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Editorial

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Are we there yet? Optimal duration of endocrine therapy in women with postmenopausal early-stage hormone receptor-positive breast cancer

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A common question during family car trips is "Are we there yet?" So too do our patients with early-stage hormone receptor-positive breast cancer ask when their endocrine therapy will end. Hormone receptor–positive breast cancer is known for its propensity for late relapse, with recurrences occurring steadily for up to 20 years (1). Over the past decade, numerous trials have contributed to the growing body of evidence that supports the use of extended-duration endocrine therapy (2-5). However, there is an ongoing need to identify the ideal duration of endocrine therapy and better define which patients benefit most from extended treatment durations.

In this issue of the Journal, Mamounas et al. (6) report 10-year results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 trial evaluating extended letrozole therapy in early-stage breast cancer in an analysis that was not prespecified in the original protocol. In this double-blind, randomized, phase 3 trial, postmenopausal women with stage I-IIIA hormone receptor–positive breast cancer who were disease free after 5 years of adjuvant endocrine therapy with either an aromatase inhibitor (AI) or tamoxifen followed by AI were randomly assigned to receive an additional 5 years of letrozole versus placebo. A total of 3966 patients enrolled between 2006 and 2010. The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS), breast cancer–free interval, distant recurrence, incidence of osteoporotic fracture, and incidence of arterial thrombotic events.

With a median follow-up of 10.3 years, the study demonstrated a statistically significant improvement in DFS with extended letrozole compared with placebo, with a hazard ratio (HR) for DFS of 0.85 (95% confidence interval [CI] = 0.74 to 0.96, $P = .01$). The 10-year DFS was 72.6% for placebo and 75.9% for letrozole, with an absolute difference of 3.3%. In the original report of NSABP B-42 with 6.9 years of median follow-up, the hazard ratio for DFS was 0.85 (95% CI = 0.73 to 0.999), with a 7-year DFS of 81.3% (95% CI = 79.3% to 83.1%) for placebo and 84.7% (95% CI = 82.9% to 86.4%) for letrozole (absolute difference of 3.4%) (5), a result that was not statistically significant. This change in statistical significance is likely due to increased events with less variance because the magnitude of treatment effect was unchanged. It is noteworthy that the magnitude of the treatment effect was preserved, suggesting a durable effect. In the current update, the authors also reported a statistically significant improvement in breast cancer–free interval (HR = 0.75, 95% CI = 0.62 to 0.91, $P = .003$, absolute difference 2.7%) and distant recurrence (HR = 0.72, 95% CI = 0.55 to 0.92, $P = .01$, absolute difference 1.8%). There was no difference in OS (HR = 0.97, 95% CI = 0.82 to 1.15). Safety analysis at 10 years showed no additional toxicity signals including arterial thrombotic events, and the osteoporotic fracture rate did not differ between treatment groups (10-year incidence 6.1% for placebo, 95% CI = 5.0% to 7.4% vs 6.6% for letrozole, 95% CI= 5.4% to 7.8%).

A key finding from the multivariable Cox model was that prior tamoxifen use was independently associated with better DFS (HR = 0.76, 95% CI = 0.66 to 0.87, $P = .001$). This suggests there was a larger reduction in recurrence risk for patients who were initially treated with tamoxifen, and patients who received an upfront AI may have benefitted less from extended durations of AI. This result is supported by a recent meta-analysis by the Early Breast Cancer Trials Collaborative Group that showed improved OS when extended AI therapy followed 5 years of tamoxifen (7).

This study has multiple strengths and adds to the growing data to support the use of extended endocrine therapy. It is the largest trial to date of continuous extended adjuvant AI therapy, demonstrating excellent retention because 3923 of 3966 patients who enrolled were available for inclusion in the efficacy analysis with a median treatment duration of 59.8 months. Though not a prespecified analysis, it provides valuable long-term follow-up. One limitation is that the authors do not report adherence, so it is difficult to assess whether the study reflects contemporary practice where the challenge of adherence to endocrine therapy is better recognized. Also worth noting is that the authors do not state how many patients received adjuvant chemotherapy and/or radiotherapy, which is reported in similar trials. However, 43% of patients were node positive compared with other extended AI trials including MA.17 (51%), SALSA (33%), DATA (67%), IDEAL (74%), and SOLE (99%) (3,4,8-10), suggesting that all trials focused on a higher-risk population. An additional challenge is that, since the study was designed, there have been major changes to clinical practice, including the use of adjuvant CDK4/6 inhibitors in high-risk patients and adjuvant bisphosphonates in postmenopausal patients, both of which have demonstrated survival advantages (11,12). Finally, the NSABP B-42 trial, like most large

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trials studying extended endocrine therapy, focused on postmenopausal patients, leaving us to speculate how best to apply these results for our premenopausal patients.

Because of the practical importance of the question of therapy duration, several key trials with variable design have examined extended endocrine therapy. Like NSABP B-42, the MA.17 trial (3) demonstrated a statistically significant improvement in DFS with a 5-year extension of letrozole. At a 6.3-year median follow-up, the 5-year DFS was 95% (95% CI = 93% to 96%) with letrozole and 91% (95% CI = 89% to 93%) with placebo (HR = 0.66, $P = .01$). The DATA trial (9) randomized patients to receive either 3 or 6 years of anastrozole treatment if they were disease free after 2-3 years on tamoxifen. There was no observed difference in DFS in this study; 10-year DFS was 69.2% (95% CI = 55.8% to 72.3%) in the 6-year group vs 66.0% (95% CI = 62.5% to 69.2%) in the 3-year group (n = 833) (HR = 0.86, 95% CI = 0.72 to 1.01, $P = .073$). Notably, no individual trial has demonstrated an OS advantage with extended AI therapy. However, the ATLAS trial did demonstrate improved OS and decreased breast cancer recurrence with extended tamoxifen treatment (2).

Several trials suggest an intermediate duration of endocrine therapy may be sufficient. The IDEAL trial (4) randomized patients to receive either 2.5 or 5 years of letrozole after 5 years of any endocrine therapy. The trial reported a reduction in risk of second primary breast but no difference in DFS between the 2.5- and 5-year groups (HR = 0.91, 95% CI = 0.74 to 1.16) or OS (HR = 1.04, 95% CI = 0.78 to 1.38). The GIM4 (13) study randomized patients who were disease free after 2 to 3 years of tamoxifen to receive an additional 2 to 3 years or 5 years of letrozole. They reported that extended treatment with 5 years of letrozole resulted in a statistically significant improvement in DFS compared with 2 to 3 years of letrozole at a median follow-up of 11.7 years (HR = 0.78, 95% CI = 0.65 to 0.93, $P = .0064$). Interestingly this also supports the observation from NSABP B-42 that extended AI therapy may be most beneficial in patients who initially receive tamoxifen. The SALSA trial (8) randomized patients who were disease free after 5 years of endocrine therapy to receive an additional 2 vs 5 years of anastrozole. There was no difference in disease progression or death at 8 years (HR = 0.99, 95% CI = 0.8 to 1.15). In aggregate, these studies suggest that, for some patients, the ideal duration of endocrine therapy may be 7 to 8 years. On the basis of these cumulative results, current American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network guidelines recommend extended therapy including an AI for patients with node-positive disease (14). ASCO guidelines also recommend consideration of extended endocrine therapy for patients with high-risk node-negative disease but acknowledge that, given the modest benefit, a personalized approach is needed for lower-risk patients. In practice, treatment durations of 7-8 years are offered primarily to intermediate-risk patients, whereas 10 years of therapy is typically recommended to high-risk patients.

Because of concern about adherence and toxicity, one study examined the use of intermittent rather than continuous AI therapy. The SOLE trial (10) randomly assigned patients who had completed 4-6 years of adjuvant endocrine therapy to receive 5 years of either continuous letrozole or intermittent letrozole (9 months "on" followed by 3 months "off"). There was no difference in DFS after a median follow-up of 60 months (HR = 1.08, 95% CI = 0.93 to 1.26, $P = .31$). This trial included only lymph node–positive patients, a high-risk population. This suggests alternative schedules may be safe and mirrors the "real world" where many patients require treatment breaks.

Sadly, none of the studies have identified methods to predict which patients benefit most from extended therapy. It is crucial to identify methods for risk stratification to prevent overtreatment and toxicity including long-term fracture risks. The Breast Cancer Index (BCI), a gene expression signature based on the molecular grade index and HOXB13/IL17BR (H/I) ratio, is one method currently under investigation. The aTTom trial (15) demonstrated that node-positive patients classified as BCI (H/I)-high derived statistically significant benefit with 10 years of tamoxifen (HR = 0.35, 95% CI = 0.15 to 0.86; 10.2% absolute risk reduction), whereas BCI (H/I)-low patients showed no statistically significant benefit from extended endocrine therapy. There also has been interest in using other genomic signatures such as Mammaprint to predict benefit from extended endocrine therapy (16). Other tools under investigation include EndoPredict, the CTS5 calculator, and the presence of circulating tumor cells or cfDNA (17-19). To date, only use of the BCI for patients with node-negative or 1-3 nodes is supported by ASCO and National Comprehensive Cancer Network guidelines (20). Given the mounting evidence to support extended endocrine therapy, including the data presented here by the NSABP B-42 trial, it will be critical to accelerate biomarker-driven research to identify optimal duration of therapy for individual patients (both premenopausal and postmenopausal) so that we can better answer their question of "Am I there yet?"

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this editorial.

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