

RAPID APPRAISAL

Name of Trial: A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer (BIG 1-98).

Reference: Thurlimann B, Keshaviah A, Coates AS, et al. New England Journal of Medicine, 2005; **353**:2747-57.

Question: What is the safety and efficacy of adjuvant letrozole compared with tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer?

Summary: This study demonstrated that in postmenopausal women with hormone receptor-positive breast cancer adjuvant letrozole therapy significantly reduced the risk of recurrent disease compared with tamoxifen (absolute difference 1.9%, NNT 53). In particular, letrozole appears to reduce the rate of appearance of distant metastases. There was no significant benefit in terms of overall survival. Patients in the tamoxifen group were more likely to have thromboembolism, vaginal bleeding or endometrial cancer, and those in the letrozole group skeletal or serious cardiovascular problems. However, interpretation of the results must take into account the relatively short follow-up period (median 25.8 months), given the natural history of the disease. Longer-term follow-up is essential to determine the potential risks/benefits and optimal duration of adjuvant therapy with letrozole.

Did the study ask a clearly focussed question?

Yes - This study was designed to compare the safety and efficacy of adjuvant letrozole (2.5mg/day) versus tamoxifen (20mg/day) in postmenopausal women with hormone receptor-positive early breast cancer, post surgery.⁽¹⁾ The study compared not only letrozole monotherapy with tamoxifen monotherapy, but also sequencing of both agents, during the first 5 years following breast cancer surgery. Participants were randomly assigned to one of 4 treatment arms; 5 years of tamoxifen, 5 years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole, or 2 years of letrozole followed by 3 years of tamoxifen. This primary analysis compared only the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially.

The primary endpoint was disease-free survival (DFS), defined as any breast cancer recurrence, invasive contralateral breast cancer; a second primary cancer; or death without a recurrence. Specified secondary endpoints included overall survival, systemic disease-free survival and safety.

Was the study design appropriate?

Yes - The Breast International Group (BIG) 1-98 study was a large randomised, phase III, double-

blind trial. Eligible patients were postmenopausal women with breast cancer that was positive for either oestrogen receptors (ER+) or progesterone receptors (PgR+), or both. Primary surgery with resulting clear margins and adequate haematologic, renal, and hepatic function were required.

In addition to the final efficacy analysis two planned interim analyses were conducted, and a Data and Safety Monitoring Committee reviewed safety bi-annually throughout the trial. Novartis distributed the study drugs and provided financial support, but placed no restrictions on the investigators with respect to trial data.

Were participants appropriately allocated to intervention and control groups?

Yes – The primary analysis was based on a total of 8,010 patients (excluding 18 who withdrew consent and did not start treatment): 4,003 in the letrozole group and 4,007 in the tamoxifen group. Randomisation was performed with the use of permuted blocks and was stratified according to the participating centre and according to whether chemotherapy had been completed before randomisation, was planned to be given concurrently with endocrine therapy, or had neither been given nor planned. The baseline characteristics of the patients, tumours and primary treatments were very similar in the two groups.

Were participants, staff and study personnel 'blind' to participants study group?

Probably - The study was conducted in a double blind fashion with respect to the study drug and active control. It is therefore likely that all patients, doctors and investigators were blind to treatment allocations as this is implied in the trial design, although the exact measures taken to ensure this at each stage are not defined.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes - A CONSORT flowchart accounted for all randomised patients up to entry into the intention-to-treat (ITT) analysis.⁽²⁾ After randomisation, 133 patients (1.7%) were deemed ineligible on the basis of medical review (41 were premenopausal, 30 had prior, concurrent or bilateral cancer, 27 had incorrectly staged cancer, 17 had negative or unknown receptor status, and 18 were ineligible for reasons not stated). All were included in the ITT analysis. Forty-seven patients did not receive treatment and were excluded from the safety analysis, and 1,717 patients who underwent hysterectomy prior to study entry were excluded from safety analyses of endometrial events. An additional 34 patients (0.4%) inadvertently received the opposite treatment for a median of 4.7 months but were evaluated according to their randomisation assignment.

Were the participants in all groups followed up and data collected in the same way?

Yes - Among patients who were alive and free of recurrence, 98.1% had a follow-up report within one year before the data cut-off. History taking and physical examination were performed at baseline, bi-annually for the first 5 years and yearly thereafter. Serum total cholesterol (TC) was measured at baseline, bi-annually for the first 3 years, yearly for the following 2 years, and 1 year after treatment ended. Haematological, blood chemistry and bilateral mammograms were performed at baseline and when medically indicated. Specific adverse events were listed and graded at each study visit.

Was the study large enough?

Yes - The primary analysis was designed to detect a 20% reduction in the risk of a DFS event (hazard ratio, 0.80) with a statistical power of 80% and a two-sided alpha level of 0.05. This design required a total of 647 DFS events, allowing for two interim efficacy analyses based on the O'Brien-Fleming boundary.⁽³⁾

How are the results presented and what is the main result?

The primary analysis was performed after 779 DFS events had been observed; 351 in the letrozole group and 428 in the tamoxifen group. Kaplan-Meier curves were presented and used to estimate DFS.⁽⁴⁾ The hazard ratios (HR) with 95% confidence intervals (CI) and p values were obtained from a Cox proportional-hazard regression model (adjusted for randomisation option and chemotherapy).⁽⁵⁾

At a median follow-up of 25.8 months, DFS was significantly greater in the letrozole group than in the tamoxifen group (HR, 0.81; 95% CI 0.70-0.93; p=0.003). This corresponds to an absolute benefit of 1.9% (8.8% vs. 10.7%) in the rate of occurrence of DFS events in favour of letrozole. Compared with tamoxifen, letrozole significantly reduced the risk of distant recurrence (HR, 0.73; 95% CI 0.60-0.88; p=0.001). The five-year estimates of DFS were 84.0% in the letrozole group and 81.4% in the tamoxifen group, corresponding to an absolute benefit of 2.6%. Overall fewer women died in the letrozole group (166 patients, 4.1%) than in the tamoxifen group (192 patients, 4.8%), but overall survival did not differ significantly between the two treatment groups (HR 0.86; 95% CI 0.70-1.06; p=0.16).

How safe were the regimens?

More patients in the letrozole group than in the tamoxifen group reported at least one protocol specified adverse event of any grade (73% vs. 64%, respectively). However the rate of serious adverse events was similar in the two groups (1.7% for both).

Fractures were significantly more frequent in the letrozole group than the tamoxifen group (5.7% vs. 4.0%, respectively, p=0.001) with a significantly shorter time to first fracture reported within four weeks after the end of treatment (p<0.001). Hypercholesterolaemia was more frequent in the letrozole group (43.6% vs. 19.2%, respectively). Tamoxifen decreased serum TC levels from baseline at 6, 12 and 24 months, whereas letrozole treatment resulted in no relevant changes over time (-12.0, -13.5 and -14.1% vs. 0, 0 and -1.8%, respectively). The overall incidence of adverse cardiac events was similar in the two groups (3.7% vs. 4.1%, respectively). However, there was a significantly increased risk of grade 3, 4 or 5 cardiac events in women taking letrozole (2.1% vs. 1.1%, p=0.001).

Compared with tamoxifen, letrozole was associated with significantly fewer thromboembolic events (1.5% vs. 3.5%, p<0.001, numbers needed to harm (NNH) = 50).

This means that treating 50 women with letrozole for just over two years would be expected to result in one thromboembolic event. Letrozole was also associated with a significantly lower rate of vaginal bleeding (3.3% vs. 6.6%, $p < 0.001$, NNH=30), fewer endometrial biopsies (2.3% vs. 9.1%, $p < 0.001$, NNH=15), and fewer invasive endometrial cancers (0.1% vs. 0.3%, NNH=500), although the latter was not statistically significant ($p = 0.18$).

How precise are the results?

This was a large, randomised phase III trial, which was well designed and conducted. Baseline characteristics were similar for both groups. All patients were accounted for with a high percentage follow-up. In terms of DFS, the results for superiority appear robust (HR 0.81) with a highly significant p value ($p = 0.003$). The 95% confidence interval is narrow and does not cross the line of no effect (0.70-0.93). The analysis included DFS events and follow-up in the sequential treatment groups that occurred up to 30 days after treatments were switched with events and follow-up in the monotherapy groups to increase the statistical power of the comparison of letrozole with tamoxifen. The HR for reducing recurrence at distant sites was also highly significant ($p = 0.001$) and did not cross the line of no effect (95% CI 0.60-0.88). Overall difference in survival between the two groups was not statistically significant ($p = 0.16$) with wide confidence intervals crossing the line of no effect (0.70-1.06). The estimates of five-year DFS were calculated using Kaplan-Meier curves. However at the point of analysis only around 1200 patients (15% of the total trial population) had reached the full 5 years of treatment. Therefore it is difficult to interpret the significance of the data extrapolated from the curve at this time point due to the small number of patients available for analysis.

Can the results be applied to the local population?

The study population comprised of postmenopausal women with hormone receptor-positive early breast cancer. The median age of patients was 61 years (range 38-90). In 41% of patients tumours had spread to the lymph nodes (node-positive), and 37% had a tumour size > 2 cm. Approximately 63% of patients had breast cancers that were ER+/PgR+, and around 20% were ER+/PgR negative. Approximately 54% of the women had breast-conserving surgery and radiotherapy, 43% had mastectomies (with or without radiotherapy), and 23% received adjuvant or neoadjuvant chemotherapy (or both). In England in 2003 there were 36,500 new cases of breast cancer in women, representing an incidence rate of 144 per 100,000 of the female population.⁽⁶⁾ Letrozole will only be prescribed for postmenopausal women, and this group

accounts for around 80% of breast cancer cases (assuming the average age of menopause is 51 years of age).⁽⁷⁾ This would equate to around 115 new cases per 100,000 population per year. Of these approximately 80% are expected to have hormone receptor-positive tumours.⁽⁸⁾ Assuming that up to 60% of these are likely to present with early stage disease this translates to around 55 patients per 100,000 each year who would be eligible for treatment with letrozole.

What is the safety and efficacy of adjuvant letrozole compared with tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer?

Tamoxifen for 5 years is currently the “gold standard” hormone therapy in the adjuvant setting for women with hormone receptor-positive early breast cancer.⁽⁹⁾ The results of this trial show that in postmenopausal women with hormone receptor-positive breast cancer adjuvant letrozole significantly reduced the risk of recurrent disease compared with tamoxifen. In particular, letrozole appears to reduce the rate of distant metastases compared to tamoxifen, a clinically relevant finding since women who develop distant metastasis have a significantly higher risk of dying from their disease.⁽¹⁰⁾ In terms of the data available at the median follow-up period of 25.8 months, the absolute difference of 1.9% in the rate of DFS events would equate to an NNT of 53. This means that for every 53 women treated with letrozole instead of the “gold standard” tamoxifen one additional woman would be alive and free from disease recurrence at just over two years.

Although this trial failed to show a significant benefit in term of overall survival, the estimated absolute difference in the rate of DFS at five years of 2.6% (extrapolated data, (NNT=38)) is similar to values reported for other aromatase inhibitors.⁽¹¹⁾ However, direct comparisons of DFS cannot be made across trials as the baseline characteristics and DFS definitions often differ.

The results of this trial indicate that letrozole and tamoxifen have different safety profiles. Fewer thromboembolic events and uterine abnormalities occurred with letrozole than tamoxifen. There is, however, an increased risk of fractures in women receiving letrozole, which is a concern, as postmenopausal women are already at increased risk of osteoporosis. There was also a higher incidence of serious cardiac events and hypercholesterolaemia in the letrozole group. These findings raise concerns regarding the long-term effects of oestrogen deprivation with respect to bone and lipid metabolism. Therefore, careful monitoring of serum lipids and bone mineral density and consideration of proactive treatment will be important adjuncts to letrozole use.

The major criticism of this trial is the relatively short follow-up period of 25.8 months, given the natural history of the disease. Longer follow-up is

necessary to ascertain whether letrozole will continue to reduce the risk of relapse for several years after cessation of treatment, as has already been shown for tamoxifen.⁽¹²⁾ From the current data it can only be concluded that there are potential benefits from using an aromatase inhibitor such as letrozole at some stage in the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer. However, questions remain regarding the optimal duration of therapy, whether tamoxifen or letrozole should be given first, or even if sequential treatment is optimal. Future analyses

of the continued BIG 1-98 study, assessing the role of sequencing, should answer these important questions.

At present, the potential long-term side effects of letrozole are undetermined; it is possible, given the concerns regarding the long-term effects of oestrogen deprivation that the toxicity profile may change with the accumulation of data. Therefore, a full adverse event profile at 5 years is essential to enable a complete comparison of the risks and benefits of adjuvant therapy with letrozole to be made.

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KEY: RCT - randomised controlled trial, MA-meta analysis, R-review.

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