Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8·1 years median follow-up

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Background Postmenopausal women with hormone receptor-positive early breast cancer have persistent, long-term risk of breast-cancer recurrence and death. Therefore, trials assessing endocrine therapies for this patient population need extended follow-up. We present an update of efficacy outcomes in the Breast International Group (BIG) 1-98 study at 8·1 years median follow-up.

Methods BIG 1-98 is a randomised, phase 3, double-blind trial of postmenopausal women with hormone receptor-positive early breast cancer that compares 5 years of tamoxifen or letrozole monotherapy, or sequential treatment with 2 years of one of these drugs followed by 3 years of the other. Randomisation was done with permuted blocks, and stratified according to the two-arm or four-arm randomisation option, participating institution, and chemotherapy use. Patients, investigators, data managers, and medical reviewers were masked. The primary efficacy endpoint was disease-free survival (events were invasive breast cancer relapse, second primaries [contralateral breast and non-breast], or death without previous cancer event). Secondary endpoints were overall survival, distant recurrence-free interval (DRFI), and breast cancer-free interval (BCFI). The monotherapy comparison included patients randomly assigned to tamoxifen or letrozole for 5 years. In 2005, after a significant disease-free survival benefit was reported for letrozole as compared with tamoxifen, a protocol amendment facilitated the crossover to letrozole of patients who were still receiving tamoxifen alone; Cox models and Kaplan-Meier estimates with inverse probability of censoring weighting (IPCW) are used to account for selective crossover to letrozole of patients (n=619) in the tamoxifen arm. Comparison of sequential treatments to letrozole monotherapy included patients enrolled and randomly assigned to letrozole for 5 years, letrozole for 2 years followed by tamoxifen for 3 years, or tamoxifen for 2 years followed by letrozole for 3 years. Treatment has ended for all patients and detailed safety results for adverse events that occurred during the 5 years of treatment have been reported elsewhere. Follow-up is continuing for those enrolled in the four-arm option. BIG 1-98 is registered at clinicaltrials.gov NCT00004205.

Findings 8010 patients were included in the trial, with a median follow-up of 8·1 years (range 0–12·4). 2459 were randomly assigned to monotherapy with tamoxifen for 5 years and 2463 to monotherapy with letrozole for 5 years. In the four-arm option of the trial, 1546 were randomly assigned to letrozole for 5 years, 1548 to tamoxifen for 5 years, 1540 to letrozole for 2 years followed by tamoxifen for 3 years, and 1548 to tamoxifen for 2 years followed by letrozole for 3 years. At a median follow-up of 8·7 years from randomisation (range 0–12·4), letrozole monotherapy was significantly better than tamoxifen, whether by IPCW or intention-to-treat analysis (IPCW disease-free survival HR 0·82 [95% CI 0·74–0·92], overall survival HR 0·79 [0·69–0·90], DRFI HR 0·79 [0·68–0·92], BCFI HR 0·80 [0·70–0·92]; intention-to-treat disease-free survival HR 0·86 [0·78–0·96], overall survival HR 0·87 [0·77–0·999], DRFI HR 0·86 [0·74–0·998], BCFI HR 0·86 [0·76–0·98]). At a median follow-up of 8·0 years from randomisation (range 0–11·2) for the comparison of the sequential groups with letrozole monotherapy, there were no statistically significant differences in any of the four endpoints for either sequence. 8-year intention-to-treat estimates (each with SE ≤1·1%) for letrozole monotherapy, letrozole followed by tamoxifen, and tamoxifen followed by letrozole were 78·6%, 77·8%, 77·3% for disease-free survival; 87·5%, 87·7%, 85·9% for overall survival; 89·9%, 88·7%, 88·1% for DRFI; and 86·1%, 85·3%, 84·3% for BCFI.

Interpretation For postmenopausal women with endocrine-responsive early breast cancer, a reduction in breast cancer recurrence and mortality is obtained by letrozole monotherapy when compared with tamoxifen montherapy. Sequential treatments involving tamoxifen and letrozole do not improve outcome compared with letrozole monotherapy, but might be useful strategies when considering an individual patient's risk of recurrence and treatment tolerability.

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See Online for webappendix

Introduction

Aromatase inhibitors are now part of standard treatment for most postmenopausal women with oestrogen-receptor-positive and/or progesterone-receptor-positive early invasive breast cancer.[1] Generally, these agents, such as letrozole, are given either alone, or in sequence, before or after tamoxifen. The BIG 1-98 trial's design allowed the comparison between tamoxifen and letrozole monotherapies, and the comparison of the sequential treatments with monotherapy.[2–5] The population included has a persistent, long-term risk of breast-cancer recurrence requiring extended follow-up.[6,7] The trial was therefore designed to include updates every 2 years of the primary analyses to monitor long-term safety and efficacy. We present updated results at a median follow-up of 8·1 years (range 0–12·4), 12 years since entry of the first patient, to provide a comparison of 5 years of letrozole versus tamoxifen monotherapy, and a direct comparison of each sequential treatment with letrozole monotherapy.

Methods

Study design

BIG 1-98 is a randomised, phase 3, double-blind trial that recruited postmenopausal women with early breast cancer positive for oestrogen receptor or progesterone receptor, or both.[2–5] Primary surgery with resulting clear margins and adequate haematological, renal, and hepatic function were required. Exclusion criteria included evidence of metastatic disease and previous or concurrent cancer other than adequately treated non-invasive breast or cervical cancer, or basal-cell or squamous-cell carcinoma of the skin within 5 years before randomisation. Enrolment included patients from 148 hospitals from 27 countries in North and South America, Australia, New Zealand, Europe, and South Africa. Ethics committees and relevant health authorities of each participating institution approved the study protocol. All patients gave written informed consent. The data and safety monitoring committee received safety data twice a year throughout the trial and reviewed predefined interim and the final efficacy analyses.

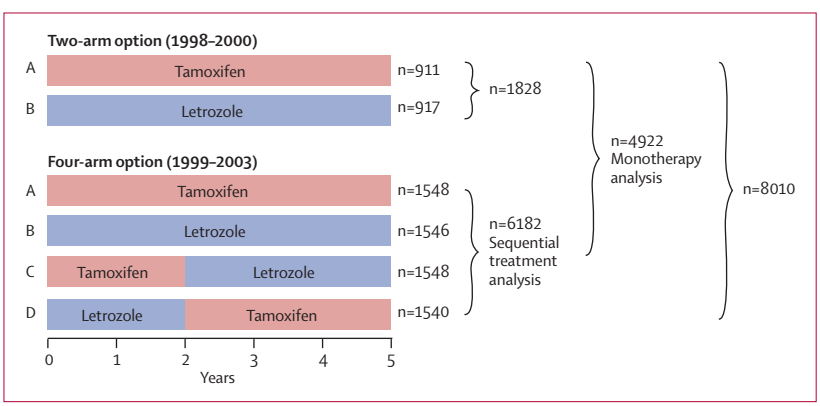

Figure 1: **Trial profile**
Of 8028 patients enrolled, 18 did not receive study treatment and withdrew consent for use of their data, leaving 8010 for the intention-to-treat population (median follow-up 8·1 years, range 0–12·4). The monotherapy analysis includes 4922 patients randomly assigned to letrozole monotherapy or tamoxifen monotherapy either as part of the two-arm or four-arm randomisation option (median follow-up 8·7 years, range 0–12·4). The sequential therapy analysis includes 6182 patients randomly assigned to one of four treatment groups as part of the four-arm randomisation option (median follow-up 8·0 years, range 0–11·2).

Randomisation and masking

Initially, from 1998 to 2000, women were randomly assigned to receive monotherapy with letrozole (Femara, Novartis, Basel, Switzerland) 2·5 mg orally daily or tamoxifen 20 mg orally daily for 5 years, and later, from 1999 to 2003, were randomly assigned to one of four groups: monotherapy with tamoxifen or letrozole for 5 years or sequential therapy consisting of letrozole for 2 years followed by tamoxifen for 3 years, or tamoxifen for 2 years followed by letrozole for 3 years (figure 1).[8] We did the randomisation centrally at the International Breast Cancer Study Group (IBCSG) randomisation centre with the use of permuted blocks, and stratified it according to the two-arm or four-arm randomisation option, participating institution, and chemotherapy use. We used the following procedure to assure concealment of the randomised assignment and masking of patients, investigators, data managers, and medical reviewers: the study drug was prepared centrally as double dummy packs containing both tamoxifen (active or placebo) and letrozole (active or placebo) tablets. Every pack included a 6-month supply of study drug and was labelled with a study drug identification number. Supplies of study drug were available at the local pharmacy of the participating site. When a patient was enrolled, the IBCSG randomisation centre provided a study drug number corresponding to the randomised treatment—either active tamoxifen or active letrozole—and the associated pack was given to the patient. Resupply was done at the subsequent 6-monthly intervals with an interactive voice recognition system to transmit a study drug identification number available in the local pharmacy corresponding to the correct treatment to be received during the next 6 months.

The 2005 results,[2] showing superiority of letrozole, led to the recommendation by the IBCSG data and safety monitoring committee, and a decision by the BIG 1-98 steering committee, to inform patients assigned to tamoxifen monotherapy of their treatment to allow informed decisions about their future care. An amendment of the protocol in April, 2005, provided letrozole treatment to any patient assigned to tamoxifen monotherapy who was disease-free, receiving or who had recently (within 6 months) stopped tamoxifen, and wishing to cross over to letrozole (selective crossover). The treatment assignment of the three letrozole-containing treatment groups remained masked.

Procedures

History taking and physical examination were done at baseline, twice a year for the first 5 years, and yearly thereafter. Haematological and blood chemical measurements and bilateral mammograms were

obtained at baseline and when medically indicated. All patients had ended study treatment by June 17, 2008, and detailed safety results for adverse events that occurred during the 5 years of treatment have been reported elsewhere.[4,5]

Endpoints

The primary study endpoint was disease-free survival, defined as the time from randomisation to the first of the following events: invasive recurrence in local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second (non-breast) primary cancer; or death without a previous cancer event. Other endpoints have been defined using STEEP criteria and include overall survival, distant recurrence-free interval (DRFI), and invasive breast cancer-free interval (BCFI).[9] The trial's primary analytic approach was intention to treat; if an event was not noted, then follow-up was censored at the date of last disease assessment.

Statistical analysis

We present two analytical populations; the monotherapy population, and the sequential treatment population (figure 1). The monotherapy population includes patients randomly assigned in the two-arm or four-arm option to receive either tamoxifen or letrozole for 5 years. The sequential treatment population includes patients randomised in the four-arm option (figure 1). The statistical design has been previously described,[8] and a CONSORT diagram is available in the webappendix (p 8).

The selective crossover to letrozole of the patients in the tamoxifen monotherapy group, after release of the primary trial results in 2005, complicates its comparison with other treatment groups in the updated analyses. Of the

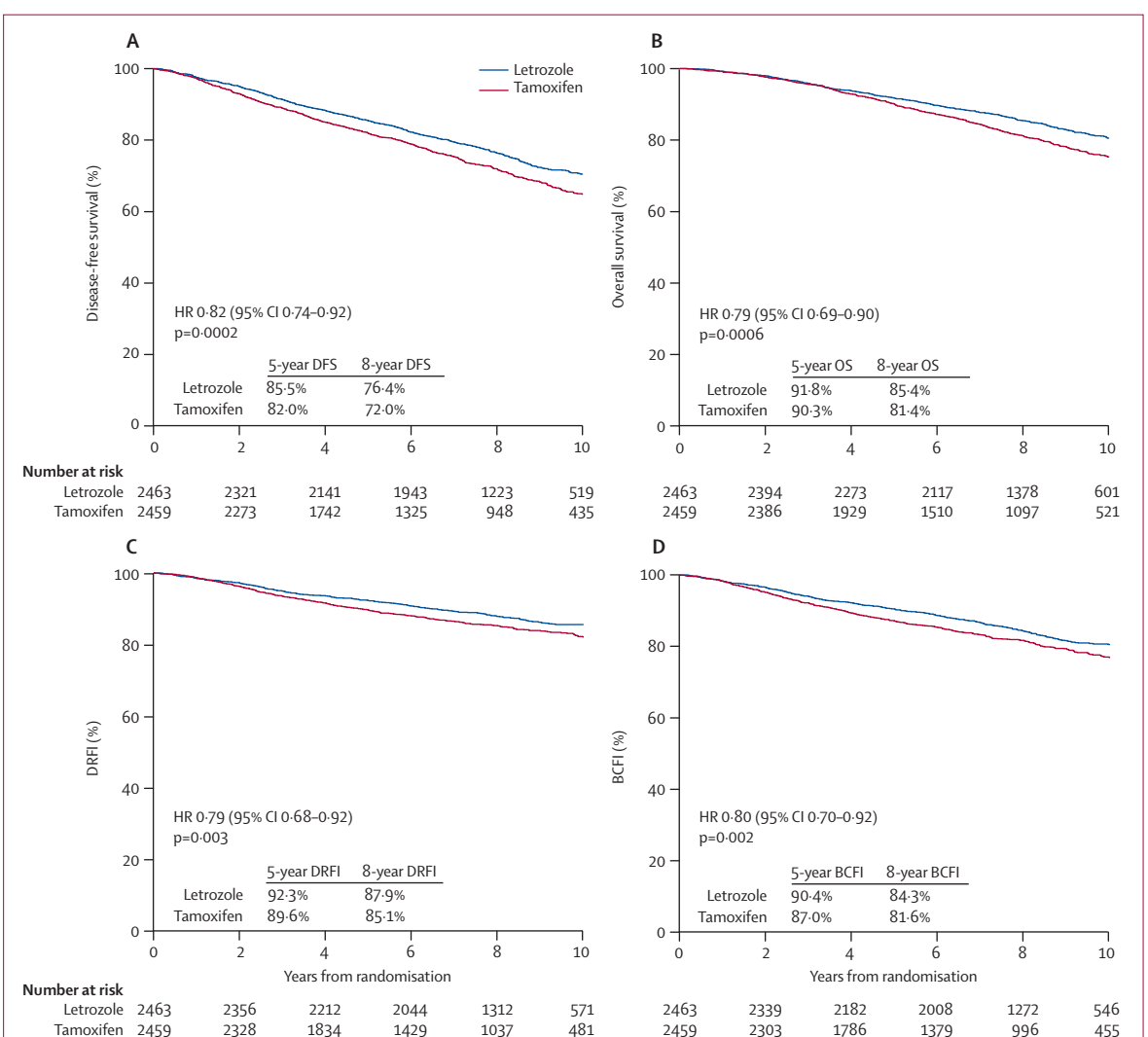

Figure 2: **Monotherapy analysis**
Inverse probability of censoring weighted Kaplan-Meier estimates of (A) disease-free survival (DFS), (B) overall survival (OS), (C) distant recurrence-free interval (DRFI), and (D) breast cancer-free interval (BCFI). Median follow-up is 8·7 years (range 0–12·4).

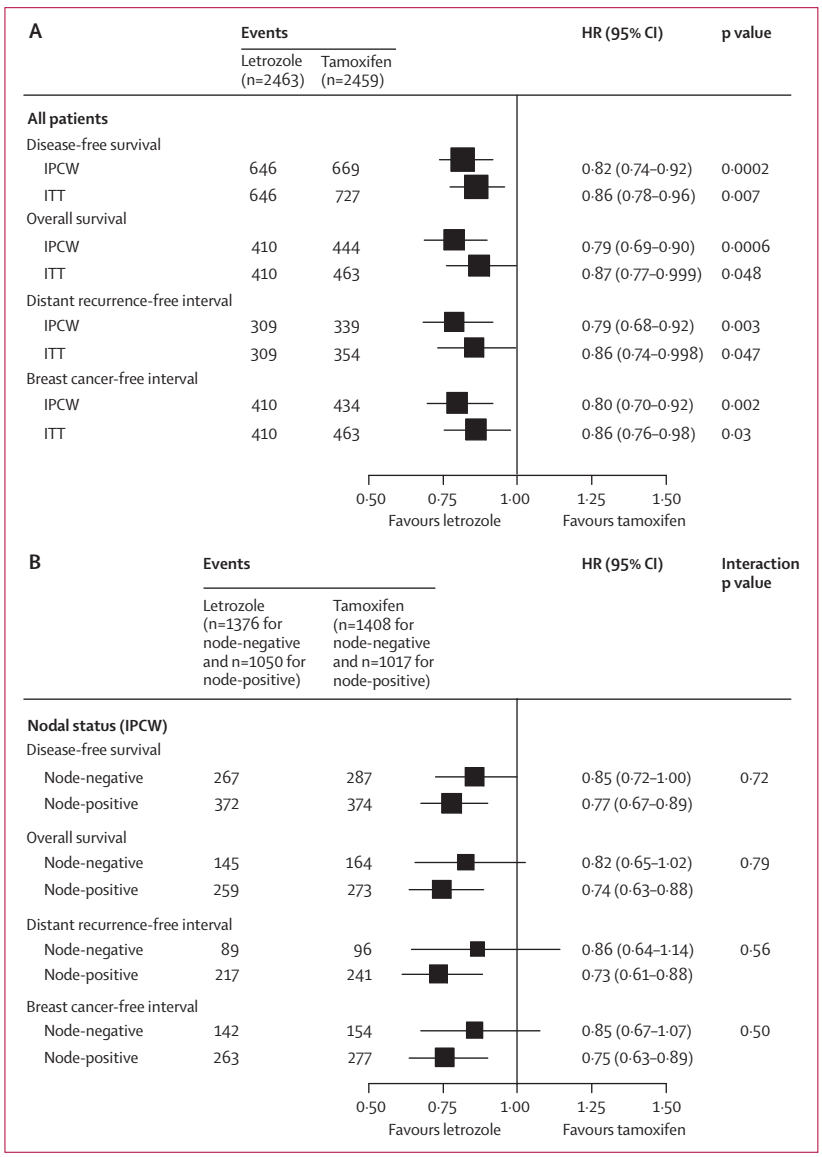

Figure 3: **Monotherapy analysis**
IPCW=inverse probability of censoring weighted. ITT=intention to treat. HRs and 95% CI comparing tamoxifen versus letrozole for four endpoints, estimated using IPCW Cox models overall and by nodal status, and estimated using unweighted Cox models to implement the ITT approach. The models were stratified by randomisation option and chemotherapy use. The size of the boxes is inversely proportional to the standard error of the HR. p values in section B refer to treatment-by-nodal-status interaction.

2459 patients assigned tamoxifen monotherapy, 619 (25%) selectively crossed over to receive letrozole before a disease-free survival event, mostly between 3 and 5 years from the start of therapy. Evidence from large, phase 3 studies has shown that patients who switched to an aromatase inhibitor after 2–3 years of tamoxifen had a survival benefit compared with patients who continued on tamoxifen for 5 years.[10] Therefore, the 25% of patients in the BIG 1-98 tamoxifen group who selectively crossed over to letrozole received a treatment known to be better than tamoxifen alone. Consequently, updated intention-to-treat analyses including tamoxifen monotherapy are likely to produce attenuated (biased) estimates of the magnitude of treatment effect. To better estimate the magnitude of the letrozole treatment effect relative to tamoxifen monotherapy had there been no selective crossover, we used inverse probability of censoring weighted (IPCW) Cox models to estimate HRs and 95% CIs.[11] IPCW modelling artificially creates a scenario of informative missing data by first censoring the follow-up of each woman at the time she crossed over, and then restoring the lost follow-up by applying weighting to the follow-up experience of women with similar characteristics who remain on tamoxifen treatment. IPCW analyses provide valid estimates, assuming no unmeasured confounders of an endpoint and selective crossover. We calculated IPCW Kaplan-Meier estimates of time-to-event distributions. For completeness, we also reported HRs, 95% CIs, and Wald χ^2 p values using unweighted Cox models to implement the intention-to-treat approach. We stratified models for the monotherapy population by randomisation option (two-arm or four-arm) and chemotherapy use; models for the sequential treatment population were stratified by chemotherapy use. We used SAS 9.2 (SAS Institute Incorporated, Cary, NC, USA).

The trial is registered with ClinicalTrials.gov, number NCT00004205.

Role of the funding source

Novartis (Basel, Switzerland), the manufacturer of letrozole, distributed the study drugs, provided financial support, and imposed no restrictions on the investigators with respect to trial data. The International Breast Cancer Study Group (IBCSG) is responsible for study design and coordination, data collection and management, medical review, data analysis, and reporting (including decision to publish). The IBCSG statistical centre had unblinded access to the database, and the IBCSG data management centre had blinded access to the database. The report was prepared by the authors, who had full access to the data and made the final decision on content. The steering committee (including a minority representation from Novartis; webappendix p 2) reviewed the manuscript and offered changes. 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

Among all 8010 patients, 2074 disease-free survival events and 1284 deaths were noted at this protocol-specified update, 12 years since trial commencement and after a median follow-up time of 8·1 years (range 0–12·4). This compares with 1569 events and 923 deaths noted at the previous 10-year update.[4] The additional 505 disease-free survival events, which were mostly recorded between 5 and 11 years from randomisation, included 279 (55%) breast cancer recurrences, 106 (21%) second non-breast malignancies, 101 (20%) deaths without previous cancer event, and 19 (4%) events that could not be reliably

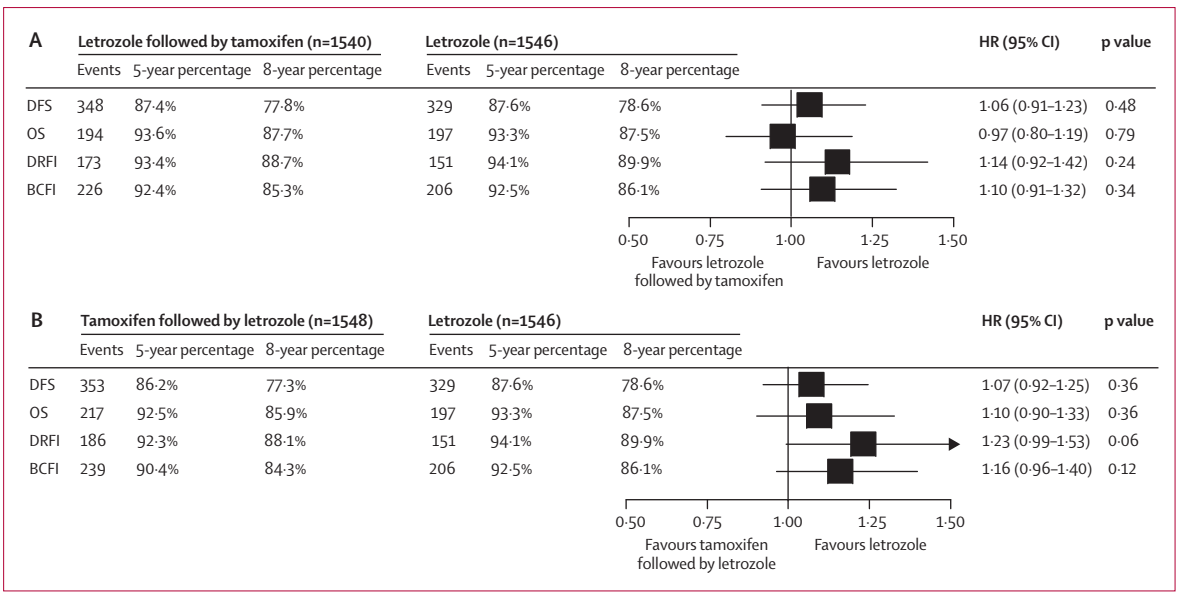

Figure 4: **Sequential treatment analysis**

DFS=disease-free survival. OS=overall survival. DRFI=distant recurrence-free interval. BCFI=breast cancer-free interval. HRs and 95% CIs comparing (A) letrozole followed by tamoxifen *vs* letrozole monotherapy, (B) tamoxifen followed by letrozole *vs* letrozole monotherapy, for the four endpoints using Cox models stratified for chemotherapy use. All analyses are by intention to treat, since the letrozole-containing regimens remained masked, and comparisons with tamoxifen alone are not shown. The size of the boxes is inversely proportional to the standard error of the HR. 5-year and 8-year estimates of endpoints were calculated with the Kaplan-Meier method, and the standard error (SE) of each estimate was ≤1·1%. The median follow-up time was 8·0 years (range 0–11·2).

classified. 5936 (74%) of 8010 patients were reported to be alive and without a disease-free survival event at their most recent follow-up. Loss to follow-up rates were low and similar across treatment groups: 260 (5%) of 4922 patients for the monotherapy analysis and 206 (3%) of 6182 patients for the sequential treatment analyses.

The monotherapy analysis cohort of 4922 patients randomly assigned to receive 5 years of tamoxifen or letrozole included 2067 (42%) with node-positive disease, 1859 (38%) with primary tumour size greater than 2 cm, 2274 (46%) who received mastectomy, and 1232 (25%) who received adjuvant or neoadjuvant chemotherapy (851 [41%] of the 2067 node-positive subgroup, 376 [14%] of the 2784 node-negative subgroup, and five [7%] of the 71 with unknown nodal status). The median age at randomisation was 61 years (range 38–90). The median follow-up for the updated analysis, which includes patients assigned to letrozole or tamoxifen monotherapy either as part of the two-arm or four-arm randomisation option, was 8·7 years (range 0–12·4). The IPCW Cox models showed a decrease in the hazard of a disease-free survival event with letrozole (HR 0·82, 95% CI 0·74–0·92; figures 2A, 3A) and a decrease in the hazard of death (HR 0·79, 0·69–0·90; figures 2B, 3A) compared with tamoxifen. There was a decrease in the hazard of a distant recurrence event with letrozole (HR 0·79, 0·68–0·92; figures 2C, 3A) and a decrease in the hazard of a breast cancer event (HR 0·80, 0·70–0·92; figures 2D, 3A). The relative treatment effects expressed as HRs were homogeneous across node-positive and node-negative subgroups (figure 3B).

The comparison of letrozole and tamoxifen monotherapies according to the intention-to-treat analysis is also shown in figure 3. The intention-to-treat analysis estimated treatment effects of smaller magnitude than the IPCW analysis, but nonetheless, also showed statistically significant improvements in disease-free survival, overall survival, DRFI, and BCFI with letrozole compared with tamoxifen (each p≤0·05). Sites of first disease-free survival event are summarised in the webappendix (p 9).

The 6182 patients randomly assigned during the four-arm option were included in the sequential treatment analysis population (figure 1). This population consisted of 2517 (41%) patients with node-positive disease, 2201 (36%) with primary tumour size greater than 2 cm, 2397 (39%) who received mastectomy, and 1586 (26%) who received adjuvant or neoadjuvant chemotherapy. The median age at randomisation was 61 years (range 38–89 years). The median follow-up for the sequential treatment analyses was 8·0 years (range 0–11·2). The sequential treatments of tamoxifen followed by letrozole and letrozole followed by tamoxifen did not significantly decrease the risk of a disease-free survival event compared with letrozole monotherapy (tamoxifen followed by letrozole HR 1·07 [95% CI 0·92–1·25]; letrozole followed by tamoxifen HR 1·06 [0·91–1·23]; figure 4). The HR for the comparison of the two sequential groups (letrozole followed by tamoxifen *vs* tamoxifen followed by letrozole) with respect to disease-free survival is 0·99 (95% CI 0·85–1·14). Figure 4 shows the estimated 8-year percentages of disease-free

	Intention to treat				Inverse probability of censoring weighted, HR (95% CI)
	Median follow-up (years)	Events	HR (95% CI)	p value	
Disease-free survival					
8-year[3]	4·3	770	0·82 (0·71–0·95)	0·007	NA
10-year[4,5]	6·3	1074	0·88 (0·78–0·99)	0·03	0·83 (0·74–0·94)
12-year	8·7	1373	0·86 (0·78–0·96)	0·007	0·82 (0·74–0·92)
Overall survival					
8-year[3]	4·3	405	0·91 (0·75–1·11)	0·35	NA
10-year[4,5]	6·3	646	0·87 (0·75–1·02)	0·08	0·82 (0·70–0·95)
12-year	8·7	873	0·87 (0·77–0·999)	0·048	0·79 (0·69–0·90)
Distant recurrence-free interval					
8-year[3]	4·3	427	0·81 (0·67–0·98)	0·03	NA
10-year[4,5]	6·3	555	0·85 (0·72–1·00)	0·05	0·80 (0·67–0·94)
12-year	8·7	663	0·86 (0·74–0·998)	0·047	0·79 (0·68–0·92)
Breast cancer-free interval					
8-year[3]	4·3	522	0·78 (0·65–0·92)	0·004	NA
10-year[4,5]	6·3	697	0·86 (0·74–0·99)	0·04	0·81 (0·70–0·94)
12-year	8·7	873	0·86 (0·76–0·98)	0·030	0·80 (0·70–0·92)

NA=not applicable. At the 8-year, 10-year, and 12-year datasets (time from randomisation of first patient), the percentages of total person-years of follow-up for the intention-to-treat tamoxifen randomised group that accumulated after selective crossover to letrozole were 0%, 7% (1040 of 14 361) and 13% (2324 of 18 208), respectively.

Table: **Monotherapy analysis: estimates of relative treatment benefit of letrozole versus tamoxifen monotherapy according to follow-up time**

survival for the three letrozole-containing regimens of the sequential treatment analysis population (webappendix p 11). Overall survival, DRFI, or BCFI did not differ for either sequence compared with letrozole monotherapy (figure 4). With 151–353 events available per treatment group depending on endpoint (figure 4), the results are underpowered to show statistical equivalence. Sites of first disease-free survival event and Kaplan-Meier estimates of the 5-year and 8-year percentages of the four endpoints (with standard errors) are summarised in the webappendix (pp 9–10).

Discussion

Although it has been 12 years since BIG 1-98 opened for accrual, disease-free survival events continue to occur in large numbers in this population of postmenopausal women with endocrine-responsive early breast cancer. The trial protocol specified that updates of the primary analyses would be done every 2 years in recognition of the prolonged, persistent hazard of breast-cancer recurrence in this population.[6] At this update, 2074 disease-free survival events were recorded in all 8010 patients, compared with 1569 at the protocol-specified update 2 years ago, a 32% increase in number of events. Statistically, these additional events during follow-up improve the precision of the treatment effect estimate for the secondary endpoints of overall survival, DRFI, and BCFI (table), and the ability to examine relative efficacy in subgroups (eg, node-positive *vs* node-negative), where the timing of the events differs. Long-term follow-up of the BIG 1-98 trial population continues, which will enable analysis of changes in patterns of events over time, including treatment-by-time interaction and carry-over effect.

The comparison of the monotherapy treatments of BIG 1-98 in this updated analysis continues to show the superiority of letrozole over tamoxifen for these patients (panel). Additionally, with more than 500 disease-free survival events recorded among the 2784 patients with node-negative disease, the updated data support that letrozole is beneficial on average in both the node-positive and the node-negative subgroups.

We presented the results using an IPCW analysis, because, compared with the intention-to-treat approach, which is known to be biased in this case, IPCW provides better estimates of the magnitude of the true treatment effect that would have been observed had there been no selective crossover.[13] Of note, the intention-to-treat analysis of the monotherapy population—which ignores the trial's provision of letrozole for a proportion of the 5 years of therapy to a quarter of the patients assigned tamoxifen—also supports letrozole as the better single-agent endocrine treatment, showing significant improvements in disease-free survival, overall survival, DRFI, and BCFI (all $p \leq 0{\cdot}05$). However, as summarised in the table, the HR for overall survival estimated by intention to treat is unchanged as compared with the previous report 2 years ago, but has narrower CIs and a p value that is now lower than the threshold of $0{\cdot}05$.

In the sequential treatment analyses, neither sequence—tamoxifen followed by letrozole nor letrozole followed by tamoxifen—showed superiority over letrozole monotherapy. As the study was not designed to test equivalence, statistical equivalence cannot be shown. Although letrozole followed by tamoxifen seemed to provide similar disease-free survival and overall survival to letrozole monotherapy (upper 95% CIs below $1{\cdot}25$), letrozole monotherapy tended to be better than tamoxifen followed by letrozole, especially for control of distant recurrence in patients at higher risk of early relapse. Therefore, overall risk and tradeoffs with respect to side-effects and other burdens will influence the preferred choice of treatment.

Whether clinical and pathological features can identify patient groups for whom it is more or less important that a 5-year programme include only or some aromatase inhibitor therapy has been described for early relapse,[14] and more recently for 5-year outcome.[15] In the recent report by Viale and colleagues,[15] we simulated the clinical approach to treatment decision-making using a synthesised assessment of risk based on multiple factors. A composite measure of prognostic risk was calculated for every patient from a Cox proportional hazards model with factors based on the 2007 St Gallen Consensus[16] (ie, number of affected lymph nodes, tumour grade, tumour size, and presence of peritumoral vascular invasion as determined by local pathology; and oestrogen receptor,

pregesterone receptor, Ki-67, and HER2 status as determined by central pathology review), plus age. The non-parametric Subpopulation Treatment Effect Pattern Plot (STEPP)[17] shows the estimates of 5-year disease-free survival for subpopulations across the continuum of risk without regard to treatment and separately by treatment (webappendix p 12).[15] As shown in the webappendix (p 12) and in the report by Viale and colleagues,[15] all four treatments had similar 5-year disease-free survival for patients at lowest risk (left end of the x-axis), the three letrozole-containing treatments had similar 5-year disease-free survival for intermediate risk (middle), whereas patients given letrozole for 5 years had better outcome for those at highest risk. The recent meta-analysis by Amir and colleagues[18] on toxic effects of adjuvant endocrine treatment for postmenopausal patients concludes that, compared with upfront aromatase inhibitor treatment given for 5 years, switching from tamoxifen to an aromatase inhibitor might offer the best balance between efficacy and toxic effects. Their analysis does not include information on the sequential treatment groups from BIG 1-98, and, particularly, does not consider the unique evidence provided by BIG 1-98 on the sequential use of upfront letrozole for 2 years followed by tamoxifen for 3 years, available in the BIG 1-98 Collaborative Group's article and appendix.[4] Upfront letrozole might be reasonable for patients at high risk for early relapse, but sequential regimens might be useful strategies for others considering treatment tolerability.

In 2005, when the first results of BIG 1-98 showed significantly improved disease-free survival for letrozole compared with tamoxifen, the BIG 1-98 steering committee, concerned for the welfare of study participants, amended the protocol to facilitate selective crossover to letrozole of patients assigned to tamoxifen. Analyses designed to provide treatment effect estimates had there been no selective crossover are not universally accepted, with some arguing that the intention-to-treat analyses, known to be substantially biased in favour of tamoxifen, are preferred. Thus, interpretation of updated comparisons of the monotherapy regimens is controversial. A median follow-up of 8 years is also too short to appreciate the full effect of the sequential regimens compared with letrozole alone and, fortunately, longer-term follow-up is continuing.

As previously reported,[4,5] patients on tamoxifen had more thromboembolic events, vaginal bleeding, hot flushes, and night sweats than did those given letrozole. Patients on letrozole had more vaginal dryness, bone fractures, osteoporosis, arthralgia or myalgia, and higher grade cardiac events than did those given tamoxifen. It is important to note that these analyses present the incidence of adverse events for one regimen (letrozole) compared with the other (tamoxifen), and it is possible that tamoxifen in particular might offer protection from cardiac or bone events. The incidences of the adverse events occurring in the sequential groups generally show results similar to the monotherapies during the time the patient was on the individual agents (ie, first 2 years or last 3 years).

The present study examined 5 years of adjuvant endocrine therapy. Patients continue to relapse after such therapy. Results from other trials have since shown the value of extended treatment with aromatase inhibitor after 5 years of tamoxifen adjuvant therapy.[19,20] The ongoing Study of Letrozole Extension (SOLE) trial[21] investigates this notion in more detail and adds the assessment of intermittent letrozole treatment as extended adjuvant therapy on the basis of promising results from pre-clinical models.[22,23]

This update of BIG 1-98 at 8·1 years median follow-up reinforces the evidence that letrozole monotherapy is better than tamoxifen in controlling breast cancer recurrence and improving survival for postmenopausal women with endocrine-responsive early breast cancer. Use of a sequence might be reasonable for patients at low-to-intermediate risk of relapse, those for whom starting or continuing letrozole is contraindicated, or in cases where 5 years of letrozole might not be available. Trials investigating endocrine treatments in hormone receptor-positive populations require an investment in

***Panel:* Research in context**

Systematic review

At the time the BIG 1-98 trial was launched in 1998, letrozole had been tested in phase 1 through phase 3 clinical trials involving more than 1200 participants. The AR/BC 2 and AR/BC 3 trials were phase 2b/3 trials for postmenopausal women with oestrogen/progesterone receptor-positive (or unknown) advanced breast cancer. These two trials established the optimal dose of letrozole at 2·5 mg, and the adverse events profile and efficacy results justified comparing letrozole to tamoxifen in the adjuvant setting. This Article presents the updated results of the BIG 1-98 trial, which was opened for accrual in 1998. BIG 1-98 was designed to compare 5 years of tamoxifen with 5 years of the aromatase inhibitor letrozole, and to compare the strategy of the sequential treatments with the monotherapy approach. These comparisons are presented in this report at 8·1 years median follow-up. At the time this trial opened, the role of aromatase inhibitors for use upfront in early breast cancer was being tested in only one other trial, the ATAC trial,[12] and no results of such therapy for this indication were available for early breast cancer. BIG 1-98 is the only trial to assess the sequence of letrozole for 2 years followed by tamoxifen for 3 years. The first results from ATAC were reported in 2002,[12] and reports of trials investigating the switching to aromatase inhibitors after 2–3 years of tamoxifen began appearing in 2003 and 2004. Thus, when BIG 1-98 was designed in 1998, one could not have predicted the highly statistically and clinically significant beneficial effects of an aromatase inhibitor compared with tamoxifen, and of switching to an aromatase inhibitor after tamoxifen compared with remaining on tamoxifen, that were reported in 2002 and later.

Interpretation

On the basis of the available evidence, aromatase inhibitor therapy should be recommended as part of adjuvant treatment for postmenopausal women with hormone receptor-positive early breast cancer. This update of BIG 1-98 shows the benefit of letrozole for 5 years compared with tamoxifen for 5 years for all endpoints studied, in both the IPCW and the intention-to-treat analyses. Neither of the sequences of letrozole and tamoxifen is better than letrozole alone, but they might represent useful strategies that can be considered on the basis of a patient's risk of recurrence, preferences, and treatment tolerability.

long-term follow-up to ensure reliable choices are made for patient care.

Contributors

MMR and AG-H participated in the data analysis and interpretation. PN and BE participated in data interpretation and acquisition of data. AG, IS, KNP, and ASC participated in trial design and data interpretation. LM, JFF, and BT participated in trial design, data interpretation, and acquisition of data. IL and AW participated in acquisition of data. MR participated in the medical review of data and data interpretation. RDG participated in the trial design and data analysis and interpretation. All authors participated in the writing and revision of the report and gave final approval for publication.

Conflicts of interest

AW had a consultant or advisory role for Novartis and BE had a consultant or advisory role for Pfizer. BT own stocks for Novartis. JFF has received honoraria from AstraZeneca; AW has received honoraria from Novartis. AG has received honoraria from Novartis and Pfizer. BT has received honoraria from AstraZeneca, Novartis. RDG has received research funding from Novartis; BE has received research funding from Novartis. AC has received travel grants from Roche and Takeda. All other authors declared no conflicts of interest.

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