Role of ErbB2 in selection for adjuvant tamoxifen or aromatase inhibitors

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Evaluation of: Rasmussen BB, Regan MM, Lykkesfeldt AE et al.: Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1–98 randomized trial. Lancet Oncol. 9, 23–28 (2008). This study analysed data after a median of 51 months follow-up from 4922 postmenopausal women with early hormone-sensitive breast cancer randomly assigned to 5 years of treatment with letrozole or tamoxifen. Tumors from 3650 (74%) patients were centrally assessed for estrogen receptor, progesterone receptor and ErbB2 status. By central assessment, 7% (257 of 3650) of tumors were classified as ErbB2-positive. Disease-free survival was significantly worse in patients with ErbB2-positive tumors (p < 0.0001). Letrozole improved disease-free survival compared with tamoxifen regardless of ErbB2 status.

Background
There are limited data available comparing tamoxifen and aromatase inhibitors in patients with ErbB2-positive or -negative cancers in the adjuvant setting and the latest data from the Breast International Group (BIG) 1–98 study are thus of great importance [1]. Not only is ErbB2 a prognostic factor in breast cancer, but it appears to predict outcome in women who receive certain types of chemotherapy and tamoxifen [2–5]. Published reports have shown that patients who are estrogen receptor (ER)-positive and ErbB2-positive have a poorer response to tamoxifen than patients who are ER-positive and ErbB2-negative [2,3]. It has been observed in neo-adjuvant studies that patients whose cancers are ErbB2-positive have a better response to the aromatase inhibitor letrozole than to tamoxifen [6]. However, it is not at all clear from these studies whether there is a greater relative benefit of letrozole compared with tamoxifen in ErbB2-positive cancers compared with ErbB2-negative tumors.

Data from a study comparing the effects of adjuvant anastrozole and tamoxifen in patients subdivided on the basis of ErbB2 status (Trans/Arimidex, Tamoxifen Alone or in Combination [ATAC]) have been presented but not yet published [7]. There were 5880 eligible patients in the ATAC study who were ER-positive and who were randomized to 5 years of adjuvant anastrozole or tamoxifen. For the analysis of the interaction of ErbB2 and treatment, blocks from 1786 patients were obtained of whom 190 had ErbB2-positive cancers. In this study, anastrozole significantly reduced events compared with tamoxifen in the ErbB2-negative group with a relative hazard ratio of 0.66, but there was no apparent benefit in the ErbB2-positive group with a relative hazards ratio of 0.92, although because of small numbers the confidence intervals (CIs) were wide. Therefore, within this study there was no suggestion that there was a greater relative benefit in the ErbB2-positive population for anastrozole.

Given the uncertainty of the relative benefits of aromatase inhibitors compared with tamoxifen in ErbB2-positive, ER-positive patients, further data are needed to determine whether there are significant interactions between ErbB2 positivity and a greater response to aromatase inhibitors compared with tamoxifen.

Results
In this randomized trial of adjuvant letrozole versus tamoxifen published in Lancet Oncology, the aim was to determine whether there was a greater beneficial effect of letrozole compared with tamoxifen in patients with ErbB2-positive, ER-positive patients. A total of 4922 patients were randomly assigned to 5 years of monotherapy with letrozole or tamoxifen and the current analysis was performed after 51 months median follow-up. Tumors were assessed centrally for ER, progesterone receptor (PgR) and ErbB2 status measured by immunohistochemistry and confirmed by fluorescence in situ hybridization (FISH). Tumors were deemed ErbB2-positive if
amplified by FISH, or for the few tumors with unassessable or unavailable FISH results if immunohistochemically classified as 3+. Hazard ratios were estimated by Cox modelling to compare the effect of letrozole with tamoxifen on disease-free survival, which was the primary end point of this study.

By central assessment, 257 of 3650 tumors that were available for ErbB2 assessment (7%) were classified as ErbB2-positive. There was a total of 3533 patients whose tumors were ER-positive, and in this group disease-free survival was poorer in patients who had ErbB2-positive tumors (n = 239) compared with those patients with ErbB2-negative tumors (n = 3294) with a hazard ratio of 2.09 (95% CI: 1.59–2.76; p < 0.0001). However, there was no statistical evidence of a greater benefit for letrozole compared with tamoxifen in ErbB2-positive compared with ErbB2-negative tumors. Letrozole improved disease-free survival regardless of ErbB2 status with an observed hazard ratio of 0.62 (95% CI: 0.37–1.03) for ErbB2-positive tumors and 0.72 (95% CI: 0.59–0.87) for ErbB2-negative tumors.

Significance
These data show that letrozole is superior to tamoxifen in terms of improving disease-free survival in patients with both ErbB2-positive and negative cancers. This study has confirmed that ErbB2 status is an independent predictor of outcome in patients with ER-positive breast cancer treated by endocrine therapy, with patients who express ErbB2 having a worse disease-free survival with an adjusted hazards ratio (adjusted for tumor size, grade, ER and PgR expression) for ErbB2-positive cancers compared with ErbB2-negative cancers of 1.69 (95% CI: 1.27–2.25).

In this study, it was clear that there was no statistically significant interaction between disease-free survival with letrozole compared with tamoxifen and PgR status. Initial data from the ATAC study had suggested that anastrozole had greater relative benefits in patients with ER-positive, PgR-negative cancers compared with patients whose cancers were both ER- and PgR-positive [8]. This was a hypothesis-generating observation as it was based on subgroup analysis, although it was not confirmed in the Trans/ATAC study where a subset of the trial patients had central PgR evaluation [7]. The letrozole adjuvant study and results from the MA17 study, comparing letrozole versus placebo after 5 years of tamoxifen [9], have shown that aromatase inhibitors are not significantly better than tamoxifen in any specific subgroup based on ER, PgR or ErbB2 expression.

While it is true in the letrozole arm that the relative reduction in events was similar for ErbB2-positive and ErbB2-negative cancers, because of the greater event rate in the ErbB2-positive cancer patients it will be interesting with further follow-up to determine whether the absolute benefit of letrozole in reducing events is greater in the ErbB2-positive patients than the ErbB2-negative patients. Currently, such small numbers of ErbB2-positive patients and small differences in the number of events between the two groups (27 events in 134 ErbB2-positive patients randomized to letrozole compared with 32 events out of 105 ErbB2-positive women randomized to tamoxifen) do not allow firm robust conclusions to be drawn. With further follow-up by combining these data with that from other trials, it may eventually be possible to determine whether despite similar relative risks the absolute risk in the ErbB2 subpopulation is such that ErbB2 positivity will be an indication for use of an aromatase inhibitor as their initial adjuvant therapy. The finding in the current study of a similar benefit in ErbB2-positive and -negative subgroups is not inconsistent with earlier observations in the neoadjuvant setting [6].

The major limitations of both this and the Trans/ATAC study are the small number of ErbB2-positive patients and the small number of events in these two patient groups. In both the ATAC and BIG 1–98 groups, many of the events in what is an older postmenopausal group are deaths from other causes and these are unlikely to be influenced by drug therapy. An analysis of breast cancer relapse-free survival should provide more precise information on the relative influence of drugs in the ErbB2-positive and -negative subgroups. However, it may be that only with a meta-analysis of the aromatase-inhibitor adjuvant trials will it be possible to come to a meaningful conclusion regarding the interaction between ErbB2 positivity and the relative benefit of different endocrine agents.

The conclusion at present is that in the adjuvant setting compared with tamoxifen letrozole is superior, irrespective of the ErbB2 status of the tumor, in improving disease-free survival and that ErbB2 status is not valuable as a selection criteria for those patients who benefit more from letrozole than from tamoxifen [10].
Future perspective

There is now clear evidence that patients benefit from adjuvant treatment with letrozole compared with tamoxifen and that these women have a 30% reduction in all events in the first 2 years and a 30% reduction in metastatic events [10]. This relative benefit of letrozole compared with tamoxifen is present in all groups, although there are some women who have very low-risk tumors where the absolute benefit of letrozole compared with tamoxifen is small. Whether such women are best treated by having 5 years of letrozole, a switching strategy starting with an aromatase inhibitor or tamoxifen and switching to the other drug after 2–3 years, or should have 5 years of tamoxifen followed by 5 years of an aromatase inhibitor, is not clear. Within the BIG 1–98 study there are two sequential arms of letrozole followed by tamoxifen or tamoxifen followed by letrozole; results from these two arms will be available next year and are awaited with interest.

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Bibliography

1. Rasmussen BB, Regan MM, Lykkefeldt AE et al.: Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1–98 randomised trial. Lancet Oncology 9, 23–28 (2008).

2. Slamon DJ, Clark GM, Wong SG, Levine WJ, Ullrich A, McGuire WL: Human breast cancer: correlation of relapse and survival with amplification of the HER2/neu oncogene. Science 235, 177–182 (1987).

3. Tandon AK, Clark GM, Chamnes GC, Ullrich A, McGuire WL: Her-2/neu oncogene protein and prognosis in breast cancer. J. Clin. Oncol. 7, 1120–1128 (1989).

4. Hayes DF, Thor AD, Dressler LG et al.: HER2 and response to paclitaxel in node-positive breast cancer. New Engl. J. Med. 357, 1496–1506 (2007).

5. Schiff R, Massarweh SA, Shou J et al.: Advanced concepts in estrogen receptor biology and breast cancer endocrine resistance: implicated role of growth factor signaling and estrogen receptor coregulators. Cancer Chemother. Pharmacol. 56(Suppl. 1), 10–20 (2005).

6. Ellis MJ, Coop A, Singh B et al.: Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB1 and/or ErbB2 positive, estrogen receptor positive primary breast cancer: evidence from a Phase III randomized trial. J. Clin. Oncol. 19, 3808–3816 (2001).

7. Dowsett M, Allred DC, on behalf of the TRANS/ATAC Investigators: Relationship between quantitative ER and PgR expression and HER2 status with recurrence in the ATAC trial. Br. J. Cancer 95, 756–766 (2006).

8. Goss PE, Ingle JN, Martinot S et al.: Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: national cancer institute of Canada clinical trials group MA.17. J. Clin. Oncol. 25(15), 2006–2011 (2007).

9. Mauriac L, Keshaviah A, Debled M et al.: Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1–98 trial. Ann. Oncol. 18, 859–867 (2007).