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

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BACKGROUND: The Breast International Group (BIG) 1-98 trial (a randomised double-blind phase III trial) has shown that letrozole significantly improves disease-free survival (DFS) compared with tamoxifen in postmenopausal women with endocrine-responsive early breast cancer. Our aim was to establish whether the benefit of letrozole versus tamoxifen differs according to the ERBB2 status of tumours. METHODS: The BIG 1-98 trial consists of four treatment groups that compare 5 years of monotherapy with letrozole or tamoxifen, and sequential administration of one drug for 2 years followed by the other drug for 3 years. Our study includes data from the 4922 patients randomly assigned to the two monotherapy treatment groups (letrozole or tamoxifen for 5 years; 51 months median follow-up [range <1 to 90 months]). A central assessment of oestrogen receptor (ER), progesterone receptor (PgR) and ERBB2 status using paraffin-embedded primary tumour material was possible for 3650 (74%) patients. ER, PgR, and ERBB2 expression were measured by immunohistochemistry (IHC) and ERBB2-positivity was confirmed by fluorescence in-situ hybridisation (FISH). Positive staining in at least 1% of cells was considered to show presence of ER or PgR expression. Tumours were deemed ERBB2-positive if amplified by FISH, or, for the few tumours with unassessable or unavailable FISH results, if they were IHC 3+. Hazard ratios (HR) estimated by Cox modelling were used to compare letrozole with tamoxifen for DFS, which was the primary endpoint, and to assess treatment-by-covariate interactions. The BIG 1-98 trial is registered on the clinical trials site of the US National Cancer Institute website http://www.clinicaltrials.gov/ct/show/NCT00004205. FINDINGS: By central assessment 7% (257 of 3650) of tumours were classified as ERBB2-positive. In 3533 patients with tumours confirmed to express ER, DFS was poorer in patients with ERBB2-positive
tumours (n=239) than in those with ERBB2-negative tumours (n=3294; HR 2.09 [95% CI 1.59-2.76]; p<0.0001). There was no statistical evidence of heterogeneity in the treatment effect according to ERBB2 status of the tumour (p=0.60 for interaction), thus, letrozole improves DFS compared with tamoxifen regardless of ERBB2 status. The observed HRs were 0.62 (95% CI 0.37-1.03) for ERBB2-positive tumours and 0.72 (0.59-0.87) for ERBB2-negative tumours. INTERPRETATION: A benefit of letrozole over tamoxifen was noted, irrespective of ERBB2 status of the tumour, and, therefore, ERBB2 status does not seem to be a selection criterion for treatment with letrozole versus tamoxifen in postmenopausal women with endocrine-responsive early breast cancer.