Clinical Trial

Lancet Oncol. 2021 Oct;22(10):1458-1467.
doi: 10.1016/S1470-2045(21)00352-1. Epub 2021 Sep 17.

Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial

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- PMID: 34543613

- DOI: 10.1016/S1470-2045(21)00352-1

Abstract

Background: The benefit of extending aromatase inhibitor therapy beyond 5 years in the context of previous aromatase inhibitors remains controversial. We aimed to compare extended therapy with letrozole for 5 years versus the standard duration of 2-3 years of letrozole in postmenopausal patients with breast cancer who have already received 2-3 years of tamoxifen.

Methods: This multicentre, open-label, randomised, phase 3 trial was done at 69 hospitals in Italy. Women were eligible if they were postmenopausal at the time of study entry, had stage I-III histologically proven and operable invasive hormone receptor-positive breast cancer, had received adjuvant tamoxifen therapy for at least 2 years but no longer than 3 years and 3 months, had no signs of disease recurrence, and had an Eastern Cooperative Oncology Group performance status of 2 or lower. Patients were randomly assigned (1:1) to receive 2-3 years (control group) or 5 years (extended group) of letrozole (2·5 mg orally once a day). Randomisation, with stratification by centre, with permuted blocks of size 12, was

done with a centralised, interactive, internet-based system that randomly generated the treatment allocation. Participants and investigators were not masked to treatment assignment. The primary endpoint was invasive disease-free survival in the intention-to-treat population. Safety analysis was done for patients who received at least 1 month of study treatment. This trial was registered with EudraCT, 2005-001212-44, and ClinicalTrials.gov, NCT01064635.

Findings: Between Aug 1, 2005, and Oct 24, 2010, 2056 patients were enrolled and randomly assigned to receive letrozole for 2-3 years (n=1030; control group) or for 5 years (n=1026; extended group). After a median follow-up of 11·7 years (IQR 9·5-13·1), disease-free survival events occurred in 262 (25·4%) of 1030 patients in the control group and 212 (20·7%) of 1026 in the extended group. 12-year disease-free survival was 62% (95% CI 57-66) in the control group and 67% (62-71) in the extended group (hazard ratio 0·78, 95% CI 0·65-0·93; p=0·0064). The most common grade 3 and 4 adverse events were arthralgia (22 [2·2%] of 983 patients in the control group vs 29 [3·0%] of 977 in the extended group) and myalgia (seven [0·7%] vs nine [0·9%]). There were three (0·3%) serious treatment-related adverse events in the control group and eight (0·8%) in the extended group. No deaths related to toxic effects were observed.

Interpretation: In postmenopausal patients with breast cancer who received 2-3 years of tamoxifen, extended treatment with 5 years of letrozole resulted in a significant improvement in disease-free survival compared with the standard 2-3 years of letrozole. Sequential endocrine therapy with tamoxifen for 2-3 years followed by letrozole for 5 years should be considered as one of the optimal standard endocrine treatments for postmenopausal patients with hormone receptor-positive breast cancer.

Funding: Novartis and the Italian Ministry of Health.

Translation: For the Italian translation of the abstract see Supplementary Materials section.