Reducing the risk of late recurrence in hormone-responsive breast cancer

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Women with early breast cancer are exposed to an ongoing risk of relapse, even after successful surgical resection of the primary tumor and, where given, radiotherapy. Adjuvant chemotherapy and/or endocrine therapy can further help to prevent relapses by targeting metastatic disease deposits, which may be present but clinically undetectable. The benefits of adjuvant therapy are well documented, and millions of relapses have undoubtedly been prevented by treatment in this setting. Adjuvant tamoxifen has proven particularly effective in preventing relapses in hormone-receptor-positive (HR+) disease, and has been the standard treatment for affected women for over 30 years. However, long-term exposure to tamoxifen is associated with an unfavorable risk/benefit profile due to decreasing efficacy and an increasing incidence of harmful side effects. Although the risk of relapse is highest during the first 2–3 years after surgery, a residual risk remains indefinitely for those women who do not experience disease relapse in these early years, and the majority of all breast cancer recurrences and deaths occur after completion of 5 years of adjuvant tamoxifen. Hence, there is a great need for additional adjuvant therapies to reduce the considerable risk of late relapses in patients with HR+ disease: until recently no agent had been shown to provide a significant benefit over no further treatment. In 2003, upon publication of the first interim analysis of the MA.17 trial, letrozole became the first agent to be shown to significantly reduce relapses in women with HR+ early breast cancer who had completed 5 years of adjuvant tamoxifen. Subsequent analyses confirmed that letrozole significantly reduced recurrences, including distant metastases, and, in patients with node-positive disease, the agent also significantly improved overall survival, with the benefit of letrozole increasing with duration of therapy, at least up to 48 months. Preliminary results from a small, open-label study suggest that extended anastrozole therapy can also improve outcomes after completion of standard adjuvant tamoxifen. Ongoing analyses from MA.17, investigating how estrogen and progesterone receptor status and the length of time since finishing tamoxifen influence the effectiveness of letrozole, and studies evaluating the safety and efficacy of 10 years of extended aromatase inhibitor therapy, will help to optimize extended adjuvant therapy and improve outcomes for women with HR+ early breast cancer.

Key words: breast cancer, extended adjuvant therapy, hormone-responsive, recurrence

introduction

Breast cancer is the most common cancer in women, with over 1 million new cases being diagnosed annually worldwide. Early diagnosis and the ongoing development of new therapies have significantly improved outcomes, and many women with early disease can now expect to survive, disease free, for several years. In some cases, treatment may even be curative. However, metastatic breast cancer is still incurable, and over 500 000 breast-cancer-related deaths occur each year, indicating the importance of preventing recurrences, particularly at distant, metastatic sites.

Surgical resection of the primary tumor, whether through mastectomy or, increasingly, breast-conserving surgery, still forms the basis of treatment for women with early breast cancer. Radiotherapy is also given in the majority of cases to help prevent local recurrences. After surgery, and depending on the estimated risk of relapse at the time of presentation, patients may also receive systemic adjuvant therapy to further reduce the risk of disease recurrence by targeting undetectable micrometastases, which may be present at distant sites. In the absence of adjuvant therapy, the estimated risk of relapse at 15 years after diagnosis is 70 and 40% in node-positive and node-negative disease, respectively. Adjuvant therapy has proven highly effective in preventing both local and distant relapses [1]. The type of adjuvant therapy given depends primarily on the presence or absence of estrogen receptors (ER) and/or progesterone receptors (PgR). Patients with hormone-receptor-positive (HR+) disease will receive endocrine therapy, whereas chemotherapy is given in the absence of HRs (HR− disease) and in addition to endocrine therapy in patients with HR+ disease considered to be at increased risk of relapse, for example in cases where the tumor has spread to the lymph nodes.

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Over the past three decades, adjuvant therapy with the selective estrogen receptor modulator, tamoxifen, has greatly improved outcomes for millions of patients worldwide with HR+ breast cancer, significantly reducing the risk of recurrence and death compared with placebo [1]. Despite the proven benefits of adjuvant tamoxifen, relapses do still occur, with the peak risk of relapse occurring in the first 2–3 years after surgery. The third-generation aromatase inhibitors (AIs) were found to further reduce the risk of relapse in postmenopausal patients with HR+ early breast cancer; the current treatment options for the prevention of these early relapses in patients with HR+ disease are discussed by Dr Thürlimann elsewhere in this supplement. Furthermore, the risk of relapse continues indefinitely after surgery, and the risk of late relapses, that is, in years 6 and beyond, is particularly high in women with HR+ disease, but adjuvant tamoxifen is limited to 5 years due to an unfavorable risk/benefit profile in later years [2]. For many years, in the absence of any agent with proven efficacy and good tolerability in women who had successfully completed 5 years of tamoxifen, these patients were exposed to a continuing risk of late relapse. Evidence from the metastatic setting, showing that AIs can achieve responses in women with relapsed disease after or during tamoxifen therapy [3–10], suggests that HR+ breast cancer remains sensitive to endocrine therapy for many years. Women who remain disease free after completion of adjuvant tamoxifen are, therefore, candidates for additional endocrine therapy to help to reduce late relapses in patients with HR+ disease.

The MA.17 trial was designed to assess whether the third-generation AI, letrozole, improved outcomes compared with placebo in women who were disease free at completion of approximately 5 years of adjuvant tamoxifen. The first interim analysis showed that starting letrozole within 3 months of finishing tamoxifen significantly reduced the risk of recurrence, including distant metastases, in postmenopausal women with HR+ disease [11]. On the basis of these findings, letrozole was licensed for the treatment of women who had completed adjuvant tamoxifen, that is, in the ‘extended adjuvant’ setting, and, for the first time, women could be offered adjuvant endocrine therapy to reduce the risk of disease recurrence beyond the first 5 years after surgery. The highly significant disease-free survival (DFS) benefit achieved by letrozole in this post-tamoxifen setting was confirmed in the final analysis, which was published in 2005 [12]. An additional, retrospective analysis has shown that the benefit achieved increases with the duration of exposure to letrozole, at least up to 48 months [13]. Following the early unblinding of MA.17, all women in the placebo arm were offered letrozole, providing the unplanned opportunity to investigate the efficacy of letrozole in women who had not received active treatment for up to 5 years. By comparing outcomes in these women and those who chose not to receive treatment following unblinding, the efficacy and safety of letrozole after a treatment-free interval can be studied, and preliminary results suggest that letrozole is effective in this situation.

This article discusses the scale of the problem of late relapses in HR+ early breast cancer and how the AIs, specifically letrozole, which is the only AI licensed in the extended adjuvant setting, are helping to prevent relapses in patients who have completed adjuvant tamoxifen. Updated analyses of data from MA.17 and the clinical implications of this pivotal study are also discussed.

**the continuing risk of late recurrence in hormone-responsive breast cancer**

Adjuvant chemotherapy and endocrine therapy have had a considerable impact on outcomes in patients with early breast cancer, preventing many recurrences and deaths in millions of women worldwide. Despite the proven benefits of adjuvant therapy, the risk of recurrence remains during treatment and continues indefinitely after completion of therapy. The risk of recurrence is not uniform across all breast cancers and differs depending on patient and disease characteristics, including age, menopausal status, HR status and extent of nodal involvement. It is becoming increasingly apparent that HR+ and HR− breast cancer are two distinct diseases: the risk of recurrence during the first 5 years after surgery is higher in HR− than HR+ disease, whereas the risk of experiencing a late relapse is higher in patients with HR+ disease (Figure 1) [14].

Tamoxifen has been the mainstay of adjuvant endocrine therapy for HR+ breast cancer for over 30 years. However, prolonged tamoxifen use is associated with acquired and de novo resistance, and the incidence of potentially fatal side effects, such as thromboembolic disease and endometrial cancer, increases with time on therapy, thus limiting tamoxifen use to 5 years. The Early Breast Cancer Trialists’ Collaborative Group meta-analysis of adjuvant tamoxifen trials has revealed that 5 years of tamoxifen, which was the accepted gold standard adjuvant endocrine therapy for over a decade, reduces the rate of recurrence by 41% and the annual rate of breast cancer death by 34%, demonstrating the clear benefit that tamoxifen confers in the first 5 years after surgery (Table 1) [1]. Tamoxifen also has a carry-over effect, with the benefit of treatment persisting for at least 5 years after successful completion of therapy. Consequently, women who have completed adjuvant tamoxifen are at a significantly lower risk of breast cancer recurrence or death.
The prevention of late relapses in patients with HR addressing the risk of late relapse completion of adjuvant tamoxifen. Results could, therefore, be greatly improved for population is 8.3% at 5 years, 17.8% at 10 years and 25.6% at 15 years after diagnosis is over twice that seen at 5 years at 15 years of adjuvant tamoxifen, the probability of disease recurrence in women with ER+ disease is 24.7 and 33.2% at 10 and 15 years after surgery, respectively, and this risk of relapse at 15 years after diagnosis is over twice that seen at 5 years (Table 1). The risk of breast cancer death in the same patient population is 8.3% at 5 years, 17.8% at 10 years and 25.6% at 15 years. Outcomes could, therefore, be greatly improved for women with HR+ disease by additional therapy after the completion of adjuvant tamoxifen.

### addressing the risk of late relapse

The prevention of late relapses in patients with HR+ disease has been studied for many years. Continued tamoxifen therapy is not recommended outside a clinical trial as recurrences and deaths occur after completion of adjuvant tamoxifen. Following 5 years of adjuvant tamoxifen, the probability of disease recurrence in women with ER+ disease is 24.7 and 33.2% at 10 and 15 years after surgery, respectively, and this risk of relapse at 15 years after diagnosis is over twice that seen at 5 years (Table 1). The risk of breast cancer death in the same patient population is 8.3% at 5 years, 17.8% at 10 years and 25.6% at 15 years. Outcomes could, therefore, be greatly improved for women with HR+ disease by additional therapy after the completion of adjuvant tamoxifen.

### efficacy of extended adjuvant therapy

MA.17 was a randomized, placebo-controlled, phase III trial to investigate the efficacy of letrozole in postmenopausal women (n = 5187) with HR+ or HR-unknown early breast cancer who had successfully completed 4.5–6 years of adjuvant tamoxifen. Women were randomized to receive 2.5 mg letrozole or placebo for 5 years, starting within 3 months of finishing tamoxifen. The primary endpoint, DFS, was defined as the time from randomization to the first recurrence of the tumor in the breast, chest wall, lymph nodes or at a distant site, or a new primary contralateral breast cancer. Secondary endpoints included overall survival (OS), quality of life (QoL) and long-term safety, assessed according to the Common Toxicity Criteria of the National Cancer Institute [11]. Bone mineral density (BMD) and lipid profiles were assessed annually in the companion studies, MA.17B [18] and MA.17L [19], respectively.

At the first interim analysis, after a median follow-up of 2.4 years, letrozole was shown to confer a highly significant benefit over placebo, reducing the risk of relapse by 43% (P = 0.00008). Subgroup analysis revealed that letrozole was effective in both node-positive and node-negative disease. Distant metastases were also reduced by letrozole therapy, occurring in 1.8 and 2.9% of patients on letrozole and placebo, respectively. OS did not differ significantly between the two treatment arms [11]. On the basis of these findings, the trial.
was unblinded; patients were made aware of the findings and those in the placebo arm were given the option of starting treatment with letrozole.

The final analysis, based on events that occurred prior to unblinding, with a median follow-up of 2.5 years, confirmed the results of the first interim analysis. DFS and distant DFS (DDFS) were significantly longer in patients on letrozole than in those on placebo. Letrozole reduced the risk of recurrence by 42% [hazard ratio 0.58, 95% confidence interval (CI) 0.45–0.76, \( P < 0.001 \)] and the risk of distant metastases by 40% (hazard ratio 0.60, 95% CI 0.43–0.84, \( P = 0.002 \)) (Figure 2) [12].

The 4-year absolute DFS benefit associated with letrozole therapy was 4.6% [12]. Letrozole prevented recurrences irrespective of nodal status, prior chemotherapy and duration of adjuvant tamoxifen (≤5 years or >5 years).

Although OS did not differ significantly between the two study arms in the intent-to-treat analysis (hazard ratio 0.82, 95% CI 0.57–1.19, \( P = 0.3 \)), letrozole significantly reduced the mortality rate in the subgroup of patients with node-positive disease (hazard ratio 0.61, 95% CI 0.38–0.98, \( P = 0.04 \)), making letrozole the first AI to demonstrate a survival advantage in early breast cancer [12]. Following publication of the results of MA.17, letrozole became the first agent licensed for the extended adjuvant treatment of women with HR+ early breast cancer.

The effectiveness of AIs in preventing late relapses has been confirmed in a preliminary analysis of the small, open-label ABCSG (Austrian Breast & Colorectal Cancer Study Group)-6a trial. Postmenopausal women with hormone-responsive breast cancer who had completed 5 years of adjuvant tamoxifen or tamoxifen plus aminoglutethimide were randomized to receive extended adjuvant anastrozole (n = 469) for 3 years; among the 387 patients randomized to anastrozole, 82 chose not to receive treatment, which resulted in considerable imbalance between the number of patients in the two treatment arms. Early results showed that extended adjuvant anastrozole therapy significantly reduced the risk of recurrence (local, contralateral or distant) by 36% compared with no treatment (hazard ratio 0.64, 95% CI 0.41–0.99, \( P = 0.048 \)), but had no effect on mortality rates [20]; these findings have yet to be presented in a peer-reviewed publication.

**Safety of extended adjuvant therapy**

Extended adjuvant letrozole therapy was well tolerated, with many side effects being predictable symptoms of estrogen deprivation. Hot flushes, arthralgia and myalgia were associated with letrozole therapy, and have been described for all AIs in the postoperative adjuvant setting [21–24]. Notably, hot flushes, which are a well-recognized symptom of the menopause, were also commonly reported in the placebo arm. Vaginal bleeding was less common in patients on letrozole than in those on placebo (\( P = 0.005 \)), but the incidence of new, patient-reported osteoporosis was higher in patients on letrozole than in those on placebo (8.1 versus 6.0%, \( P = 0.003 \)) (Table 2).

Bone loss is a predictable consequence of the near-complete depletion of circulating estrogen levels achieved by all third-generation AIs. However, in MA.17, the fracture rate did not differ significantly between the letrozole and placebo arms (5.3 versus 4.6%, respectively, \( P = 0.25 \)).

Detailed analysis of the effects of extended adjuvant letrozole on bone turnover and BMD in the MA.17B companion study also suggested that letrozole is associated with some bone loss; at 24 months, a significantly greater decrease in BMD at the total hip (letrozole versus placebo: –3.6 versus –0.71%, \( P = 0.044 \)) and lumbar spine (letrozole versus placebo: –5.35 versus –0.70%, \( P = 0.008 \)) was reported in patients on letrozole compared with those on placebo [18]. Of note, the incidence of osteoporosis in the MA.17B study, as assessed by BMD measurement, was considerably lower than that of patient-reported osteoporosis in the core trial. In MA.17B, no patient was identified as becoming osteoporotic based on total hip BMD, whereas a trend for more cases of osteoporosis in patients on letrozole than on placebo was reported with the lumbar spine (L2–L4) BMD measurements (4.1 versus 0%, respectively, \( P = 0.064 \)) [18].

Exploratory subgroup analyses revealed that women who were osteopenic at the time of starting letrozole were more likely to experience a significant drop in BMD over the course of the study than those with BMD in the normal range [18].

Letrozole was not associated with an increased risk of cardiovascular disease (CVD; 5.8 versus 5.6%, letrozole versus placebo, \( P = 0.76 \)) or hypercholesterolemia (16 versus 16%, letrozole versus placebo, \( P = 0.79 \)) compared with placebo.
optimum duration of extended adjuvant therapy

Following the demonstration that extended adjuvant letrozole significantly improves outcomes in postmenopausal women who have completed adjuvant therapy with tamoxifen, a retrospective analysis was performed to assess whether the duration of exposure to letrozole had an impact on the benefit achieved. All events that occurred up to the point of unblinding were included in the analysis, which used a non-parametric kernel smoothing method to estimate the hazard rates for DFS, DDFS and OS at 6, 12, 24, 36 and 48 months of follow-up. From these, the hazard ratios were determined for letrozole versus placebo at these timepoints.

The hazard rate for recurrence was shown to gradually increase over time for patients in the placebo arm, whereas, in the letrozole arm, a small peak in the hazard rate was seen at 24 months, which gradually decreased thereafter for the duration of the study. Consequently, the hazard ratios for DFS and DDFS decreased with duration of therapy, with the benefit in favor of letrozole increasing significantly between 6 and 48 months (DFS: \( P < 0.0001 \); DDFS: \( P = 0.0013 \) (Table 3) [13]. The hazard ratios for OS did not vary significantly over time (\( P = 0.33 \)), but were always <1, that is, favoring letrozole [13].

The association between the duration of exposure to letrozole and efficacy was also studied in patient subgroups according to nodal status. In patients with node-positive disease (\( n = 2360 \)), the benefit in terms of DFS (\( P = 0.0004 \)), DDFS (\( P = 0.0005 \) and OS (\( P = 0.038 \) increased significantly between 6 and 48 months (Table 3). Similarly, the decrease in hazard ratios over time in favor of letrozole reached significance for DFS (\( P = 0.027 \)), but the trend for increasing benefit over time did not reach statistical significance for DDFS (\( P = 0.22 \)) or OS (\( P = 0.34 \)) in patients with node-negative disease (\( n = 2568 \)).

The findings from MA.17 support the concept that HR+ early breast cancer retains sensitivity to endocrine therapy for longer than the standard 5-year adjuvant treatment period, and may have implications for future therapeutic guidelines. National Comprehensive Cancer Network guidelines recommend the use of extended adjuvant letrozole therapy for 5 years [26]. The American Society for Clinical Oncology (ASCO) guidelines, however, recommend giving extended adjuvant letrozole for at least 2.5 years [27], consistent with the median follow-up at the final analysis of the MA.17 trial. The observation that the benefit achieved with letrozole increases with duration of therapy, at least up to 4 years, suggests that extended adjuvant therapy should not be terminated before this time. The optimum duration of extended adjuvant therapy is still not known, and is being studied in the ongoing MA.17R trial, in which patients who have completed 5 years of extended adjuvant therapy as participants in MA.17 or in the community are re-randomized to receive either placebo or a further 5 years of letrozole. Thus, the safety and efficacy of up to 10 years of letrozole treatment, and the potential for extending adjuvant endocrine therapy for up to 15 years, is under investigation.

post-unblinding analysis

The early unblinding of MA.17 left several questions unanswered, such as the optimum duration of therapy and long-term tolerability. However, unblinding did allow a further unplanned analysis to be performed, that is, investigation of whether the length of time without active therapy since completion of tamoxifen affected the response to extended adjuvant letrozole, and also allowed further investigation of long-term toxicities associated with letrozole therapy. The effect of letrozole was assessed in women initially randomized to receive placebo who then elected to start letrozole after unblinding of the trial: these women had been on placebo for up to 5 years. This ‘post-unblinding’ analysis examined the effect of letrozole in two cohorts: patients randomized to receive placebo who started letrozole after unblinding of the study (placebo–letrozole), and patients randomized to receive placebo who chose to continue without active therapy (placebo) [28]. Of the 2268 women initially randomized to receive placebo who were free from recurrence at the time of unblinding, 1655 started letrozole therapy and 613 chose not to start treatment. Initial analysis of post-unblinding cohorts, with a median follow-up of 54 months, showed that starting letrozole therapy significantly reduced the risk of relapse by

Table 3. Increasing benefit with duration of extended adjuvant letrozole, up to 48 months of therapy, in the intent-to-treat and node-positive patient populations in the MA.17 trial [13]

<table>
<thead>
<tr>
<th>Population</th>
<th>Hazard ratio (let versus placebo)</th>
<th>Hazard ratio (let versus placebo)</th>
<th>Hazard ratio (let versus placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
<td>48 months</td>
<td>( P ) value</td>
</tr>
<tr>
<td>DFS</td>
<td>0.59</td>
<td>0.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DDFS</td>
<td>0.51</td>
<td>0.21</td>
<td>0.0013</td>
</tr>
<tr>
<td>OS</td>
<td>0.87</td>
<td>0.79</td>
<td>0.33</td>
</tr>
</tbody>
</table>

ITT, Intent-to-treat; N+, node positive; N−, node negative; let, letrozole.
69% (hazard ratio for DFS 0.31, 95% CI 0.18–0.55, P < 0.0001) compared with no further therapy [29]. Letrozole was well tolerated, and, importantly, was not associated with an increased risk of fractures or CVD [29]. It is important to note that, unlike the core MA.17 trial, the post-unblinding analysis is not a randomized trial; nonetheless, this study suggests that starting letrozole after a prolonged treatment-free interval following completion of standard adjuvant tamoxifen significantly improves outcomes, and could, therefore, have important implications for the clinical management of patients with HR+ early breast cancer.

**Influence of ER and PgR status on response to extended adjuvant therapy**

Low tumor ER levels and/or PgR negativity are associated with poor response to tamoxifen therapy [30]. However, whether the level of ER expression and/or the PgR status of the primary tumor affect outcomes in women receiving adjuvant or extended adjuvant AI therapy is not yet known. An exploratory, retrospective analysis of the influence of ER/PgR status of the primary tumor on the efficacy (DFS, DDFS and OS) of extended adjuvant letrozole in MA.17 is currently underway. Assessment of ER/PgR status at local laboratories, with receptor positivity defined as ≥ 210 fmol/mg protein, or a positive result by immunohistochemical analysis, has been performed on tumors from 4653 patients. Preliminary analysis suggests that letrozole is most effective in patients with ER+/PgR+ disease, in which a 51% reduction in the risk of relapse (hazard ratio 0.49, 95% CI 0.36–0.67) and a 47% reduction in the risk of distant metastases were achieved [31]. Notably, letrozole also reduced the risk of death by 42% in the subgroup of patients with ER+/PgR+ tumors, who accounted for over 80% of all patients included in the analysis. A statistically significant interaction between ER+/PgR+ and ER+/PgR− status was reported for DFS (P = 0.02), with strong trends for DDFS (P = 0.06) and OS (P = 0.09). Although these data suggest that extended adjuvant letrozole may be of particular benefit in patients with ER+/PgR+ disease, these results should be interpreted with caution as this was an unplanned, retrospective analysis in which receptor levels were measured in local laboratories.

**Discussion and conclusions**

Despite earlier diagnosis through screening programs and advances in the treatment of early breast cancer, the risk of the cancer recurring after primary treatment persists indefinitely for affected women. Whereas the risk of early relapse is greater for women with HR− than HR+ tumors, late relapses are more common in HR+ than HR− disease. Adjuvant endocrine therapy with tamoxifen prevents many recurrences in women with HR+ disease during the first 5 years after surgery, but the efficacy of tamoxifen decreases over time and longer tamoxifen therapy is not recommended, leaving patients with an ongoing risk of late recurrence. The MA.17 trial identified letrozole as the first agent to significantly improve outcomes after successful completion of adjuvant tamoxifen. After a median follow-up of only 30 months, letrozole significantly reduced relapses, including distant metastases, in the study population, and significantly improved survival in patients with high-risk, node-positive disease.

The results of MA.17 have altered clinical practice. International guidelines now recommend extended adjuvant letrozole therapy for women who have completed standard adjuvant tamoxifen. Although the advantages of extended adjuvant letrozole are well accepted, the optimum duration of therapy and possible late side effects are still unknown. It is now apparent that the benefit gained increases with the length of time the patient has been taking letrozole, at least up to 48 months, which suggests that patients should remain on letrozole for at least 4 years, consistent with the treatment guidelines from the National Comprehensive Cancer Network [26].

Recent, updated analyses of data from MA.17 may bring about further changes in the clinical management of early breast cancer. In the core MA.17 trial, all patients started letrozole within 3 months of completing standard adjuvant tamoxifen. Unblinding of the trial at the first interim analysis enabled an unplanned investigation of the benefits of letrozole in women who had been without active therapy for up to 5 years after finishing tamoxifen, that is, in those patients initially randomized to the placebo arm who chose to start letrozole at study unblinding. Analysis of the post-unblinding patient cohorts demonstrated that letrozole significantly reduced the risk of relapse compared with no further treatment. These findings suggest that all postmenopausal women who have completed standard adjuvant tamoxifen should be considered for late extended adjuvant letrozole therapy, even after a prolonged treatment-free interval.

How levels of ER and PgR expression affect the response to AI therapy is currently unclear. Studies comparing the efficacy of AIs and tamoxifen as postoperative adjuvant therapy suggest that PgR status may influence the responsiveness of ER+ tumors to AI therapy. Current data from this setting, based on local assessment of tumor HR levels, suggest that, whereas PgR status does not affect the efficacy of letrozole in ER+ tumors [24], anastrozole may be more effective in ER+/PgR− than ER+/PgR+ disease [32]. Centralized review of HR status in BIG 1-98 has confirmed that letrozole is effective regardless of PgR status [33]; to date, BIG 1-98 is the only trial to have confirmed tumor ER/PgR status centrally. On the other hand, the findings of an exploratory retrospective analysis of data from MA.17 suggest that the response to letrozole may differ depending on ER/PgR expression in the primary tumor. In the extended adjuvant setting, the benefit of letrozole appeared to be greater in the subgroup of patients with ER+/PgR+ tumors than in those with ER+/PgR− tumors, although the ER+/PgR− group contained very few patients and confidence intervals were wide. Most of the relapses in ER+/PgR− disease seem to occur earlier in the course of disease. Furthermore, the unplanned, retrospective nature of this analysis, and the measurement of HR levels locally rather than at a central laboratory, make it difficult to draw conclusions from these results, and basing treatment decisions on ER/PgR status is not currently recommended. Central review of ER/PgR status in MA.17 is planned and will provide further insights into the influence of ER and/or PgR status on the response to extended adjuvant letrozole therapy.
Extended adjuvant letrozole was generally well tolerated, with most side effects being predictable consequences of estrogen deprivation, such as hot flushes and bone loss, which have also been reported with AI use in the upfront adjuvant setting [22–24]. Data from the MA.17b bone companion study suggest that the incidence of osteoporosis is actually lower than that based on patient self-diagnosis [18], and that screening may identify patients most at risk of bone loss, in whom additional interventions may be beneficial. ASCO guidelines for the management of bone loss in patients on AIs are available [34] and include lifestyle alterations, dietary supplements and, where necessary, bisphosphonate use. Notably, there was no evidence that extended adjuvant letrozole increases the risk of hypercholesterolemia or CVD compared with placebo.

These findings indicate that HR+ early breast cancer remains hormone responsive for at least 10–15 years after primary therapy and demonstrate that stopping endocrine therapy 5 years after surgery is no longer an acceptable option for all patients with HR+ disease. Under its current license, extended adjuvant letrozole enables patients to receive adjuvant therapy for up to 10 years, and recent data from MA.17 indicate that, in the absence of a recurrence, letrozole should be continued for at least 4 years. It is possible that, in the future, postmenopausal women with HR+ early breast cancer may receive lifelong endocrine therapy to prevent disease recurrence and breast cancer deaths. However, studies assessing the long-term safety and efficacy of endocrine agents are required. Further studies, such as the MA.17R re-randomization study will investigate the optimum duration of therapy. Patients in MA.17R will receive extended adjuvant letrozole for up to 10 years, and will, therefore, have received a total of up to 15 years of uninterrupted adjuvant endocrine therapy.

disclosures

Professor Čufer has reported no financial relationships with companies whose products are mentioned in this supplement.

references