Use of letrozole after aromatase inhibitor-based therapy (NRG Oncology/NSABP B-42): a randomised, double-blind, placebo-controlled phase 3 trial

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Summary

Background The optimal duration of extended therapy with aromatase inhibitors in patients with postmenopausal breast cancer is unknown. In the NSABP B-42 study, we aimed to determine whether extended letrozole treatment improves disease-free survival after 5 years of aromatase inhibitor-based therapy in women with postmenopausal breast cancer.

Methods This randomised, double-blind, placebo-controlled, phase 3 trial was done in 158 centres in the USA, Canada, and Ireland. Postmenopausal women with stage I–IIIA hormone receptor-positive breast cancer, who were disease-free after about 5 years of treatment with an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor, were randomly assigned (1:1) to receive 5 years of letrozole (2·5 mg orally per day) or placebo. Randomisation was stratified by pathological node status, previous tamoxifen use, and lowest bone mineral density T score in the lumbosacral spine, total hip, or femoral neck. The primary endpoint was disease-free survival, defined as time from randomisation to breast cancer recurrence, second primary malignancy, or death, and was analysed by intention to treat. To adjust for previous interim analyses, the two-sided statistical significance level for disease-free survival was set at 0·0418. This study is registered with ClinicalTrials.gov, number NCT00382070, is active, and is no longer enrolling patients.

Findings Between Sept 28, 2006, and Jan 6, 2010, 3966 patients were randomly assigned to receive letrozole (n=1983) or placebo (n=1983). Follow-up information was available for 3903 patients for the analyses of disease-free survival. Median follow-up was 6·9 years (IQR 6·1–7·5). Letrozole treatment did not significantly improve disease-free survival (339 disease-free survival events were reported in the placebo group and 292 disease-free survival events were reported in the letrozole group; hazard ratio 0·85, 95% CI 0·73–0·999; p=0·048). 7-year disease-free survival estimate was 81·3% (95% CI 79·3–83·1) in the placebo group and 84·7% (82·9–86·4) in the letrozole group. The most common grade 3 adverse events were arthralgia (47 [2%] of 1933 patients in the placebo group *vs* 50 [3%] of 1941 patients in the letrozole group) and back pain (44 [2%] *vs* 38 [2%]). The most common grade 4 adverse event in the placebo group was thromboembolic event (eight [<1%]) and the most common grade 4 adverse events in the letrozole group were urinary tract infection, hypokalaemia, and left ventricular systolic dysfunction (four [<1%] each).

Interpretation After 5 years of aromatase inhibitor-based therapy, 5 years of letrozole therapy did not significantly prolong disease-free survival compared with placebo. Careful assessment of potential risks and benefits is required before recommending extended letrozole therapy to patients with early-stage breast cancer.

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Introduction

Patients with hormone receptor-positive, early-stage breast cancer are at risk of recurrence long after the first 5 years after diagnosis of breast cancer. In an overview analysis of the Early Breast Cancer Trialist's Collaborative Group,[1,2] about half of the recurrences and more than two-thirds of the deaths from breast cancer occurred more than 5 years after diagnosis.

Extended adjuvant endocrine therapy with either tamoxifen or an aromatase inhibitor after 5 years of initial tamoxifen treatment has been shown to improve disease-free survival in early-stage breast cancer.[3–6] In one large trial,[5] breast cancer-specific mortality and overall survival were also improved with extended adjuvant endocrine therapy. However, studies investigating the benefit of extending adjuvant aromatase inhibitor therapy beyond 5 years have only recently been reported, with mixed results.[7–11]

In the NSABP B-42 trial (henceforth referred to as B-42), we aimed to determine whether 5 years of letrozole treatment would improve disease-free survival in patients who had remained free of breast cancer after completing 5 years of endocrine therapy with either an aromatase

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Research in context

Evidence before this study

Results from clinical trials and overview analyses have established that patients with hormone receptor-positive, early-stage breast cancer are at considerable risk of recurrence long after the first 5 years from diagnosis of breast cancer. We searched PubMed when we designed this study, in March, 2005, to identify randomised clinical trials of adjuvant endocrine therapy in English. At that time, use of adjuvant tamoxifen for 5 years was the standard of care for patients with premenopausal breast cancer. Clinical trials such as the aTTom and ATLAS studies investigated extended adjuvant tamoxifen therapy for 10 years compared with 5 years, but had not reported results at the time we designed this study. These two trials showed that 10 years of tamoxifen improved disease-free survival (and breast cancer-specific mortality in the ATLAS trial), compared with 5 years of tamoxifen. For postmenopausal patients, several clinical trials had shown significant improvement in disease-free survival with the use of aromatase inhibitors, compared with 5 years of tamoxifen. Three different approaches had been used for the incorporation of aromatase inhibitors in the adjuvant setting, all three compared with the standard of 5 years of tamoxifen: 5 years of an upfront aromatase inhibitor (as assessed in the ATAC and BIG-1-98 trials), 2–3 years of an aromatase inhibitor after 2–3 years of tamoxifen (as assessed in the ABCSG-8/ARNO 95 and the ITA trials), or 5 years of an aromatase inhibitor after 5 years of tamoxifen (as assessed in the MA.17 and B-33 trials). All three approaches yielded significant improvements in disease-free survival compared with 5 years of adjuvant tamoxifen. Although the MA.17 and B-33 trials assessed extended aromatase inhibitor therapy after 5 years of tamoxifen, at the time our trial started the benefit of extending adjuvant aromatase inhibitor therapy for longer than 5 years in patients who had received 5 years of an aromatase inhibitor or 2–3 years of tamoxifen followed by 2–3 years of an aromatase inhibitor was unknown. Therefore, the NSABP B-42 (B-42) trial aimed to determine whether extending therapy past 5 years would improve disease-free survival in these patients.

Added value of this study

The B-42 trial showed that letrozole therapy did not significantly prolong disease-free survival after 5 years of hormonal therapy. However, extended letrozole therapy resulted in a significant reduction in breast cancer recurrence and distant recurrence. The B-42 results might appear discordant with those recently reported from the NCIC MA.17R trial, which showed a significant improvement in disease-free survival with extended letrozole therapy in patients who had already received 5 years of letrozole (preceded in most participants by 5 years of tamoxifen treatment). However, disease-free survival in MA.17R included only breast cancer recurrence and contralateral breast cancer as events, which is the definition of breast-cancer-free interval by the STandardized definitions for Efficacy End points (STEEP) criteria. When the disease-free survival endpoint is defined more closely to the STEEP criteria by including deaths as first event in MA.17R, a smaller and non-significant improvement in disease-free survival was observed with extended letrozole treatment. The results of the B-42 trial are further corroborated by two other randomised trials (DATA and IDEAL), which compared longer and shorter durations of extended aromatase inhibitor therapy.

Implications of all the available evidence

Considering all available evidence, it seems that the benefit from extended aromatase inhibitor therapy is modest. Therefore, careful assessment of potential risks and benefits is required before recommending extended letrozole therapy to patients with early-stage breast cancer who are disease-free after 5 years of hormonal therapy, primarily with an aromatase inhibitor. Further research is needed to identify biological markers that might predict risk of late recurrence or magnitude of benefit from extended aromatase inhibitor therapy, to optimise selection of candidates for extended aromatase inhibitor therapy.

inhibitor or initial tamoxifen for up to 3 years followed by an aromatase inhibitor for the remainder of the first 5 years.

Methods

Study design and participants

This was a randomised, double-blind, placebo-controlled, phase 3 trial done in 158 centres in the USA, Canada, and Ireland. Eligible patients were postmenopausal women with histologically confirmed, oestrogen-receptor-positive or progesterone-receptor-positive invasive ductal carcinoma (by local assessment), stage I–IIIA at diagnosis, who were disease-free after about 5 years of endocrine therapy consisting of either an aromatase inhibitor or tamoxifen for 3 years or less followed by an aromatase inhibitor for the remainder of the first 5 years. For study purposes, we defined postmenopausal as 56 years or older with no spontaneous menses for at least 12 months before study entry, or age 55 or younger with no spontaneous menses for at least 12 months before study entry and a documented oestradiol concentration in the postmenopausal range according to local institutional or laboratory standards, or a previous documented bilateral oophorectomy.

In order to have a predominantly letrozole-treated population for enrolment in the study, we provided an optional registration programme that offered patients with a minimum history of 2 years of previous hormonal therapy (either tamoxifen for ≤3 years or an aromatase inhibitor) letrozole at no cost until completion of 5 years of initial adjuvant endocrine therapy.

Eligible patients had either had breast-conserving therapy or mastectomy with axillary lymph-node staging. Estimated life expectancy was not an eligibility criterion, although the protocol suggested that investigators

should consider women who had a life expectancy of less than 10 years—apart from in relation to the diagnosis of breast cancer—as potentially unsuitable candidates for the trial. Patients were required to have Eastern Cooperative Oncology Group performance status of 0–1 and must have consented to participate by signing and dating an appropriate institutional review board-approved consent form that conformed to federal and institutional guidelines.

Participants had to be randomly assigned to study treatment within 6 months of the completion of adjuvant hormonal therapy; they were required to have had adjuvant hormonal therapy after breast cancer diagnosis over a duration of 57–63 months from the first dose, regardless of the number of missed doses. Participants could have no clinical evidence of recurrent breast cancer at randomisation, and had to have had bilateral mammogram (when applicable) and bone mineral density testing within the preceding year. They had to have had a result for total cholesterol of grade 1 or lower as defined by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 within the preceding 1 or 2 years, depending on the patient's history of hypercholesterolaemia, use of cholesterol-lowering interventions, or risk factors for cardiovascular events.

Patients were ineligible for inclusion in the study if they had a history of non-traumatic osteoporotic fracture, bilateral breast cancer including ductal carcinoma in situ, other malignancies (except carcinoma in situ of the colon or cervix, melanoma in situ, or squamous or basal cell carcinoma of the skin) unless they had been disease-free for at least 5 years before randomisation and were deemed at low risk of recurrence by their physician. Patients who were taking sex hormone therapy or therapy with any hormonal drug for management of osteoporosis were ineligible unless they discontinued such therapy before study entry. Administration of any investigational study drug within 30 days before study entry also made a patient ineligible.

The study was approved by local human investigations committees or institutional review boards in accordance with assurances filed with and approved by the Department of Health and Human Services. Written, informed consent was required from each participant.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either letrozole or matching placebo (appendix p 2). Assignment to the treatment groups was stratified by pathological node status at diagnosis (negative *vs* positive), use of tamoxifen as a component of initial adjuvant therapy (no *vs* yes), and lowest bone mineral density T score in the lumbosacral spine, total hip, or femoral neck (–2·0 or less *vs* higher than –2·0 SD) with a biased-coin minimisation algorithm.[12] Randomisation was done centrally by the statistical centre (Pittsburgh, PA, USA). Patients and investigators were masked to treatment group assignment. Letrozole and matching placebo was supplied in bottles and each bottle was labelled letrozole 2·5 mg or placebo.

Procedures

Patients received either letrozole 2·5 mg or placebo oral tablet once daily, beginning within 30 days after randomisation and ending 5 years from the date of the first dose, regardless of any missed doses. If patients developed grade 3–4 high cholesterol, the study drug had to be suspended until total cholesterol returned to grade 1 or lower. The study drug had to be discontinued for any of the following events: grade 1 or worse stroke or transient ischaemic attack; grade 2 or worse acute coronary syndrome or cerebrovascular ischaemia; grade 3 or worse myocardial infarction, peripheral ischaemia, or visceral arterial ischaemia; or if osteoporotic fracture occurred with a T score less than –2·5 while the patient was taking bisphosphonates or other medication for osteoporosis. Patients were required to have an annual physical examination during the study. Patients were followed up with physical examinations every 6 months during therapy and every 12 months thereafter. Bilateral mammogram was required every 12 months and bone mineral density testing was required every 2 years during study treatment. The frequency of lipid testing was decided on a patient-by-patient basis. Adverse events (according to the CTCAE version 3.0 and then according to version 4.0 from the beginning of January, 2011) were assessed every 6 months during study therapy and 6 months after the last administered dose of the investigational study drug.

Outcomes

The primary endpoint was disease-free survival, defined as time from randomisation to breast cancer recurrence, second primary malignancy, or death.

Secondary endpoints were overall survival (time from randomisation to death from any cause), breast-cancer-free interval (time from randomisation to local, regional, or distant recurrence of breast cancer, or contralateral breast cancer as a first event), distant recurrence (time from randomisation to distant recurrence of breast cancer), incidence of osteoporotic fractures (defined as Colles', hip, or spinal fractures), and incidence of arterial thrombotic events as defined by CTCAE version 4.0 (grade ≥1 stroke or transient ischaemic attack; grade ≥2 acute coronary syndrome or cerebrovascular ischaemia; grade ≥3 myocardial infarction, peripheral ischaemia, or visceral arterial ischaemia; and grade ≥4 selected thromboembolic events [cerebrovascular event, arterial insufficiency]).

See Online for appendix

Pathology reports from the study sites were reviewed centrally to confirm breast cancer recurrence, contralateral breast cancer, or second non-breast primary malignancy. All time-to-event endpoints were measured from the date of randomisation to the date of diagnosis of the specified event. Patients who were otherwise

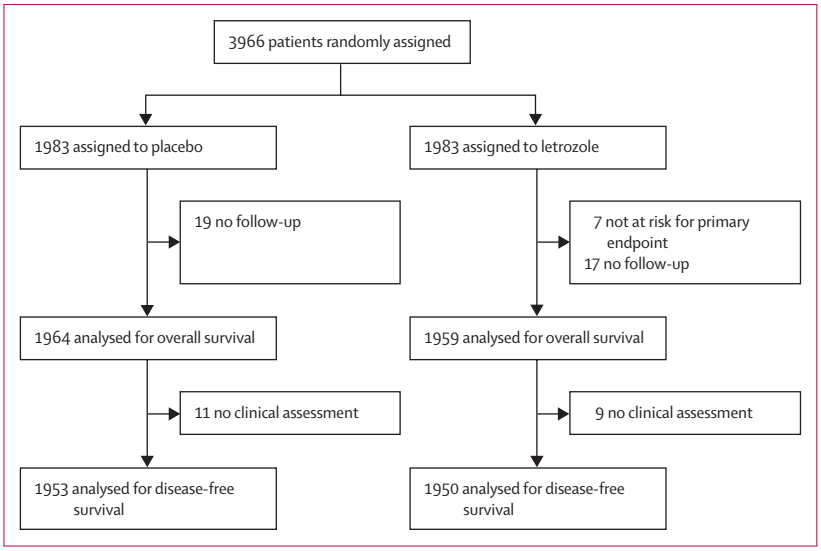

Figure 1: **Trial profile**

event free were censored at the date of last follow-up. Additionally, for the breast-cancer-free interval endpoint, other second primary cancers and death without evidence of recurrence were treated as censored events. Clinical assessment was required for determining patients' status for all endpoints except overall survival.

Statistical analysis

The study was designed to have at least 80% power to detect a 20% reduction in the annual disease-free survival hazard rate with letrozole compared with placebo using a 0·05 two-sided significance level. 3840 patients were to be enrolled. Definitive analysis was planned after the report of the 631st disease-free-survival event for both treatment groups combined. Four formal interim analyses were prespecified in the statistical analysis plan, scheduled for after 126, 252, 379, and 505 events were observed. We originally used symmetric stopping boundaries based on the O'Brien-Fleming method.[13] We added futility boundaries for the third and fourth interim analyses[14] according to recommendations from the data monitoring committee. We used the original O'Brien-Fleming method for the one-sided lower boundary for superiority. To adjust for the previous four interim analyses and account for alpha spending, we used an adjusted two-sided significance level of 0·0418 for the primary analysis.

We assessed differences in primary and secondary endpoints between treatment groups using stratified log-rank tests, controlling for stratification variables.[15] We calculated hazard ratios (HRs) and corresponding 95% CIs on the basis of a stratified Cox proportional hazards model for all time-to-event endpoints.[16] We tested the assumption of proportionality of hazards for each time-to-event outcome.[17] When the proportional hazards assumption was not satisfied, we used a so-called change point for the relative risk technique to identify the optimal timepoint to divide the time interval into the regions in which the proportionality of the hazards holds.[15] In secondary analyses, we used the proportional hazards model to estimate and control for the effect of additional prognostic factors. For the analyses of secondary endpoints, we considered two-sided p values of less than 0·05 to be significant. We tested for the presence of treatment-by-covariate interactions, with a two-sided p-value of less than 0·01 indicating significance. We also did a post-hoc analysis of the effect of letrozole on disease-free survival by bisphosphonate use at baseline.

For illustration purposes, we estimated the distribution of disease-free survival and overall survival endpoints using the Kaplan-Meier method[18] and used the cumulative incidence function to estimate the proportions of breast-cancer-free interval, distant recurrence, osteoporotic fractures, and arterial thrombotic events over time to account for competing risks.[19] We also present the point estimates and corresponding 95% CIs at the median follow-up time. Second primary cancers (other than breast) and death without evidence of recurrence were considered as competing events in estimating cumulative incidence of breast-cancer-free interval events. We considered death as first event as a competing event in estimating cumulative incidence of distant recurrence, osteoporotic fractures, and arterial thrombotic events.

Definitive analysis, which was triggered by observing 631 disease-free survival events, was based on the intention-to-treat principle, with all randomly assigned patients analysed, regardless of eligibility or protocol compliance. We excluded patients with no follow-up and those not at risk for the primary endpoint (metastases at time of randomisation or first non-death event within 30 days from randomisation) from all analyses. We did all statistical analyses using SAS (version 9.4). The analyses reported include all data received as of Aug 25, 2016.

This study is registered with ClinicalTrials.gov, number NCT00382070.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. EPM, HB, and J-HJ had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 28, 2006, and Jan 6, 2010, 3966 patients were randomly assigned at 158 participating institutions (figure 1; appendix pp 3–6). Median time from original diagnosis to random assignment was 5·6 years (IQR 5·4–5·8). Distribution of baseline characteristics was well balanced between the two treatment groups (table 1). The median duration of aromatase inhibitor treatment in all patients in the first 5 years after diagnosis was 60 months (IQR 40–60); median duration of

aromatase inhibitor treatment was 36 months (31–47) for women previously treated with tamoxifen and 60 months (60–61) for women not previously treated with tamoxifen. Seven patients assigned to the letrozole group were excluded from all analyses because they were not at risk for the primary endpoint, and 36 patients (19 in the placebo group, 17 in the letrozole group) were excluded from all analyses because there were no available follow-up data. Of 3923 patients with follow-up data, 20 (1%) did not have a clinical assessment for the duration of the follow-up (11 in the placebo group, nine in the letrozole group) and were therefore excluded from the analyses of all disease-related endpoints except for overall survival. Median duration of follow-up for the 3923 patients included in the analyses was 6·9 years (IQR 6·1–7·5).

Median duration of treatment was 59·8 months (IQR 32·6–60·0) in the placebo group and 59·8 months (32·3–60·0) in the letrozole group. Of 3923 patients, 47 (1%) did not begin study treatment (30 in the placebo group, 17 in the letrozole group). Overall, 1228 (63%) of 1964 patients in the placebo group and 1181 (60%) of 1959 patients in the letrozole group completed 5 years of therapy in this study, as defined by the protocol. The main reasons for treatment discontinuation were withdrawal or refusal (250 [13%] of 1964 patients in the placebo group vs 271 [14%] of 1959 patients in the letrozole group), adverse events (140 [7%] vs 189 [10%]), disease progression (102 [5%] vs 81 [4%]), other complicating disease or death (53 [3%] vs 52 [3%]), and declining bone density or osteoporotic fracture (16 [1%] vs 27 [1%]).

There were 631 disease-free survival events recorded among 3903 patients included in the analyses of disease-free survival (339 events in the placebo group *vs* 292 events in the letrozole group). Letrozole treatment did not significantly increase disease-free survival compared with placebo (HR 0·85, 95% CI 0·73–0·999; p=0·048). The 7-year disease-free survival point estimates were 81·3% (95% CI 79·3–83·1) for placebo and 84·7% (95% CI 82·9–86·4) for letrozole (figure 2A).

The primary differences in the frequency of disease-free survival events between the placebo and letrozole groups were observed in distant recurrence (87 *vs* 61 events) and in contralateral breast cancer (59 *vs* 30 events; table 2).

There were 310 deaths during the study (146 in the placebo group and 164 in the letrozole group). There was no significant difference in overall survival with letrozole compared with placebo (HR 1·15, 95% CI 0·92–1·44; p=0·22). 7-year overall survival point estimates were 92·3% (95% CI 90·9–93·5) for placebo and 91·8% (90·4–93·0) for letrozole (figure 2B). 93 patients died from breast cancer (47 in the placebo group, 46 in the letrozole group; appendix p 7).

There were 306 breast-cancer-free interval events (179 in the placebo group, 127 in the letrozole group). There was a significant reduction in breast-cancer-free interval events in the letrozole group compared with placebo (HR 0·71, 95% CI 0·56–0·89, p=0·0027). The 7-year cumulative incidence of breast-cancer-free interval events was 10% (95% CI 8·6–11·5) in the placebo group and 6·7% (5·6–8·0) in the letrozole group (figure 3A).

There were 175 distant recurrences (102 in the placebo group, 73 in the letrozole group; appendix p 8). There was a significant 28% reduction in the rate of distant recurrences in the letrozole group compared with placebo (HR 0·72, 95% CI 0·53–0·97, p=0·030). However, there was non-proportionality of hazards in the treatment groups (p=0·012) with a change point for the relative risk of 4·1 years. We observed no difference in the risk of distant recurrence events before 4·1 years (HR 1·00,

	Placebo group (n=1983)	Letrozole group (n=1983)
Age at randomisation, years		
<60	675 (34·0%)	685 (34·5%)
≥60	1308 (66·0%)	1298 (65·5%)
Race		
White	1840 (92·8%)	1848 (93·2%)
Black	81 (4·1%)	70 (3·5%)
Asian	39 (2·0%)	39 (2·0%)
Other or unknown	23 (1·2%)	26 (1·3%)
Pathological node status		
Negative	1134 (57·2%)	1145 (57·7%)
Positive	849 (42·8%)	838 (42·3%)
Lowest bone mineral density T score		
–2·0 or less	493 (24·9%)	489 (24·7%)
Higher than –2·0	1490 (75·1%)	1494 (75·3%)
Duration of tamoxifen before randomisation, months		
0	1212 (61·1%)	1207 (60·9%)
1 to 12	164 (8·3%)	150 (7·6%)
13 to 24	254 (12·8%)	259 (13·1%)
25 to 36	353 (17·8%)	367 (18·5%)
Surgery type		
Lumpectomy	1208 (60·9%)	1201 (60·6%)
Mastectomy	775 (39·1%)	782 (39·4%)
HER2 status		
Positive	278 (14·0%)	287 (14·5%)
Negative	1547 (78·0%)	1546 (78·0%)
Not done or unknown	158 (8·0%)	150 (7·6%)
Duration of aromatase inhibitor before randomisation, months		
≤36	412 (20·8%)*	399 (20·1%)
37 to 48	192 (9·7%)	207 (10·4%)
49 to 60	992 (50·0%)	970 (48·9%)
>60	387 (19·5%)	407 (20·5%)

Data are n (%). *Duration was unknown for one patient in this category.

Table 1: **Baseline characteristics**

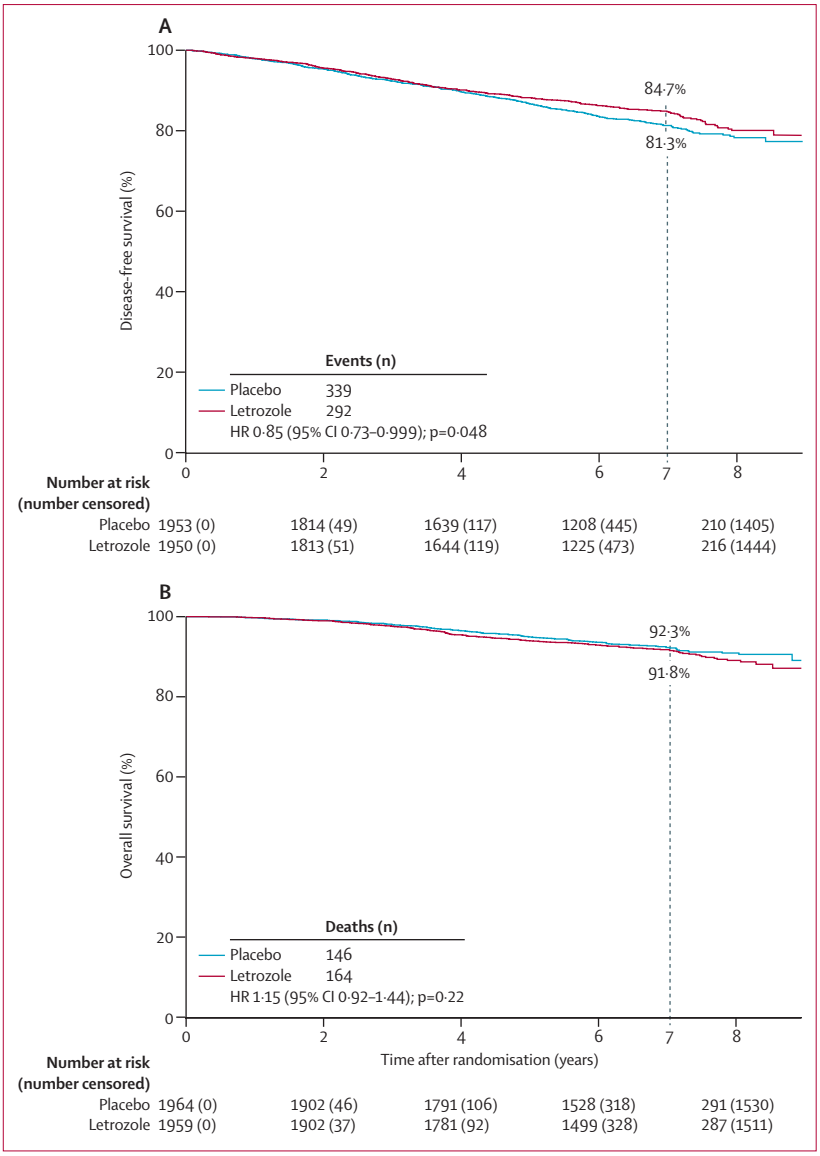

Figure 2: **Disease-free survival (A) and overall survival (B)**
HR=hazard ratio.

	Placebo group (n=1953)	Letrozole group (n=1950)
Distant recurrence	87 (4·5%)	61 (3·1%)
Local recurrence	33 (1·7%)	36 (1·8%)
Contralateral breast cancer	59 (3·0%)	30 (1·5%)
Second non-breast primary cancer	112 (5·7%)	104 (5·3%)
Death	48 (2·5%)	61 (3·1%)
Total first event	339 (17·4%)	292 (15·0%)
Alive, event free	1614 (82·6%)	1658 (85·0%)

Data are n (%).

Table 2: **Type of first events**

95% CI 0·70–1·42, p=0·98), but there was a significant reduction in the rate of distant recurrence events in the letrozole group as compared with placebo after 4·1 years (0·32, 0·17–0·59, p=0·0003). The 4-year cumulative incidence of distant recurrences was 3·2% (95% CI 2·5–4·0) in the placebo group and 3·1% (2·4–4·0) in the letrozole group. 7-year cumulative incidence of distant recurrences was 5·8% (95% CI 4·7–7·0) in the placebo group and 3·9% (3·1–4·9) in the letrozole group (figure 3B).

There were 169 osteoporotic fractures (78 in the placebo group and 91 in the letrozole group), with no significant difference in the development of osteoporotic fractures between groups (HR 1·19, 95% CI 0·88–1·60, p=0·27). 7-year cumulative incidence of osteoporotic fractures was 4·8% (95% CI 3·8–6·0) in the placebo group and 5·4% (4·3–6·6) in the letrozole group.

There were 130 reported arterial thrombotic events (59 in the placebo group and 71 in the letrozole group). Although treatment with letrozole did not result in a significant overall increase in arterial thrombotic events compared with placebo (HR 1·21, 95% CI 0·85–1·70, p=0·29), a proportionality of the hazards assumption was not satisfied (p=0·007). We identified a change point of 2·5 years for the relative risk of arterial thrombotic events. There was no significant difference in the risk of arterial thrombotic events with letrozole compared with placebo before 2·5 years (HR 0·55, 95% CI 0·30–1·01, p=0·054), but a significant increase in risk after 2·5 years (1·85, 1·18–2·88, p=0·0069). The 2·5-year cumulative incidence of arterial thrombotic events was 1·6% (95% CI 1·1–2·2) in the placebo group and 0·9% (0·5–1·4) in the letrozole group. 7-year cumulative incidence was 3·4% (2·6–4·4) in the placebo group and 4·0% (3·1–5·0) in the letrozole group (figure 3C).

The effect of treatment on disease-free survival persisted in the multivariable analysis (HR 0·86, 95% CI 0·73–1·00; p=0·0501) after adjustment for the prognostic factors of age (p<0·0001), pathological node status (p=0·0005), previous tamoxifen use (p=0·0035), and type of surgery (p=0·0098; table 3).

There were no significant differences in the effect of letrozole on disease-free survival by age, pathological node status, previous tamoxifen use, type of surgery, or lowest bone mineral density score (figure 4). The effect of letrozole was similar for different categories of age and pathological node status. Although no significant treatment by factor interactions were identified, the effect of letrozole seemed more pronounced in patients who had received previous tamoxifen versus those who had not, in those who had mastectomy versus lumpectomy, and in those with lowest bone mineral density score of –2·0 or lower versus higher than –2·0. Additionally, the absolute 7-year differences between treatment groups were small for disease-free survival (2·1–6·4%), breast-cancer-free interval event (2·8–4·5%), and distant recurrences (0·6–4·6%; table 4).

In a post-hoc analysis, 1393 (35·7%) of patients reported using bisphosphonates at baseline (701 in the placebo group and 692 in the letrozole group): 577 (60·5%) of 954 patients with a lowest bone mineral density score of –2 or lower (294 in the placebo group, 283 in the letrozole group) and 816 (27·7%) of 2949 patients with a lowest bone mineral density score of higher than –2 (407 in the placebo group and 409 in the letrozole group) used bisphosphonates at baseline. The effect of treatment among bisphosphonate users at baseline was consistent with the overall treatment effect in those with lowest bone mineral density score of –2·0 or lower (HR 0·76, 95% CI 0·51–1·12) and in those with lowest bone mineral density score of higher than –2·0 (0·92, 0·64–1·32). Among 1393 participants taking bisphonates at baseline, 1381 (99%) planned to continue bisphosphonate use during and after randomisation.

Toxicity information was available for 3874 (99%) of 3923 patients with available follow-up data (1933 [98%] of patients in the placebo group and 1941 [99%] of patients in the letrozole group) and was similar between both groups (table 5; appendix pp 9–19). The most common grade 3 adverse events were arthralgia (47 [2%] in the placebo group, 50 [3%] in the letrozole group) and back pain (44 [2%] in the placebo group, 38 [2%] in the letrozole group). The most common grade 4 adverse event in the placebo group was thromboembolic event (eight [<1%]) and the most common grade 4 events in the letrozole group were urinary tract infection, hypokalaemia, and left ventricular systolic dysfunction (four [<1%] each). For 104 (3%) patients, their worst adverse event was grade 4 (53 in the placebo group, 51 in the letrozole group) and for 51 (1%), a grade 5 adverse event was their worst event (26 in the placebo group, 25 in the letrozole group). There were 21 serious adverse events reported among 18 patients that were reported by study staff as possibly or probably related to treatment (eight in the placebo group, ten in the letrozole group; appendix p 20). Among these 21 serious adverse events, four were grade 3 events (one in the placebo group, three in the letrozole group), 16 grade 4 events (seven in the placebo group, nine in the letrozole group), and one grade 5 left ventricular systolic dysfunction reported in the letrozole treatment group. The most frequent drug-related serious adverse event reported among patients randomly assigned to the placebo group was a thromboembolic event (three events, grade 4). The most frequent drug-related serious adverse events reported among patients randomly assigned to receive letrozole were other nervous system disorders (two events, grade 4).

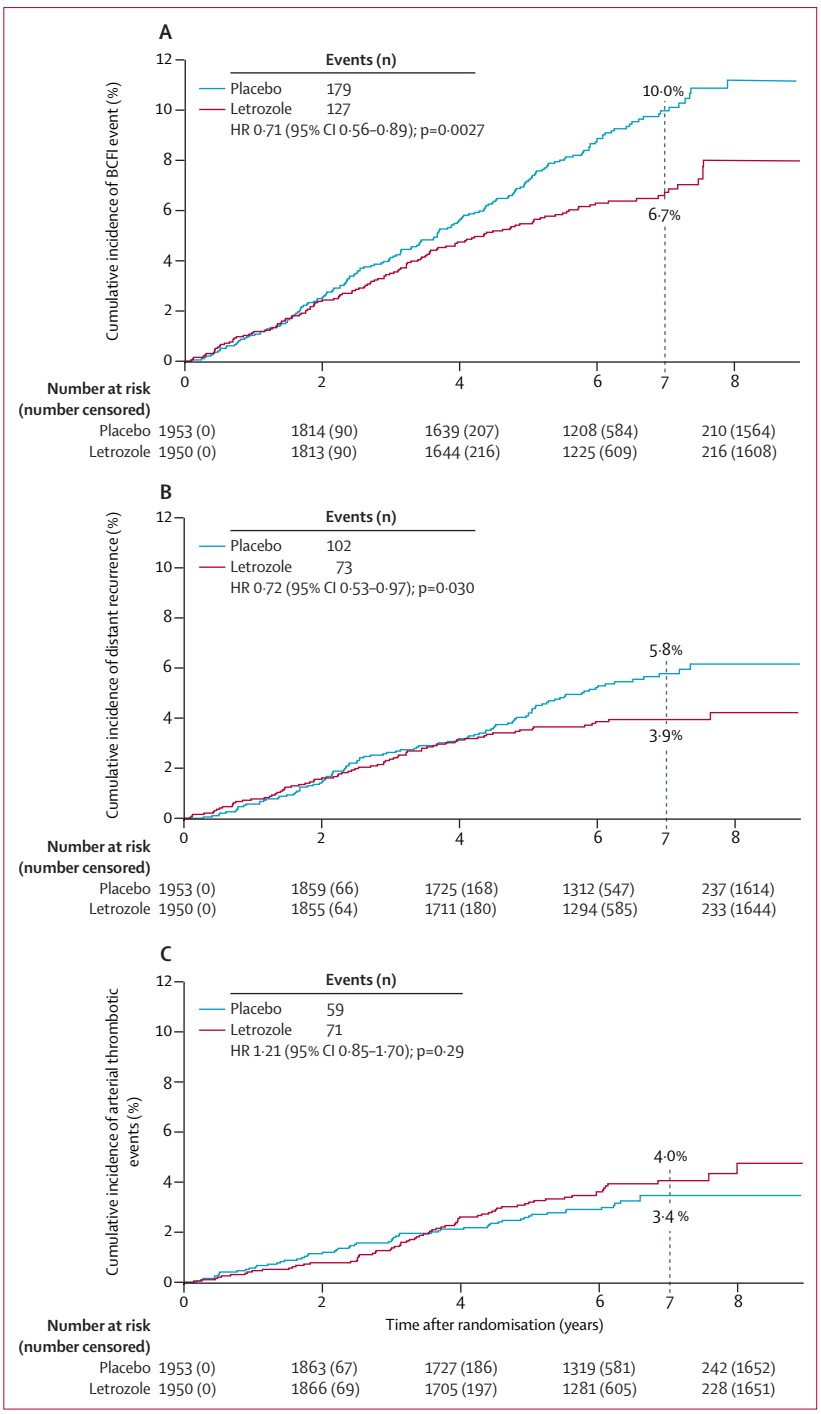

Figure 3: **Cumulative incidence of secondary outcomes**
(A) Cumulative incidence of breast-cancer-free interval (BCFI). (B) Cumulative incidence of distant recurrence. (C) Cumulative incidence of arterial thrombotic events. HR=hazard ratio.

Discussion

To our knowledge, the NSABP B-42 trial is the largest to investigate extended adjuvant aromatase inhibitor therapy in patients who were disease-free after 5 years of endocrine therapy, most of whom had been treated with an aromatase inhibitor. Our findings did not show a significant prolongation of disease-free survival with extended letrozole therapy. At first glance, our results appear discordant with those reported from the MA.17R trial,[7] which enrolled 1918 postmenopausal women with primary breast cancer who were free of recurrent disease

after receiving 4·5–6 years of adjuvant aromatase inhibitor therapy, preceded in most patients by 5 years of tamoxifen treatment. In MA.17R, patients were randomly assigned to receive 5 years of placebo or letrozole within 2 years of completion of aromatase inhibitor therapy.

	Number of patients (n=3903)	Number of disease-free survival events	Hazard ratio (95% CI); p value
Treatment			
Placebo	1953	339 (17·4%)	..
Letrozole	1950	292 (15·0%)	0·86 (0·73–1·00); p=0·0501
Age, years			
<60	1344	163 (12·1%)	..
≥60	2559	468 (18·3%)	1·55 (1·29–1·86); p<0·0001
Pathological node status			
Negative	2240	322 (14·4%)	..
Positive	1663	309 (18·6%)	1·33 (1·13–1·56); p=0·0005
Received tamoxifen			
No	2377	421 (17·7%)	..
Yes	1526	210 (13·8%)	0·78 (0·66–0·92); p=0·0035
Surgery type			
Lumpectomy	2374	348 (14·7%)	..
Mastectomy	1529	283 (18·5%)	1·24 (1·05–1·45); p=0·0098

Table 3: **Multivariable analysis for disease-free survival**

With a median follow-up of 6·9 years and 165 disease-free survival events reported, the study showed a significant reduction in disease-free survival events in favour of letrozole (HR 0·66, p=0·01; 5-year disease-free survival was 91% in the placebo group, 95% in the letrozole group). However, the definition of disease-free survival in MA.17R included only breast cancer recurrence and contralateral breast cancer as events, which corresponds to the STandardized definitions for Efficacy End points (STEEP)[20] breast-cancer-free interval-definition employed in B-42 (HR 0·71, p=0·003). In a disease-free survival analysis[7] that also included deaths from any cause as first events, but not other non-breast second primary cancers, the MA.17R trial did not show a significant improvement with extended letrozole (HR 0·80, p=0·06; 5-year disease-free survival was 88% in the placebo group, 90% in the letrozole group). Neither the MA.17R nor B-42 trials showed significant differences in overall survival with extended letrozole treatment. Thus, although extended letrozole treatment significantly reduced recurrence and distant recurrence in both trials, only a modest, non-significant reduction in disease-free survival as defined by the STEEP criteria was achieved.[20] Although reductions in breast cancer recurrence reflect the biological effect of extended-duration endocrine therapy, traditionally defined disease-free survival captures the overall clinical effect in the study populations of postmenopausal patients, some with pre-existing comorbidities and at risk of non-breast cancer-related events.

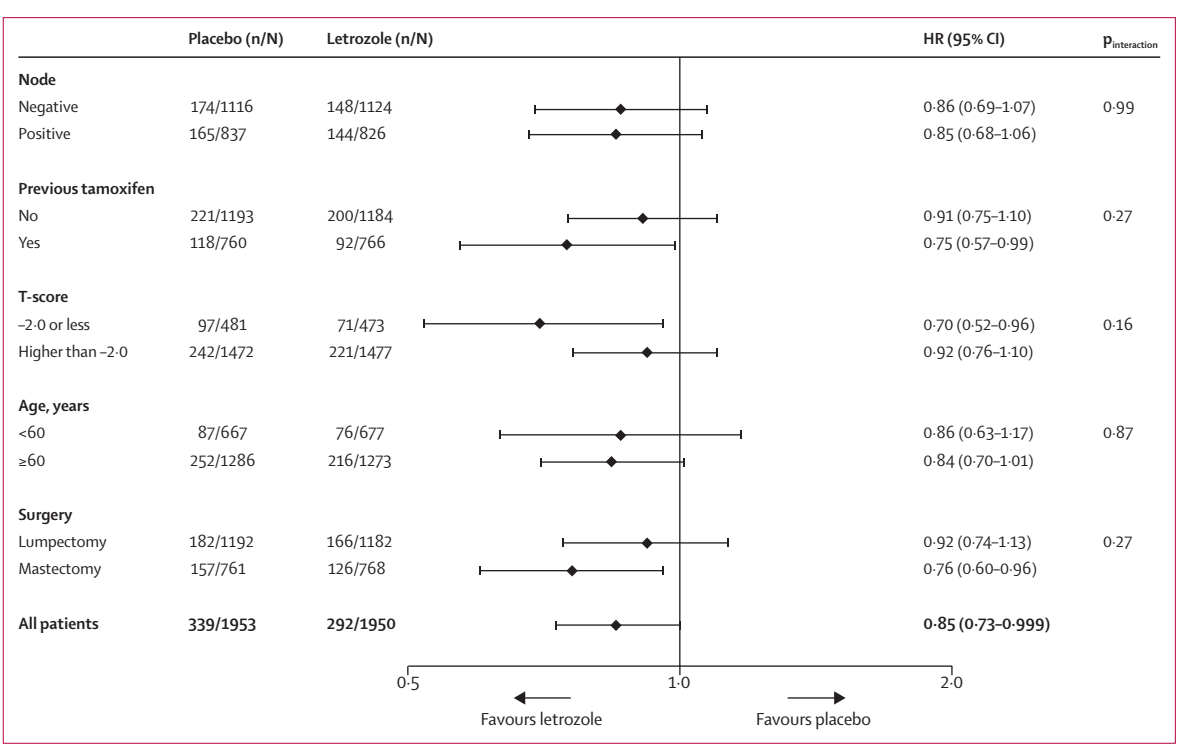

Figure 4: **Subgroup analyses of disease-free survival**
n is the number of events and N is the number of patients. HR=hazard ratio.

	7-year disease-free survival		7-year cumulative incidence, breast-cancer-free interval		7-year cumulative incidence, distant recurrence	
	Placebo	Letrozole	Placebo	Letrozole	Placebo	Letrozole
Pathological node status						
Negative	83·4% (80·9–85·7)	86·5% (84·2–88·5)	8·2% (6·5–10·0)	5·3% (4·0–6·8)	3·6% (2·5–4·9)	2·2% (1·4–3·2)
Positive	78·4% (75·2–81·3)	82·4% (79·4–85·0)	12·4% (10·1–15·0)	8·7% (6·8–10·8)	8·7% (6·8–10·9)	6·3% (4·7–8·2)
Previous tamoxifen						
No	79·8% (77·1–82·1)	82·0% (79·4–84·3)	9·9% (8·2–11·8)	6·8% (5·4–8·5)	5·9% (4·5–7·4)	3·6% (2·6–4·9)
Yes	83·7% (80·6–86·3)	88·8% (86·2–91·0)	10·0% (7·8–12·5)	6·5% (4·8–8·5)	5·6% (4·0–7·6)	4·4% (3·1–6·1)
Lowest bone mineral density T score						
–2·0 or less	77·9% (73·4–81·7)	84·3% (80·2–87·6)	9·3% (6·9–12·3)	5·7% (3·6–8·5)	7·3% (5·1–9·9)	2·7% (1·5–4·6)
Higher than –2·0	82·4% (80·1–84·4)	84·9% (82·8–86·7)	10·2% (8·5–11·9)	7·1% (5·8–8·5)	5·3% (4·1–6·6)	4·3% (3·3–5·5)
Age, years						
<60	86·0% (82·9–88·6)	88·1% (85·2–90·5)	9·5% (7·3–12·1)	6·7% (4·9–8·9)	5·9% (4·2–8·0)	4·3% (2·9–6·2)
≥60	78·8% (76·3–81·2)	83·0% (80·6–85·1)	10·2% (8·5–12·1)	6·7% (5·4–8·3)	5·7% (4·4–7·2)	3·7% (2·8–4·9)
Surgery type						
Lumpectomy	83·4% (80·9–85·6)	85·7% (83·3–87·7)	8·7% (7·0–10·5)	6·2% (4·8–7·9)	3·1% (2·2–4·3)	2·5% (1·7–3·5)
Mastectomy	78·0% (74·6–81·0)	83·3% (80·3–85·9)	12·0% (9·6–14·6)	7·5% (5·7–9·5)	10·0% (7·8–12·4)	6·1% (4·5–8·1)

Data are % (95% CI).

Table 4: **7-year disease-free survival and cumulative incidence of breast cancer-free interval and distant recurrence**

The results from B-42 are corroborated by two other randomised trials of extended adjuvant endocrine therapy that have recently reported their results: the DATA trial[9] and the IDEAL trial.[8] In the DATA trial,[9] postmenopausal women with hormone receptor-positive early-stage breast cancer and no signs of disease recurrence after 2–3 years of adjuvant tamoxifen were randomly assigned to receive either 3 or 6 years of anastrozole. The primary study endpoint was disease-free survival starting more than 3 years after random assignment (adapted disease-free survival). Of 1860 eligible patients, 1660 were disease-free 3 years after random assignment. The 5-year adapted disease-free survival was 83·1% (95% CI 80·0–86·3) in the 6-year group and 79·4% (76·1–82·8) in the 3-year group (HR 0·79, 95% CI 0·62–1·02; p=0·066). On the basis of these findings, the authors did not recommend the use of extended adjuvant aromatase inhibition after 5 years of sequential endocrine therapy in all postmenopausal women with hormone-receptor-positive breast cancer. In the IDEAL trial,[8] postmenopausal patients with hormone-receptor-positive breast cancer were randomly allocated to receive either 2·5 or 5 years of letrozole after the initial 5 years of any endocrine therapy. 1824 patients were assigned to receive either 2·5 years (n=909) or 5 years (n=915) of letrozole treatment. With a median follow-up of 6·6 years, there was no significant difference in disease-free survival between the two groups (HR 0·92, 95% CI 0·74–1·16). No significant differences were reported in overall survival or distant metastasis-free survival between groups, but a significant reduction in the occurrence of second primary breast cancer was associated with 5 years of extended treatment (HR 0·39, 95% CI 0·19–0·81). The authors concluded that there was no superiority of 5 years over 2·5 years of extended adjuvant letrozole therapy after an initial 5 years of adjuvant endocrine therapy. Because both of the above trials assessed shorter differences in the duration of extended endocrine therapy compared with the B-42 trial (2·5–3 years *vs* 5 years), their findings of no significant disease-free survival improvement with the longer regimen are not surprising in the context of the B-42 results.

More recently, two other trials (ABCSG-16[11] and SOLE[10]) investigated extended adjuvant aromatase inhibitor therapy in women with postmenopausal breast cancer. In the ABSCG-16 trial,[11] 3484 postmenopausal women with stage I–III, hormone-receptor-positive breast cancer who had completed 5 years of endocrine therapy with tamoxifen, an aromatase inhibitor, or tamoxifen followed by an aromatase inhibitor, were randomly assigned to receive 2 years or 5 years of anastrozole. With median follow-up of 106 months, there were no significant differences in disease-free survival between the two groups (HR 1·007, 95% CI 0·87–1·16; p=0·925). The authors concluded that two additional years of anastrozole were sufficient for efficacy after 5 years of adjuvant endocrine therapy, because five additional years of anastrozole did not yield additional outcome benefit and did add toxicity. In the SOLE multicentre, open-label, randomised, phase 3 trial,[10] 4884 postmenopausal women with hormone-receptor-positive, lymph-node-

	Placebo group (n=1933)				Letrozole group (n=1941)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Total	219 (11%)	418 (22%)	53 (3%)	26 (1%)	263 (14%)	486 (25%)	51 (3%)	25 (1%)
Arthralgia	253 (13%)	47 (2%)	0	0	296 (15%)	50 (3%)	0	0
Myalgia	99 (5%)	19 (1%)	0	0	133 (7%)	16 (1%)	0	0
Back pain	0	44 (2%)	0	0	0	38 (2%)	0	0
Fracture	0	29 (2%)	0	0	0	36 (2%)	2 (<1%)	0
Hypertension	0	27 (1%)	2 (<1%)	0	0	27 (1%)	1 (<1%)	0
Dyspnoea	0	22 (1%)	1 (<1%)	0	0	29 (1%)	2 (<1%)	0
Thromboembolic event	15 (1%)	9 (<1%)	8 (<1%)	0	11 (1%)	9 (<1%)	1 (<1%)	0
Hot flushes	0	16 (1%)	0	0	0	28 (1%)	0	0
Cataract	0	20 (1%)	0	0	0	21 (1%)	0	0
Urinary tract infection	0	17 (1%)	2 (<1%)	0	0	18 (1%)	4 (<1%)	0
Atrial fibrillation	0	16 (1%)	1 (<1%)	0	0	20 (1%)	0	0
Fatigue	0	17 (1%)	0	0	0	20 (1%)	0	0
Syncope	0	16 (1%)	0	0	0	21 (1%)	0	0
Anaemia	0	11 (1%)	5 (<1%)	0	0	17 (1%)	2 (<1%)	0
Lung infection	0	13 (1%)	2 (<1%)	4 (<1%)	0	14 (1%)	0	0
Myocardial infarction	0	11 (1%)	2 (<1%)	2 (<1%)	0	11 (1%)	1 (<1%)	0
Dizziness	0	15 (1%)	0	0	0	11 (1%)	0	0
Diarrhoea	0	16 (1%)	0	0	0	9 (<1%)	0	0
Heart failure	0	6 (<1%)	1 (<1%)	1 (<1%)	0	14 (1%)	2 (<1%)	1 (<1%)
Pain	0	11 (1%)	0	0	0	14 (1%)	0	0
Depression	0	4 (<1%)	6 (<1%)	0	0	12 (1%)	2 (<1%)	0
Hyperglycaemia	0	8 (<1%)	0	0	0	14 (1%)	2 (<1%)	0
Skin infection	0	12 (1%)	0	0	0	11 (1%)	1 (<1%)	0
Headache	0	11 (1%)	0	0	0	12 (1%)	0	0
Abdominal pain	0	9 (<1%)	0	0	0	13 (1%)	0	0
Left ventricular systolic dysfunction	0	5 (<1%)	2 (<1%)	0	0	10 (1%)	4 (<1%)	1 (<1%)
Other infections	0	15 (1%)	0	1 (<1%)	0	5 (<1%)	0	0
Other surgical and medical procedures	0	11 (1%)	0	0	0	10 (1%)	0	0
Hyponatraemia	0	11 (1%)	2 (<1%)	0	0	6 (<1%)	1 (<1%)	0

Table 5: **Most common adverse events**

positive, and operable breast cancer who had completed 4–6 years of adjuvant endocrine therapy were randomly assigned to receive either continuous letrozole for 5 years or intermittent letrozole for 9 months followed by a 3-month break in years 1–4 and then continuous letrozole for all 12 months of year 5. After a median follow-up of 60 months, there was no significant difference in disease-free survival between the two groups (HR 1·08, 95% CI 0·93–1·26; p=0·31) and incidence of adverse events was similar between the two groups.[10] Thus, the results of the SOLE trial support the safety of intermittent administration of extended aromatase inhibitor therapy. These two trials help to refine the optimal duration of extended aromatase inhibitor therapy after 5 years of endocrine therapy.

Our finding in the B-42 trial that most of the reduction in distant recurrence events occurred after 4 years is of interest and is also a potential limitation of this study, because this reduction with extended letrozole therapy might continue to increase with additional follow-up. At the same time, the increase in arterial thrombotic events with letrozole after 2·5 years requires additional follow-up to determine whether the incidence of arterial thrombotic events will continue to increase. A systematic review[21] of randomised controlled trials that compared aromatase inhibitors and tamoxifen as primary adjuvant endocrine

therapy in postmenopausal women showed that longer duration of aromatase inhibitor use was associated with increased odds of developing cardiovascular disease (odds ratio 1·26, p<0·001) and bone fractures (1·47, p<0·001) but decreased odds of venous thrombosis (0·55, p<0·001) and endometrial carcinoma (0·34, p<0·001). Furthermore, 5 years of aromatase inhibitor use was associated with an increased odds of death without recurrence as compared with 5 years of tamoxifen alone or tamoxifen for 2–3 years followed by an aromatase inhibitor for 2–3 years, although this was not statistically significant (1·11, p=0·09). These observations might partially explain the absence of benefit in overall survival in any of the extended aromatase inhibitor trials, despite the observed reductions in breast cancer recurrence in B-42 and MA.17R.

Given the modest effect of extended letrozole on disease-free survival, it is important to identify patient subgroups at increased risk of recurrence or those who might receive greater proportional benefit from extended endocrine therapy. Our multivariable analysis showed that age, pathological node status, previous tamoxifen use, and type of surgery were independent predictors of disease-free survival. The effect of extended letrozole was more pronounced in patients who had had a mastectomy, those who had received previous tamoxifen, and those with a lowest bone mineral density score of –2·0 or less; however, these differences in treatment effect were not statistically significant. Furthermore, there was no evidence to suggest that the effect of extended letrozole treatment was associated with bisphosphonate use at baseline. Thus, in the B-42 trial, baseline clinico-pathological factors and patient and treatment characteristics did not help predict any subgroups of patients that might benefit from extended endocrine therapy.

During the past few years, several attempts have been made to refine risk of late recurrence of breast cancer after 5 years of endocrine therapy. These attempts include the development of clinico-pathological algorithms,[22] assessment of circulating tumour cell counts,[23] and assessment of several commercially available genomic classifiers, some of which might also predict which patients could benefit from extended endocrine therapy.[24–29] Incorporating such approaches into the clinical decision-making algorithm for recommending extended endocrine therapy could improve patient selection and optimise the risk-to-benefit ratio. Correlative science studies using B-42 tumour tissue are currently being planned.

Our findings suggest that careful assessment of the risks and potential benefits of extended letrozole therapy is required before recommending this treatment to any patients with early-stage breast cancer. This assessment should include patient and tumour characteristics, existing comorbidities, information about bone mineral density, and tolerance of aromatase inhibitor treatment in the initial 5 years of treatment for breast cancer.

Contributors

EPM, HB, J-HJ, CEG, PR, and NW contributed to study design and manuscript preparation. BCL, CEG, PR, SMS, and DLW contributed to study development and implementation. EPM, BCL, PR, and CEG contributed to study monitoring. HB and J-HJ contributed to data collection, data management, and data analysis. EPM, HB, CEG, PR, and NW contributed to data interpretation. SP contributed the correlative science section for the study. EPM, LF, MJG, SLC, AMB, JMW, GSS, SRD, TES, JLW, and ECMcC contributed to patient recruitment. EPM, HB, CEG, PR, and NW contributed to the preparation and writing of the manuscript. All authors contributed to, reviewed, and approved the final manuscript.

Declaration of interests

EPM served as a consultant and speaker for Genomic Health Inc, and consultant for Biotheranostics, outside the submitted work. CEG reports grants from the National Cancer Institute during the conduct of the study, personal fees from Celgene and Myriad, and other from AstraZeneca, outside the submitted work. SKC reports grants from National Surgical Adjuvant Breast and Bowel Project during the conduct of the study. AMB reports personal fees from Novartis outside the submitted work. JMW reports personal fees from Genomic Health Inc, Biotheranostics, Roche, and Pfizer, outside the submitted work. SMS reports reports other from AstraZeneca, non-financial support from Caris Life Sciences, personal fees and non-financial support from Daiichi-Sankyo, grants, personal fees, and non-financial support from Genentech/Roche, personal fees from Genomic Health, personal fees and non-financial support from Cardinal Health, personal fees and non-financial support from Inivata Ltd, grants, personal fees and non-financial support from Eli Lilly & Company, non-financial support from nanoString Technologies, personal fees and non-financial support from Pieris Pharmaceuticals, personal fees and non-financial support from Tocagen, personal fees and non-financial support from Novartis, grants from Puma Biotechnology, grants and personal fees from Pfizer, and grants from Merrimack Pharmaceuticals, outside the submitted work. BCL, HB, J-HJ, PR, LF, MLG, GSS, SRD, TES, JLW, EMMcC, SP, DLW, and NW declare no competing interests.

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References

1 Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; **351:** 1451–67.

2 Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med* 2017; **377:** 1836–46.

3 Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; **349:** 1793–802.

4 Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol* 2008; **26:** 1965–71.

5 Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; **381:** 805–16.

6 Gray RG, Rea DW, Handley K, et al. ATTom: randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer—preliminary results. *Proc Am Soc Clin Oncol* 2008; **26** (abstr 513).

7 Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med* 2016; **375:** 209–19.

8 Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). *J Natl Cancer Inst* 2018; published online Jan 1. DOI:10.1093/jnci/djx134.

9 Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. *Lancet Oncol* 2017; **18:** 1502–11.

10 Colleoni M, Luo W, Karlsson P, et al. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2018; **19:** 127–38.

11 Gnant M, Steger G, Greil R, et al. A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial. San Antonio Breast Cancer Symposium, San Antonio, TX, Dec 5–9, 2017. GS3-01 (abstr).

12 White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978; **37:** 849–57.

13 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35:** 549–56.

14 Anderson JR, High R. Alternatives to the standard Fleming, Harrington, and O'Brien futility boundary. *Clin Trials* 2011; **8:** 270–76.

15 Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. In: Dietz K, Gail M, Krickeberg K, Samet J, Tsiatis A, eds. Statistics for biology and health. Springer: New York, 2003.

16 Cox DR. Regression models and life-tables (with discussion). *J Royal Stat Society B* 1972; **34:** 187–202.

17 Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993; **80:** 557–72.

18 Kaplan EL, Meier P. Nonparametric-estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.

19 Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Hoboken: J Wiley, 2002.

20 Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol* 2007; **25:** 2127–32.

21 Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst* 2011; **103:** 1299–309.

22 Dowsett M, Sestak I, Regan MM, et al. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor-positive breast cancer treated with 5 years of endocrine therapy: CTS5. *J Clin Oncol* 2018; **36:** 1941–48.

23 Sparano JA, O'Neill A, Alpaugh K, et al. Circulating tumor cells (CTCs) five years after diagnosis are prognostic for late recurrence in operable stage II-III breast cancer. San Antonio Breast Cancer Symposium, San Antonio, TX, Dec 5–9, 2017. GS6-03 (abstr).

24 Dubsky P, Brase JC, Jakesz R, et al. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. *Br J Cancer* 2013; **109:** 2959–64.

25 Wolmark N, Mamounas EP, Baehner FL, et al. Prognostic impact of the combination of recurrence score and quantitative estrogen receptor expression (ESR1) on predicting late distant recurrence risk in estrogen receptor-positive breast cancer after 5 years of tamoxifen: results from NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-28 and B-14. *J Clin Oncol* 2016; **34:** 2350–58.

26 Sgroi DC, Sestak I, Cuzick J, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *Lancet Oncol* 2013; **14:** 1067–76.

27 Filipits M, Nielsen TO, Rudas M, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. *Clinical Cancer Res* 2014; **20:** 1298–305.

28 Blok EJ, Bastiaannet E, van den Hout WB, et al. Systematic review of the clinical and economic value of gene expression profiles for invasive early breast cancer available in Europe. *Cancer Treat Rev* 2018; **62:** 74–90.

29 Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. *J Natl Cancer Inst* 2013; **105:** 1036–42.