Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background In animal models of breast cancer, resistance to continuous use of letrozole can be reversed by withdrawal and reintroduction of letrozole. We therefore hypothesised that extended intermittent use of adjuvant letrozole would improve breast cancer outcome compared with continuous use of letrozole in postmenopausal women.

Methods We did the multicentre, open-label, randomised, parallel, phase 3 SOLE trial in 240 centres (academic, primary, secondary, and tertiary care centres) in 22 countries. We enrolled postmenopausal women of any age with hormone receptor-positive, lymph node-positive, and operable breast cancer for which they had undergone local treatment (surgery with or without radiotherapy) and had completed 4–6 years of adjuvant endocrine therapy. They had to be clinically free of breast cancer at enrolment and without evidence of recurrent disease at any time before randomisation. We randomly assigned women (1:1) to treatment groups of either continuous use of letrozole (2·5 mg/day orally for 5 years) or intermittent use of letrozole (2·5 mg/day orally for 9 months followed by a 3-month break in years 1–4 and then 2·5 mg/day during all 12 months of year 5). Randomisation was done by principal investigators or designee at respective centres through the internet-based system of the International Breast Cancer Study Group, was stratified by type of previous endocrine therapy (aromatase inhibitors only *vs* selective oestrogen receptor modulators only *vs* both therapies), and used permuted block sizes of four and institutional balancing. No one was masked to treatment assignment. The primary endpoint was disease-free survival, analysed by the intention-to-treat principle using a stratified log-rank test. All patients in the intention-to-treat population who initiated protocol treatment during their period of trial participation were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT00553410, and EudraCT, number 2007-001370-88; and long-term follow-up of patients is ongoing.

Findings Between Dec 5, 2007, and Oct 8, 2012, 4884 women were enrolled and randomised after exclusion of patients at a non-adherent centre, found to have inadequate documentation of informed consent, immediately withdrew consent, or randomly assigned to intervention groups in error. 4851 women comprised the intention-to-treat population that compared extended intermittent letrozole use (n=2425) with continuous letrozole use (n=2426). After a median follow-up of 60 months (IQR 53–72), disease-free survival was 85·8% (95% CI 84·2–87·2) in the intermittent letrozole group compared with 87·5% (86·0–88·8) in the continuous letrozole group (hazard ratio 1·08, 95% CI 0·93–1·26; p=0·31). Adverse events were reported as expected and were similar between the two groups. The most common grade 3–5 adverse events were hypertension (584 [24%] of 2417 in the intermittent letrozole group *vs* 517 [21%] of 2411 in the continuous letrozole group) and arthralgia (136 [6%] *vs* 151 [6%]). 54 patients (24 [1%] in the intermittent letrozole group and 30 [1%] in the continuous letrozole group) had grade 3–5 CNS cerebrovascular ischaemia, 16 (nine [<1%] *vs* seven [<1%]) had grade 3–5 CNS haemorrhage, and 40 (19 [1%] *vs* 21 [1%]) had grade 3–5 cardiac ischaemia. In total, 23 (<1%) of 4851 patients died while on trial treatment (13 [<1%] of 2417 patients in the intermittent letrozole group *vs* ten [<1%] of 2411 in the continuous letrozole group).

Interpretation In postmenopausal women with hormone receptor-positive breast cancer, extended use of intermittent letrozole did not improve disease-free survival compared with continuous use of letrozole. An alternative schedule of extended adjuvant endocrine therapy with letrozole, including intermittent administration, might be feasible and the results of the SOLE trial support the safety of temporary treatment breaks in selected patients who might require them.

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Introduction

Adjuvant extended endocrine therapy with the aromatase inhibitor letrozole after 5 years of tamoxifen has been endorsed for postmenopausal women with hormone receptor-positive (oestrogen receptor-positive, progesterone receptor-positive, or both) breast cancer.[1,2] However, the magnitude of the beneficial effect of 5 years of extended letrozole use in postmenopausal women who have

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Research in context

Evidence before this study

We did a systematic literature database search on PubMed using the terms "adjuvant", "breast cancer", "clinical trial", "extended", "postmenopausal", and "letrozole" without any language restriction at the time the protocol was finalised on July 6, 2007. Only one phase 3 study of extended adjuvant letrozole in this patient population was identified. This study showed improved disease-free survival for 5 years of letrozole therapy in women who have completed 5 years of tamoxifen therapy. We repeated the same literature search on June 13, 2017. Three additional phase 3 studies were identified. One study reported improved disease-free survival for letrozole administered for 10 years. The second study, not yet published, did not show a significant improvement in disease-free survival for patients who had completed 5 years of adjuvant endocrine therapy and received 5 years of extended letrozole. The results of a third trial were presented but not yet published, showing no clear advantage for 5 years of extended letrozole compared with a shorter duration of extended treatment. On the basis of the results of these trials, adjuvant extended endocrine therapy with 5 years of letrozole seemed to be a feasible treatment option for postmenopausal women with hormone receptor-positive (oestrogen receptor-positive or progesterone receptor-positive, or both) breast cancer at intermediate or high risk of relapse.

Added value of this study

To our knowledge, the SOLE trial is the first to directly compare extended intermittent letrozole use with extended continuous letrozole use. We showed that in postmenopausal women with hormone receptor-positive breast cancer, extended use of intermittent letrozole is feasible, and represents a possible option in selected patients who could benefit from temporary treatment breaks—namely, those who have side-effects during extended endocrine treatment.

Implications of all the available evidence

The magnitude of the beneficial effect of extended letrozole use in postmenopausal women who previously received an aromatase inhibitor during the first 5 years is low and should be weighed against the side-effects. The results of the SOLE trial support additional treatment options of extended adjuvant letrozole. The intermittent administration of extended adjuvant letrozole is an attractive approach considering potentials for reduced economic cost and improved quality of life. Continued follow-up to further investigate the value of intermittent extended letrozole in subgroups defined by previous adjuvant endocrine therapy is ongoing.

previously received an aromatase inhibitor for 5 years is low. One study[3] reported improved disease-free survival with 5 years of extended letrozole, supporting the use of an aromatase inhibitor for 10 years, whereas another study[4] reported no significant improvement in disease-free survival for patients who had already completed 5 years of adjuvant endocrine therapy with either tamoxifen or an aromatase inhibitor. On the basis of available data, recent treatment recommendations suggest the use of an aromatase inhibitor for 10 years be discussed on a personalised basis.[5]

Evidence from animal models suggests that resistance to letrozole can be reversed by discontinuing treatment, supporting an alternating on–off letrozole treatment as a strategy to prolong sensitivity to the endocrine treatment.[6] This effect might be related to the capacity of oestradiol to induce programmed cell death in breast cancer cells that have developed resistance following extensive anti-hormonal therapy. In particular, cells that are deprived of oestrogen for several years initially start to grow spontaneously in cellular models.[7] Even minimal concentrations of oestrogen, similar to those achievable through interruptions of treatment with aromatase inhibitors, produce a cytocidal effect on these cells that are exhaustively deprived of oestrogen.[7–9]

In 2007, the International Breast Cancer Study Group (IBCSG) started a randomised, phase 3 trial—the Study of Letrozole Extension (SOLE)—for postmenopausal women with node-positive, hormone receptor-positive, early breast cancer who remained free of relapse after 4–6 years of adjuvant endocrine therapy. On the basis of findings from preclinical studies, the trial was designed to evaluate whether extended intermittent use of adjuvant letrozole improves disease-free survival versus continuous use of letrozole. In this paper, we report the results of this primary analysis.

Methods

Study design and participants

We did a multicentre, open-label, randomised, parallel, phase 3 trial in 240 centres (academic, primary, secondary, and tertiary care centres) of the Breast International Group-affiliated cooperative groups in 22 countries (appendix p 8). Women of any age were eligible for the trial as long as they were postmenopausal. Postmenopausal status was defined as meeting the following criteria: women of any age who had had a bilateral oophorectomy (including radiation castration confirmed by subsequent amenorrhoea for longer than 3 months) and were amenorrhoeic for longer than 3 months; those aged 55 years or younger with biochemical evidence of definite postmenopausal status (oestradiol, follicle-stimulating hormone, and luteinising hormone in the postmenopausal range); and those aged 56 years or older who, if they had any evidence of ovarian function, had to have the same biochemical evidence of definite postmenopausal status. Eligible women must have previously

had unilateral, lymph node-positive, steroid hormone receptor-positive (oestrogen receptor-positive, progesterone receptor-positive, or both) operable breast cancer, for which they had undergone local treatment (surgery with or without radiotherapy) with no known clinical residual locoregional disease. They had to be clinically free of breast cancer at enrolment without evidence of recurrent disease at any time before randomisation, could have any Eastern Cooperative Oncology Group performance status score, and had to have completed 4–6 years of previous adjuvant endocrine therapy with aromatase inhibitors, selective oestrogen receptor modulators (SERMs), or a sequential combination of both within the past year. Patients were eligible if they had received any type of previous adjuvant therapy and were allowed to have been on bisphosphonates for treatment of bone loss, but those who had a bone fracture due to osteoporosis at any time during previous endocrine therapy were not eligible. Patients also had to have clinically adequate hepatic function and could not have had previous bilateral breast cancer or a previous or concomitant malignancy. We also excluded patients with non-malignant systemic diseases (eg, cardiovascular disease) that would prevent long-term follow-up and those with psychiatric disorders that could compromise protocol compliance.

Ethics committees and appropriate national health authorities from each centre approved the protocol, and all patients provided written informed consent. The trial protocol is available online.

Randomisation and masking

Patients were randomly assigned (1:1) to unmasked treatment groups of either continuous letrozole or intermittent letrozole, and this sequence was generated centrally by the randomisation office of the Frontier Science & Technology Research Foundation at the IBCSG Data Management Center (Amherst, NY, USA). Randomisation was done with permuted blocks sizes of four and institutional balancing, and was stratified by previous adjuvant endocrine therapy (aromatase inhibitors only *vs* SERMs only *vs* both aromatase inhibitors and SERMs). The participating centres' principal investigator and authorised co-investigators enrolled patients, and the principal investigator or designee (which might have been a cooperative group representative) accessed the IBCSG's internet-based randomisation system to register patients to obtain the treatment assignment. In this trial, no-one was masked to treatment assignment.

Procedures

Before patients were randomly assigned, in order to verify their disease-free status, haematology and blood chemistry tests within 2 months of randomisation, bilateral mammography within 1 year of randomisation, and chest x-ray before randomisation (no specified timepoint) were recommended, and bone scan was to be done at baseline if clinically indicated. After randomisation, patients either received continuous letrozole (2·5 mg/day orally for 5 years) or intermittent letrozole (2·5 mg/day orally during the first 9 months of years 1–4, followed by a 3-month break in each of these years, and then 2·5 mg/day during all 12 months of year 5). All patients completed treatment at 60 months from randomisation. Dose reductions were not permitted. Treatment compliance was assessed by case report forms, which collected the dates of beginning and end of all letrozole interruptions that lasted more than 1 month in duration.

We assessed patients for their disease status every 6 months during years 1–5, and annually thereafter with physical examinations, haematology and blood chemistry tests, and imaging as medically indicated at each study visit during treatment. Additionally, we systematically queried for 14 targeted adverse events using the National Cancer Institute Common Terminology Criteria for adverse events (version 3.0) at each study visit during treatment. In the subset of patients enrolled in the prospectively defined quality-of-life substudy, the quality-of-life assessments, which included the 18-item Breast Cancer Prevention Trial Symptom Scales[10] and nine further symptom-specific and global quality-of-life indicators,[11,12] were done at baseline and at 6, 12, 18, and 24 months after randomisation (appendix p 7). All patients continued in the study until they withdrew consent, were lost to follow-up, or died.

Outcomes

The primary endpoint was disease-free survival defined as the time from randomisation to the first appearance of one of the following investigator-assessed events: invasive recurrence of breast cancer (local, regional, or distant), invasive contralateral breast cancer, second non-breast invasive cancer, or death without recurrence or second cancer; and each reported event was centrally reviewed by the IBCSG Medical Affairs. Secondary endpoints were breast cancer-free interval, defined as the time from randomisation to the recurrence of invasive breast cancer (local, regional, or distant) or invasive contralateral breast cancer; distant recurrence-free interval, defined as the time from randomisation to the recurrence of breast cancer at a distant site (in the statistical analysis plan, this endpoint replaced distant disease-free survival for consistency with the standardised definitions for time-to-event efficacy endpoints [STEEP] criteria[13]); overall survival, defined as time from randomisation to death from any cause; sites of first disease-free survival event; second (non-breast) malignancies; deaths without prior cancer event; and assessment of adverse events. For patients who did not have an endpoint event for breast cancer-free or distant recurrence-free interval, the times were censored at the date of the last follow-up visit or date of death without an endpoint event. For the analysis of overall survival, the endpoint was censored at the date at which the patient

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See **Online** for appendix

For the **trial protocol** see http://www.ibcsg.org/public/documents/forjournals/ibcsg_35-07/35-07_protocol.pdf

was last known to be alive. Finally, the trial included a prospectively defined quality-of-life substudy.

Statistical analysis

The 4-year disease-free survival was assumed to be 90% in the continuous letrozole group on the basis of the 91·8% disease-free survival in the node-positive subgroup of the MA.17 trial of extended letrozole adjuvant treatment in patients with hormone receptor-positive breast cancer.[14] The MA.17 disease-free survival estimate of 91·8% was adjusted downwards to account for differences in events defining disease-free survival between the two trials (MA.17 included only breast cancer recurrence and contralateral breast cancer as events, whereas SOLE also included invasive second non-breast malignancies and deaths without cancer as events). The sample size was determined to provide 80% power to detect a 20% reduction in the risk of a disease-free survival event associated with intermittent letrozole use compared with continuous letrozole use (hazard ratio [HR] 0·80) using a two-sided 0·05 level significance test. A group sequential design was used, with two interim analyses (at approximately 40% and 70% events) and the primary analysis targeting 647 disease-free survival events. At each interim analysis and at the primary analysis, testing was done with O'Brien-Fleming boundaries and reviewed by the IBCSG Data and Safety Monitoring Committee. Enrolment of 4800 patients was planned (1600 patients per year for 3 years), with approximately 5 years of additional follow-up and assuming 5% dropout by 4 years.

Analyses were performed by the intention-to-treat principle after the exclusion of patients who were enrolled at a non-adherent centre, found to have inadequate documentation of informed consent, immediately withdrew consent, or randomly assigned to intervention groups in error. Kaplan-Meier estimates of time-to-event endpoints were calculated, using Greenwood's formula for standard errors, and pointwise 95% CIs were obtained with use of complementary log-log transformation of the survivor function. The log-rank test and Cox proportional hazards regression, stratified according to previous adjuvant endocrine therapy, were used for hypothesis testing and to estimate HRs with 95% CIs.

In prespecified secondary endpoint analyses, a multivariable model adjusting for patient, disease and treatment factors (age and body-mass index at randomisation; tumour size and grade; number of positive lymph nodes; oestrogen receptor, progesterone receptor, and HER2 status of the primary tumour; type of previous endocrine therapy; duration of previous endocrine therapy; and the time since the cessation of previous endocrine therapy), and heterogeneity of the treatment effect according to subgroups was investigated by tests of treatment-by-covariate interaction of the same factors. These methods that did not account for competing risks were used for breast cancer-free interval and distant recurrence-free interval because the proportion of competing events (ie, deaths without a previous cancer event) was anticipated to be small.

All patients in the intention-to-treat population who initiated protocol treatment during their period of trial participation were included in the safety analyses. Adverse events are reported as the maximum grade recorded during the treatment period, with 95% exact binomial CIs for the adverse events. Quality-of-life scores were first transformed so that each score ranged from 0 to 100, with higher numbers reflecting a better condition, and were then quantified as the change from baseline. This analysis used mixed-effects regression modelling of all timepoints and contrasted the two treatment groups at 12 months and 24 months. The sample size for the quality-of-life substudy was estimated on the basis of a between-group comparison of the change from baseline to 12 months in the hot flushes or flashes scale, estimating that 676 patients were needed to achieve 90% power to detect an effect size of 0·25 between the two groups on the basis of a two-sided 0·05 level *t* test. Additional information about the SOLE quality-of-life substudy is included in the appendix (p 7).

We used SAS (version 9.4) with SAS/STAT (version 14.1) for statistical analyses. This study is registered with

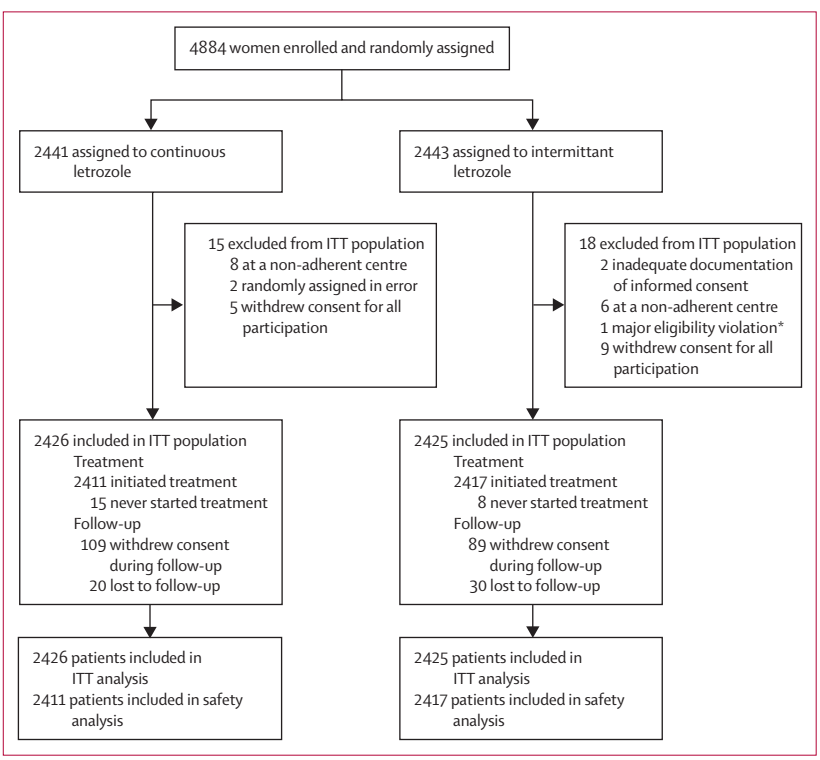


Figure 1: **Trial profile**
For 93 (38%) of the 248 patients who withdrew consent or were lost to follow-up, continued submission of disease recurrence and survival status from medical records or updates were obtained from tumour and vital registries according to the protocol follow-up schedule. ITT=intention to treat. *Treatment with letrozole was inappropriate for this patient because of major eligibility violation; patient received less than 1 month of treatment when the issue was identified, and protocol treatment and participation were stopped at that time.

ClinicalTrials.gov, number NCT00553410, and EudraCT, number 2007-001370-88.

Role of the funding source

IBCSG was responsible for the study design, randomisation, collection and management of data, medical review, data analyses, and reporting of data. The IBCSG Data and Safety Monitoring Committee did reviews twice per year. Novartis, the manufacturer of letrozole, donated the study drug and provided financial support but did not impose restrictions on the trial data. MC, WL, and MMR had full access to all the data. The steering committee, which included employees of Novartis, reviewed and approved the manuscript content. The corresponding author had final responsibility to submit for publication.

Results

Between Dec 5, 2007, and Oct 8, 2012, we randomly assigned 4884 postmenopausal women to receive continuous letrozole (n=2441) or intermittent letrozole (n=2443; figure 1). The population analysed by the intention-to-treat principle included 4851 women (2426 in the continuous letrozole group and 2425 in the intermittent group) after exclusion of 33 women after randomisation (15 from the continuous letrozole group and 18 from the intermittent letrozole group; figure 1). Baseline patient

	Continuous letrozole (n=2426)	Intermittent letrozole (n=2425)
Age at randomisation (years)		
<55	688 (28%)	671 (28%)
55–59	504 (21%)	496 (20%)
60–64	451 (19%)	471 (19%)
65–69	400 (16%)	375 (15%)
≥70	383 (16%)	412 (17%)
Median age (IQR)	60 (54–67)	60 (54–67)
Race		
White	2199 (91%)	2211 (91%)
Black	10 (<1%)	9 (<1%)
Asian	119 (5%)	121 (5%)
Other	97 (4%)	83 (3%)
Unknown	1 (<1%)	1 (<1%)
Body-mass index at randomisation		
Normal (<25 kg/m²)	853 (35%)	922 (38%)
Overweight (25 to <30 kg/m²)	886 (37%)	805 (33%)
Obese (≥30 kg/m²)	574 (24%)	572 (24%)
Unknown	113 (5%)	126 (5%)
Menopausal status at diagnosis		
Premenopausal	470 (19%)	477 (20%)
Perimenopausal	90 (4%)	87 (4%)
Postmenopausal	1859 (77%)	1849 (76%)
Unknown	7 (<1%)	12 (<1%)
Number of positive lymph nodes		
0	24 (1%)	31 (1%)
1–3	1609 (66%)	1599 (66%)
4–9	536 (22%)	571 (24%)
≥10	254 (10%)	222 (9%)
Unknown	3 (<1%)	2 (<1%)
Tumour grade		
1	441 (18%)	483 (20%)
2	1270 (52%)	1265 (52%)
3	606 (25%)	567 (23%)
Unknown	109 (4%)	110 (5%)
Tumour size		
≤2 cm	1141 (47%)	1154 (48%)
>2 cm	1272 (52%)	1262 (52%)
Unknown	13 (1%)	9 (<1%)
(Table 1 continues in next column)		
(Continued from previous column)		
HER2 status		
Negative	1805 (74%)	1842 (76%)
Positive	441 (18%)	371 (15%)
Unknown HER2 status or HER2 test not done	180 (7%)	212 (9%)
Hormone receptor status		
ER-positive and PgR-positive	1889 (78%)	1854 (76%)
ER-positive and PgR-negative	416 (17%)	439 (18%)
ER-positive and PgR-unknown	72 (3%)	80 (3%)
ER-negative and PgR-positive	47 (2%)	51 (2%)
Other or unknown	2 (<1%)	1 (<1%)
Previous chemotherapy		
No	451 (19%)	476 (20%)
Yes	1974 (81%)	1949 (80%)
Unknown	1 (<1%)	0
Local therapy		
Mastectomy with radiotherapy	830 (34%)	794 (33%)
Mastectomy without radiotherapy	329 (14%)	359 (15%)
Breast-conserving surgery with radiotherapy	1243 (51%)	1250 (52%)
Other	24 (1%)	22 (1%)
Previous endocrine therapy		
SERMs only	435 (18%)	438 (18%)
SERMs and AIs	977 (40%)	979 (40%)
AIs only	1014 (42%)	1008 (42%)
Duration of previous endocrine therapy		
<4·5 years	412 (17%)	400 (16%)
4·5–5·5 years	1790 (74%)	1809 (75%)
>5·5 years	222 (9%)	215 (9%)
Unknown	2 (<1%)	1 (<1%)
Time from end of previous endocrine therapy to randomisation		
≤1 month	1747 (72%)	1702 (70%)
>1 month	679 (28%)	723 (30%)

Data are n (%), unless otherwise specified. ER=oestrogen receptor. PgR=progesterone receptor. SERMs=selective oestrogen receptor modulators. AIs=aromatase inhibitors.

Table 1: **Baseline characteristics**

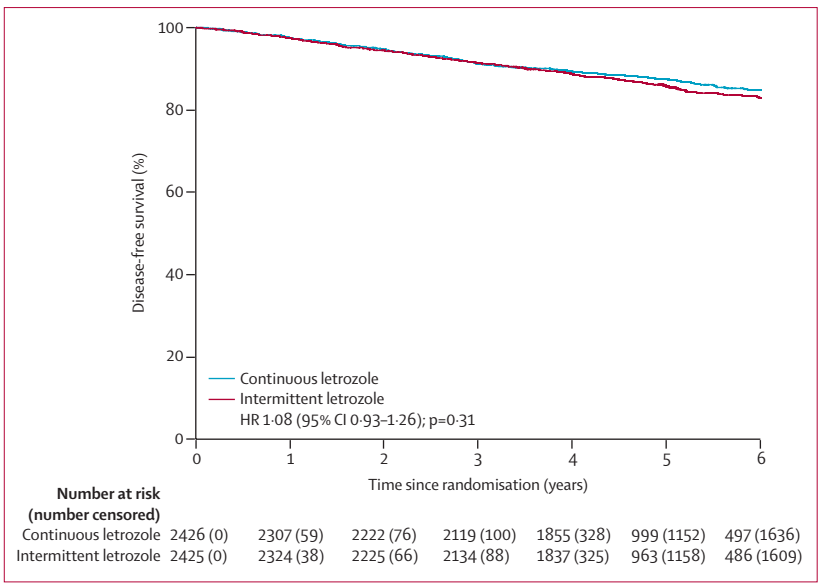


Figure 2: **Disease-free survival after median follow-up of 60 months**
HR=hazard ratio.

characteristics were well balanced between the two groups (table 1). Median age at randomisation was 60 years (IQR 54–67) in both groups (table 1). Before randomisation, a total of 2022 (42%) of 4851 patients had received aromatase inhibitors only and 873 (18%) had received SERMs only. Overall median duration of previous endocrine therapy for both groups was 5·0 years (IQR 4·7–5·1).

The visit cutoff date was Oct 31, 2016, and the database lock date for analysis was Feb 8, 2017. After a median follow-up of 60 months (IQR 53–72), disease-free survival events were reported in 665 (14%) of 4851 patients overall (346 [14%] of 2425 patients in the intermittent letrozole group and 319 [13%] of 2426 in the continuous letrozole group). Disease-free survival did not differ between the groups: the estimated 5-year disease-free survival was 85·8% (95% CI 84·2–87·2) in the intermittent letrozole group versus 87·5% (86·0–88·8) in the continuous letrozole group (HR 1·08, 95% CI 0·93–1·26; p=0·31; figure 2). The sites of disease-free survival events did not differ substantially between the groups; a full breakdown of event sites by treatment group is in the appendix (p 9). Distant sites were involved for 318 (7%) of 4851 patients, and 169 (4%) patients had second non-breast invasive malignancies (appendix p 9); in total, 239 (36%) of 665 disease-free survival events were not related to breast cancer.

Planned subgroup analyses did not indicate heterogeneity of treatment effect on disease-free survival across patient subgroups according to type of previous endocrine therapy (figure 3A), or by age at randomisation; body-mass index; tumour size; tumour grade; oestrogen receptor, progesterone receptor, and HER2 status of the primary tumour; number of positive lymph nodes; duration of previous endocrine therapy; and time since the cessation of previous endocrine therapy (appendix pp 10, 11). A multivariable model adjusting for the same factors provided a result consistent with the primary analysis of disease-free survival, showing no significant difference in disease-free survival between the treatment groups (HR 1·07, 95% CI 0·92–1·25). Further exploratory and data-driven analyses of subgroups are beyond the scope of this primary report of the trial and, therefore, are not reported.

Similar to the results for the primary efficacy endpoint, none of the secondary efficacy endpoints differed significantly between the two treatment groups (figure 3). Breast cancer events were reported in 431 (9%) of 4851 patients (214 [9%] of 2425 patients in the intermittent letrozole group and 217 [9%] of 2426 in the continuous letrozole group), and did not differ significantly between the two groups (HR 0·98, 95% CI 0·81–1·18; p=0·84). The estimated proportion of patients free from breast cancer at 5 years was 90·9% (95% CI 89·6–92·1) in patients in the intermittent letrozole group compared with 91·2% (89·9–92·3) in those in the continuous letrozole group (figure 4A). Distant recurrence was reported in 338 (7%) of 4851 patients (159 [7%] of 2425 in the intermittent letrozole group and 179 [7%] of 2426 in the continuous letrozole group) and did not differ significantly between the groups (HR 0·88, 95% CI 0·71–1·09; p=0·25). The estimated proportion of patients free from distant recurrence at 5 years was 93·2% (95% CI 92·0–94·2) in the intermittent letrozole group versus 92·5% (91·3–93·5) in those given continuous letrozole (figure 4B).

At data cutoff, 316 (7%) of 4851 patients had died (146 [6%] of 2425 in the intermittent letrozole group and 170 [7%] of 2426 in the continuous letrozole group; figure 3D): 198 deaths occurred after a breast cancer event (83 *vs* 115), 49 occurred after a second non-breast malignancy (24 *vs* 25), 55 were confirmed without a previous cancer event (33 *vs* 22), and 14 occurred with incomplete knowledge of breast cancer recurrence status (6 *vs* 8). Overall survival did not differ significantly between the treatment groups (HR 0·85, 95% CI 0·68–1·06; p=0·16); etimated 5-year overall survival was 94·3% (95% CI 93·2–95·2) in the intermittent letrozole group versus 93·7% (92·6–94·7) in the continuous letrozole group (figure 4C). Subgroup analyses for breast cancer-free interval, distant recurrence-free interval, and overall survival for heterogeneity of treatment effect according to type of previous endocrine therapy are shown in figure 3.

23 (<1%) of 4851 patients never started their assigned treatment and 3390 (70%) had stopped treatment at the time of analysis, with similar patterns of permanent treatment discontinuation in the two treatment groups (appendix p 12). The reasons for early discontinuation were indicated as adverse events or side-effects for 706 (15%) of 4851 patients (333 [14%] of 2425 in the

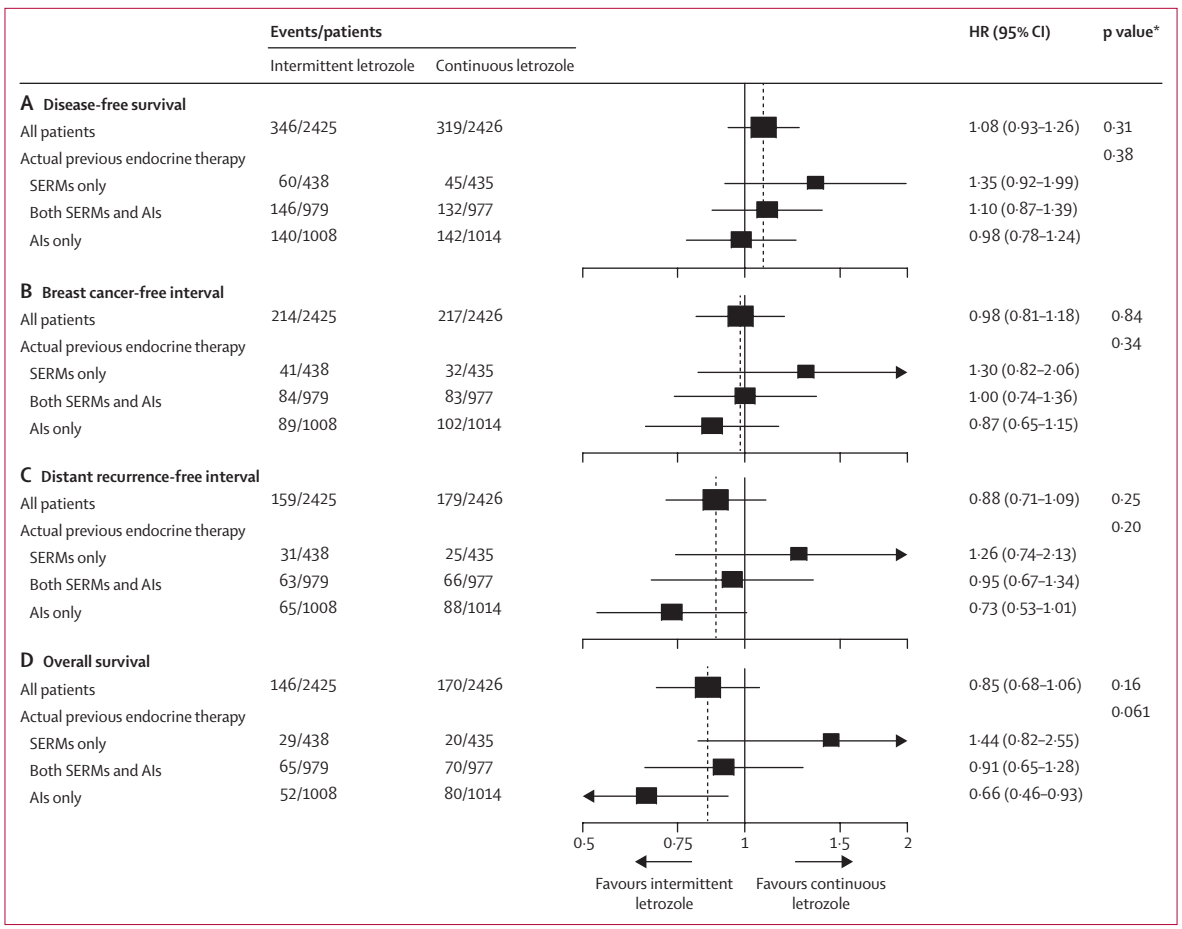
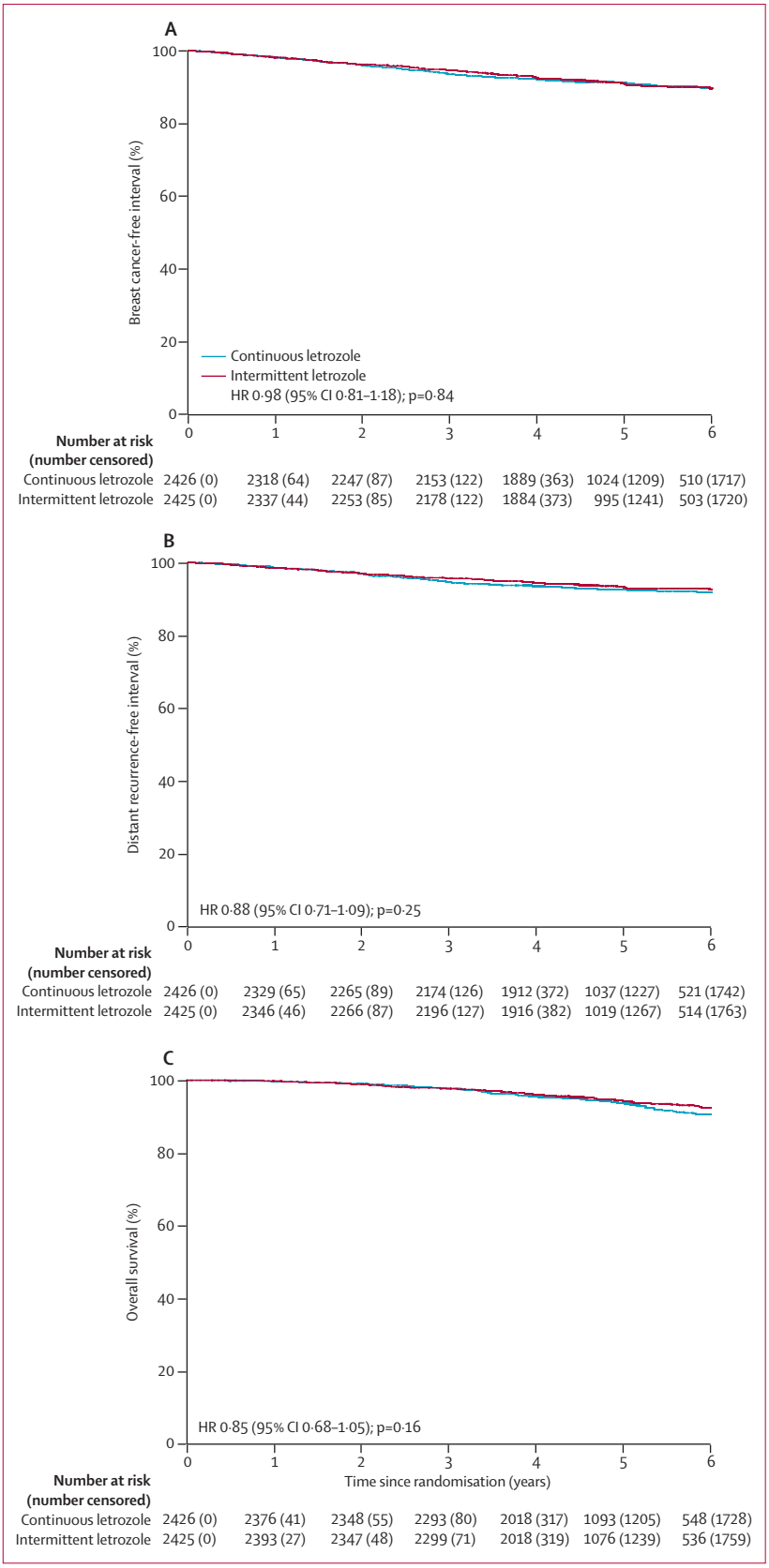


Figure 3: **Primary and secondary efficacy endpoints, in all patients and by type of previous endocrine therapy**
Cox proportional-hazards models were used for the comparisons of (A) disease-free survival, (B) breast cancer-free interval, (C) distant recurrence-free interval, and (D) overall survival, according to type of previous endocrine therapy. The vertical dashed lines represent the overall HR estimate for each endpoint. The size of the squares is inversely proportional to the standard error of the HR. HR=hazard ratio. SERMS=selective oestrogen receptor modulators. AIs=aromatase inhibitors. *The p values for the comparisons in all patients were from stratified log-rank tests; the p values for the assessment of treatment-effect heterogeneity were from tests of treatment by previous endocrine therapy interaction.

intermittent letrozole group *vs* 373 [15%] of 2426 in the continuous letrozole group) and as patient's decision for 327 (7%) patients (173 [7%] *vs* 154 [6%]). In patients assigned to intermittent letrozole who initiated treatment, 2020 (84%) of 2417 patients interrupted letrozole use during year 1, 1877 (89%) of 2115 interrupted letrozole use in year 2, 1747 (89%) of 1955 interrupted letrozole use in year 3, and 1599 (87%) of 1831 interrupted letrozole use in year 4 according to protocol (ie, every 9 months [within a month of either side] since randomisation, with discontinuation lasting for 3 months [within 0·5 months of this duration]; the denominator is the number of patients on protocol treatment at the beginning of the respective year). At the end of each scheduled interruption, 1981 (98%) of 2020 in year 1, 1827 (97%) of 1877 in year 2, 1693 (97) of 1747 in year 3, and 1460 (91%) of 1599 in year 4 resumed treatment according to protocol. Non-protocol interruptions were similar in the two groups (appendix pp 12, 13).

The profile of adverse events was as expected for letrozole and was similar between the two groups. Targeted adverse events of grade 3 or worse, as characterised by the worst grade during the 5-year treatment period, were reported for 876 (36·2%; 95% CI 34·3–38·2) of 2417 patients who received intermittent letrozole compared with 833 (34·5%; 32·7–36·5) of 2411 who received continuous letrozole (table 2). Evidence of osteopenia or osteoporosis (T-score less than –1) was reported in 1146 (47·5%; 95% CI 45·5–49·5) of 2417 patients who received intermittent letrozole versus 1130 (46·9%; 44·9–48·9) of 2411 patients who received continuous letrozole; and fractures of any cause were reported for 198 (8·2%; 7·2–9·4) versus 214 (8·9%; 7·8–10·1).

The most common grade 3–5 targeted adverse events were hypertension (584 [24%] of 2417 patients in the intermittent letrozole group *vs* 517 [21%] of 2411 patients in the continuous letrozole group) and arthralgia



(136 [6%] *vs* 151 [6%]). Grade 3–5 CNS cerebrovascular ischaemia was reported in 54 patients overall (24 [1%] in the intermittent letrozole group *vs* 30 [1%] in the continuous letrozole group), CNS haemorrhage in 16 (nine [<1%] *vs* seven [<1%]), and cardiac ischaemia in 40 (19 [1%] *vs* 21 [1%]). In total, 23 (<1%) of 4851 patients died while on trial treatment (13 [<1%] of 2417 patients in the intermittent letrozole group *vs* ten [<1%] of 2411 in the continuous letrozole group), although a clear relationship with the treatment cannot be established.

Of the 4851 patients in the intention-to-treat population, 956 were enrolled in the prospectively planned quality-of-life substudy at 61 centres in nine countries between Dec 5, 2007, and July 26, 2012. One patient in the intermittent letrozole group had quality-of-life data completely missing and was thus excluded from the quality-of-life analysis; therefore, the final number of patients analysed in the quality-of-life substudy was 955 (455 in the continuous letrozole group and 500 in the intermittent letrozole group). Patients who participated in the quality-of-life substudy tended to be younger women, more often premenopausal at diagnosis, than those who did not participate (median age 58 years [IQR 53–66] *vs* 60 years [54–67]; 255 [27%] of 955 who participated *vs* 869 [22%] of 3896 who did not participate) and were more likely to have received previous SERMs only rather than aromatase inhibitors only or both of these therapies (254 [27%] of 955 *vs* 619 [16%] of 3896). The distributions of disease characteristics were similar between those who participated and those who did not (data not shown).

Changes in patient-reported symptoms and quality-of-life indicators between baseline and 12 months—ie, at the end of the first interruption in patients assigned intermittent letrozole—were small but showed a consistent pattern of less worsening in quality of life in those assigned to the intermittent letrozole group than in those assigned to the continuous letrozole group. Patients receiving intermittent letrozole reported significantly less worsening in vaginal problems (between-group difference in mean change score from baseline was 4 [95% CI 1–8]; p=0·017), musculoskeletal pain (3 [0–6]; p=0·023), sleep disturbance (5 [1–9]; p=0·0073), physical wellbeing (4 [1–8]; p=0·0080), and mood (4 [0–7]; p=0·026) than those receiving continuous letrozole. At 24 months (ie, after the second interruption), patients in the intermittent letrozole group reported a greater improvement in hot flushes (3 [95% CI 0–6]; p=0·025) than those assigned continuous letrozole. Changes in the other quality-of-life endpoints did not differ significantly between the treatment groups at 24 months (data not shown).

Figure 4: **Breast cancer-free interval (A), distant recurrence-free interval (B), and overall survival (C) after median follow-up of 60 months**
HR=hazard ratio.

	Continuous letrozole (n=2411)				Intermittent letrozole (n=2417)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Hot flushes	1240 (51%)	70 (3%)	..	..	1217 (50%)	59 (2%)	..	..
Insomnia	983 (41%)	59 (2%)	0	..	961 (40%)	52 (2%)	0	..
Fatigue	1025 (43%)	58 (2%)	0	..	954 (39%)	47 (2%)	1 (<1%)	..
Fractures	148 (6%)	65 (3%)	1 (<1%)	0	136 (6%)	60 (2%)	2 (<1%)	0
Osteoporosis	1113 (46%)	17 (<1%)	0	0	1119 (46%)	26 (1%)	1 (<1%)	0
Myalgia	841 (35%)	54 (2%)	0	..	818 (34%)	51 (2%)	1 (<1%)	..
Arthralgia	1506 (62%)	151 (6%)	0	..	1453 (60%)	131 (5%)	5 (<1%)	..
Bone pain	634 (26%)	57 (2%)	1 (<1%)	..	613 (25%)	44 (2%)	2 (<1%)	..
Depression	767 (32%)	49 (2%)	4 (<1%)	1 (<1%)	762 (32%)	53 (2%)	8 (<1%)	0
CNS cerebrovascular ischaemia	11 (<1%)	17 (<1%)	12 (<1%)	1 (<1%)	8 (<1%)	10 (<1%)	13 (<1%)	1 (<1%)
CNS haemorrhage	4 (<1%)	6 (<1%)	1 (<1%)	0	4 (<1%)	6 (<1%)	2 (<1%)	1 (<1%)
Hypertension	539 (22%)	511 (21%)	6 (<1%)	0	493 (20%)	579 (24%)	5 (<1%)	0
Cardiac ischaemia	15 (<1%)	16 (<1%)	5 (<1%)	0	23 (<1%)	10 (<1%)	7 (<1%)	2 (<1%)
Thrombosis or embolism	8 (<1%)	11 (<1%)	7 (<1%)	0	9 (<1%)	14 (<1%)	6 (<1%)	0

Data are frequency (%) of patients. ..=grades 4 or 5 of these adverse events do not exist.

Table 2: **Maximum grade of targeted adverse events reported during the 5-year treatment period**

Discussion

Contrary to previous findings in animal models,[6] our study showed that intermittent letrozole use did not improve disease-free survival compared with continuous letrozole use when given as extended adjuvant therapy in postmenopausal women with hormone receptor-positive early breast cancer.

The outcome of this trial might be partly related to the short period of interruption of letrozole use chosen. The 3 months interruption after 9 months of therapy was selected arbitrarily, although based on several clinical and preclinical observations. Long-term oestradiol and oestrone suppression has been recorded after a single administration of letrozole in healthy postmenopausal women.[15] In these women, oestradiol suppression was maintained for 2 weeks after a single dose of letrozole. Moreover, the response to letrozole discontinuation of breast tumours transplanted into athymic mice was observed after 6 weeks of treatment interruption, when treatment was started again.[6] Finally, a clinical effect of high-dose oestrogen therapy following exhaustive anti-hormonal therapy has been noted after 3 months of treatment in postmenopausal patients with advanced breast cancer.[16] We also noted that 11–16% of patients each year in the intermittent letrozole group did not interrupt therapy at the appropriate time or duration in years 1–4 according to protocol; although 85–90% adherence with endocrine therapy is very high, missed interruptions would have the effect of making the two groups more similar than they should be. The median 60 months of follow-up might also have contributed to these findings because it might not be long enough, and continued follow-up of the SOLE trial is ongoing.

Two trials have previously tested the use of extending letrozole from 5 years to 10 years of adjuvant treatment with aromatase inhibitors. In the MA.17R trial,[3] a beneficial effect of letrozole versus placebo was recorded, with improvement in disease-free survival and a favourable toxicity profile. However, the patient population differed to that in the present study because around 80% of participants in MA.17R had received tamoxifen before letrozole. The NRG Oncology/NSABP B-42 trial[4] did not meet its primary endpoint of improved disease-free survival with extended letrozole, although significant improvements in breast cancer-free interval and distant recurrence-free interval were recorded. Extended use of letrozole did not increase the risk of osteoporotic fractures, but the risk of arterial thrombotic events was increased after 2·5 years of extended treatment in the NSABP B-42 trial.[4] These results suggest that extended letrozole treatment only provides a small amount of benefit that needs to be weighed against increased side-effects.

Previous trials[3,4] evaluating extended adjuvant letrozole treatment included women with both lymph node-negative and lymph node-positive disease, all of whom were free of breast cancer after adjuvant endocrine therapy. The present study, the largest on extended adjuvant therapy involving an aromatase inhibitor, differs from those previously mentioned in that it focuses exclusively on an initially node-positive population. Despite this selection criterion, in the current event-based analysis, after a median follow-up of 60 months only 14% of patients had disease-free survival events and only 9% had breast cancer events. In retrospect, a major limitation of our trial was probably the use of a classical disease-free survival definition, including both breast cancer and non-breast cancer events, as a substantial number of non-breast cancer events were recorded in both treatment groups,

therefore interfering with the possibility to detect any significant difference in disease-free survival between treatment groups. Caution should be heeded not to compare the 4-year or 5-year estimates of primary endpoints between this trial and previous trials because the endpoints differ in their definitions of events; however, the use of different endpoints does not in itself bias the estimates of treatment effect.

Another key difference across trials evaluating extended adjuvant letrozole is the age distribution of participants. The most apparent reason for heterogeneity of age is the eligibility for previous endocrine therapy: those trials requiring previous aromatase inhibitor therapy would involve older patients because they would have been postmenopausal at diagnosis, whereas those trials allowing previous aromatase inhibitors or SERMs probably contain younger patients because patients who are premenopausal and have received 5 years of SERMs are eligible. The role of age and previous endocrine therapy in relation to the heterogeneity of the extended adjuvant endocrine therapy trial results should be investigated in a meta-analysis.

The SOLE study investigated extended letrozole use in three patient cohorts defined by previous adjuvant endocrine therapy. Randomisation was stratified according to use of SERMs only, aromatase inhibitors only, or both SERMs and aromatase inhibitors during the first 4–6 years of endocrine therapy. For the 2022 postmenopausal women receiving up-front treatment with aromatase inhibitors only, our subgroup analysis showed that the extension with intermittent letrozole to 10 years had a pattern towards reduced risk of breast cancer events and death compared with the continuous administration of letrozole. By contrast, no such effect was observed for intermittent letrozole in the cohort that had received both SERMs and aromatase inhibitors, and a trend to a detrimental effect was noted in patients who had previously received SERMs only. Based on preclinical data, the driver of the change in oestradiol function has been postulated to be prolonged oestrogen deprivation, as is the case in patients on previous treatment with aromatase inhibitors only, rather than extensive anti-hormonal therapy.[17] Moreover, a specific adaptation to oestrogen deprivation induced by letrozole has been shown in animal models that can explain the resistance to aromatase inhibitors and the results observed in the SOLE trial according to previous endocrine therapy. In particular, studies done on cells isolated from tumours treated with letrozole for a prolonged time showed a change in the balance of growth factors' cascade during letrozole use and a restoration to hormonal signalling when the aromatase inhibitor was withdrawn.[18,19] Caution is required in the interpretation of these subgroup analyses because, despite the consistent trend across endpoints, the interactions between previous endocrine therapy and treatment assignment were not significant. However, the results do support the safety of a pause in the treatment in patients whose previous adjuvant therapy included only an aromatase inhibitor.

Any risk reduction from extended adjuvant endocrine therapy must be balanced with toxicities and effects on quality of life. No significant differences in the targeted adverse events were observed between the two treatment groups, in particular for grade 3–5 adverse events. The profiles of adverse events in both groups are in agreement with findings from previous studies,[3,4] with no unexpected serious adverse events in either group. Besides the absence of between-group differences with respect to the side-effect profile, the overall quality-of-life assessment showed that intermittent administration of letrozole had less worsening of symptoms and quality-of-life indicators than did continuous administration of letrozole. Although these changes were not large, there was a consistent pattern in favour of intermittent administration. These findings are important for women with endocrine side-effects during extended treatment. However, a limitation of the present quality-of-life substudy is that the observed results might not be generalisable because only 20% of patients were selected to participate in this analysis, and participants tended to be younger women who were premenopausal at diagnosis and more often received previous SERMs only (rather than aromatase inhibitors only or both SERMs and aromatase inhibitors) as compared with non-participants. The quality-of-life analyses focused on the changes from baseline to 12 months and 24 months, immediately following the interruption in the intermittent letrozole group; additional quality-of-life data across the 6, 12, 18, and 24 months will be reported separately.

A notable finding from the SOLE trial is that the rates of adherence to letrozole were similar for both groups, and not inferior to results reported in other extended adjuvant endocrine therapy trials, which might be related to enrolment in these trials of patients who were recurrence-free and had tolerated 4–6 years of previous endocrine therapy. This finding supports the feasibility of extended treatment with aromatase inhibitors through different schedules, including intermittent administration.[20]

Modelled analyses have indicated that extended adjuvant letrozole is a cost-effective treatment option when compared with no further treatment.[21] However, issues related to the costs of therapies in the adjuvant setting are relevant both in low-income and high-income countries.[22] According to the recommendation for 10 years of endocrine therapy for many women, the cost implications become even more relevant. The intermittent use of letrozole might be an attractive approach considering the reduced economic cost and spared resources of 12 fewer months of treatment during interruptions, possibly improving existing socioeconomic disparities in patients with breast cancer.[23]

From the current analysis, we conclude that extended treatment with intermittent letrozole did not improve disease-free survival versus treatment with continuous letrozole. The safety, quality-of-life, and efficacy results of the intermittent administration provide clinically relevant information about extended adjuvant endocrine therapy with letrozole and support the safety of this option for temporary treatment breaks in selected patients who might require them.

Contributors

MC, PK, and AGol were responsible for the conception and study design, recruitment of patients, collection and assembly of data, data analysis and interpretation, result interpretation, and manuscript drafting. WL was responsible for collection and assembly of data, data analysis and interpretation, result interpretation, and manuscript drafting. JC and SA were responsible for conception and study design, recruitment of patients, data analysis and interpretation, result interpretation, and manuscript drafting. GJ was responsible for recruitment of patients and result interpretation. PN and M-PG were responsible for recruitment of patients. EH, ES, and SO'R were responsible for recruitment of patients and collection and assembly of data. CK and MR-P were responsible for collection and assembly of data and data analysis and interpretation. AT was responsible for the conception and study design and recruitment of patients. SL was responsible for collection and assembly of data, data analysis and interpretation, and manuscript drafting. JG was responsible for manuscript drafting. KK was responsible for data analysis and interpretation, result interpretation, and manuscript drafting. CM and BM were responsible for collection and assembly of data. VDL was responsible for recruitment of patients, collection and assembly of data, and result interpretation. TR was responsible for recruitment of patients, collection and assembly of data, and data analysis and interpretation. HB was responsible for recruitment of patients, data analysis and interpretation, and manuscript drafting. KR and JB were responsible for the conception and study design, data analysis and interpretation, and manuscript drafting. GV was responsible for collection and assembly of data, data analysis and interpretation, and result interpretation. RDG was responsible for the conception and study design and result interpretation. ASC was responsible for the conception and study design, result interpretation, and manuscript drafting. ADL was responsible for data analysis and interpretation and manuscript drafting. MMR was responsible for the conception and study design, collection and assembly of data, data analysis and interpretation, result interpretation, and manuscript drafting. All authors, including AGom and RM, were responsible for reviewing and revising the manuscript and the final approval of the manuscript.

Declaration of interests

MC has received fees from AstraZeneca, Pierre Fabre, Pfizer, OBI Pharma, Puma Biotechnology, and Celldex advisory board participation; and has received honoraria from Novartis, all outside the submitted work. PK has received personal fees from Novartis advisory board participation, outside the submitted work. JC has received fees from Novartis, Specialized Therapeutics Australia, and Eisai advisory board participation, outside the submitted work. SA has received fees from Novartis, Pfizer, and Roche advisory board participation, outside the submitted work. GJ has received grants from Novartis during the conduct of the study; grants, personal fees, and non-financial support from Novartis and Roche; personal fees and non-financial support from Pfizer and Lilly; and personal fees from Celgene, Amgen, Bristol-Myers Squibb, and Biotechnology, all outside the submitted work. M-PG has received research funding from Novartis during the conduct of the study; and grants from Novartis, Pfizer, and Roche, outside the submitted work. ES has received personal fees from Novartis advisory board participation, outside the submitted work. CK has received fees from Novartis, Pfizer, and Roche advisory board participation, outside the submitted work. SO'R has received honorarium and advisory board fees from Novartis during the conduct of the study and outside the submitted work. TR has received personal fees from Roche, Novartis, and Lilly advisory board participation; travel grants from Roche and Amgen; and personal fees from Pfizer, all outside the submitted work. RDG and MMR have received research funding to the International Breast Cancer Study Group from Novartis during the conduct of the study; and research funding from Novartis, Pfizer, Ipsen, Merck, Celgene, Ferring, Roche, AstraZeneca, all outside the submitted work. ADL has received grants from AstraZeneca, Novartis, and Pfizer; personal fees from AstraZeneca, Bayer, Celgene, Daichii-Sankyo, Eisai, Genomic Health, Ipsen, Lilly, Novartis, Pfizer, Pierre Fabre, Puma Biotechnology, and Roche; and non-financial support from AstraZeneca, Daichii-Sankyo, Genomic Health, Ipsen, Lilly, Novartis, Pfizer, Pierre Fabre, Puma Biotechnology, and Roche, all outside the submitted work. MMR has received research funding from Veridex and OncoGenex, all outside the submitted work. All other authors declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Colleoni M, Luo W, Karlsson P, et al, on behalf of the SOLE Investigators. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017; published online Nov 17. http://dx.doi.org/10.1016/S1470-2045(17)30715-5.

Colleoni et al., Extended adjuvant intermittent versus continuous letrozole in postmenopausal breast cancer (SOLE; IBCSG 35-07 / BIG 1-07): an international, open-label, randomized, phase 3 trial

WEB EXTRA MATERIAL

Section 1:

APPENDIX: Study of Letrozole Extension (SOLE) Trial Investigators and the International Breast Cancer Study Group Participants

SOLE Steering Committee: M Colleoni (Chair); S Aebi, J Chirgwin, P Karlsson (Co-Chairs); M Andre (Novartis), M Bellet, L Blacher, A Coates, A Di Leo, R Gelber, M Gnant, A Goldhirsch, A Hiltbrunner, G Jerusalem, C Kamby, R Kammler, I Kössler, K Kuroi, S Loibl, W Luo, R Maibach, B Müller, P Neven, M Rabaglio, M Regan, B Ruepp, K Scott, H Shaw, E Simoncini, A Thompson, G Viale, D Zardavas

IBCSG Scientific Committee: M Colleoni (Chair), A Di Leo (Co-Chair)

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Section 2: Supplementary Methods of SOLE Quality-of-Life Substudy

The prospectively-defined quality-of-life (QoL) substudy was activated at the start of the parent trial on November 8, 2007. Selected IBCSG centers participated. All patients were eligible, with the exception of patients with physical impairment that would interfere with assessment, or inability to read any of the languages available for the assessment forms. The target QoL enrollment goal was met as of November 30, 2010, and the substudy enrollment was closed as of December 31, 2010. However enrollment continued until July 26, 2012 at centers enrolling patients into a second SOLE substudy; because that substudy had 1:3 enrollment of patients assigned to continuous versus intermittent letrozole, the total enrollment in the QoL substudy included greater number of patients assigned to intermittent letrozole.

The sample size for the QoL substudy was estimated based on a between-group comparison of the change from baseline to 12 months in the hot flushes/flashes scale, estimating 676 patients to achieve 90% power to detect an effect size of 0.25 between the two groups using a two-sided 0.05 level t-test. To allow for a 10% non-compliance rate, the target enrollment was inflated to 744 patients. The baseline assessments were to be completed prior to randomisation in order to eliminate any differential anticipatory effects on baseline scores and to help ensure compliance with the protocol requirements.

Of the 4851 patients in the intention-to-treat population, 956 patients participated in QoL substudy at 61 centers in 9 countries. One patient had QoL data completely missing and therefore was excluded from QoL analysis. As compared with the 3896 non-QoL ITT patients, those patients included in the QoL analysis tended to be younger premenopausal women (median age 58 vs. 60; 26.8% vs. 22.8% pre/perimenopausal) and more often received prior SERMs only rather than AIs or both SERM/AI (26.6% vs 15.9% prior SERMs only); distributions of disease characteristics were similar (data not shown).

Section 3: Supplementary Tables and Figures

Table S1. Number of enrolling centers and number of patients enrolled in the SOLE trial, according to cooperative group and country.

Cooperative Group/Country		Centers	Patients	
		N	N	%
Total		*240*	*4884*	*100.0*
ABCSG	Austria	17	180	3.7
DBCG	Denmark	13	441	9.0
GBG	Germany	35	291	6.0
IBCSG	Australia (ANZBCTG)	22	353	7.2
	Belgium	25	1029	21.1
	Chile (GOCCHI)	10	140	2.9
	France	3	30	0.6
	Hungary	2	155	3.2
	India	1	16	0.3
	Italy	13	578	11.8
	New Zealand (ANZBCTG)	2	19	0.4
	Peru	1	66	1.4
	Russia	2	43	0.9
	Slovenia	1	24	0.5
	South Africa	4	56	1.1
	Sweden	7	209	4.3
	Switzerland	23	318	6.5
	USA	4	40	0.8
CTI (formerly ICORG)	Ireland	12	111	2.3
JBCRG	Japan	15	192	3.9
SOLTI	Spain	13	271	5.5
SCTBG	Scotland	15	322	6.6

Table S2. Sites of first disease-free survival (DFS) event, overall and according to treatment assignment. The 4851 patients in the intention-to-treatment analysis population have been observed for a median follow-up of 60 months.

	Treatment Assignment				Overall	
	Continuous Letrozole		Intermittent Letrozole			
	N	%	N	%	N	%
Number of patients ITT	*2426*	*100.0*	*2425*	*100.0*	*4851*	*100.0*
DFS event	319	13.1	346	14.3	665	13.7
Site of first DFS event:						
Breast cancer events as site of first DFS event	215	8.9	211	8.7	426	8.8
Local	20	0.8	22	0.9	42	0.9
Contralateral breast ± above	17	0.7	27	1.1	44	0.9
Regional ± above	10	0.4	12	0.5	22	0.5
Soft tissue / distant lymph nodes ± above	5	0.2	9	0.4	14	0.3
Distant bone ± above	56	2.3	52	2.1	108	2.2
Distant viscera ± above	107	4.4	89	3.7	196	4.0
Second (non-breast) malignancy	74	3.1	95	3.9	169	3.5
Death without prior cancer event	22	0.9	33	1.4	55	1.1
Death with recurrence suspected	1	0.0	2	0.1	3	0.1
Death with no recurrence information	7	0.3	5	0.2	12	0.2

Figure S1. Cox proportional hazards model results of disease-free survival (DFS) treatment comparisons for all patients and according to subgroups. Median follow-up was 60 months. The solid vertical line is placed at 1.08, the hazard ratio (HR) estimate for all patients. The x-axis is scaled according to the natural logarithm of the HR. The size of the box is inversely proportional to the standard error of the HR.

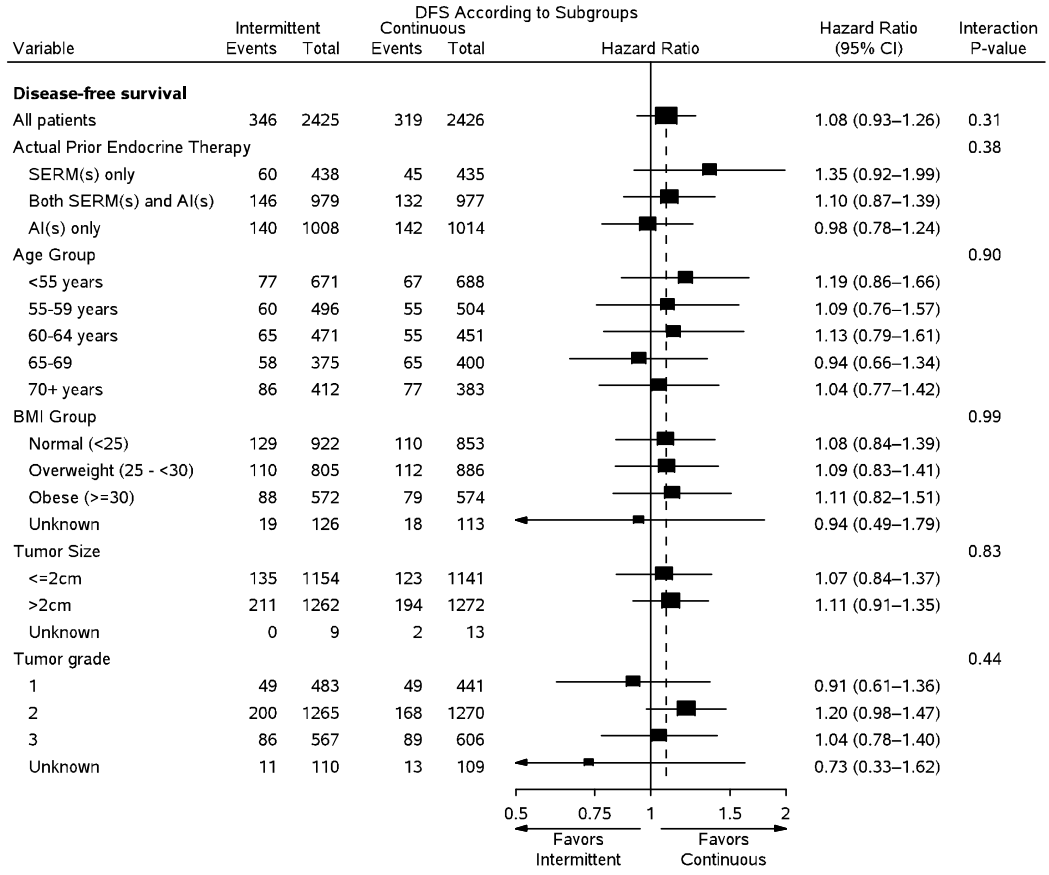
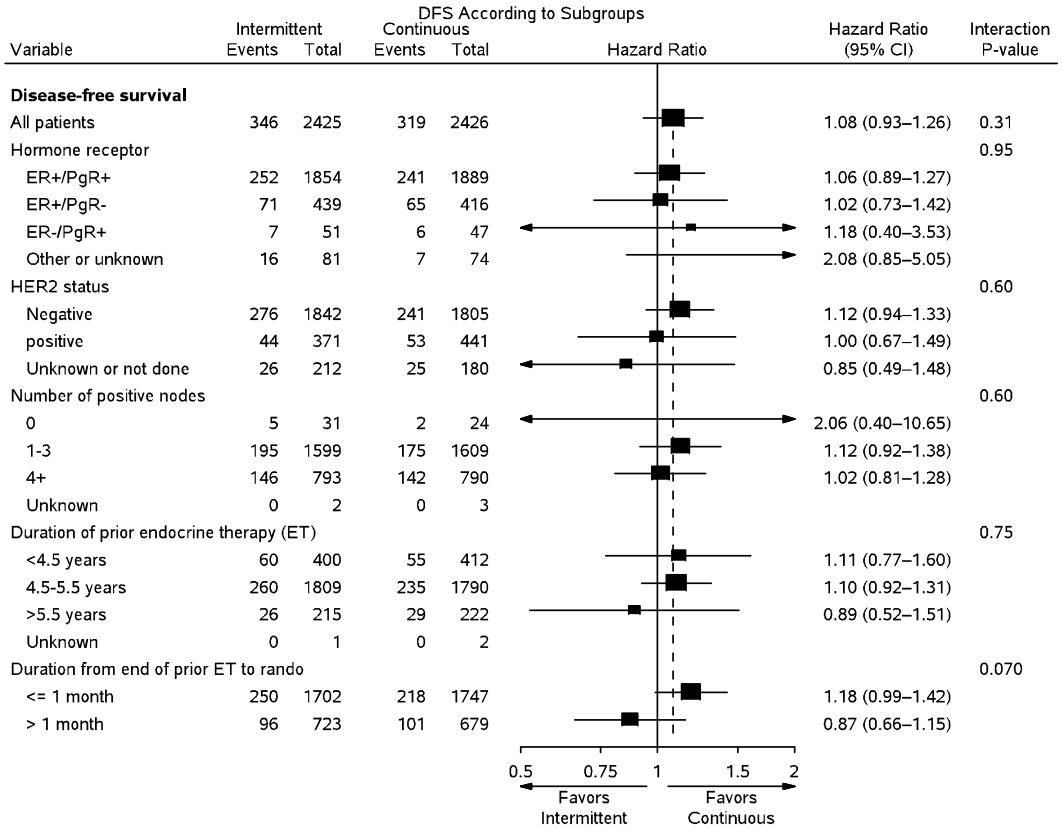


Figure S1 continued

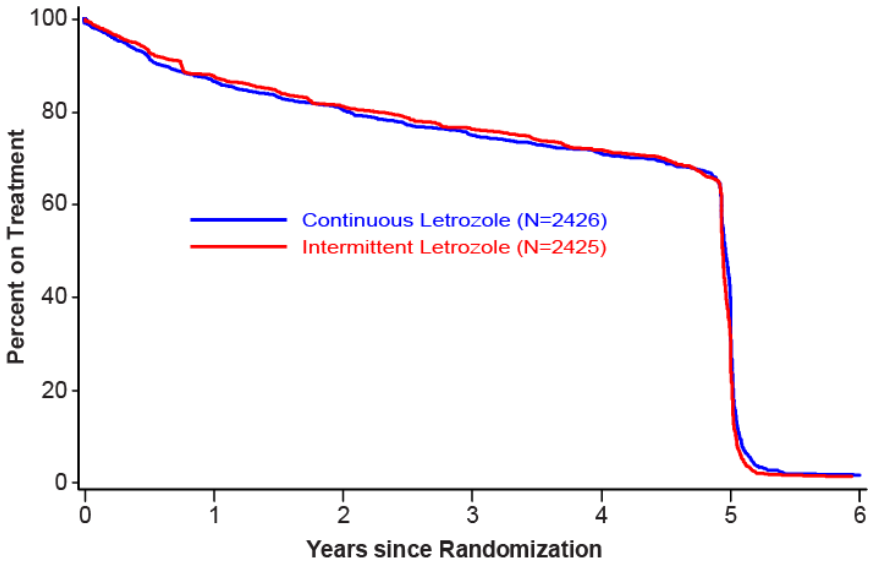


*P-Value for “All Patients” is the stratified log-rank test; for other variables, P-Value is test of heterogeneity of the treatment effect across subgroups, using test of treatment-by-variable interaction from stratified Cox model, with “unknown” or “other” group omitted from the test.

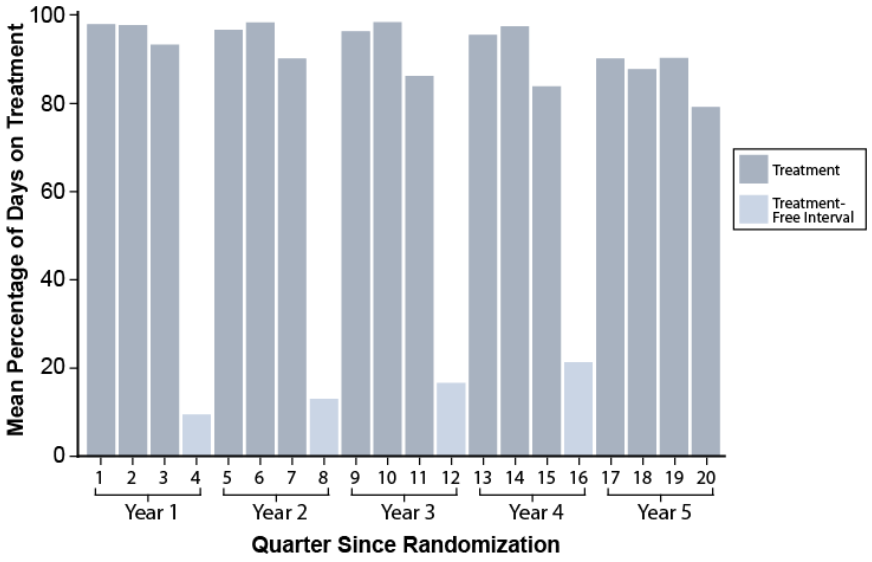
Abbreviations: CI denotes confidence interval; SERM=selective estrogen receptor modulator; AI=aromatase inhibitor; BMI=body mass index; ER=estrogen receptor; PgR=progesterone receptor; ET=endocrine therapy

Figure S2: Treatment adherence in the SOLE trial. (A) Time from randomisation to permanent treatment discontinuation of protocol treatment for any reason, according to treatment assignment; at the time of analysis 1438 patients had not yet discontinued. (B) Percentage of days on letrozole, in 3-monthly intervals since randomisation, among 2425 patients assigned to intermittent letrozole. (C) Percentage of days on letrozole, in 3-monthly intervals since randomisation, among 2426 patients assigned to continuous letrozole.

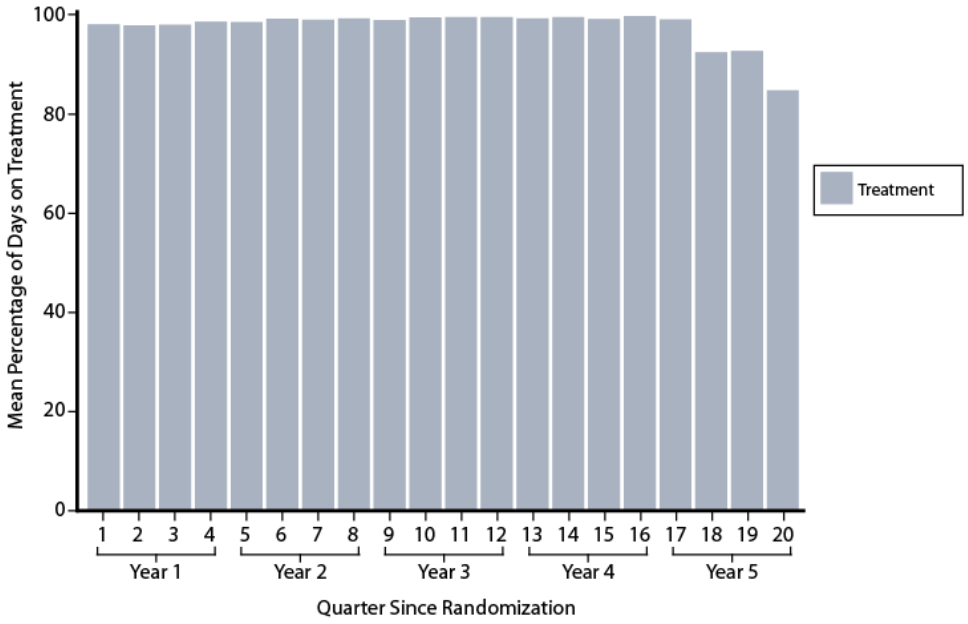
(A)



(B)



(C)


Mean Percentage of Days on Treatment
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Year 1
Year 2
Year 3
Year 4
Year 5
Quarter Since Randomization
Treatment