The Optimal Duration and Selection of Adjuvant Endocrine Therapy for Breast Cancer: How Long Is Enough?

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OVERVIEW

Women with estrogen receptor (ER)+ early breast cancer (BC) are at continuing risk of relapse up to at least 15 years after diagnosis, despite being on adjuvant endocrine therapy for approximately 5 years. Extended adjuvant endocrine therapy with an aromatase inhibitor (AI) after 5 years of tamoxifen further reduces the risk of recurrence in postmenopausal women. More recently, continuing tamoxifen for 10 years has also been shown to further reduce the risk of recurrence compared with 5 years. There are no direct comparative data on the relative merits of extended tamoxifen compared with an AI; indirect evidence suggests that an AI may have increased efficacy but a greater adverse effect on quality of life. Results are awaited on the need for continuing front-line adjuvant AIs for more than 5 years. The next challenge is to determine which patients will benefit from this long-term treatment. Currently, tumor size, nodal involvement, and gene expression profile as measured by the PAM50 Risk of Recurrence (ROR) score have all been shown to have prognostic significance for late recurrence beyond 5 years.

ADJUVANT TAMOXIFEN

The first randomized trials of adjuvant tamoxifen for early BC began in the mid-1970s and compared 1 to 2 years of tamoxifen with no endocrine treatment.1-3 Early results showed a reduction in recurrences in the tamoxifen arms, but these occurred mainly during the treatment period, with little or no carryover benefit thereafter. This led to the hypothesis that treatment of longer duration might further improve results.4 Concurrent data from animal models suggested that the effect of tamoxifen was cytostatic rather than cytotoxic,5 further suggesting that adjuvant tamoxifen should be continued indefinitely to maximize the effect. These initial clinical and preclinical observations led to an arbitrary duration of 5 years being chosen for many subsequent adjuvant tamoxifen trials.6

The Oxford EBCTCG meta-analyses have demonstrated a clear reduction in mortality in women treated with tamoxifen for approximately 5 years, with the proportional risk reductions little affected by age or node status.7,8 The most recent Oxford overview, with a median follow-up of 13 years, showed that in ER+ disease, tamoxifen for about 5 years achieves a reduction of yearly BC mortality by about one-third throughout the first 15 years.8 This indicates a clear carryover rate for many years after discontinuation (rate ratio [RR] = 0.70; p < 0.00001), including 0.53 in years 0 to 4 and 0.68 in years 5 to 9, with no subsequent loss of the gains made during the first decade. Over all time periods the recurrence rate reduction averaged 39% (RR = 0.61 for any recurrence, and 0.62 for contralateral disease incidence; both 2p < 0.00001).8 After year 10 there was no convergence of the recurrence curves (RR = 0.97 in years 10 to 14), indicating that 5 years of tamoxifen can prevent a high proportion of recurrences and potentially cure many patients, rather than simply delay an inevitable event.

Tamoxifen Duration: 5 Years or Less

In the early 1980s the Swedish Breast Cancer Cooperative Group started a multicenter, randomized trial that demonstrated the superiority of 5 years of adjuvant tamoxifen versus 2 years in the treatment of postmenopausal women with ER+ early BC.9 This additional benefit was confirmed in the Cancer Research United Kingdom “Over 50s” trial involving 3,499 women with early BC between age 51 and 81.10 Direct and indirect comparisons from overview analyses have also shown a greater mortality reduction with approximately 5 years tamoxifen versus 2 years and further reinforce these results.7,8

Of note, the reductions in recurrence and mortality during
years 0 to 4 in patients with ER+ disease were almost as great in trials of only 1 to 2 years as in trials of approximately 5 years of tamoxifen, and the additional benefit of 5 years only emerged during years 5 to 9. Approximately 18% of patients assigned to 5 years treatment discontinued therapy within 2 years, suggesting that with full compliance the benefit of 5 years over 2 would have been greater. The rate ratio for BC death of 0.70 (standard error = 0.06) in the overview analyses by allocated treatment suggests that with full compliance, 5 years of tamoxifen would reduce 15-year BC mortality rates by one-third or more.

**Long-Term Risk of Relapse**

BC is characterized by a very long natural history and some women remain at risk of late recurrence, with an annual rate of relapse in excess of 2% for at least 15 years after diagnosis, even after 5 years of tamoxifen. A similar risk remains for at least 10 years for postmenopausal women who have received 5 years of an AI. The Oxford overview analyses likewise show that at least 50% of recurrences occur more than 5 years after diagnosis. The challenge, therefore, has been to determine whether there is any outcome advantage in continuing adjuvant endocrine therapy for more than 5 years.

**Tamoxifen Beyond 5 Years**

Results of early, relatively small, trials assessing tamoxifen treatment for more than 5 years were inconclusive. A combined analysis, including 1,588 patients, failed to show any significant benefit of 10 years of tamoxifen over 5 years.

Indeed, the largest of these trials, the NSABP B-14 extension study, randomly assigned more than 1,100 patients in remission after 5 years of tamoxifen to either a further 5 years of tamoxifen or placebo, and actually showed a significant adverse effect for those continuing tamoxifen. At 7 years of follow-up, disease-free survival (DFS) was 82% for those on placebo versus 78% for those continuing tamoxifen (p = 0.03).

This suggestion that prolonged tamoxifen had an adverse effect was supported by experimental data showing that, in some instances, prolonged exposure to tamoxifen eventually has an agonistic rather than antagonistic effect on BC growth, inducing tumor dependence or resistance.

For many years, BC specialists were relaxed in the belief that 5 years of adjuvant therapy was optimal. Although further, much larger, trials were underway, a clinical alert from the U.S. National Cancer Institute stated that “all available evidence indicates that 5 years of tamoxifen is a reasonable standard for the adjuvant setting” for all women of any age with invasive hormone receptor–positive BC.

Attitudes have recently changed, however, with results from these larger trials. In the first, the international ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trial, 12,894 women with early BC who had completed 5 years of tamoxifen were randomly assigned to continue tamoxifen to 10 years or to stop at 5 (Table 1). Results from the 6,846 women with known ER+ disease showed that 10 years of tamoxifen further reduced the risk of relapse (p = 0.002), BC mortality (p = 0.01), and all-cause mortality (p = 0.01) compared with approximately 5 years. Much of this benefit seemed to accrue late: there was only a modest reduction in recurrence rates during the 5 extra years of tamoxifen compared with a much greater carryover benefit during the following 5 years after completion of 10 years of tamoxifen.

Likewise, a reduction in mortality only emerged after completion of 10 years of tamoxifen. The benefit of continuing tamoxifen for a further 5 years is therefore achieved first by the carryover benefit from the first 5 years and then by the additional benefit of a further 5 years, giving a total estimated relapse risk reduction of 39% (p < 0.0001) and risk reduction of BC mortality of 36% (p < 0.0001). After 10 years of treatment, this estimated risk was reduced by 30% for relapse (2p = 0.01) and 48% for mortality (2p < 0.0001), continuing for at least 5 years. These carryover benefits contribute substantially to the cumulative benefits of treatment, particularly because toxic effects mostly occur during the active treatment period. The most important adverse events (AE) noted with 10 years of treatment were an increased risk of endometrial cancer (RR = 1.74) and pulmonary embolism (RR = 1.87). Reassuringly, there was there no increased incidence of strokes, and there was a decreased incidence of ischemic heart disease (RR = 0.76). Overall, the benefits of extended tamoxifen substantially outweighed the risks.

A second trial of similar design, aTTom (Adjuvant Tamoxifen: To Offer More?), randomly assigned 6,953 U.K. women in continuous remission after 5 years of tamoxifen to a further 5 years or to stop (Table 1). The results reinforced

**KEY POINTS**

- Women with early-stage estrogen receptor (ER)+ breast cancer have a continuing risk of relapse that extends up to at least 15 years despite the use of adjuvant therapy.
- Recent evidence shows that tamoxifen for up to 10 years in patients with ER+ BC further reduces recurrence and BC mortality compared with 5 years. The additional gain only emerges after 10 years.
- There is also strong evidence in postmenopausal women that extended adjuvant endocrine therapy with an aromatase inhibitor (AI) after approximately 5 years of tamoxifen also further reduces the risk of recurrence and improves survival, at least in those with node-positive disease. There are no direct comparative data on the relative merits of extended tamoxifen versus an AI.
- Results are awaited on the need for continuing front-line adjuvant AIs for more than 5 years, but circumstantial evidence suggests that there will probably be further benefit.
- An important challenge is to determine which patients will benefit from this long-term treatment. Currently, tumor size, nodal involvement, and gene expression profile as measured by the PAM50 Risk of Recurrence score have all been shown to have prognostic significance for late recurrence beyond 5 years.
<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-Up</th>
<th>Population</th>
<th>DFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA.17</td>
<td>5 yr</td>
<td>Postmenopausal HR+EBC who had received 4.5 to 6 yr of adjuvant T therapy</td>
<td>0.68 (0.56, 0.83), p &lt; 0.001</td>
<td>0.99 (0.79, 1.24), p = 0.83</td>
</tr>
<tr>
<td>Double-Blind</td>
<td>64-mo follow-up</td>
<td>IPCW 0.52 (0.45, 0.61), p &lt; 0.001</td>
<td>IPCW 0.61 (0.52, 0.71), p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>L vs. Placebo</td>
<td></td>
<td>SCC* 0.58 (0.47-0.72), p &lt; 0.001</td>
<td>SCC* 0.76 (0.60, 0.96), p = 0.02</td>
<td></td>
</tr>
<tr>
<td>ABCSG Trial 6a</td>
<td>5 yr</td>
<td>Postmenopausal HR+EBC who had received 3 yr of adjuvant T therapy, with or without AG, for the first 2 yr of therapy</td>
<td>0.62 (0.40, 0.96), p = 0.031</td>
<td>0.75 (0.62, 0.90), p = 0.01</td>
</tr>
<tr>
<td>Open-Label</td>
<td>62.3-mo follow-up</td>
<td>10 yr RR 0.90 (0.79, 1.02), p = 0.10</td>
<td>BC mortality: 5-9 yr RR 0.97 (0.79, 1.18), p = 0.74</td>
<td></td>
</tr>
<tr>
<td>NSABP-33</td>
<td>1 yr</td>
<td>Postmenopausal HR+EBC who were disease-free after 5 yr of adjuvant T</td>
<td>0.68, p = 0.07</td>
<td>NA</td>
</tr>
<tr>
<td>Double-Blind</td>
<td>30-mo follow-up</td>
<td>&gt; 10 yr RR 0.75 (0.62, 0.90), p = 0.01</td>
<td>BC mortality: &gt; 10 yr RR 0.71 (0.58-0.88), p = 0.002</td>
<td></td>
</tr>
<tr>
<td>E (5 yr) vs. Placebo (5 yr)</td>
<td></td>
<td>All years log-rank = 0.002</td>
<td>Any death RR 0.87 (0.78, 0.97), p = 0.01</td>
<td></td>
</tr>
<tr>
<td>ATLAS23</td>
<td>5 yr</td>
<td>Pre- and postmenopausal women with ER+EBC who had already been taking T for 5 yr (in the context of ATLAS trial total n = 12,894)</td>
<td>5-9 yr RR 0.90 (0.79, 1.02), p = 0.10</td>
<td>Any death RR 0.87 (0.78, 0.97), p = 0.01</td>
</tr>
<tr>
<td>Open-Label</td>
<td></td>
<td>Absolute reduction at yr 15: 3.7%</td>
<td>Death with recurrence RR 0.83 (0.72, 0.96), p = 0.01</td>
<td></td>
</tr>
<tr>
<td>T for Additional 5 yr (10 yr) vs. Stop T (5 yr)</td>
<td></td>
<td>BC mortality: All years RR 0.85 (0.77, 0.94), p = 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aTTom24</td>
<td>5 yr</td>
<td>Invasive EBC who had already been taking T for 5 yr, 2,755 ER+ (39%) and 4,198 ER untested (61%) (estimated 80% ER+ if status unknown)</td>
<td>RR 0.85 (0.76-0.95), p = 0.003</td>
<td>Death without recurrence RR 0.78 (0.78, 0.86), p = 0.24</td>
</tr>
<tr>
<td>Open-Label</td>
<td></td>
<td>Absolute reduction 4%</td>
<td>BC mortality: &gt; 10 yr RR 0.75 (0.63, 0.90), p = 0.007</td>
<td></td>
</tr>
<tr>
<td>T for Additional 5 yr vs. No Further Treatment</td>
<td></td>
<td>BC mortality: All years RR 0.88 (0.74, 1.03), p = 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled Analysis ATLAS+ aTTom</td>
<td>10 yr</td>
<td>10,543 ER+ from ATLAS plus 6,934 ER+ from aTTom</td>
<td>NA</td>
<td>BC mortality: 5-9 yr RR 0.97 (0.84, 1.15)</td>
</tr>
<tr>
<td>T 10 vs. 5 yr</td>
<td></td>
<td>BC mortality: &gt; 10 yr RR 0.75 (0.65-0.86), p = 0.000004</td>
<td>BC mortality: All years RR 0.85 (0.77, 0.94), p = 0.001</td>
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</tbody>
</table>

**Abbreviations:** A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; AI, aromatase inhibitor; BC, breast cancer; CI, confidence intervals; DFS, disease-free survival; E, exemestane; EBC, early breast cancer; ER, estrogen receptor; HR, hazard ratio; HR+ hormone receptor-positive; IPCW, Inverse probability of censoring weighted; L, letrozole; mo, months; n, number; NA, not available; OS, overall survival; RR, rate ratio; SCC, approach proposed by Shao, Chang, and Chow*; T, tamoxifen; vs., versus; yr, year.


**Analysis of patients with ER+ disease only.**

**Figures are derived from the abstract [24] and the presentation at the 2013 ASCO Annual Meeting, available online.**

**IPCW estimate of the effect in patients with ER+ disease.**
those from ATLAS. The BC recurrence rate was 16.7% in the 10-year study group compared to 19.3% in the 5-year study group. As in the ATLAS trial, there was a time-dependent reduced risk of recurrence with 10 years of tamoxifen with an RR of 0.99 during years 5 to 6, 0.84 during years 7 to 9, and 0.75 subsequently. Longer treatment also reduced BC mortality in a time-dependent fashion, with an RR of 1.03 during years 5 to 9 and 0.77 later; likewise, the overall mortality rate ratio was 1.05 during years 5 to 9 and 0.86 later. Non-BC mortality was little affected (457 vs. 467 deaths, RR = 0.94). The most serious AE of long-term tamoxifen was an increase in endometrial cancer: in the long and short treatment arms of the trial was unblinded, allowing patients in the control arm to switch to letrozole. At a median follow-up of 30 months a relative reduction in recurrence risk of 42% emerged with letrozole.31 Letrozole significantly reduced the risk of distant metastases in patients with both node-negative and -positive disease (p = 0.002), and significantly improved OS by 39% in patients with node-positive disease (HR 0.61, p = 0.04).

A more recent IPCW (inverse probability of censoring weighted) Cox model analysis adjusting for the effects of treatment cross-over showed that patients initially assigned to receive letrozole had a hazard ration of 0.52 for DFS, 0.51 for distant DFS (DDFS) and 0.61 for OS (all p < 0.0001) at a median follow-up of 64 months.33

Subgroup analyses of MA.17 showed that letrozole had similar benefits in older (> age 70, 1,323 patients, 26%) versus younger (< age 60) patients without any increase in toxicity compared with placebo. Importantly, the 877 women premenopausal at diagnosis experienced significantly greater DFS benefit on letrozole (HR 0.26) than the 4,289 women who were postmenopausal at time of initial diagnosis (HR 0.67, p = 0.03 for interaction).34 Therefore, premenopausal patients with BC who have become menopausal by the end of adjuvant tamoxifen also benefit significantly from extended adjuvant therapy.

The optimal duration of extended adjuvant AI therapy remains unclear. An exploratory analysis suggested that the HR continues to fall for DFS and DDFS but not for OS out to 48 months, indicating that the benefit of letrozole increases with longer exposure.35 The 66% cross-over rate in MA.17 from placebo to letrozole after unblinding offered the chance of testing whether starting an AI after a sizeable treatment gap could still be of any benefit.36 At a median follow-up of 5.3 years, a significant reduction in recurrence risk (adjusted HR 0.37, p < 0.0001) and a significant 61% improvement in DDFS (p = 0.004) was found in the 1,579 patients who switched to letrozole compared with the 804 who did not, despite the former having more adverse prognostic factors. These results suggest that AI therapy started more than 7 years after diagnosis can still reduce the risk of late relapse in hormone receptor–positive BC.

**ADJUVANT AIs**

The development of AIs has provided an alternative strategy to tamoxifen by preventing the synthesis of endogenous estrogens in postmenopausal women and in premenopausal women in whom ovarian function has been suppressed.25,26 The so-called third-generation AIs, anastrozole, letrozole and exemestane, have all been shown to have modestly superior efficacy to tamoxifen as adjuvant endocrine therapy, and these have become the first-choice standard of care for postmenopausal women with ER+ BC.12,27-29

**Extended Adjuvant Letrozole Therapy after 5 Years of Tamoxifen**

AIs are usually given for approximately 5 years simply because that was the practice with tamoxifen. A groundbreaking trial, NCIC-CTG MA.17/BIG 1–97 (usually referred to as MA.17), tested the effectiveness of 5 years of letrozole versus placebo after completion of the standard 4 to 6 years of adjuvant tamoxifen in postmenopausal women in continuous remission (Table 1).30

At a median follow-up of 2.4 years, a highly significant reduction in the risk of recurrence was seen in the letrozole arm (DFS hazard ratio [HR] 0.57, p = 0.00008).30 Following this, the trial was unblinded, allowing patients in the control arm to switch to letrozole. At a median follow-up of 30 months a relative reduction in recurrence risk of 42% emerged with letrozole.31 Letrozole significantly reduced the risk of distant metastases in patients with both node-negative and -positive disease (p = 0.002), and significantly improved OS by 39% in patients with node-positive disease (HR 0.61, p = 0.04). A more recent IPCW (inverse probability of censoring weighted) Cox model analysis adjusting for the effects of treatment cross-over showed that patients initially assigned to receive letrozole had a hazard ration of 0.52 for DFS, 0.51 for distant DFS (DDFS) and 0.61 for OS (all p < 0.0001) at a median follow-up of 64 months.33

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**Other Extended Adjuvant Therapy Trials with AIs**

Other trials have investigated the role of extended adjuvant AI therapy (Table 1). In the Austrian Breast and Colorectal Cancer Study Group (ABCSD) Trial 6a, 856 ER+ postmenopausal patients who were disease-free after 5 years of adjuvant tamoxifen (with or without aminoglutethimide) were randomly assigned to receive either 3 years of anastrozole or no further treatment.37 At a median follow-up of 62 months, anastrozole further reduced the risk of a BC event (locoregional recurrence, distant recurrence, or contralateral BC) by 38% (HR 0.62, p = 0.031). There was no statistically significant difference in OS.
The NSABP-B33 trial investigated extended adjuvant therapy with exemestane in postmenopausal women with clinical T1–3N1M0 BC who were disease-free after 5 years of adjuvant tamoxifen.38 This trial closed prematurely after the publication of the results of MA.17, but at 30 months of median follow-up, ITT analysis showed a trend toward improvement in 4-year DFS (91% vs. 89%; RR 0.68; p = 0.07) and a statistically significant improvement in 4-year recurrence-free survival (RFS; 96% vs. 94%; RR 0.44; p = 0.004).

Finally, the Adjuvant Post-Tamoxifen Exemestane versus Nothing Applied (ATENA) trial comparing exemestane with observation after 5 years of previous tamoxifen was also closed prematurely after recruiting only 448 patients.39

An EBCTCG meta-analysis of these trials confirmed that extended adjuvant AI treatment was associated with an absolute 2.9% decrease in BC recurrence (relative decrease, 43%; p < 0.00001), and an absolute 0.5% decrease in BC mortality (relative decrease, 27%; p = 0.11) at a median follow-up of 2.5 years, with the magnitude of these effects probably underestimated because of cross-over after unblinding.40

Side Effects with Extended Adjuvant AI Therapy

The Quality of Life (QoL) Questionnaire (MENQOL), completed at baseline, 6 months, and annually by 70% (3,612 of 5,187) of patients in the MA.17 study, showed that hot flashes, anorexia, arthralgia, myalgia, and alopecia were more common on the treatment arm.31,41 In the overall population treatment was well tolerated; 4.5% of the women on letrozole group discontinued treatment because of toxicity, compared with 3.6% of the women on the placebo (p = 0.019).30 Overall, older patients discontinued treatment more frequently (24% of patients age 70 and older, 18% of patients age 60 or younger, and 19% of patients age 61 to 69; p = 0.0003).42

Conversely, more women under age 60 discontinued treatment specifically for toxicity in the letrozole versus the placebo group (5% vs. 3%, respectively; p = 0.008). A more recent analysis of women who were premenopausal at diagnosis and yet eventually treated with extended adjuvant letrozole showed significantly worse QoL measures than those on placebo, including role function-physical (p = 0.02), general health (p = 0.04), vitality domains (p = 0.001), and physical overall scale (p = 0.04).44

Comparison between letrozole and placebo showed no significant difference in the incidence of cardiovascular events or hypercholesterolemia.31

An increased risk of osteoporosis as a result of profound estrogen depletion and accelerated bone resorption was also seen in MA.17 among women treated with letrozole compared to placebo (8.1% vs. 6.0%, p = 0.003), but there was no significant increase in bone fractures (5.3% vs. 4.6%; p = 0.25).31,43

Up-Front AI Adjuvant Therapy for More Than 5 Years

The MA.17 and similar trials described above are among the most important in the recent history of adjuvant endocrine therapy because they demonstrate a proof of principle that therapy for more than 5 years further reduces the risk of long-term relapse. In reality, however, most postmenopausal women are now started on an AI up front and not after several years of tamoxifen. Do they also benefit from continuing their AI beyond 5 years?

Several ongoing studies are investigating this issue and are summarized in Table 2.44

While results of these are awaited, what advice can be given to the practicing clinician? It is our view that there is likely to be further benefit from continuing an AI for more than 5 years, by extrapolation from the recent large trials of extended tamoxifen therapy (ATLAS and aTTom) and of an AI after 5 years tamoxifen (including, in particular, MA.17). The improved outcome of front-line AIs over tamoxifen is modest and unlikely to eliminate the risk of late relapse. We therefore currently recommend continuing an AI beyond 5 years in women at significant initial risk of relapse (see below) with the caveat that our recommendation is based on extrapolated data.

UNRESOLVED ISSUES

Extended Adjuvant Therapy with Tamoxifen or an AI?

There are no randomized data on this important issue, and indeed it would take large numbers of patients and many years to obtain such data. Indirect comparisons between the ATLAS and aTTom trials on the one hand and MA.17 for patients initially premenopausal on the other suggest that letrozole may be more effective than tamoxifen. In the ATLAS trial, the benefit in DFS for a further 5 years of tamoxifen had a hazard ratio of 0.87 (p = 0.01), and emerged only after year 10 (HR for DFS 0.75).23 In contrast, MA.17 reported that letrozole during years 5 to 10 significantly improved DFS with a greater HR than for ATLAS, both during the treatment period (HR for DFS 0.58) and thereafter (HR for DFS 0.68; both p = 0.001).31,33,35 Adjusting for cross-over, both studies reported an OS benefit at 10 years for extended adjuvant therapy (HR 0.71 for ATLAS and 0.61 for MA.17 by IPCW); both were statistically significant (p = 0.0016 and 0.001, respectively).23,33

Another source of indirect data comes from a group of trials in which patients on adjuvant tamoxifen were randomly assigned to switching to an AI after 2 to 3 years versus continuing tamoxifen for 5 years.45-48 These consistently showed an outcome benefit from the switch, and by extrapolation this might argue for switching to letrozole after 5 years of tamoxifen rather than continuing tamoxifen.

Balanced against this, there is probably a higher risk of side effects and impaired QoL by switching to an AI. The younger patient subgroup that switched from tamoxifen to letrozole in MA.17 (representing the age range of patients most likely to be affected by this decision) experienced a significantly worse QoL than those on placebo.

In the absence of direct comparative data, our current clinical policy therefore is to continue tamoxifen beyond 5 years in women at moderate risk of relapse and those who remain premenopausal, but to recommend a switch to an AI for those at initial high risk (see below).
### TABLE 2. Ongoing Randomised Phase III Clinical Trials of Extended Aromatase Inhibitor Therapy

<table>
<thead>
<tr>
<th>Study and Design</th>
<th>Primary Objective (Secondary Objectives)</th>
<th>N</th>
<th>Population (Treatment Received Pre-Enrollment)</th>
<th>Arms at Randomization</th>
<th>Study Number</th>
<th>Status in ClinicalTrials.gov*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA.17R Double-Blind</td>
<td>DFS (OS, safety, contralateral BC, quality of life)</td>
<td>1,918</td>
<td>Prior 4.5-6 yr of AI, with or without prior T</td>
<td>L (5 yr) vs. placebo (5 yr)</td>
<td>NCT00754845</td>
<td>Active, not recruiting</td>
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<tr>
<td>SALS A Open-Label</td>
<td>DFS (OS, rate of fracture occurrence, contralateral BC)</td>
<td>3,486</td>
<td>Any endocrine therapy (4-6 yr)</td>
<td>A (5 yr) vs. A (2 yr)</td>
<td>NCT00295620</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>LEAD Open-Label</td>
<td>DFS (OS, safety)</td>
<td>4,050</td>
<td>T (2-3 yr)</td>
<td>L (5 yr) vs. L (2-3 yr)</td>
<td>NCT01064635</td>
<td>Recruiting</td>
</tr>
<tr>
<td>DATA Open-Label</td>
<td>DFS (OS, safety, contralateral BC)</td>
<td>1,900</td>
<td>T (2-3 yr)</td>
<td>A (6 yr) vs. A (3 yr)</td>
<td>NCT00301457</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>NSABP-B42 Double-Blind</td>
<td>DFS (OS, BCFI, distant recurrence, osteoporotic-related fractures, arterial thrombotic events)</td>
<td>3,966</td>
<td>AI or T→AI³ (total 5 yr)</td>
<td>L (5 yr) vs. placebo (5 yr)</td>
<td>NCT00382070</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>SOLE Open-Label</td>
<td>DFS (OS, distant DFS, BCFI, sites of 1st DFS failure, distant recurrence, 2nd [nonbreast] malignancies, deaths without prior cancer events, adverse events)</td>
<td>4,800</td>
<td>Any endocrine therapy* (5 yr)</td>
<td>L (5 yr) vs. intermittent* (5 yr)</td>
<td>NCT00533410</td>
<td>Active, not recruiting</td>
</tr>
</tbody>
</table>

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; BCFI, breast cancer-free interval; DFS, disease-free survival; L, letrozole; LEAD, Letrozole Adjuvant Therapy Duration trial; SALS A, Secondary Adjuvant Long-Term Study with Arimidex trial; DATA, Different Durations of Anastrozole after Tamoxifen trial; OS, overall survival; SOLE, Study of Letrozole Extension trial; n, number; T, tamoxifen; vs., versus; yr, year.

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Who Needs Extended Adjuvant Endocrine Therapy?

The large majority of patients in continuing remission after 5 years of endocrine therapy do not, of course, experience relapse. In the MA.17 trial, the 4-year DFS (i.e., year 9 since initial diagnosis) in the placebo group was 87%.³⁰ In the ATLAS trial, the cumulative incidence of BC recurrence among patients with ER+ disease who stopped treatment at 5 years was only 14.5% at 10 years after diagnosis and 25.1% after 15 years.²³ The challenge is to select which patients are likely to benefit from long-term treatment.

The ATLAS trial showed no significant heterogeneity in the proportional risk reduction with respect to patient or tumor characteristics or site of first recurrence.²³

The MA.17 trial showed that the OS benefit from extended endocrine therapy was restricted to patients with lymph node-positive disease who received letrozole (HR 0.61, p = 0.04)²³ and a subsequent analysis suggested a greater benefit in patients with both ER+ and progesterone receptor (PgR)-positive tumors.⁴⁹

In a subset (940 patients) of patients randomly assigned to the monotherapy arms of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial,⁵₀ a multivariate analysis found node status and tumor size to be the only individual factors that added prognostic information in years 5 to 10 (node status: \( \chi^2 = 21.72, p < 0.001 \); tumor size: \( \chi^2 = 10.52, p = 0.001 \)). Fifty no further prognostic information was added by grade and receptor status, despite the fact that ER and PgR status had proven to be significant prognostic variables for years 1 to 5.

An immunohistochemical (IHC) marker score (IHC4) and two gene expression profile tests (OncoType DX Recurrence Score [RS] and PAM50 Risk of Recurrence [ROR]) were also assessed specifically for predicting outcome in years 5 to 10.⁵²–⁵⁴ ROR was the strongest molecular prognostic factor in predicting late recurrence and discriminating patients into low and high risk for late distant recurrence (\( \chi^2 = 16.29; p < 0.001 \)); IHC4 (\( \chi^2 = 7.41 \)) and RS (\( \chi^2 = 5.55 \)) were only weakly prognostic in this period (years 5 to 10).²³

More recently, the same group confirmed that ROR score added prognostic information to the clinical treatment score in all patients and subgroups in the 5 to 10 year follow-up period, in univariate and multivariate analyses. In combined analysis of 2,137 women in remission at year 5 from two cohorts (transATAC and ABCSG8 cohorts) the risk of distant recurrence in years 5 to 10 was significantly different for three risk groups: low (5.7%, 95% CI [4.5%, 7.2%]), intermediate (14.6%, 95% CI [12.0%, 17.6%]), and high (29.3%, 95% CI [25.5%, 33.6%]).⁵⁵ The authors suggested that the ROR score might be used to separate patients into risk groups and to select patients who could benefit most from extended hormone therapy.

Table 3 summarizes the main studies on other molecular assays (optimized to predict the risk of relapse in the context of patients treated with endocrine therapy) which have been tested in their ability to predict late relapse.⁵¹,⁵⁵–⁶¹

The prognostic EndoPredict (EP) score, a multigene score that combines the expression levels of proliferative genes and the ER gene (ESR1) signaling/differentiation-associated genes, was tested in 1,702 postmenopausal women treated with 5 years of adjuvant endocrine treatment. It showed that
the high EP group has a higher risk of early (0 to 5 years; HR 2.73, p = 0.001) as well as late relapse (HR 2.87, p = 0.013) and the significance was maintained when adjusted for clinico-pathologic variables in multivariate analysis.57 In the group with low EP, the risk of a distant event in the interval from 5 to 10 years was 3.71% (0.89% to 6.52%). A combined score including EP, node status, and tumor size (EPclin) performed very powerfully in defining a low-risk group associated with only 1.8% probability of distant metastasis from year 5 to 10.57 However, the group of patients defined by the pathologic variable in whom the assay is truly informative and clinically useful remains unclear.

The prognostic performance of the HOXB13/IL17BR (H/I) biomarker, already known to predict recurrences risk in patients with ER+ lymph node–negative BC,62 was tested in a nested case-control design of 83 recurrences matched to 166 non-recurrences from patients treated with letrozole and placebo within MA.17.58 In the absence of extended letrozole therapy, high H/I identifies a subgroup of patients with ER+ disease-free after 5 years of tamoxifen who are at risk for late recurrence. When extended endocrine therapy with letrozole is prescribed, high H/I predicts benefit from therapy and a decreased probability of late disease recurrence (odds ratio 0.35, p = 0.007).

Further research into applying molecular features and gene expression scores to standard clinico-pathologic criteria for tailoring extended endocrine therapy is now a high priority.

**CONCLUSION**

There is now strong evidence that both tamoxifen for up to 10 years in patients of any age with ER+ BC and an AI for 5 years in postmenopausal women who have already had 5 years tamoxifen further reduces recurrence and BC mortality. Currently there are no direct comparative data on the relative efficacies of these extended adjuvant therapy options. Likewise, there is not yet any direct evidence for continuing up-front AI therapy for more than 5 years, but circumstantial data suggest that there is likely to be a gain here too.

An important research challenge is now to identify which patients are likely to benefit from this type of long-term therapy. Preliminary data suggest that molecular approaches including gene expression platforms such as ROR may add to classical clinical parameters including tumor size and node status at diagnosis.

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**TABLE 3. Summary of the Main Studies Testing Molecular Assays Tested to Predict Risk of Late Relapse**

<table>
<thead>
<tr>
<th>References, Year of Publication</th>
<th>Patient Cohort(s)</th>
<th>Endocrine Treatment</th>
<th>Nodal Status</th>
<th>Biomarker(s) Assessed</th>
<th>Group at High Risk for Late Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sestak et al, 201351</td>
<td>ATAC</td>
<td>T or A</td>
<td>Node-negative and positive</td>
<td>IHC4, RS, ROR (from PAM50)</td>
<td>High ROR</td>
</tr>
<tr>
<td>Sestak et al, 201355</td>
<td>transATAC ABCSG8 Trial</td>
<td>T or T followed by A</td>
<td>Node-negative and positive</td>
<td>ROR</td>
<td>High ROR</td>
</tr>
<tr>
<td>Dubsky et al, 201357</td>
<td>ABCSG6 Trial ABCSG8 Trial</td>
<td>T or T followed by A</td>
<td>Node-negative and positive</td>
<td>EndoPredict (EP), EPclin (including tumour size and nodal status)</td>
<td>High EP, High EPclin</td>
</tr>
<tr>
<td>Sgroi et al, 201358</td>
<td>MA.17</td>
<td>T followed by L</td>
<td>Node-negative</td>
<td>HOXB13/IL17BR (H/I)</td>
<td>High HOXB13/IL17BR (H/I)</td>
</tr>
<tr>
<td>Sgroi et al, 201359</td>
<td>ATAC</td>
<td>T or A</td>
<td>Node-negative</td>
<td>BCI (linear combination model), HOXB13/IL17BR (H/I), MGI IHC4, RS</td>
<td>Intermediate/high BCI, High HOXB13/IL17BR (H/I)</td>
</tr>
<tr>
<td>Bianchini et al, 201360</td>
<td>Public data sets</td>
<td>T</td>
<td>Node-negative and positive</td>
<td>Combination of proliferation (MKS, GGI) and ERS markers</td>
<td>High-proliferation/high, ERS Low-proliferation/low ERS</td>
</tr>
<tr>
<td>Zhang et al, 201361</td>
<td>Stockholm cohort and institutional cohorts</td>
<td>T (2 or 5 yr)</td>
<td>Node-negative</td>
<td>BCI (linear combination model)</td>
<td>Intermediate/high BCI</td>
</tr>
</tbody>
</table>

Modified with permission from Bianchini et al.56

Abbreviations: A, anastrozole; ABCSG, Austrian Breast and Colorectal Cancer Study Group; BCI, Breast Cancer Index; ERclin, combined EndoPredict and clinical variables; ERS, estrogen-related genes; GGI, Genomic Grade Index (MapQuant DX); HOXB13/IL17BR (H/I), homeobox B13/interleukin 17 receptor B two-gene ratio; IHC4, combination of four immunohistochemical markers; L, letrozole; MGI, Molecular Grade Index; MKS, Mitotic Kinase Score; ROR, Risk Of Recurrence (Prosigma); RS, Recurrence Score (Oncotype DX); T, tamoxifen.

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