

ORIGINAL ARTICLE

## Continuous versus intermittent extended adjuvant letrozole for breast cancer: final results of randomized phase III SOLE (Study of Letrozole Extension) and SOLE Estrogen Substudy<sup>☆</sup>

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**Background:** Late recurrences in postmenopausal women with hormone receptor-positive breast cancers remain an important challenge. Avoidance or delayed development of resistance represents the main objective in extended endocrine therapy (ET). In animal models, resistance was reversed with restoration of circulating estrogen levels during interruption of letrozole treatment. This phase III, randomized, open-label Study of Letrozole Extension (SOLE) studied the effect of extended intermittent letrozole treatment in comparison with continuous letrozole. In parallel, the SOLE estrogen substudy (SOLE-EST) analyzed the levels of estrogen during the interruption of treatment.

**Patients and methods:** SOLE enrolled 4884 postmenopausal women with hormone receptor-positive, lymph node-positive, operable breast cancer between December 2007 and October 2012 and among them, 104 patients were enrolled in SOLE-EST. They must have undergone local treatment and have completed 4–6 years of adjuvant ET. Patients were randomized between continuous letrozole (2.5 mg/day orally for 5 years) and intermittent letrozole treatment (2.5 mg/day for 9 months followed by a 3-month interruption in years 1–4 and then 2.5 mg/day during all of year 5).

**Results:** Intention-to-treat population included 4851 women in SOLE ( $n = 2425$  in the intermittent and  $n = 2426$  in the continuous letrozole groups) and 103 women in SOLE-EST ( $n = 78$  in the intermittent and  $n = 25$  in the continuous

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letrozole groups). After a median follow-up of 84 months, 7-year disease-free survival (DFS) was 81.4% in the intermittent group and 81.5% in the continuous group (hazard ratio: 1.03, 95% confidence interval: 0.91-1.17). Reported adverse events were similar in both groups. Circulating estrogen recovery was demonstrated within 6 weeks after the stop of letrozole treatment.

**Conclusions:** Extended adjuvant ET by intermittent administration of letrozole did not improve DFS compared with continuous use, despite the recovery of circulating estrogen levels. The similar DFS coupled with previously reported quality-of-life advantages suggest intermittent extended treatment is a valid option for patients who require or prefer a treatment interruption.

**Key words:** breast cancer, endocrine therapy, letrozole, estrogen

## INTRODUCTION

Late recurrences in postmenopausal women with hormone receptor-positive breast cancers led to the extension of adjuvant endocrine therapy (ET), with aromatase inhibitors (AIs) such as letrozole<sup>1</sup> or selective estrogen receptor modulators (SERMs) such as tamoxifen, from 5 to 10 years. Different trials explored the benefit of extended adjuvant ET in postmenopausal women who completed 5 years of treatment.<sup>2-5</sup> The benefit of this extended treatment, in particular after prior use of AIs in the adjuvant setting, however, is rather modest especially in terms of reduction of distant metastases and the recommendations for 10 years of adjuvant therapy remain controversial.<sup>6-11</sup>

In early breast cancers, secondary resistance is defined as a relapse after at least 2 years of ET or during the first year after the end of adjuvant ET. Mechanisms of resistance involve aberrations in estrogen receptor (ER) signaling inducing overactivation of the pathway leading to cell cycle activation. For example, mutation in *ESR1* gene coding for ER, occurred in around 20%-40% of metastatic breast cancers previously treated with ET.<sup>12</sup>

Animal model studies showed that resistance to AIs can be reversed by intermittent treatment with letrozole, suggesting prolongation of the sensitivity of tumoral cells to AIs due to the restoration of estrogen levels during the interruption of the treatment.<sup>13</sup> Indeed, cells deprived of estrogen for several years showed a spontaneous growth *in vitro* and the addition of minimal concentrations of estrogens induced a cytotoxic effect demonstrating a pro-apoptotic role of estrogens in breast cancer cells.<sup>14-17</sup>

Based on these data, in 2007 the International Breast Cancer Study Group (IBCSG) launched a randomized, phase III trial, the Study of Letrozole Extension (SOLE). SOLE was designed to compare continuous letrozole for 5 years with intermittent letrozole over a 5-year period among postmenopausal women who were disease-free following 4-6 years of prior adjuvant ET with SERM(s) and/or AI(s) for endocrine-responsive node-positive operable breast cancer. The hypothesis was that introducing 3-month treatment-free intervals during the course of 5 years of extended letrozole would reflect the results seen in animal models and improve disease-free survival (DFS). Thus, the statistical design tested superiority rather than non-inferiority.

In 2017, the primary analysis after 5 years median follow-up reported that extended intermittent letrozole therapy

did not improve DFS compared with continuous treatment.<sup>18</sup> Some limitations in the study could explain the outcome of this trial. In that analysis, while 14% of patients had DFS events, only 9% developed breast cancer events. Therefore, follow-up continued until 1 year after all patients had completed therapy, increasing the median follow-up to 84 months for the final analysis presented here.

The underlying hypothesis required that the chosen interval without treatment actually allowed restoration of circulating estrogen levels. Therefore, the SOLE estrogen substudy (SOLE-EST) was conducted to document changes of circulating estrogen levels before and during the initial 3-month treatment interruption and its relationship with some baseline clinical factors, quality of life, and grip strength. Results of this substudy are presented here for the first time and to the best of our knowledge represent the first trial to measure the modification of circulating estrogen levels during an interruption of extended ET in patients with breast cancer.

## METHODS

### Study design and participants

SOLE [registered at [ClinicalTrials.gov](https://ClinicalTrials.gov) (NCT00553410) and EudRACT (2007-001370-88)] was a multinational, open-label, phase III, randomized clinical trial in 240 centers of the Breast International Group-affiliated cooperative groups from 22 countries ([Supplementary Appendix](#), available at <https://doi.org/10.1016/j.annonc.2021.07.017>). Postmenopausal women of any age were eligible. They must have had unilateral, lymph node-positive, steroid hormone receptor-positive (estrogen and/or progesterone receptor-positive) operable breast cancer. They had no known clinical residual locoregional disease after local treatment (surgery with or without radiotherapy) and were clinically free of breast cancer at enrollment, without evidence of recurrence at any time before randomization. Eligible women had completed 4-6 years of prior adjuvant ET with AI or SERM alone or a sequential use of both agents. More details of eligibility criteria of the SOLE study were previously described.<sup>18</sup> Enrollment started at the end of 2007 and the last patient was randomized 8 October 2012 for a total of 4884 patients.

SOLE-EST was activated in three countries (Belgium, Australia, and Italy). A total of 104 patients enrolled

between 31 January 2011 and 12 July 2012 at 14 participating centers (*Supplementary Appendix*, available at <https://doi.org/10.1016/j.annonc.2021.07.017>). All eligible patients randomized to SOLE from these centers were to be offered participation in SOLE-EST, but inclusion was not mandatory.

Ethics committees and appropriate national health authorities from each center approved the protocol and all patients provided written informed consent.

### Procedures

Eligible patients for SOLE were randomly assigned 1 : 1 to receive continuous (orally 2.5 mg/day for 5 years) or intermittent letrozole (orally 2.5 mg/day for 9 months followed by 3 months interruption in years 1–4 and 2.5 mg/day during year 5, *Supplementary Figure S1*, available at <https://doi.org/10.1016/j.annonc.2021.07.017>). For the SOLE-EST substudy, patients who had been randomized to continuous or intermittent letrozole use were enrolled in a ratio of 1 : 3. Details on randomization were previously described.<sup>18</sup> Patients completed treatment at 60 months from randomization. The median duration of follow-up from randomization was 84 months (range, <1 month to 105 months). Patients were assessed every 6 months during years 1–5 and thereafter annually for their disease status and to record 14 specified adverse events [using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0)] at each study visit during the 5-year treatment period.

For patients enrolled in the SOLE-EST substudy, quality-of-life assessments were carried out at baseline and at 6, 12, 18, and 24 months after randomization (detailed in a previous report).<sup>19</sup> Grip strength was measured using the Martin vigorimeter (a modified sphygmomanometer) at 0, 9, and 12 months. To carry out the hand grip test, the patients were asked to squeeze the balloon of a modified sphygmomanometer three times with maximal force and the maximal values of three trials of each hand were used for evaluation. Serum samples were obtained at four time points (0, 9, 10.5, and 12 months, *Supplementary Figure S1*, available at <https://doi.org/10.1016/j.annonc.2021.07.017>) using provided blood collection kits and stored locally at –20°C. Estrogen levels [ $17\beta$ -estradiol (E2), estrone (E1), and estrone sulfate (E1S)] and sex hormone binding globulin were measured using a highly sensitive assay in a central laboratory (Reproductive Endocrine Research Laboratory of Frank Stanczyk, Los Angeles, CA).

### Outcomes

The primary endpoint was DFS, defined as the time from randomization to the first appearance of invasive recurrence of breast cancer, invasive contralateral breast cancer, second non-breast invasive cancer, or death without recurrence or second cancer. Secondary endpoints were breast cancer-free interval (time from randomization to the recurrence of invasive breast cancer); distant recurrence-free interval (DRFI, time from randomization to the

recurrence of breast cancer at a distant site); and overall survival (OS, time from randomization to death from any cause). In the absence of an endpoint event, the times were censored at the date of the last follow-up visit or date of death without an endpoint event. For OS, the endpoint was censored at the date the patient was last known alive.

In SOLE-EST, levels of E2, E1, and E1S were summarized over time. The primary endpoints studied the percentage change of E2 from baseline at 9, 10.5, and 12 months from randomization, and the percentage change from 9 to 10.5 and 12 months, which characterized E2 recovery after letrozole interruption. The secondary assessments included correlations between baseline characteristics, quality of life score changes (between 6 and 12 months) and grip strength changes (between 9 and 12 months) with recovery of E2 levels.

### Statistical considerations

Determination of sample size and statistical analysis for the SOLE trial and the SOLE-EST are detailed in the *Supplementary Material*, available at <https://doi.org/10.1016/j.annonc.2021.07.017>. The primary analysis used an intention-to-treat approach of all randomized patients except in certain situations of inadequate consent or trial procedures. Kaplan–Meier estimates of 7-year times to event, stratified log-rank tests and stratified Cox model estimates of hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Subgroup analyses estimated treatment effect HRs according to selected patient and prior treatment characteristics hypothesized as possibly associated with variability in estrogen levels [age and body mass index (BMI) at randomization, last (most recent) type of prior ET, duration of prior AI, and interval from end of prior ET until randomization; *Table 1*]. Recovery of E2 during the interruption from letrozole in the intermittent group was tested using the Wilcoxon signed rank test. Associations of selected characteristics with baseline E2 and changes in E2 during the interruption used linear regression and linear-mixed models, respectively, using natural log-transformed E2 values because of skewed distribution.

## RESULTS

### Cohorts and baseline characteristics

During the SOLE enrollment period, 4884 postmenopausal women were randomized to receive continuous or intermittent letrozole. After randomization, 33 women were excluded from the analysis (due to inadequate informed consent and non-compliant center) and based on the principle of intention-to-treat the analyzed population included 4851 patients ( $n = 2426$  assigned to continuous and 2425 assigned to intermittent letrozole; *Figure 1*). Among them, 104 women were enrolled in the SOLE-EST substudy, but one patient had no samples collected and was excluded from all SOLE-EST analyses.

The median age at randomization in the SOLE and SOLE-EST populations was 60 years old [interquartile range (IQR): 53–69 years in SOLE and IQR: 53–67 years in SOLE-EST] and

**Table 1.** Selected patient and prior treatment characteristics of the SOLE-EST substudy population (103 patients) according to treatment assignment and in the overall SOLE intention-to-treat (ITT) population

	SOLE-EST substudy						Overall ITT	
	Treatment assignment		Overall					
	Continuous letrozole	Intermittent letrozole	N	%	N	%	N	%
Number of patients	25	100.0	78	100.0	103	100.0	4851	100.0
Age at randomization, years								
<55	6	24.0	23	29.5	29	28.2	1359	28.0
55-59	6	24.0	13	16.7	19	18.4	1000	20.6
60-64	3	12.0	15	19.2	18	17.5	922	19.0
65-69	5	20.0	12	15.4	17	16.5	775	16.0
≥70	5	20.0	15	19.2	20	19.4	795	16.4
BMI at randomization								
Normal (<25)	12	48.0	27	34.6	39	37.9	1774	36.6
Overweight (25 to <30)	7	28.0	31	39.7	38	36.9	1690	34.8
Obese (≥30)	6	24.0	20	25.6	26	25.2	1147	23.6
Unknown	—	—	—	—	—	—	240	4.9
Type of menopause <sup>a</sup>								
Bilateral oophorectomy	4	16.0	22	28.2	26	25.2	—	—
Chemotherapy-induced amenorrhea	7	28.0	8	10.3	15	14.6	—	—
Natural menopause before breast cancer diagnosis	13	52.0	41	52.6	54	52.4	—	—
Natural menopause since breast cancer diagnosis	1	4.0	7	9.0	8	7.8	—	—
Last (most recent) type of prior ET								
AI	23	92.0	72	92.3	95	92.2	3854	79.4
SERM	2	8.0	6	7.7	8	7.8	997	20.6
Duration of prior AI								
<6 months	2	8.0	5	6.4	7 <sup>b</sup>	6.8	930 <sup>b</sup>	19.2
6 months to <2 years	—	—	3	3.8	3	2.9	323	6.7
2 to <3 years	5	20.0	14	17.9	19	18.4	812	16.7
3 to <4 years	3	12.0	10	12.8	13	12.6	515	10.6
≥4 years	15	60.0	46	59.0	61	59.2	2265	46.7
Unknown	—	—	—	—	—	—	6	0.1
Duration from end of prior ET to randomization								
≤1 month	20	80.0	61	78.2	81	78.6	3452	71.2
>1 month	5	20.0	17	21.8	22	21.4	1399	28.8

AI, aromatase inhibitor; BMI, body mass index; ET, endocrine therapy; SERM, selective estrogen receptor modulator; SOLE, Study of Letrozole Extension; SOLE-EST, SOLE estrogen substudy.

<sup>a</sup> Type of menopause was only collected for SOLE-EST participants.

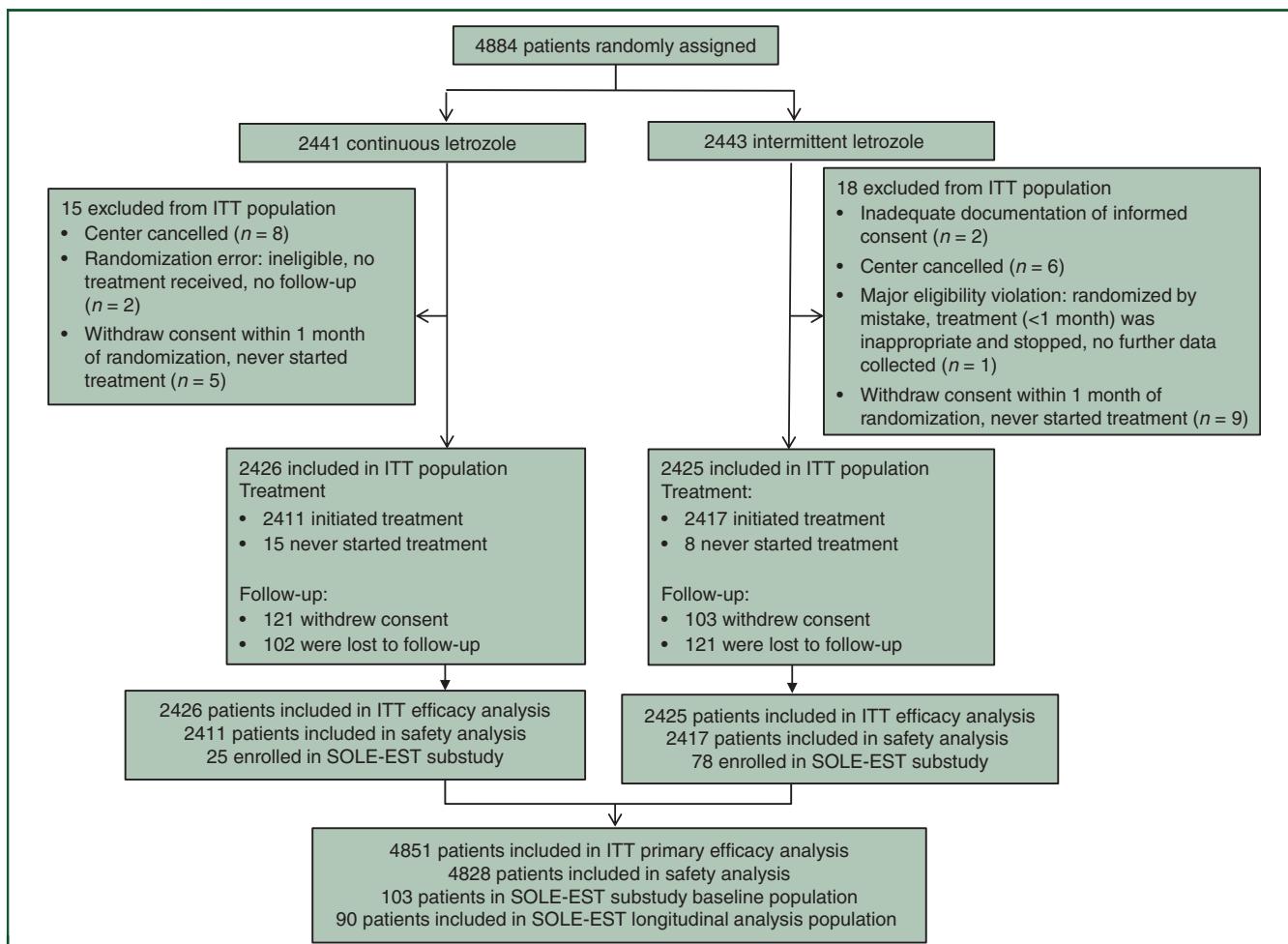
<sup>b</sup> A total of 873/930 and 6/7 patients had prior SERM only in the ITT and SOLE-EST populations, respectively.

more than the half of the women were overweight or obese (58.4% in SOLE and 62.1% in SOLE-EST). A higher proportion of the SOLE-EST population had AI as the most recent prior ET (92.2%) than in the overall SOLE population (79.4%). Duration from the end of prior therapy to randomization was quite similar (71.2% of patients in SOLE had ≤1 month of therapy interruption versus 78.6% in SOLE-EST). Baseline characteristics were homogeneous between continuous and intermittent letrozole treatment groups in SOLE ([Supplementary Table S1](#), available at <https://doi.org/10.1016/j.annonc.2021.07.017>) and in SOLE-EST ([Table 1](#)).

### SOLE study

In the SOLE population, during the additional 2 years of follow-up since first analysis, 258 patients (5.3%) developed a DFS event. During the median 84 months of follow-up, a total of 923 women (19%, 470 assigned intermittent and 453 assigned continuous letrozole) experienced a DFS event. No difference between treatment groups was observed (HR: 1.03, 95% CI: 0.91-1.17, [Figure 2A](#)). The estimated 7-year DFS was 81.4% (95% CI: 79.0% to 83.0%) among patients assigned intermittent letrozole compared

with 81.5% (95% CI: 79.8% to 83.1%) among patients assigned continuous letrozole. The sites of first DFS event did not differ meaningfully between the treatment groups, although the distant metastases were numerically lower in the intermittent treatment group (183/2425) compared with continuous treatment (201/2426; [Supplementary Table S2](#), available at <https://doi.org/10.1016/j.annonc.2021.07.017>). None of the secondary endpoints showed statistically significant differences between intermittent and continuous letrozole treatments. The estimated 7-year breast cancer-free interval was 88.6% (95% CI: 87.2%-89.9%) among patients with intermittent letrozole compared with 88.0% (95% CI: 86.5% to 89.3%) among patients with continuous letrozole (HR: 0.99, 95% CI: 0.84-1.17, [Figure 2B](#)). The estimated 7-year DRFI was 91.6% (95% CI: 90.4% to 92.7%) among patients with intermittent letrozole compared with 90.4% (95% CI: 89.1% to 91.6%) among patients with continuous letrozole (HR: 0.91, 95% CI: 0.76-1.10, [Figure 2C](#)). Deaths were reported for 501 patients [238 in the intermittent group and 263 in the continuous letrozole group (HR: 0.89, 95% CI: 0.75-1.06, [Figure 2D](#))]. The estimated 7-year OS was 90.6% (95% CI:

**Figure 1.** Flow diagram of SOLE trial and SOLE-EST substudy participation.

The data of patients who withdrew consent or were lost to follow-up during SOLE conduct were analyzed until the time at which data submission ceased. ITT, intention to treat; SOLE, Study of Letrozole Extension; SOLE-EST, SOLE estrogen substudy.

89.3% to 91.8%) among patients assigned intermittent letrozole compared with 89.6% (95% CI: 88.2% to 90.8%) among patients assigned continuous letrozole.

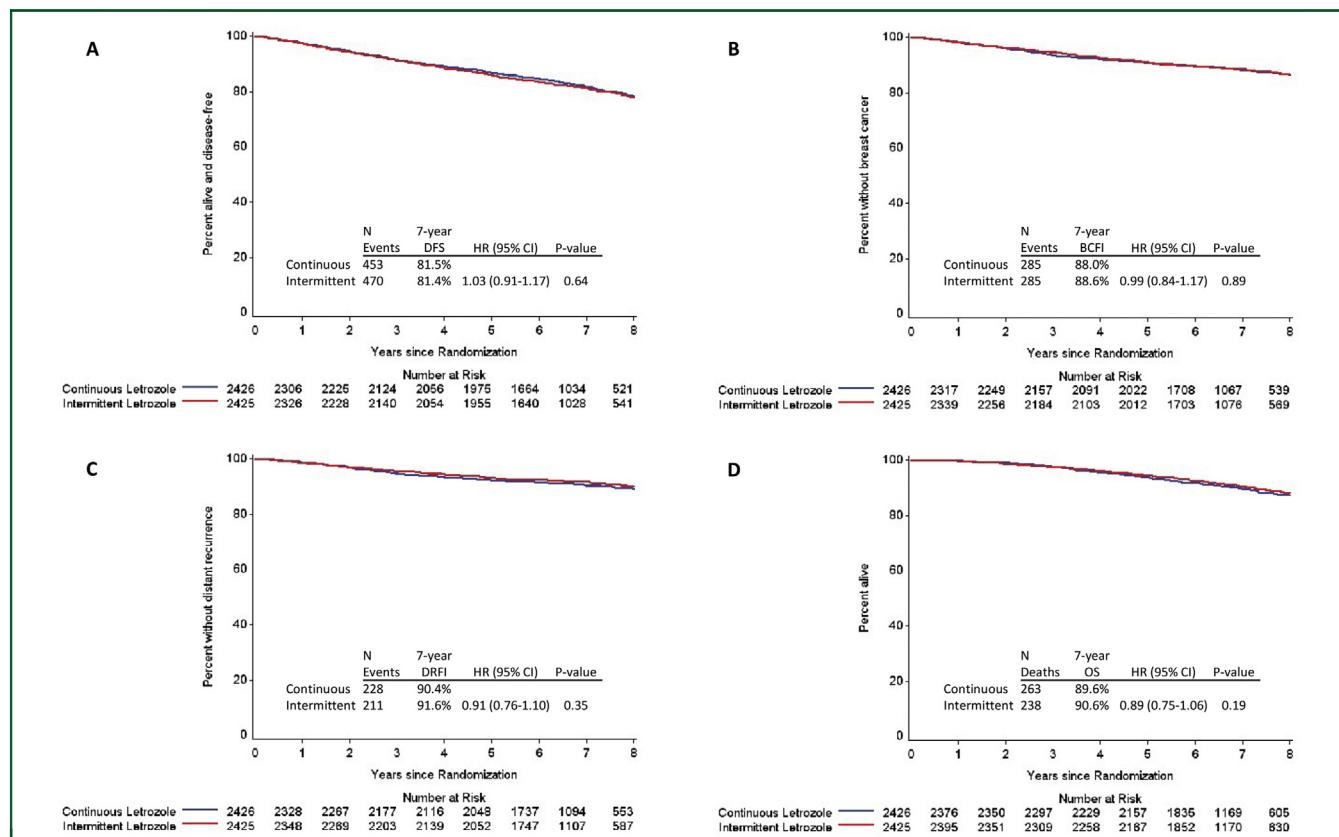
Subgroup analyses based on selected characteristics did not show any significant heterogeneity in treatment effect HRs for the four endpoints (Figure 3; Supplementary Figure S2, available at <https://doi.org/10.1016/j.annonc.2021.07.017>). DRFI showed a tendency to be better in the intermittent letrozole group if the most recent prior ET was AI and if longer duration of prior AI, and worse with recent SERM or shorter duration of AI or youngest age. However, subpopulation treatment effect pattern plot (STEPP) analysis of the efficacy of treatment across prior AI duration (Supplementary Figure S3, available at <https://doi.org/10.1016/j.annonc.2021.07.017>) did not reveal a consistent pattern in the difference between treatments groups, as prior AI duration ranged from no or minimal prior AI up to  $\geq 5$  years of prior AI.

The frequency of adverse events during treatment did not show any new safety signal (Supplementary Table S3, available at <https://doi.org/10.1016/j.annonc.2021.07.017>).

### SOLE-EST substudy

In SOLE-EST, blood samples were obtained from 103 patients at baseline. The levels of E2, E1, and E1S showed some expected variability according to select characteristics, observing a lower circulating E2 concentration in older women, those most recently treated by AI, with longer duration of AI, or more recently ceased prior ET (Supplementary Table S4, available at <https://doi.org/10.1016/j.annonc.2021.07.017>). E2 was slightly higher in overweight women.

There were 90/103 patients (21 continuous, 69 intermittent, Supplementary Figure S4, available at <https://doi.org/10.1016/j.annonc.2021.07.017>) who had baseline and one or more samples at 9, 10.5, and/or 12 months and could be included in analyses of hormone levels over time (Figure 4). Median estrogen level reductions between randomization and 9 months of letrozole treatment were similar in both groups of patients (median  $\sim 30\%$  for E2, 60% for E1, and 35% for E1S; data not shown). At month 12, patients with intermittent letrozole treatment showed a recovery of estrogen concentration while patients with



**Figure 2. Primary and secondary endpoints after median follow-up of 84 months.**

(A) Disease-free survival; (B) breast cancer-free interval; (C) distant recurrence-free survival; and (D) overall survival.

continuous treatment showed the same reduction of estrogen as after 9 months of treatment (median change of E2 level at 12 months compared with 9 months: 141% (IQR: 55% to 238%) in the intermittent group versus 2.2% (IQR: -13% to 46%) in the continuous treatment group, *Supplementary Table S5*, available at <https://doi.org/10.1016/j.annonc.2021.07.017>). An increase in E2 for the intermittent group was observed already at 10.5 months (median 123%; IQR 67% to 216%). The change of E2 level between month 9 and 10.5 and/or 12 did not show any correlation with select characteristics, except potentially for BMI. Overweight or obese women had a greater recovery of the E2 level during the interruption of letrozole than those of normal weight (*Supplementary Tables S6 and S7*, available at <https://doi.org/10.1016/j.annonc.2021.07.017>). These patients also had greater decreases in E2 between baseline and month 9 (data not shown). Changes in quality-of-life measures and grip strength did not show any relation with change of estrogen level in women assigned to intermittent letrozole treatment (*Supplementary Table S7*, available at <https://doi.org/10.1016/j.annonc.2021.07.017>).

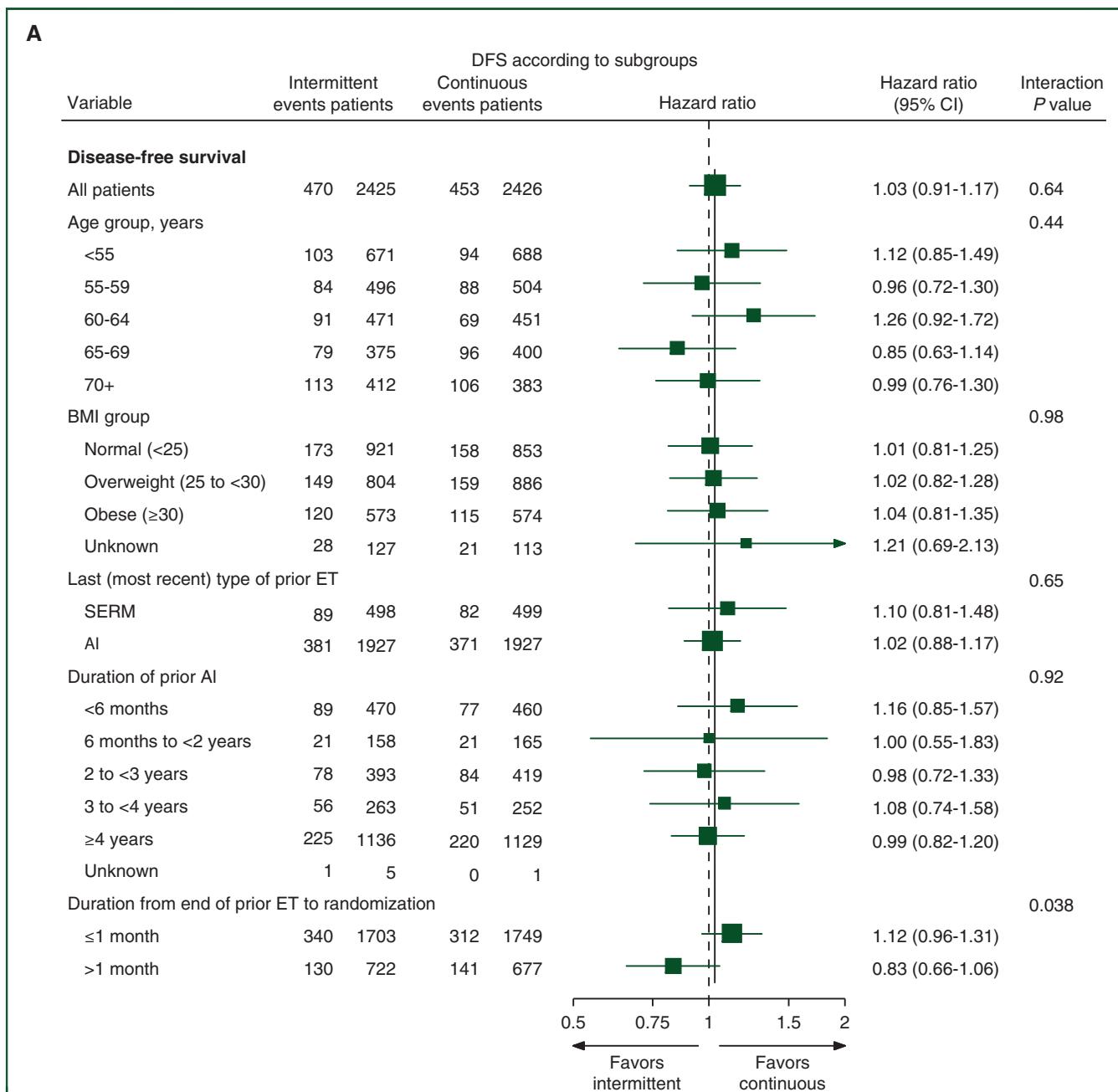
## DISCUSSION

In 2007 when the present trial was started, the benefit of extending adjuvant ET to 10 years was under evaluation in

different phase III international trials<sup>1,3-5</sup> for postmenopausal women with hormone receptor-positive breast cancers.

Based on evidence in animal models,<sup>13</sup> we decided to explore the potential benefit of allowing recovery of circulating estrogen levels by interrupting extended adjuvant letrozole in comparison with a continuous treatment. First analyses of SOLE carried out after 5 years median follow-up did not show an improvement in DFS in patients assigned intermittent letrozole treatment.<sup>18</sup> The final analyses presented here were conducted after the addition of 2 years of follow-up, with median 7 years, and confirmed the previous results. The small number of events reported during the additional 2 years of follow-up demonstrated that the late recurrence rate after ET remains relatively low and prolongation of follow-up would be unlikely to demonstrate an advantage of late intermittent therapy. SOLE was not designed as a non-inferiority study. Had it been so, the observed CIs of the HR for DFS with intermittent therapy (0.91-1.17) would fit within the success parameters of most non-inferiority trials. Importantly, as reported elsewhere,<sup>19</sup> patients assigned to the intermittent treatment reported less worsening in symptom-specific and global quality of life.

The apoptosis induction of estrogen has been previously shown in tumoral cell models and in animal xenograft models.<sup>14-16</sup> Although the xenograft model used reversed

**Figure 3. Disease-free survival and distant recurrence-free interval hazard ratios according to selected characteristics.**

(A) Disease-free survival. (B) Distant recurrence-free interval. Stratified Cox proportional hazards models were used for the estimation of disease-free survival and distant recurrence-free interval hazard ratios between treatment groups, according to selected characteristics. The vertical solid lines represent the overall hazard ratio estimate for each endpoint. The size of the squares is inversely proportional to the standard error of the hazard ratio.

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-characteristic interaction.

AI, aromatase inhibitor; BMI, body mass index; CI, confidence interval; DRFI, distant recurrence-free interval; ET, endocrine therapy; SERM, selective estrogen receptor modulator.

acquired resistance of tumoral cells to letrozole,<sup>20,21</sup> other environmental factors could influence tumoral cells *in vivo* which could potentially explain the failure of the present study to demonstrate a parallel improvement. One remaining question was whether the chosen 3-month interruption of letrozole was sufficient to allow restoration of estrogen levels in blood. The SOLE-EST substudy was therefore conducted in 14 centers from three countries (Belgium, Italy, and Australia) to answer this question and to

analyze the relationship between estrogen levels and clinical factors. The large variability of estrogen levels observed at baseline could be explained by some clinical factors, such as older or overweight women and by the type, duration, and interval from previous ET. Indeed, as expected, patients who received tamoxifen as principal first ET showed two times higher estrogen levels compared with patients who received AI. SOLE-EST demonstrated that even after only 6 weeks interruption of letrozole, estrogen levels increased in

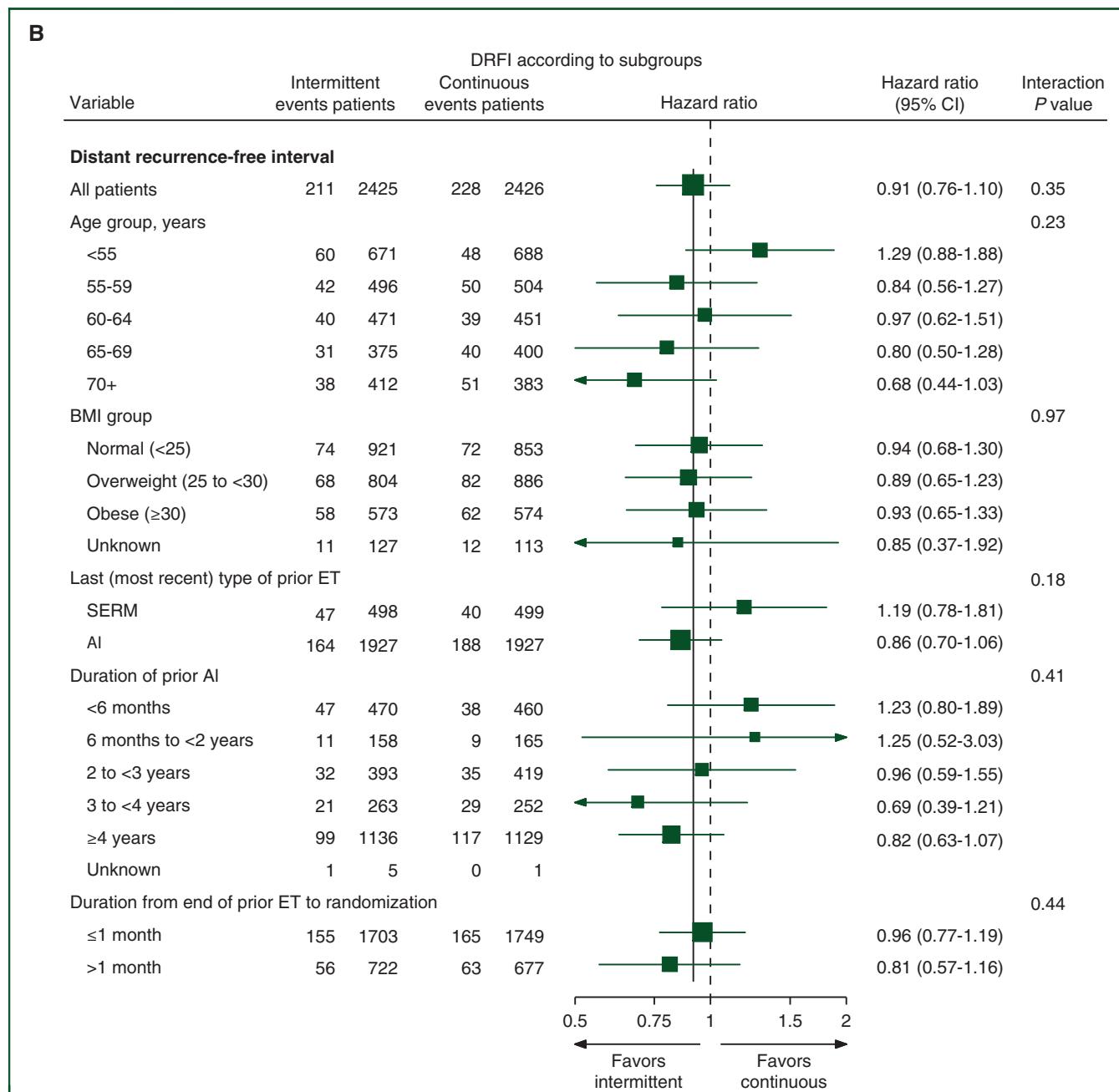


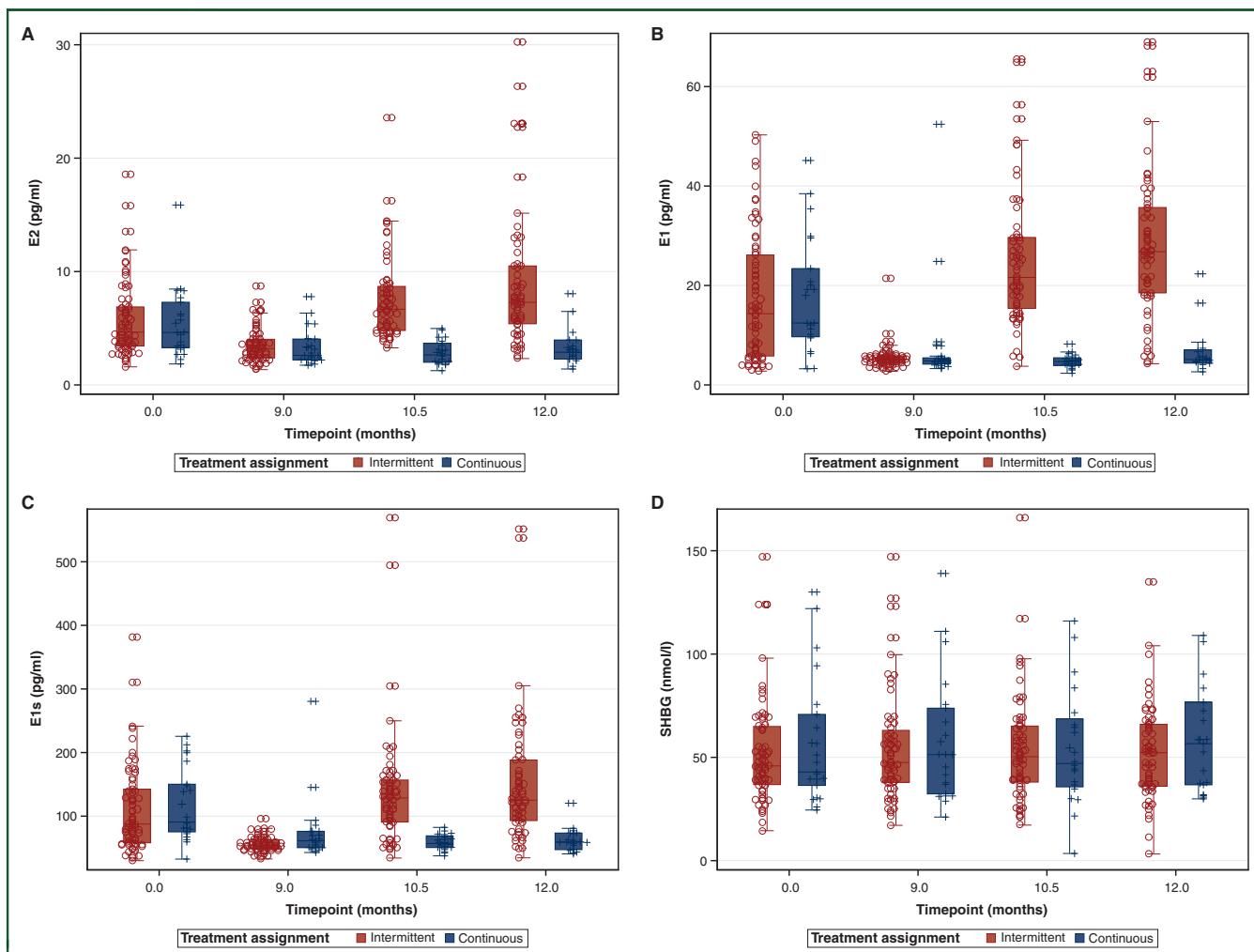
Figure 3. Continued.

patients with a recovery to a level comparable with baseline. The estrogen level remained high until the resumption of treatment. In a parallel study, Balduzzi et al.<sup>22</sup> also showed recovery of estrogen levels during a break of 3 months of adjuvant letrozole therapy. The study, however, did not analyze the relation between estrogen levels and outcomes. In SOLE-EST, estrogen level modification was not significantly associated with clinical effects of treatment measured by quality-of-life scales or grip strength.

Different studies analyzed the effect of intermittent anti-androgen hormonal treatment of advanced prostate cancer.<sup>23,24</sup> As in SOLE, OS was similar to that in the continuous treatment group.<sup>23</sup>

Moreover, in a phase II trial, Ellis et al.<sup>25</sup> showed that treatment with low doses of estradiol allowed lower adverse effects than high doses with the same result on metastatic breast cancer. So, the level of recovery of estrogen could also influence the outcome of patients.

The better understanding of mechanisms leading to endocrine resistance in breast cancer has allowed the development of new targeted therapies.<sup>12</sup> It is now clear that mechanisms of resistance include aberrations in the expression of ER leading to the up-regulation of its downstream pathways.<sup>26</sup> Mutation in the *ESR1* gene coding for ER occurred in 20%-40% of metastatic breast cancers treated by ET.<sup>12</sup> An interruption of this treatment could



**Figure 4. Estrogen levels over time according to treatment assignment.**

(A) 17 $\beta$ -Estradiol (E2), (B) estrone (E1), (C) estrone sulfate (E1s), and (D) sex hormone binding globulin (SHBG) levels measured over time in the intermittent (red;  $n = 78$ ) and continuous (blue;  $n = 25$ ) letrozole groups during the first year of treatment. SHBG was used as control.

allow the loss of the mutation or delay its appearance and subsequent resistance. Among the downstream effectors of the ER pathway, the cyclin-dependent kinase 4/6 (CDK4/6) complex, which controls cell cycle progression, represents a new promising target in adjuvant ET.<sup>27</sup> Some phase III trials testing a combination of adjuvant ET, such as AIs, with CDK4/6 inhibitors have been reported with contradictory results after just 2-3 years median follow-up.<sup>28-30</sup> Longer follow-up of these studies is needed. The combination of intermittent letrozole with CDK4/6 inhibitors has not been evaluated.

As reported in the previous publication, ~70% of patients completed the 5 years of letrozole therapy with similar patterns of early permanent discontinuation in the treatment groups.<sup>18</sup> Moreover, in the intermittent letrozole therapy group, 11%-16% of patients did not interrupt therapy at the appropriate time or duration each year. Although this noncompliance of treatment was expected, it could mask outcome differences between continuous or intermittent therapy in the study.

In conclusion, SOLE indicates that intermittent letrozole treatment did not show superiority, in terms of DFS,

compared with continuous therapy in the extended adjuvant setting. Despite a large number of patients enrolled in this study, the small proportion of DFS events observed during the follow-up time did not reveal differences between treatment groups. Clinically, the association of similar outcomes with modest improvements in quality of life will be reassuring to patients and clinicians, who may, for various reasons, need or choose to interrupt extended adjuvant therapy.

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## DATA SHARING

After publication, access to de-identified individual participant data may be requested by researchers by submitting a proposal (to [stat\\_center@ibcsg.org](mailto:stat_center@ibcsg.org)), which will be reviewed for scientific merit and feasibility in accordance with IBCSG guidelines for collaborative research and data sharing policy.

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