seem to apply to the adjuvant and advanced cancer settings.

Although disease-free survival remains very similar in both the anastrozole and tamoxifen groups at 62 months' follow-up, a clear difference in overall survival has emerged. The exploratory analyses that we present provide insight into the potential causes of the surprising overall survival disadvantage for the anastrozole group. We feel confident that ascertainment bias did not affect the collection of data for postrelapse treatment and secondary events because these analyses were not prospectively planned and the data requests were sent to

the centres without providing any explanation for the request. Our data show that after the initial disease recurrence event, women receiving tamoxifen were more likely to be switched to an aromatase inhibitor than were those in the anastrozole group. This finding is consistent with standard clinical practice in adjuvant endocrine therapy, wherein disease recurrence while on one agent is followed by switching of therapy to a different endocrine agent.[43] For patients in the tamoxifen group, switching to an aromatase inhibitor might have reduced their risk of future recurrence and death. By contrast, patients in the anastrozole group switched to second-line endocrine therapy (ie, not an aromatase inhibitor) seem to have had worse survival outcomes. These two factors might have combined to bias overall survival in favour of the tamoxifen group. Ongoing studies such as SOFT (NCT00066690) and TEXT (NCT00066703)[44] will provide further insight into this clinically important question. In addition to the potential effect of secondary therapy after recurrence, anastrozole efficacy might have been affected by patient body-mass index, resulting in reduced efficacy in overweight and obese patients because of incomplete suppression of oestrogen production in peripheral body fat.[45]

Currently, more than 96% of the women enrolled in ABCSG-12 are alive, emphasising that the treatment regimens and duration used are appropriate for this patient population. On the basis of the results of this study, combination of zoledronic acid with adjuvant endocrine therapy (ovarian suppression plus tamoxifen) should be considered for premenopausal women with low-or-moderate-risk, early-stage, hormone-receptor-positive breast cancer. In fact, recent European Society for Medical Oncology clinical practice guidelines for primary breast cancer[27] recommend that treatment with zoledronic acid might be appropriate for prevention of bone loss and reduction of the risk of breast-cancer recurrence in premenopausal women receiving endocrine therapy and postmenopausal women receiving aromatase inhibitors.

Contributors

MG and RJ designed the ABCSG-12 protocol. MG, HS, RJ, and WK were responsible for trial conception and design. MG, BM, HS, GL-E, DH, CM, RJ, MS, MH, GP, TB, HE, WE, WK, PD, GH, E-PF, and RG took part in data collection. MG, HS, GL-E, RJ, HE, GS, PD, CF, and RG analysed and interpreted the data. MG and PD drafted the report. MG, BM, HS, GL-E, DH, CM, MS, MH, TB, HE, GS, WK, GH, E-PF, CF, and RG critically revised the report. MG and CF did the statistical analysis. MG and RJ obtained funding. BM, HS, GL-E, RJ, MH, GP, TB, HE, PD, and E-PF provided administrative, technical, or material support. MG, GL-E, RJ, GP, GS, PD, and RG provided supervision.

Conflicts of interest

MG has received research support from and has served as a consultant for AstraZeneca, Novartis, and Pfizer, and has received lecture fees and honoraria for participation on advisory boards from AstraZeneca, Novartis, Sanofi-Aventis, Roche, Schering, Amgen, and Pfizer. GL-E has received lecture fees from AstraZeneca and Novartis. RJ has served as a consultant for and received honoraria for participation on advisory boards from AstraZeneca, Roche, and Sanofi-Aventis, and has received lecture fees from AstraZeneca, Roche, and Sanofi-Aventis. MS has received lecture fees from AstraZeneca and Novartis. GP has received travel grants and lecture fees from AstraZeneca, Novartis, Roche, and GlaxoSmithKline. HE has received honoraria for participation on advisory boards and lecture fees from AstraZeneca and Novartis. WE has received consultancy fees and travel support from Novartis and AstraZeneca and lecture fees from Novartis, Sanofi-Aventis, and Roche. GS has received lecture fees from AstraZeneca, Novartis, Roche, and Amgen. PD has received consultancy fees from Novartis and Genomic Health, lecture fees and payment for development of educational presentations from Novartis and Pfizer, and travel expenses from AstraZeneca, Novartis, Roche, and Pfizer. GH has received travel expenses from Novartis. RG has served as a consultant for and received honoraria for participation on advisory boards from Novartis and AstraZeneca. All other authors declare that they have no conflicts of interest.

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