The standard adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer is 5 years of tamoxifen. Nevertheless, recurrences and side-effects restrict its usefulness. The aromatase inhibitor anastrozole was compared with tamoxifen for 5 years in 9366 postmenopausal women with localised breast cancer. After a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival (575 events with anastrozole vs 651 with tamoxifen, hazard ratio 0.87, 95% CI 0.78–0.97, p=0.01) and time-to-recurrence (402 vs 498, 0.79, 0.70–0.90, p=0.0005), and significantly reduced distant metastases (324 vs 375, 0.86, 0.74–0.99, p=0.04) and contralateral breast cancers (35 vs 59, 42% reduction, 12–62, p=0.01). Almost all patients have completed their scheduled treatment, and fewer withdrawals occurred with anastrozole than with tamoxifen. Anastrozole was also associated with fewer side-effects than tamoxifen, especially gynaecological problems and vascular events, but arthralgia and fractures were increased. Anastrozole should be the preferred initial treatment for postmenopausal women with localised hormone-receptor-positive breast cancer.

Figure: (A) Efficacy endpoints for all patients and hormone-receptor-positive patients and (B) time-to-recurrence in hormone-receptor-positive patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>All patients</th>
<th>HR+ patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>0.87</td>
<td>0.83</td>
</tr>
<tr>
<td>Time-to-recurrence</td>
<td>0.79</td>
<td>0.74</td>
</tr>
<tr>
<td>Time-to-distant-recurrence</td>
<td>0.86</td>
<td>0.84</td>
</tr>
<tr>
<td>Overall survival</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Time to breast cancer death</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>Contralateral breast cancer*</td>
<td>0.58</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Hazard ratio 0.74 (95% CI 0.64–0.87) p=0.0002

Proportion with recurrence (%)

Numbers at risk:

- Anastrozole: 2618 2540 2468 2355 2268 2014 830
- Tamoxifen: 2598 2516 2398 2304 2189 1932 774

Absolute difference

- Anastrozole: 2618 2540 2468 2355 2268 2014 830
- Tamoxifen: 2598 2516 2398 2304 2189 1932 774

The standard adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer is 5 years of tamoxifen. Nevertheless, recurrences and side-effects restrict its usefulness. The aromatase inhibitor anastrozole was compared with tamoxifen for 5 years in 9366 postmenopausal women with localised breast cancer. After a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival (575 events with anastrozole vs 651 with tamoxifen, hazard ratio 0.87, 95% CI 0.78–0.97, p=0.01) and time-to-recurrence (402 vs 498, 0.79, 0.70–0.90, p=0.0005), and significantly reduced distant metastases (324 vs 375, 0.86, 0.74–0.99, p=0.04) and contralateral breast cancers (35 vs 59, 42% reduction, 12–62, p=0.01). Almost all patients have completed their scheduled treatment, and fewer withdrawals occurred with anastrozole than with tamoxifen. Anastrozole was also associated with fewer side-effects than tamoxifen, especially gynaecological problems and vascular events, but arthralgia and fractures were increased. Anastrozole should be the preferred initial treatment for postmenopausal women with localised hormone-receptor-positive breast cancer.
recurrence is in addition to the 47% risk reduction previously shown for 5 years of tamoxifen versus placebo in adjuvant studies. No significant differences were noted in effect according to subgroup at the 1% level, and the hazard rate was lower for anastrozole in all subgroups except for patients who were hormone-receptor-negative or whose hormone-receptor status was unknown.

Absolute differences in recurrence rates increased over time, even beyond 5 years of scheduled treatment, suggesting that there is a carryover effect for anastrozole similar to that observed for tamoxifen, at least in the short-term (figure 1B). The benefits of anastrozole were seen at all times after the first year of follow-up. In particular, the high hazard rate seen in years 1–3 for tamoxifen was substantially suppressed by anastrozole. We noted a significant overall benefit in time-to-distant-recurrence for anastrozole (324 vs 375 events, hazard ratio 0.86, 95% CI 0.74–0.99, p=0.04), with a similar trend in the subset of hormone-receptor-positive patients (0.84, 0.70–1.00, p=0.06).

The incidence of contralateral breast cancer was substantially reduced by anastrozole compared with tamoxifen (all patients 35 vs 59, 42% reduction, 95% CI 12–62, p=0.01; hormone-receptor-positive patients 53%, 25–71, p=0.001). Since tamoxifen shows a 50% reduction in the occurrence of these tumours in hormone-receptor-positive patients compared with placebo, the findings from the ATAC study suggest that anastrozole treatment might prevent 70–80% of hormone-receptor-positive tumours in women at high risk of breast cancer.

831 women died; 500 (60%) after recurrence of breast cancer and 331 (40%) without recurrence and due to other causes. Overall survival was similar for anastrozole and tamoxifen (hazard ratio 0.97, 95% CI 0.85–1.12, p=0.07); a 12% reduction in deaths from breast cancer in the anastrozole group was not significant (0.88, 0.74–1.05; p=0.2). However, since the trial population had a relatively good prognosis (5695 [61%] of patients were lymph-node-negative and 5959 [64%] had tumours 2 cm or smaller in diameter), it is too early to expect a difference in survival. For example, it took at least 7 years to show a significant survival advantage for tamoxifen versus placebo in previous adjuvant studies. The significant reductions in recurrence and distant recurrence associated with anastrozole strongly suggest that a reduction in deaths from breast cancer will eventually be seen.

Since almost all patients have completed their scheduled 5 years of therapy, the safety and tolerability data during treatment can be deemed final. Withdrawals due to adverse events were significantly less common with anastrozole (344, 11·1%) than with tamoxifen (442, 14·3%; p=0.0002). Drug-related serious adverse events were also significantly less common with anastrozole (146, 4·7%) than with tamoxifen (271, 9·0%; p<0·0001).

Treatment with anastrozole was associated with significant reductions in the incidence of endometrial cancer, thromboembolic events, ischaemic cerebrovascular events, vaginal bleeding, hot flushes, and vaginal discharge, compared with tamoxifen (table). Tamoxifen was associated with fewer fractures and less arthralgia than was anastrozole. Fracture rates per 1000 woman-years were 22·6 for anastrozole and 15·6 for tamoxifen (hazard ratio 1·44, 95% CI 1·21–1·68, p<0·0001). The incidence of hip fracture was low and similar for anastrozole and tamoxifen (table). Findings of several studies show that bisphosphonates are effective in maintaining bone density in women with breast cancer. The risk ratios for all the prespecified adverse events in the present report were similar to those noted in previous analyses, suggesting that the safety profile of anastrozole remains unchanged during the 5-year treatment period. No new safety concerns emerged.

This analysis of the ATAC trial confirms the efficacy and tolerability benefits of anastrozole as initial adjuvant treatment for postmenopausal women with localised breast cancer. The results are only applicable to anastrozole, since it is unknown how differences between the aromatase inhibitors affect their clinical usefulness. Results from studies evaluating anastrozole or exemestane after 2–3 years of adjuvant tamoxifen, compared with continuing tamoxifen, suggest that it is reasonable to switch patients currently on tamoxifen.
localised breast cancer. The present data suggest that it is not appropriate to wait 5 years to start an aromatase inhibitor. Furthermore, the higher rates of recurrence (especially in years 1–3), and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen, lend support to the approach of offering the most effective and well tolerated therapy at the earliest opportunity. 5 years of anastrozole should now be considered as the preferred initial adjuvant endocrine treatment for post-menopausal women with hormone receptor-positive localised breast cancer.

Conflict of interest statement
A Howell has received honoraria and appeared on speakers’ bureaux for AstraZeneca. M Baum has received travel grants, honoraria for lectures, and occasional consultancy fees for AstraZeneca. A Buzdar has received research grants, travel awards, and honoraria from AstraZeneca. J Cuzick is statistical consultant to, and has received research funds from, AstraZeneca. M Dowsett has received paid consultancy from AstraZeneca and is in receipt of grants from AstraZeneca for work done in his laboratory. J F Forbes has received honoraria from AstraZeneca, Novartis, and Lilly for attendance at advisory board meetings. He is responsible for the undertaking of clinical trials by the Australia New Zealand Breast Cancer Trials Group, which have been supported by education/research grants from various pharmaceutical companies.

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References