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E19. Letrozole: a new partner in the fight against relapses from endocrine-responsive breast cancer

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MA.17 is a phase III randomised, double-blind, placebo-controlled trial of letrozole (Femara®) in post-menopausal women with primary breast cancer, who were disease-free after completion of 5 years (4.5–6) of adjuvant tamoxifen. 5187 patients were randomised to receive either oral placebo or oral letrozole 2.5 mg, daily for 5 years. The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS), long-term safety and quality of life. Two interim analyses were scheduled after 171 and 342 events. The protocol included strict, pre-planned stopping rules; early termination had to be considered at a nominal significance level of P=0.0008. At the first interim analysis, which took place after a median follow-up of 2.4 years, 132 events had occurred in the placebo arm, 75 in the letrozole arm. The letrozole-to-placebo hazard ratio was 0.57, with a 95% Confidence Interval (CI) of 0.43–0.75 (P=0.00008). The 4-year DFS was 93% in the letrozole arm and 87% in the placebo arm.

This first interim analysis with its striking results prompted the independent data and safety monitoring committee to recommend unblinding of the trial and to share the results with the participants (1). Patients in the placebo group were offered to switch to letrozole.

Five years of post-operative tamoxifen therapy is still considered the standard approach for women diagnosed with hormone receptor (HR)-positive breast cancer (2). So far, longer durations of adjuvant tamoxifen have not been shown to be beneficial and have been associated with increased risks of tamoxifen-induced endometrial cancer and thromboembolic disease (3). Another important observation is that a significant proportion of breast cancer recurrences (roughly 40–50%) occur more than 5 years post-surgery (4). Taken together, these observations provided a rationale for the assessment of other agents with demonstrated efficacy in breast cancer, such as the aromatase inhibitors, to be tested for extended adjuvant therapy in an attempt to further improve patient survival.

The effectiveness of 5 years of letrozole therapy in post-menopausal women with breast cancer who have completed 5 years of tamoxifen therapy has been explored in this large international trial, with the enrolment of 5187 women (1). At the first interim analysis, there were 207 local or distant recurrences of breast cancer or new primary cancers in the contralateral breast – 75 in the letrozole group and 132 in the placebo group. When analysed by site of recurrence, letrozole was found to be superior to placebo and to result in fewer locoregional, but also distant recurrences. Distant metastases are a surrogate for survival as they almost inevitably lead to mortality. Fewer patients in the letrozole arm (14) than in the placebo arm (26) experienced a new primary tumour in the contralateral breast.

At the time of analysis, a total of 42 women in the placebo group and 31 women in the letrozole group had died (P=0.25 for the comparison of overall survival). Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group, but vaginal bleeding was less frequent. There were new diagnoses of osteoporosis (as reported by patients and unverified) in 5.8% of the women in the letrozole group and 4.5% of the women in the placebo group (P=0.07); the rates of fracture were similar.

Companion studies to MA.17 will be analysed: annual bone mineral density (BMD) in 226 patients, lipid profiles in around 320 patients, quality of life (QOL) as assessed by Short Form (SF)-36 and the Menopause-Specific Quality of Life (Menqol) questionnaires in approximately 3500 women.

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At this first interim analysis, the estimated 4-year DFS was higher in the letrozole arm (93%) than in the placebo arm (87%), with an absolute 6% difference. Interestingly both node-negative and node-positive patients experienced improvement in DFS with an absolute 3-year difference of 3% for node-negative and 7% for node-positive disease. The observation that there is increasing difference in favour of letrozole over time suggests this difference could be even more apparent with more prolonged follow-up, leading to a survival difference.

Despite the short median follow-up, these results are impressive and unlikely to be the subject of a ''reversal of fortune''. Continued follow-up of the trial's participants will be ensured, while women in the ''control'' group currently have the option to start letrozole therapy at no cost.

This landmark trial will have a significant impact on endocrine adjuvant treatment strategies for the next 10 years. In daily clinical practice, before the final results of the study are available, the decision to offer letrozole after 5 years of tamoxifen should be individualised.

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