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Letter

Comment on "Anastrozole (Arimidex™) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results" by J.-M. Nabholtz et al.☆

In the recently published manuscript, "Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results" [1], no survival difference was noted between anastrozole and tamoxifen in the first-line treatment of 1021 postmenopausal women with advanced breast cancer in terms of the proportion of patients dead at 2 years (31.1 versus 32.0%), or at median follow-up of 43.7 months (55.1 versus 55.9%) nor in terms of median time to death (39.2 versus 40.1 month) [1]. In view of the fact that there were no significant differences in the other efficacy endpoints (response rate [ORR], time to progression [TTP]), this is not a surprising finding [2].

In the discussion of the data, the authors refer to a similar phase-III trial of letrozole versus tamoxifen ($N=916$); however, they did not quote the complete analysis of this trial, which we recently published in the *Journal of Clinical Oncology* [3]. In this comparison of letrozole versus tamoxifen, letrozole was associated with a significantly higher ORR and TTP than the anti-oestrogen. While this trial only showed a numerical overall survival (OS) benefit for letrozole (median 34 versus 30 months, $P=0.53$ see Fig. 1), letrozole did significantly decrease the risk of death throughout the first 2 years on treatment—as was apparent in the Kaplan–Meier curves and from the prospectively planned statistical analysis at 6 monthly intervals following randomisation (2-year-survival: 62 versus 57%, $P=0.0246$).

This early survival advantage of letrozole over tamoxifen indicates that the OS results might have been confounded by the crossover design of this trial: approximately 50% of patients in both arms crossed over to the other agent upon progression on their 1st-line treatment. Exploratory analyses confirmed this theory: When censoring time-to-death at crossover in the intent-to-treat (ITT) population, thus attempting to exclude the effect of crossover, letrozole led to a significant survival advantage of 1 year over tamoxifen (median OS 42 versus 30 months).

Such an early survival benefit was not demonstrated in the anastrozole trials described by Nabholtz and colleagues despite the fact that a lower percentage of patients (25%) crossed over to the other agent, which would make it easier to detect differences.

Nabholtz and colleagues subsequently argue that the actual duration of survival in both arms of the anastrozole trials is somewhat higher than that observed in the letrozole first-line study. Comparisons of data across different trials is generally inappropriate, as such comparisons may be confounded by biases. In the letrozole trial, more women had visceral metastases than in the anastrozole trials (45% versus 39%) and 10% of patients had already undergone prior chemotherapy for advanced disease; i.e. two detectable confounders in favour of the anastrozole trial.

In summary, letrozole is the only aromatase inhibitor which has proven significantly greater efficacy, including an early survival benefit, over tamoxifen in the first-line treatment of advanced breast cancer in postmenopausal women.

References

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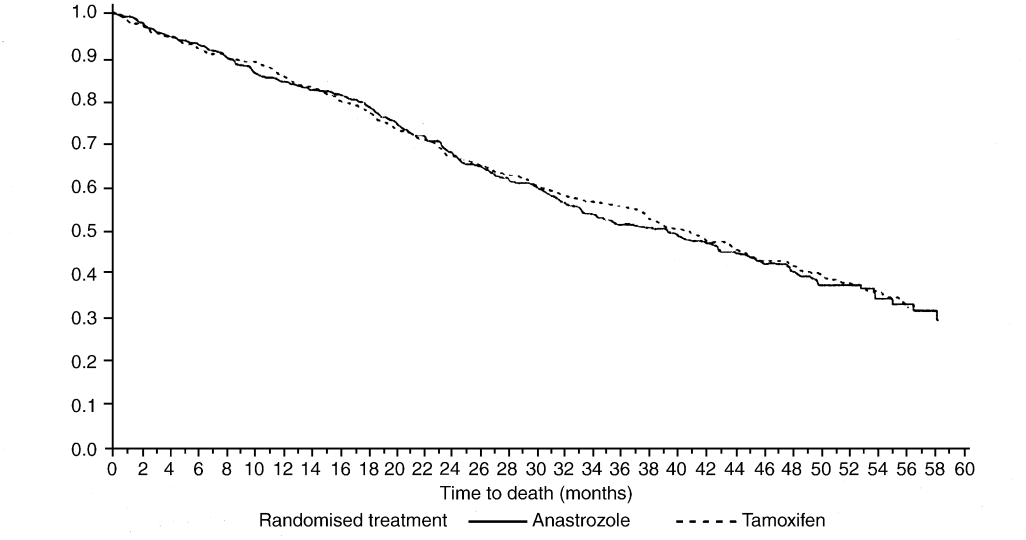

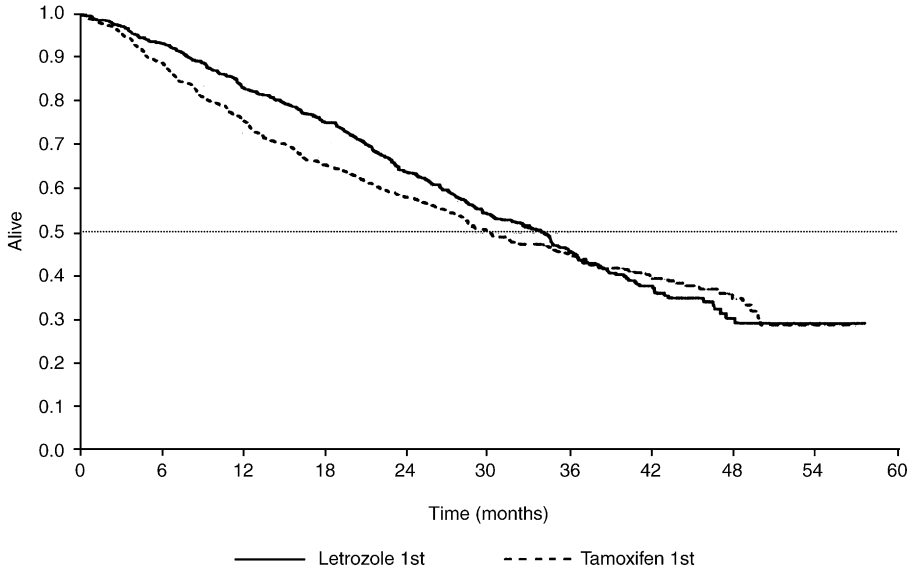

Fig. 1. Anastrozole versus Tamoxifen: Kaplan–Meier Plot of time to death in the overall population ($N=1021$) [1]. Letrozole versus Tamoxifen: Kaplan–Meier Plot of time to death in the overall population ($N=916$) [3].