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

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Following primary treatment for early breast cancer, systemic adjuvant therapy is given to reduce the risk of recurrence by targeting any undetectable micrometastatic deposits. Adjuvant systemic treatment may include endocrine therapy, chemotherapy and antibody therapy, depending on the presence or absence of hormone receptors, HER2 status and the estimated risk of relapse. In recent years, an increasing number of tumor characteristics have been identified that influence the risk of relapse and the likelihood of achieving the desired outcome with a given therapy. Hence, choosing the optimum therapy for early breast cancer is becoming an increasingly complicated task. Decision tools have been developed that can be used by physicians to select the most appropriate therapy on an individual basis. Treatment recommendations are, therefore, based on available data from a large number of sources. Hormone-receptor positivity (HR+) is the primary factor when considering whether or not patients should receive adjuvant endocrine therapy. For several decades, tamoxifen has been the gold standard of endocrine therapy, and has significantly reduced recurrences and deaths among the millions of women with HR+ breast cancer worldwide. However, prolonged use of tamoxifen is associated with potentially life-threatening side effects, and resistance is a common problem. In fact, many women will experience disease relapse while on tamoxifen. In particular, the peak of early relapses that occurs in the first 2–3 years after surgery is not prevented by tamoxifen. The third-generation aromatase inhibitors (AIs), letrozole, anastrozole and exemestane, have recently been shown to significantly improve outcomes compared with tamoxifen in large, randomized, controlled trials; however, how the AIs should be incorporated into adjuvant therapy to optimize outcomes requires further investigation. Clinical differences between the AIs, and whether tumor estrogen/progesterone receptor status and HER2 overexpression affect the response to AI therapy, are among the questions that remain to be answered. Ongoing and future studies will help to address these questions and, together with improved patient and disease profiling, will help physicians to optimize adjuvant treatment for individual patients.

Key words: adjuvant endocrine therapy, aromatase inhibitors, breast cancer, hormone-responsive

Introduction

Adjuvant therapy plays a key role in the effective management of early breast cancer, and has significantly improved outcomes for millions of women with this disease. Following initial resection of the primary tumor, there is an ongoing risk of recurrence, and systemic adjuvant therapy aims to prevent relapses by targeting undetectable disease deposits that may be present at locoregional or distant sites. The peak risk of recurrence occurs during the first 2–3 years after surgery [1], and the decision of whether or not adjuvant therapy should be given depends largely on the estimated risk of recurrence in the individual patient. Disease characteristics that have been shown to predict for early disease relapse include grade 3 tumor pathology, low estrogen-receptor (ER) expression and an increasing number of involved lymph nodes [1, 2].

The type of adjuvant therapy given depends on tumor and patient characteristics, and may consist of endocrine therapy, chemotherapy or both. Patients with tumors overexpressing HER2/neu may also receive treatment with the monoclonal antibody, trastuzumab. The responsiveness of tumors to hormones, due to the presence of hormone receptors, remains the most important consideration when choosing adjuvant therapy, and identifies patients who would be expected to benefit from endocrine therapy, either alone or after chemotherapy. An increasing number of parameters have been identified that influence response to therapy, which are now being used by physicians to identify the optimal treatment strategy on an individual basis.

Adjuvant therapy has been shown to reduce the risk of local and distant recurrences and prolong survival [3], and many patients with early breast cancer can now expect to survive for a decade or longer after diagnosis. Despite the undeniable benefits of adjuvant therapy, many patients will experience disease relapse while on treatment. Tamoxifen has been the
mainstay of adjuvant endocrine therapy for hormone-receptor-positive (HR+) disease for many years, and has significantly improved outcomes for millions of women worldwide [3]; however, relapses occur over a period of more than 20 years, the early peak of recurrences persists despite tamoxifen, and resistance to tamoxifen is a common problem. Serious adverse events have also been associated with tamoxifen, which, along with a reported lack of efficacy when used for more than 5 years, has limited the duration of tamoxifen treatment to 5 years. Although this treatment limit may be revised in light of results from the ongoing ATTom (Adjuvant Tamoxifen Treatment Offer More) and ATLAS (Adjuvant Tamoxifen Longer Against Shorter) trials, which are investigating the optimum duration of tamoxifen therapy, there remains a need for more effective and better tolerated endocrine treatments to further improve outcomes for patients with HR+ early breast cancer. In recent years, the third-generation aromatase inhibitors (AI) have demonstrated greater efficacy and at least equivalent tolerability to tamoxifen in the adjuvant setting, and are now an essential part of adjuvant endocrine therapy in postmenopausal women with HR+ breast cancer. This article discusses the information and tools available to help physicians to select the most appropriate treatment for HR+ disease on an individual basis, and summarizes data from large clinical trials showing that the AIs achieve significantly better outcomes than tamoxifen as postoperative adjuvant therapy.

**treatment decision-making in early breast cancer**

Information is available from several sources to help physicians to decide which treatment to prescribe, including data from individual clinical trials, meta-analyses of clinical trial data (e.g. from the Early Breast Cancer Trialists’ Collaborative Group), and national and international guidelines (American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN], St Gallen International Expert Consensus Panel) [4–6]. Although guidelines are useful, they are derived from expert opinions and provide little in the way of quantitative guidance. Additionally, due to the large number of parameters that might influence treatment selection (Table 1), it is difficult to produce accurate prognostic estimates for individual patients. For these reasons, decision tools, such as Adjuvant! (www.adjuvantonline.com), have been created.

**Table 1.** Prognostic factors used to estimate the risk of relapse in early breast cancer

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>Tumor-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>ER/PgR status</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Nodal involvement (yes/no)</td>
</tr>
<tr>
<td>Race</td>
<td>Number of involved nodes</td>
</tr>
<tr>
<td></td>
<td>Tumor size</td>
</tr>
<tr>
<td></td>
<td>Tumor grade</td>
</tr>
<tr>
<td></td>
<td>Vascular invasion</td>
</tr>
<tr>
<td></td>
<td>HER2/neu status</td>
</tr>
</tbody>
</table>

PgR, progesterone receptor.

Adjuvant! is a web-based tool that can be used to estimate baseline prognosis, the efficacy of different treatments, and predicted 10-year survival for an individual patient, using data from national databases, clinical trial overviews, individual trials and other sources [7, 8]. Adjuvant! integrates complex information about prognosis, treatment efficacy, some aspects of toxicity and mortality rates to provide a quantitative perspective on how a selected treatment is likely to benefit a particular patient. The risks and benefits of different therapy options are displayed clearly, enabling the doctor to make an informed decision regarding the best therapy on an individual basis. Furthermore, the information can be easily presented to the patient, allowing them to be involved in the decision-making process. Adjuvant! has several limitations, such as the categorical use of tumor size, tumor ER expression or nodal involvement subgroups, subjectivity of variables (e.g. histological grade), failure to consider progesterone receptor (PgR) and HER2/neu status, and the limited knowledge available about the long-term efficacy and safety of some therapies. The most important drawback is that the magnitude of treatment benefit is based on the average therapy effects in patients with ‘average’ disease, as observed in clinical trials. However, these limitations apply to guidelines and decision-making tools.

Despite the introduction of new decision-making aids, guidelines are more widely used by doctors to help choose the optimal treatment for a patient. According to the guidelines from the 2005 St Gallen International Expert Consensus Panel [6] and the recent St Gallen update [9], selection of adjuvant therapy should be based primarily on tumor endocrine responsiveness, three categories of which have been defined: endocrine responsive, endocrine non-responsive, and tumors of uncertain endocrine responsiveness. These categories are then further divided according to menopausal status. Finally, patients are divided into low-, intermediate- and high-risk categories, according to nodal status, tumor size and grade, patient age, and the two newly accepted prognostic factors, HER2/neu overexpression/amplification and vascular invasion [6].

**adjuvant treatment for early breast cancer**

Adjuvant therapy may consist of chemotherapy, endocrine therapy, or chemotherapy followed by endocrine therapy, depending on the hormone responsiveness of the tumor and the estimated risk of relapse. Trastuzumab will be given to patients with HER2 overexpressing tumors, as appropriate. Endocrine therapy is the standard treatment for postmenopausal women with HR+ disease. Premenopausal women with HR+ disease will receive adjuvant endocrine therapy with tamoxifen, but it is unclear whether these women will also require surgical or medical induction of the menopause to stop ovarian hormone production. The role of ovarian suppression or ablation is currently being investigated by the International Breast Cancer Study Group in SOFT (Suppression of Ovarian Function Trial). Cytotoxic chemotherapy is recommended for patients with HR− disease and is also given prior to endocrine therapy for patients with...
HR+ disease who are at increased risk of relapse, such as those with involved lymph nodes at diagnosis and patients who have uncertain endocrine responsiveness despite an ER+ primary tumor.

Tamoxifen has been the mainstay of adjuvant endocrine therapy for HR+ disease for over 30 years. Meta-analyses, carried out at 5-year intervals, have demonstrated that 5 years of adjuvant tamoxifen significantly reduces the risk of recurrence and death [3]. Furthermore, the benefit of tamoxifen continues beyond the 5-year treatment period; the risks of breast cancer recurrence and breast-cancer-related death are lower in women who have completed tamoxifen therapy compared with those who have not received tamoxifen, for up to 15 years after surgery [3]. Although treatment with tamoxifen has substantially improved outcomes in women with HR+ early breast cancer, the risk of disease recurrence is not eliminated, and the peak of early relapses persists. In fact, approximately half of all relapses and two-thirds of deaths are not prevented by 5 years of tamoxifen treatment [3].

Acquired or de novo resistance to tamoxifen occurs in many patients, but predictors of tamoxifen resistance are poorly defined, making it difficult to identify patients who are less likely to benefit from tamoxifen treatment. Furthermore, tamoxifen is associated with problematic and potentially life-threatening adverse events, such as thromboembolic disease and invasive endometrial cancer [10], the majority of which occur during the first 2.5 years of therapy [11]. The failure of tamoxifen to prevent many early relapses, and the risk of serious side effects, highlight the need for more effective endocrine therapies with better safety profiles to improve outcomes in patients with early breast cancer.

**adjuvant trials of AIs in the postoperative setting**

In recent years, the third-generation AIs have demonstrated greater efficacy than tamoxifen as postoperative adjuvant therapy for postmenopausal women with HR+ early breast cancer, and at least equivalent tolerability. On the basis of these findings, the AIs are now displacing tamoxifen monotherapy as the adjuvant endocrine treatment of choice for most patients. The efficacy and safety of adjuvant AI therapy has been studied in large, randomized, controlled trials; three types of AI studies have been conducted: upfront treatment, a therapy switch strategy for patients already receiving tamoxifen, and prospectively planned sequential therapy.

Upfront substitution of 5 years of tamoxifen with letrozole or anastrozole has been investigated in the BIG (Breast International Group) 1-98 and ATAC (Anastrozole, Tamoxifen Alone or in Combination) trials, respectively. In these trials, with randomization taking place before the initiation of adjuvant therapy (Figure 1), analyses included all events over the 5-year treatment period. Three trials, IES (Intergroup Exemestane Study), ITA (Italian Tamoxifen Anastrozole) and ARNO (Arimidex–Nolvadex), have examined switching to an AI in patients already taking tamoxifen (Figure 1), with randomization being performed after 2–3 years of tamoxifen. Sequential therapy trials investigate a preplanned strategy of tamoxifen followed by an AI, or vice versa, compared with 5 years of continuous tamoxifen or AI therapy. Importantly, in contrast to a switching strategy, patients in sequential trials are randomized to treatment arms immediately after surgery. In addition to the upfront treatment arms, BIG 1-98 is investigating 2 years of tamoxifen plus 3 years of letrozole, and 2 years of letrozole followed by 3 years of tamoxifen. The amended TEAM (Tamoxifen and Exemestane Adjuvant Multicenter) trial is comparing sequential tamoxifen–exemestane therapy with 5 years of exemestane (Figure 1).

These two sequential trials are ongoing and have yet to report findings. A third sequential trial, ABCSG (Austrian Breast and Colorectal Cancer Study Group)-8, is also ongoing, and is comparing 2 years of tamoxifen followed by 3 years of anastrozole and 5 years of tamoxifen (Figure 1). A preliminary analysis of ABCSG-8 data has recently been reported, assessing the efficacy of therapy switch (i.e. excluding events in the first 2 years) and sequential treatment strategies (i.e. including all events). A per-protocol combined analysis of data from ABCSG-8 and ARNO has also been reported. For this combined analysis, as randomization in ARNO was performed after 2 years of tamoxifen, only events that occurred in ABCSG-8 after the point of switching therapy were included. The combined ABCSG-8/ARNO trial, therefore, investigated a switching, not a sequential strategy.

The difference between the point of randomization in therapy switch and sequential strategies has important implications for interpretation of data. The ITA, IES and...
ARNO trials examined the benefit of switching to an AI after a period of tamoxifen treatment. In these trials, patients who were disease free after receiving 2–3 years of tamoxifen were randomized to an AI or continued tamoxifen at the point of switching therapy. This strategy excludes patients who experience an early relapse in the first 2–3 years of adjuvant therapy, and only includes events that occur after 2–3 years of tamoxifen, thus selecting a trial population with proven, endocrine-responsive disease and a relatively favorable prognosis. As sequential trials (i.e. the sequential arms of BIG 1-98, and ABCSG-8 and TEAM) performed randomization after surgery, analysis of data from these trials counts all events that occur during the 5-year treatment period, including early relapses in patients with higher-risk disease; substitution trials also include all patients irrespective of the risk of relapse.

**upfront substitution of tamoxifen with an AI**

The BIG 1-98 and ATAC trials showed that the AIs, letrozole and anastrozole, respectively, are more effective postoperative adjuvant therapies than tamoxifen for preventing relapses in postmenopausal women with HR+ early breast cancer.

**the ATAC trial**

In the ATAC trial, 9366 postmenopausal women with operable early breast cancer (HR+, HR− or HR-unknown) who had completed primary treatment were randomized to tamoxifen (n = 3116), anastrozole (n = 3125) or combined tamoxifen/anastrozole therapy (n = 3125) for 5 years. The primary endpoint was disease-free survival (DFS), defined as the time to local or distant recurrence, new primary breast cancer or death from any cause. Secondary endpoints included time to recurrence (TTR), time to distant recurrence (TTDR; time from randomization to distant recurrence or death due to breast cancer) and overall survival (OS) [12]. Following the first analysis, the combination arm was discontinued due to inferior efficacy compared with anastrozole, and no benefit compared with tamoxifen; subsequent results were, therefore, reported for approximately 6000 patients.

The treatment completion analysis of ATAC, after a median follow-up of 68 months, confirmed that anastrozole was superior to tamoxifen, reducing the risk of relapse by 13% in the intent-to-treat (ITT) population (P = 0.01). TTR (P = 0.0005) and TTDR (P = 0.04), but not distant DFS (defined as the first occurrence of distant recurrence or death for any reason), were longer in patients taking anastrozole than in those receiving tamoxifen (Table 2) [13, 14]. Anastrozole also significantly decreased the incidence of contralateral breast cancer compared with tamoxifen (42% reduction, P = 0.01; Table 2) in the ITT population [13]. The improvements were seen within 1 year of starting treatment, and anastrozole substantially reduced the peak of early relapses that occurs in years 1–3 of adjuvant tamoxifen therapy. However, anastrozole did not reduce deaths [hazard ratio 0.97, 95% CI (confidence interval) 0.85–1.12, P = 0.7] or breast cancer deaths (hazard ratio 0.88, 95% CI 0.74–1.05, P = 0.2) [13].

Anastrozole conferred a greater benefit over tamoxifen in the subgroup of patients with HR+ disease (Table 2), with significant increases in DFS (P = 0.005) and TTR (P = 0.0002) and a reduction in the incidence of contralateral breast cancer (P = 0.001) (Table 2). The absolute benefit in DFS seen with anastrozole in the HR+ population was 2.5% at 5 years. However, anastrozole did not significantly reduce the risk of distant metastases in patients with HR+ disease (Table 2); neither distant DFS (hazard ratio 0.93, 95% CI 0.80–1.07) [14] nor TTDR (P = 0.06) were significantly improved compared with tamoxifen. OS did not differ between the two treatment arms; 296 and 301 deaths occurred in patients on anastrozole and tamoxifen, respectively. In further retrospective subgroup analyses, the benefits of anastrozole over tamoxifen in the ITT population were not seen in patients at increased risk of relapse; that is, patients with node-positive disease and patients who had previously received adjuvant chemotherapy [15].

**BIG 1-98**

BIG 1-98 is a randomized, double-blind, multicenter trial comparing adjuvant letrozole and tamoxifen. Over 8000 women with confirmed HR+ early breast cancer were randomized immediately after surgery to one of four treatment arms: tamoxifen for 5 years, letrozole for 5 years, tamoxifen for 2 years followed by letrozole for 3 years, or letrozole for 2 years followed by tamoxifen for 3 years. The primary endpoint was DFS, defined as the time from randomization to the first occurrence of invasive recurrence in local, regional or distant sites, contralateral invasive breast cancer, second non-breast cancer, or death from any cause. The BIG 1-98 definition of DFS was more stringent than that of ATAC, which did not include secondary non-breast cancers, but did include *in situ* cancers as a recurrent event, making differences in DFS harder

### Table 2. The benefits of upfront anastrozole in the ITT and HR+ populations after 68 months’ median follow-up in the ATAC trial [13]

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ITT population Hazard ratio (95% CI)</th>
<th>P value</th>
<th>HR+ population Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>0.87 (0.78–0.97)</td>
<td>0.01</td>
<td>0.83 (0.73–0.94)</td>
<td>0.005</td>
</tr>
<tr>
<td>TTR</td>
<td>0.79 (0.70–0.90)</td>
<td>0.0005</td>
<td>0.74 (0.64–0.87)</td>
<td>0.0002</td>
</tr>
<tr>
<td>CLBC</td>
<td>0.58 (NR)</td>
<td>0.01</td>
<td>0.47 (NR)</td>
<td>0.001</td>
</tr>
<tr>
<td>TTDR</td>
<td>0.86 (0.74–0.99)</td>
<td>0.04</td>
<td>0.84 (0.70–1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Distant DFS</td>
<td>0.94 (0.83–1.06)</td>
<td>NR</td>
<td>0.93 (0.80–1.07)</td>
<td>NR</td>
</tr>
<tr>
<td>OS</td>
<td>0.97 (0.85–1.12)</td>
<td>0.7</td>
<td>0.97 (0.83–1.14)</td>
<td>NR</td>
</tr>
</tbody>
</table>

CI, confidence interval; CLBC, contralateral breast cancer; NR, not reported.
to demonstrate in BIG 1-98 than in ATAC. Secondary endpoints included OS, systemic DFS (excluding locoregional and contralateral events) and time to distant metastases. Additional endpoints, defined in the statistical analysis plan, included DFS without secondary non-breast malignancies, and TTR (defined as DFS excluding second, non-breast cancers and patients who died without a recurrence of breast cancer) [17].

The primary core analysis of BIG 1-98 compared upfront letrozole \( (n = 4003) \) and tamoxifen \( (n = 4007) \), and included all events in the monotherapy arms, plus events in the sequential therapy arms, up to 30 days after the point of changing therapy. The median follow-up of this first analysis was 25.8 months. Letrozole significantly improved DFS compared with tamoxifen (hazard ratio 0.81, 95% CI 0.70–0.93, \( P = 0.003 \)) (Figure 2), achieving a 19% reduction in the relative risk of relapse, and an estimated absolute risk reduction of 2.6% at 5 years. The cumulative incidence of breast cancer events was significantly reduced in patients taking letrozole compared with those receiving tamoxifen (3.4% reduction at 5 years, \( P < 0.001 \); Figure 2) [16]. Importantly, unlike anastrozole, which did not reduce distant recurrences in patients with HR+ disease, letrozole achieved a highly significant, 27% reduction in the risk of developing distant metastases, which are strongly associated with death from breast cancer (hazard ratio 0.73, 95% CI 0.60–0.88, \( P = 0.001 \)). This reduction in distant metastases became evident early in the study; after a median of 25 months of follow-up the recurrence rate at all distant sites (soft tissue/nodes, bone and viscera) was lower in the letrozole arm than in the tamoxifen arm [17]. Fewer deaths were observed in patients randomized to letrozole than in those randomized to tamoxifen (166 versus 192, respectively, \( P = 0.16 \)) after 25.8 months' follow-up [16]. Longer follow-up in this trial may reveal a survival benefit with upfront letrozole. As metastatic breast cancer is incurable, it is reasonable to expect that the early reduction in the risk of distant metastases seen with upfront letrozole may translate into a survival advantage with longer follow-up.

Preplanned subgroup analyses demonstrated that the benefit achieved by letrozole in the whole study population was also seen in patients with higher-risk disease. Compared with tamoxifen, letrozole significantly reduced the risk of recurrence by 29% \( (P < 0.001) \) in patients with node-positive disease, and by 30% \( (P = 0.01) \) in patients who had received prior adjuvant chemotherapy [16].

## Als in a therapy switch strategy

Patients who had successfully completed 2–3 years of tamoxifen were recruited to the IES, and were randomized to either switch to exemestane \( (n = 2352) \) or continue on tamoxifen \( (n = 2327) \) for the remaining 2–3 years of adjuvant treatment. Similarly, in the small, open-label ITA study, higher-risk patients \( (n = 448) \) with confirmed ER+ disease, who had already taken 2–3 years of tamoxifen therapy, were randomized to receive either anastrozole or tamoxifen for the remainder of the 5-year treatment period. In the ABCSG-8 and ARNO trials, patients received 2 years of tamoxifen followed by 3 years of anastrozole or continued tamoxifen, with analysis at 2 years, that is from the point of randomization \( (ARNO, n = 979) \) or from the point of therapy switch \( (ABCSCG-8, n = 3700) \). As discussed above, owing to the time of randomization, patients in trials investigating a therapy switch have a more favorable prognosis than patients in substitution or sequential therapy trials.

The IES demonstrated that switching to exemestane after 2–3 years of tamoxifen significantly improved DFS, time to contralateral breast cancer and time to distant metastases compared with 5 years of tamoxifen therapy. At the second interim analysis, after a median follow-up of 30.6 months, switching to exemestane reduced the risk of relapse by 32% \( (P = 0.0005) \), equating to an estimated absolute benefit of 4.7% at 3 years after randomization [18]. OS did not differ between the two treatment arms.

The first mature analysis of IES, at a median follow-up of 55 months, which was presented at the ASCO meeting in 2006, confirmed the initial findings. In the ITT population, a significant, 24% reduction in the risk of relapse \( (P = 0.0001) \) was achieved by switching to exemestane (Table 3) [18, 19]; significant increases in time to contralateral breast cancer \( (P = 0.04) \) and TTDR \( (P = 0.03) \) were also seen in patients who switched to exemestane compared with patients who remained on tamoxifen.

Patients with ER+ or ER-unknown disease were eligible for inclusion into IES, but 122 patients with unknown ER status at study entry were subsequently found to have ER– disease. When additional analyses were performed, after exclusion of patients with ER– disease, the results for DFS, time to contralateral breast cancer and TTDR were similar to those seen in the ITT population (Table 3). However, whereas no significant difference in OS was seen between the treatment
Switching to exemestane after 2–3 years of adjuvant tamoxifen improved outcomes in patients recruited to the IES [18, 19].

The combined analysis of the ABCSG-8 and ARNO trials has also demonstrated that switching to anastrozole after 2 years of tamoxifen significantly improved EFS compared with continued tamoxifen. After a median follow-up of 28 months, the risk of relapse was reduced by 40% (P = 0.0009) in patients who switched to anastrozole, corresponding to an absolute 3.1% at 3 years from randomization. A significant, 39% reduction in the risk of distant metastases was also reported in patients who switched to anastrozole (P = 0.0067). OS did not differ significantly between the treatment arms (P = 0.16). Subgroup analyses showed that the significant benefit of switching to anastrozole was seen in patients with node-negative disease (46% risk reduction, P = 0.0065) but not in those with node-positive disease (33% risk reduction, P = 0.061) [21].

A combined analysis of the data from the three trials investigating the benefits of switching to anastrozole (ITA, ARNO and ABCSG-8) reported a significant improvement in OS (29% reduction in the mortality rate, P = 0.038) in patients who switched onto anastrozole [22]. However, this analysis should be viewed with caution as important differences exist between the three trials, including the point of randomization (after 2–3 years of tamoxifen in ARNO and ITA, and after surgery in ABCSG-8), the duration of tamoxifen treatment prior to switching onto anastrozole (2 years in ABCSG-8 and ARNO, and 2–3 years in ITA), primary endpoint definitions (DFS in ITA, EFS in ABCSG-8 and ARNO), and inclusion/exclusion criteria. Furthermore, the largest trial, ABCSG-8, did not show a survival advantage in patients who switched onto anastrozole compared with those who continued on tamoxifen (42 versus 44 deaths, respectively) [22]. It should be noted that questions regarding the methodology of this analysis were raised when the data were first presented in 2005.

Although the ARNO trial was designed to be analyzed in combination with data from ABCSG-8, an interim analysis of data from ARNO alone has recently been reported. Switching to anastrozole after 2 years of tamoxifen significantly improved EFS (hazard ratio 0.66, 95% CI 0.44–1.00, P = 0.049) and OS (hazard ratio 0.53, 95% CI 0.29–0.99, P = 0.045), at a median follow-up of 30.1 months [23]. However, only 979 patients were included in ARNO, the majority of whom (74%) had low-risk, node-negative disease, and the reported improvement in survival is based on a very small difference of 13 events in 979 patients (15 deaths in the anastrozole arm versus 28 deaths in the tamoxifen arm).

### Alts in a sequential treatment strategy

Sequential therapy trials compare 5 years of continuous tamoxifen or AI therapy with a preplanned sequence of tamoxifen followed by an AI or an AI followed by tamoxifen. In these trials randomization is performed after surgery, that is, before initiation of endocrine therapy and, therefore, all patients are included, irrespective of the risk of relapse. To date, a preliminary analysis of data from the ABCSG-8 trial provides the only information regarding the efficacy of sequential tamoxifen–AI therapy.

Preliminary analysis of the ABCSG-8 trial data demonstrated that, at 30 months’ median follow-up, switching to anastrozole reduced the risk of recurrence by 37% (P = 0.01), that is, excluding events in the first 2 years of treatment. In contrast, when events that occurred during the first 2 years were included in the analysis, as prospectively defined, only a non-significant 24% reduction in the risk of recurrence was reported in patients taking sequential tamoxifen–anastrozole therapy (hazard ratio 0.76, P = 0.07) [24]. This illustrates the importance of including early events in efficacy analyses, and also highlights the importance of selecting the treatment strategy (i.e. upfront or sequential AI therapy) immediately after surgery, when the treatment decision on adjuvant endocrine therapy has to be made.

Further information regarding the efficacy of sequential therapies will be provided by two ongoing trials. The sequential arms of BIG 1-98 are examining the effects of 2 years’ tamoxifen followed by 3 years’ letrozole therapy, as well as the novel strategy of 2 years’ letrozole followed by 3 years’ tamoxifen. Results from the sequential arms of BIG 1-98 are expected in 2008. The TEAM trial was originally designed as a substitution trial comparing 5 years of
exemestane and 5 years of tamoxifen, but following publication of the IES data showing a benefit of switching to exemestane, the TEAM protocol was altered and patients in the tamoxifen arm switched onto exemestane after 2–3 years. Hence, the amended TEAM trial is now comparing 5 years of exemestane with sequential tamoxifen–exemestane therapy. Mature analyses from ABCSG-8 will also provide further insights into the benefits of sequencing tamoxifen and AIs in the adjuvant setting.

**hormone receptor status and response to adjuvant AI therapy**

Tumor hormone-receptor positivity identifies patients who can be predicted to benefit from endocrine therapy. However, there is increasing evidence that HR+ breast cancer describes a heterogeneous group of diseases, and the benefit achieved from endocrine therapy is not the same in all patients. It has been suggested that ER levels (high or low) and the presence or absence of PgRs may influence the response to endocrine therapy, but the relationship between tumor PgR status and responsiveness to AIs is currently unclear. [This issue has been clarified by the centralized analysis of receptor status in the ATAC and BIG 1-98 trials [38].]

Early data from adjuvant trials suggested that, among patients with ER+ tumors, anastrozole may be more effective in PgR– than PgR+ disease. Retrospective subgroup analysis of the influence of ER/PgR status (based on local assessment) on TTR in the ATAC trial demonstrated that the benefit of anastrozole over tamoxifen was greater in patients with ER+/PgR– tumors than in patients with ER+/PgR+ (Table 4) or ER+/PgR-unknown disease. The interaction between PgR status and response to treatment was highly significant ($P = 0.0004$) in patients with ER+ tumors [25]. In ABCSG-8/ARNO, subgroup analysis also suggested that the benefits of switching to anastrozole were more pronounced in patients with ER+/PgR– tumors (hazard ratio 0.42, 95% CI 0.19–0.92) than in patients with ER+/PgR+ disease (hazard ratio 0.66, 95% CI 0.46–0.93), but the difference between the two subgroups was not statistically significant [21].

In contrast to these findings, local assessment of tumor receptor status in patients enrolled in the BIG 1-98 trial suggested that letrozole was equally beneficial in ER+/PgR+ and ER+/PgR– disease (Table 4) [16]. These findings have recently been verified in an ongoing centralized review of hormone receptor status. Central laboratory analysis of samples from almost 4400 patients from BIG 1-98 confirmed that letrozole is effective in patients with ER+ tumors, irrespective of PgR status (Table 4) [26]. Switching to exemestane was also shown to be beneficial to patients with ER+ tumors, regardless of PgR status (ER+/PgR–, hazard ratio 0.58; ER+/PgR+, hazard ratio 0.66) [18]. Available data suggest that anastrozole may be most effective in ER+/PgR– tumors, whereas letrozole and exemestane are equally effective in ER+/PgR+ and ER+/PgR– disease. However, the influence of PgR status on responsiveness to AIs, and whether the different AIs are effective in different tumor subtypes, require confirmation, and treatment decisions based on PgR status are not currently recommended.

**HER2 status and response to adjuvant AI therapy**

HER2/neu overexpression has been associated with poor prognosis and may also predict for resistance to tamoxifen [27, 28]. The relationship between HER2/neu status and the response to AIs has not been widely investigated. In the neoadjuvant setting, letrozole has been shown to be equally effective in HER2/neu+ and HER2/neu– tumors, although this was a retrospective subgroup analysis of a relatively small trial [29]. Results from the centralized review of receptor status in BIG 1-98, based on a relatively small number of patients with HER2/neu+ tumors, show that the prognosis of these patients is less favorable with both letrozole and tamoxifen therapy (Table 4) [26]. Longer follow-up and further investigations are needed to elucidate the interaction of ER, PgR and HER2, and to clarify the role of tamoxifen and AIs in HER2-overexpressing breast cancer.

**tolerability of adjuvant endocrine therapy**

In addition to efficacy, good long-term safety is important for the widespread acceptance of AIs as adjuvant treatment for early breast cancer. A brief summary of the adverse events described in the AI clinical trials is presented here, and a more

### Table 4. Efficacy of AIs according to PgR and HER2/neu status in ER+ breast cancer. Anastrozole was initially reported to be particularly effective in ER+/PgR– tumors, whereas letrozole is equally effective in ER+ tumors, irrespective of PgR status [25, 26]

<table>
<thead>
<tr>
<th>Study</th>
<th>AI</th>
<th>Endpoint</th>
<th>ER+/PgR+ Hazard ratio (95% CI)</th>
<th>ER+/PgR– Hazard ratio (95% CI)</th>
<th>ER+/HER2+ Hazard ratio (95% CI)</th>
<th>ER+/HER2– Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>Ana</td>
<td>TTR</td>
<td>0.84 (0.69–1.02) $^a$ P = 0.07</td>
<td>0.43 (0.31–0.61) $^a$ P = 0.0001</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Let</td>
<td>DFS</td>
<td>0.84 (0.69–1.03) $^a$ P = 0.09</td>
<td>0.83 (0.62–1.10) $^a$ P = 0.18</td>
<td>0.68 (0.33–1.41)$^b$</td>
<td>0.72 (0.56–0.91)$^b$</td>
</tr>
</tbody>
</table>

$^a$Local pathological assessment.

$^b$Central pathological assessment.

NR, not reported.
The AI trials. As described above, all trials comparing postmenopausal women without breast cancer to that seen in demonstrated a similar incidence of cardiovascular events in [35, 36]. In addition, epidemiological studies have cardiovascular disease compared with women taking placebo not have an increased risk of hypercholesterolemia or patients receiving tamoxifen, an expected decrease in cholesterol over the 5-year treatment period, whereas in letrozole, there was no change in the mean level of measurements in the BIG 1-98 study: in patients taking This interpretation is supported by the serial cholesterol cardioprotective [33] effects, and the apparent increases in hypercholesterolemia and cardiovascular events among women taking AIs may be, at least in part, attributable to the lack of tamoxifen’s beneficial effects in these patients. This interpretation is supported by the serial cholesterol measurements in the BIG 1-98 study: in patients taking letrozole, there was no change in the mean level of cholesterol over the 5-year treatment period, whereas in patients receiving tamoxifen, an expected decrease in cholesterol levels of 10–15% was seen. Furthermore, in the MA.17 study, women taking extended adjuvant letrozole did not have an increased risk of hypercholesterolemia or cardiovascular disease compared with women taking placebo [31, 34]. Longitudinal studies have also failed to provide any evidence of a detrimental effect of AIs on lipid metabolism [35, 36]. In addition, epidemiological studies have demonstrated a similar incidence of cardiovascular events in postmenopausal women without breast cancer to that seen in the AI trials. As described above, all trials comparing adjuvant AIs with tamoxifen have demonstrated a small increase in cardiovascular disease associated with AIs. Hence, further studies are required to clarify the effects of AIs on lipid metabolism and the cardiovascular system.

discussion and conclusions
Systemic adjuvant endocrine therapy is an essential part of breast cancer treatment, providing long-term benefits for women with HR+ disease. For many years, tamoxifen was the first-choice drug in the adjuvant setting, but data from large, randomized clinical trials have now demonstrated the superiority of AIs over tamoxifen when given upfront or after successful completion of 2–3 years of tamoxifen. Due to significant reductions in the risk of relapse and an acceptable safety profile, the AIs are displacing tamoxifen monotherapy as the gold standard endocrine adjuvant treatment in most patients. Updated treatment guidelines from ASCO, St Gallen and NCCN now recommend the inclusion of an AI in adjuvant breast cancer treatment for postmenopausal women with HR+ disease [4–6].

Although AIs are clearly more effective than 5 years of tamoxifen, when given upfront or after a successful period of tamoxifen therapy, the optimum therapeutic strategy for AIs has not yet been determined. In oncology, when treating patients with the intention to cure their disease, it is established practice to give the most effective therapy first. In patients who have an intermediate or high risk of relapse, the peak of breast cancer recurrence occurs in the first 2–3 years after surgery, even in patients taking tamoxifen; giving an AI upfront will reduce these early relapses. Results from the ATAC and BIG 1-98 trials provide data in favor of giving anastrozole or letrozole upfront, and letrozole has been shown to be particularly beneficial to patients who are at increased risk of early relapse. Furthermore, upfront letrozole reduces the risk of early distant metastases, which can be expected to translate into a survival benefit with longer follow-up, as metastatic disease is incurable and distant relapse is a strong predictor of death from breast cancer. For patients who remain disease free after 2–3 years of tamoxifen, switching to an AI clearly improves outcomes, and may increase survival. However, as yet, there are no convincing data to suggest that starting a patient on tamoxifen with the intention of changing to an AI after 2–3 years (sequential therapy) has a similar benefit over 5 years of tamoxifen as upfront treatment with the same AI. Results from TEAM, the sequential arms of BIG 1-98, and ABCSG-8, will provide additional information on the benefits of sequential tamoxifen–AI therapy. In addition, BIG 1-98 is the only trial investigating the reverse sequence of letrozole for 2 years followed by tamoxifen for 3 years.

Tamoxifen is a highly effective drug and is still required for adjuvant therapy in pre- or perimenopausal women. Tamoxifen may also still be suitable in some postmenopausal patients, such as those with low-risk disease. However, predictors of early relapse are still poorly defined, and, as AIs have shown to be at least equivalent to tamoxifen in all patients regardless of the risk of relapse, all physicians should discuss the available data with patients starting adjuvant endocrine therapy.
Clinically relevant differences between the AIs also require further investigation. Results of subgroup analyses, although limited in their usefulness, can—particularly if confirmed in an independent data set—provide some indications regarding which subgroup of patients may be most suitable for a particular treatment. A recent retrospective analysis of BIG 1-98 data has identified several factors that predict for early recurrence, including tumor size, ER/PgR status and node positivity [37]. A significant interaction was seen between nodal involvement, which is associated with a higher risk of relapse [1], and response to treatment. In adjuvant trials, upfront letrozole, but not anastrozole, demonstrated superiority over tamoxifen in patients with node-positive disease and patients who had received prior chemotherapy, generating the hypothesis that upfront letrozole may be a more effective treatment than anastrozole for patients at higher risk of early relapse. The importance of PgR status on response to endocrine therapy is still unclear. Although retrospective analyses of the ATAC study have suggested that anastrozole may be particularly beneficial in patients with ER+PgR– tumors [21, 25], this effect was not seen in the BIG 1-98 study. Thus, treatment decisions based on ER/PgR status are not currently recommended as they are based on cross-trial comparisons.

AIs were well tolerated across the adjuvant trials, with predictable side effects reflecting the near-complete depletion of estrogen achieved by these highly effective agents. Adverse events associated mainly with AI therapy, including myalgia, arthralgia and bone loss, are usually more manageable than the more unpredictable side effects associated with tamoxifen, such as endometrial cancer and thromboembolic disease. There is currently no evidence of tolerability differences between the individual AIs, nor between different treatment strategies.

Differences in efficacy and safety between the three AIs can only be determined by direct head-to-head comparisons in randomized trials. The ongoing FACE (Femara versus Anastrozole Clinical Evaluation) trial is a multicenter, open-label, randomized study comparing the efficacy and safety of letrozole and anastrozole in postmenopausal women with HR+, node-positive early breast cancer. Patients (n = 4000) are randomized to either anastrozole or letrozole daily for 5 years, within 12 weeks of surgery, or within 4 weeks of completing adjuvant chemotherapy (Figure 3). The primary endpoint, DFS, is defined as time to local, regional or distant recurrence, contralateral breast cancer or death from any cause, and secondary endpoints are OS, breast cancer survival, time to distant metastases, and time to contralateral breast cancer; safety and tolerability will also be compared. All analyses in the FACE trial will be performed and reviewed by independent parties and by an independent data monitoring committee. In addition to the FACE trial, a direct comparison between upfront exemestane and anastrozole in over 6800 women with HR+ breast cancer has recently completed accrual (MA.27 trial).

In conclusion, AIs are now the preferred option for postoperative adjuvant endocrine therapy for most postmenopausal women with hormone-sensitive early breast cancer, and significantly improve outcomes compared with tamoxifen. In the absence of direct comparisons of the different treatment strategies, the optimal use of AIs remains unknown. Current data suggest that all postmenopausal women who are candidates for adjuvant therapy should have the opportunity to discuss upfront AI therapy with their doctor, as there is no evidence to suggest that delaying initiation of the most effective treatment has any benefit. Patients currently taking tamoxifen should be given the option of switching to an AI in order to further reduce the risk of recurrence and avoid the problematic adverse effects associated with tamoxifen. Ongoing studies, including BIG 1-98, will help to answer important questions regarding AI therapy, including the optimum treatment strategy, clinical equivalence of different AIs and the impact of PgR and HER2/neu status, and will help to maximize the potential of these highly effective drugs.

disclosures
Professor Thu¨ rlimann has reported that he holds Novartis stock and has received honoraria as a speaker for Astra Zeneca, Novartis and Pfizer.

references