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Anastrozole (Arimidex™) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results

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Abstract

We present an initial survival analysis and an update of the safety data of the North American and Tamoxifen or Arimidex™ Randomized Group Efficacy and Tolerability (TARGET) double-blind, randomised, multicentre studies which compared anastrozole with tamoxifen as first-line treatment in postmenopausal patients with oestrogen receptor and/or progesterone receptor-positive (ER+/PR+) or receptor-unknown advanced breast cancer (ABC). At a median follow-up of 43.7 months, 56.0% of patients in the anastrozole group and 56.1% of patients in the tamoxifen group had died. The proportion of patients dead at 2 years was 31.1 and 32.0% in the anastrozole and tamoxifen groups, respectively. In the ER+/PR+ subgroup, 55.1 and 55.9% of patients had died and median time to deaths (TTD) were 40.8 and 41.3 months in the anastrozole and tamoxifen groups, respectively. Both agents remained well tolerated, with fewer reports of vaginal bleeding (anastrozole versus tamoxifen, 1.0% versus 2.5%) and thromboembolic events (anastrozole versus tamoxifen, 5.3% versus 9.0%) in the anastrozole group versus the tamoxifen group. Hot flushes and vaginal dryness were reported marginally less in the tamoxifen group compared with the Anastrozole group. Although no improvement in survival was observed, the favourable profile of anastrozole with respect to efficacy (TTP) and tolerability [Cancer 92 (2001) 2247] support the use of anastrozole in advance of tamoxifen as the first-line therapy choice in postmenopausal women with ABC.

Keywords: Anastrozole; Breast cancer; Postmenopause; Tamoxifen

1. Introduction

Approximately two-thirds of breast cancers are oestrogen-dependent [1], and will regress following oestrogen deprivation. For the past 25 years, the oestrogen receptor antagonist, tamoxifen, has been successfully used to treat postmenopausal women with breast cancer [2]. Despite its proven efficacy, tamoxifen is associated with a number of well-recognised tolerability issues and there is a risk of developing resistance [2]. Alternative therapies have therefore been developed, including the aromatase inhibitors (AIs). The AIs work by blocking the conversion of androgens to oestrogen and were developed for use in patients where ovarian function had ceased naturally, surgically or pharmacologically.

Anastrozole is a potent and selective third-generation non-steroidal AI given orally once daily (od) (1 mg), and as second-line therapy, following tamoxifen, showed a significant survival advantage over megoestrol acetate for the treatment of postmenopausal women with advanced breast cancer (ABC) [3] More recently, the North American [4] and TARGET (Tamoxifen or Arimidex™ Randomized Group Efficacy and Tolerability) [5] double-blind, randomised, multicentre studies—which were designed to compare the efficacy and tolerability of anastrozole 1 mg od with tamoxifen 20

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mg od for the first-line treatment of ABC in postmenopausal women—showed that anastrozole was at least as effective as tamoxifen for certain key efficacy parameters. In the North American trial [4], where 89% of women were known to have oestrogen and/or progesterone receptor-positive (ER+/PR+) tumours, anastrozole was significantly superior to tamoxifen for time to disease progression (TTP) (anastrozole vs tamoxifen, median 11.1 months versus 5.6 months, $P=0.005$) and clinical benefit (CB = complete response + partial response + stabilisation $\geqslant$24 weeks: anastrozole = 59%; tamoxifen = 46%, two-sided $P=0.0098$, retrospective analysis). In the TARGET trial [5], where only 45% of women had ER+/PR+ tumours, anastrozole was at least as effective as tamoxifen regarding TTP (anastrozole vs tamoxifen, median 8.2 months versus 8.3 months, $P=0.941$). Both trials [4,5] reported fewer thromboembolic events and vaginal bleeding in those patients in the anastrozole arm compared with those patients in the tamoxifen arm.

The combined results of the North American and TARGET trials showed that anastrozole was significantly superior to tamoxifen with regards to TTP in those patients with ER+/PR+ tumours (anastrozole versus tamoxifen, median 10.7 months versus 6.4 months, $P=0.022$) [6]. Treatments were well tolerated, with anastrozole leading to significantly fewer venous thromboembolic ($P=0.043$) events, and fewer reports of vaginal bleeding compared with tamoxifen. We report the first survival data and an update of the safety data from the combined analysis of these trials.

2. Patients and methods

2.1. Trial design

The TARGET and North American trials were both randomised, double-blind, parallel-group, double-dummy and multicentre trials, similar in design and prospectively planned for combined analysis. The primary objectives of each trial were objective response, TTP and tolerability. The secondary objectives were time to treatment failure, time to death (TTD), duration of tumour response and duration of CB. All patients were followed until objective progression and/or death, irrespective of the treatment received. The first efficacy analyses were carried out at a median duration of follow-up of 18.2 months. Full descriptions of the trial designs are published elsewhere [4–6].

2.2. Treatment programme

Patients from 97 centres in North America and 83 centres in Europe, Australia, New Zealand, South America and South Africa were entered into the study and randomised to one of the two treatment groups (anastrozole 1 mg, tamoxifen 20 mg). Patients were randomised to receive a daily dose of two tablets (one was active and the other was placebo).

2.3. Patient population

Eligibility criteria are published in full elsewhere [4–6], but, in brief, all patients had to be suitable for first-line endocrine therapy. Patients were postmenopausal and had locally advanced or metastatic breast cancer, with ER+/PR+ tumours or tumours of unknown receptor status. All patients provided informed written consent, and ethics committee approval was obtained at each site prior to initiation of treatment.

2.4. Statistics

TTD was defined as the number of days from the date of randomisation to the date of death from any cause. Any patient who had not died at the time of data cut-off or who was lost to follow-up was censored at the date of their last contact. Median TTD was estimated using the Kaplan–Meier method in the overall population and in the subgroup of patients with ER+/PR+ tumours. Median TTD at 24 months of treatment in the overall population and in the ER+/PR+ subgroup are also presented. The primary analysis was carried out on an intention-to-treat basis using an unadjusted Cox's regression model with treatment factor only. The secondary analysis was performed using the Cox's regression model adjusting for baseline covariates. Supportive analysis was also performed on a per-protocol basis using both the adjusted and unadjusted Cox's regression models. For each analysis, statistical non-inferiority was defined as the lower one-sided 95% Confidence Limit (CL) of the hazard ratio (HR) being $\geqslant$0.8. A subgroup analysis of TTD was carried out in patients with ER+/PR+ tumours. Safety assessments (in prespecified categories) were summarised by treatment received for the combined trial population. Safety was updated in line with the survival update, and no formal statistical analyses were carried out.

3. Results

A total of 1021 patients were randomised into the two studies and included in the combined analysis (anastrozole 1 mg: $n=511$; tamoxifen 20 mg: $n=510$) (Fig. 1). Patient's characteristics were similar in both treatment groups and are published elsewhere [6]. Briefly, in both the anastrozole and tamoxifen groups, a total of 59.9% of patients were hormone receptor-positive and 33.3% of patients had received prior adjuvant endocrine therapy. The median duration of follow-up was 43.7 months. Approximately 25% of patients following disease

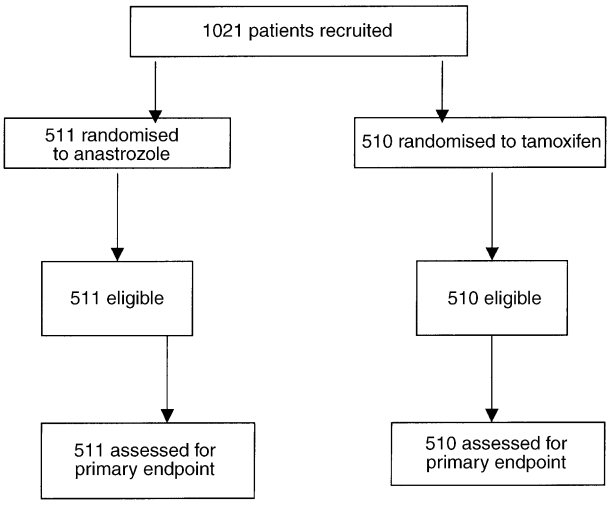


Fig. 1. Consort flowchart.

progression received the alternate hormonal therapy: 27% of patients in the anastrozole arm received tamoxifen as a second-line therapy and 26% in the tamoxifen arm received anastrozole as second-line therapy. The remaining patients received alternative second-line therapies (for anastrozole and tamoxifen, respectively, 30 and 17% received radiotherapy, 39 and 23% received chemotherapy, 46 and 30% received further hormonal therapies, 28 and 14% received other therapies and 36 and 17% received no further therapy; some patients received more than one therapy).

3.1. Survival

3.1.1. Overall population

In the combined analysis of the overall population, at a median follow-up of 43.7 months, 286/511 (56.0%) and 286/510 (56.1%) patients in the anastrozole and tamoxifen groups, respectively, had died (Table 1). The median TTD was 39.2 months in the anastrozole group and 40.1 months in the tamoxifen group (HR = 0.97, lower 95% CL = 0.84) (Fig. 2).

The proportion of patients dead at 2 years was 31.1% (159/511) and 32.0% (163/510) in the anastrozole and tamoxifen groups, respectively (Table 1). Further breakdown at earlier time points was not performed as it was considered to be statistically inappropriate.

3.1.2. ER+/PR+ subgroup

In the ER+/PR+ subgroup analysis, at a median follow-up of 43.7 months, 168/305 (55.1%) patients in the anastrozole group and 171/306 (55.9%) patients in the tamoxifen group had died. The median TTD was again similar in the anastrozole arm (40.8 months) compared with the tamoxifen arm (41.3 months) (HR = 1.00, lower 95% CL = 0.83) (Fig. 3).

The proportion of patients dead at 2 years was 31.8% (97/305) and 31.0% (95/306) in the anastrozole and tamoxifen groups, respectively (Table 1).

3.2. Safety

Exposure to treatment was noticeably longer for the anastrozole-treated than for the tamoxifen-treated patients (median duration of treatment was 10.9 months for anastrozole and 8.3 months for tamoxifen). There were no differences in the frequency of adverse events between the anastrozole and tamoxifen groups. While on the study treatment, 2.4% (24/1017) of patients died from causes related to breast cancer, and only 2.0% (20/1017) died because of an adverse event. After study treatment, a further 44.1% (448/1017) of the patients have died from causes related to breast cancer and 6.3% (64/1017) have died from causes unrelated to breast cancer. The

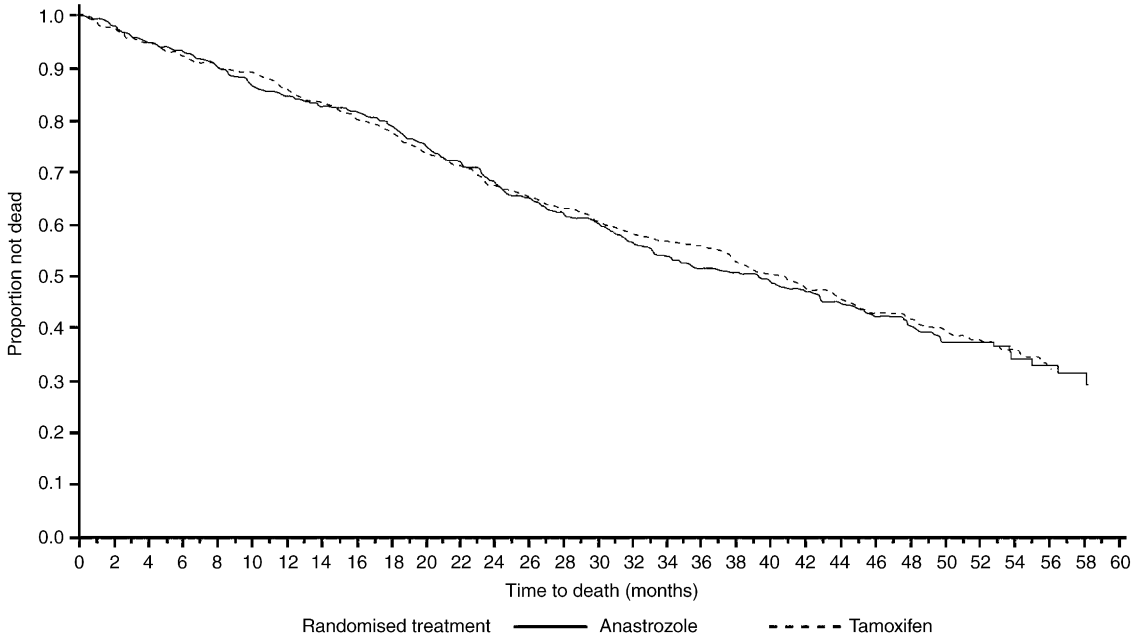
Table 1
Survival status for all patients in the TARGET and North American trial, separately and combined

Survival status	Number (%) of patients					
	TARGET trial		North American Trial		Combined data	
	Anastrozole (1 mg) (n = 340)	Tamoxifen (20 mg) (n = 328)	Anastrozole (1 mg) (n = 171)	Tamoxifen (20 mg) (n = 182)	Anastrozole (1 mg) (n = 511)	Tamoxifen (20 mg) (n = 510)
Overall population						
Total death (no. (%))	190 (55.9)	180 (54.9)	96 (56.1)	106 (58.2)	286 (56.0)	286 (56.1)
Median time to death (months)	38.5	40.9	40.4	38.5	39.2	40.1
Hazard ratio[a]	0.94		1.02		0.97	
Lower 95% CL[a]	0.79		0.81		0.84	
Total deaths at 24 months of treatment (no. (%))	NA		NA		159 (31.1)	163 (32.0)
ER+/PR+ subgroup						
Total deaths at 24 months of treatment (no. (%))	NA		NA		97 (31.8)	95 (31.0)

CL, Confidence Limit; TARGET, Tamoxifen or Arimidex™ Randomized Group Efficacy and Tolerability.

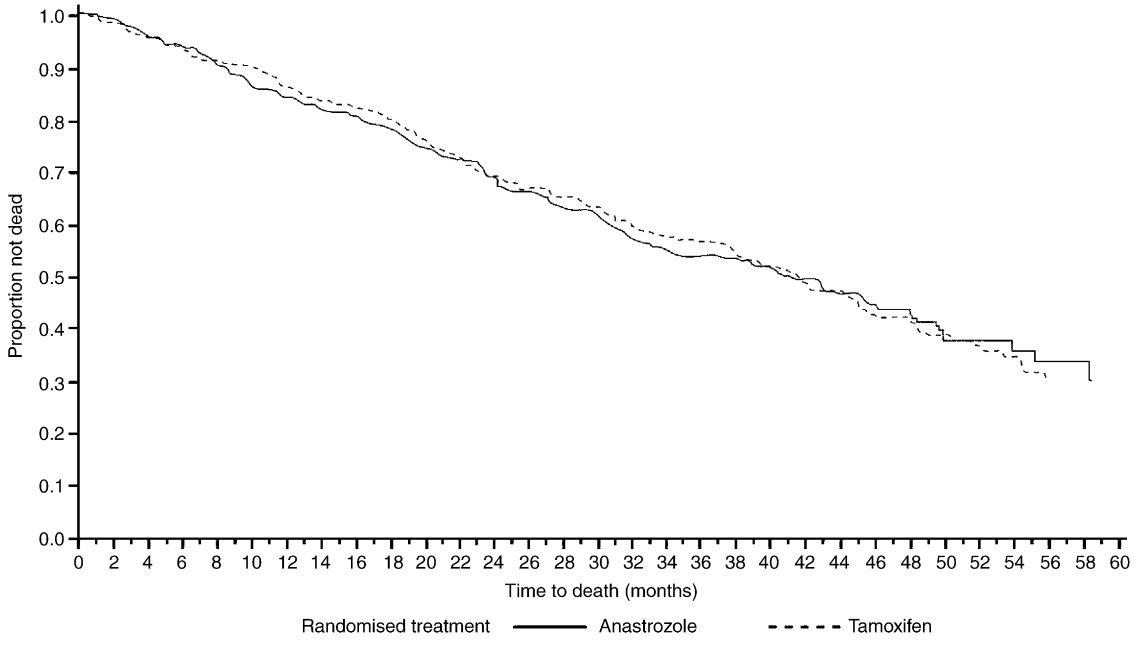
[a] Treatment comparison: tamoxifen 20 mg versus anastrozole 1 mg was performed using an unadjusted Cox regression model with treatment factor only. ER+/PR+, oestrogen receptor and/or progesterone receptor-positive subgroup; NA, not available; subanalysis not performed at 24 months.

incidence of adverse events leading to withdrawal was low (5.4% (55/1017)) and was similar for both treatment groups (Table 2). No notable differences were observed between the groups in terms of prespecified adverse events (Table 3). Vaginal bleeding and thromboembolic events were lower in the anastrozole group compared with the tamoxifen group (number (%) of patients with vaginal bleeding: anastrozole versus tamoxifen, 5 (1.0) versus 13 (2.5); thromboembolic events: anastrozole versus tamoxifen, 27 (5.3) versus 46 (9.0)). Hot flushes and vaginal dryness were higher in the anastrozole group compared with the tamoxifen group (hot flushes: anastrozole versus tamoxifen, 139 (27.5) versus 123 (24.1); vaginal dryness: anastrozole versus tamoxifen, 16 (3.2) versus 11 (2.2)).



Months:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
At risk:	1021	995	965	940	911	886	856	833	811	785	744	711	672	642	614	592	551	511	463	412	363	316	274	228	199	151	110	76	49	31	15

Fig. 2. Kaplan–Meier plot of time to death in the combined analysis of the overall population.



Months:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60
At risk:	611	602	583	570	550	532	513	498	489	474	450	433	410	397	381	369	338	314	286	253	217	187	163	130	113	87	66	42	26	18	8

Fig. 3. Kaplan–Meier plot of time to death in the combined analysis of the ER+/PR+ subgroup.

Table 2
Overview of patients with adverse events

Category[a]	Anastrozole ($n=506$)		Tamoxifen ($n=511$)		Total ($n=1017$)	
Any AE	*422*	*(83.4)*	*432*	*(84.5)*	*854*	*(84.0)*
Drug-related	211	(41.7)	212	(41.5)	423	(41.6)
Serious AE	*111*	*(21.9)*	*116*	*(22.7)*	*227*	*(22.3)*
Drug-related	13	(2.6)	23	(4.5)	36	(3.5)
Withdrawal	*457*	*(90.3)*	*468*	*(91.6)*	*925*	*(91.0)*
Due to AE	27	(5.3)	28	(5.5)	55	(5.4)
Drug-related	10	(2.0)	13	(2.5)	23	(2.3)
Due to serious AE	17	(3.4)	20	(3.9)	37	(3.6)
Drug-related	4	(0.8)	8	(1.6)	12	(1.2)
Death	*285*[c]	*(56.3)*	*287*	*(56.2)*	*572*	*(56.2)*
During treatment[b]	26	(5.1)	19	(3.7)	45	(4.4)
Due to AE	13	(2.6)	7[d]	(1.4)	20	(2.0)
After treatment	259	(51.2)	268	(52.4)	527	(51.8)
Unrelated to breast cancer	39	(7.7)	25	(4.9)	64	(6.3)

AE, adverse event.

[a] Patients may fall into more than one category.

[b] Death during treatment included all deaths occurring within 14 days of treatment cessation and any death due to an adverse event that had an onset within 14 days of treatment cessation.

[c] One patient randomised to treatment with anastrozole but who received tamoxifen therapy subsequently died.

[d] An additional patient treated with tamoxifen died as a result of breast cancer following an adverse event (heart failure).

Table 3
Incidence of adverse events defined by prespecified categories

Adverse event category	Irrespective of causality		Irrespective of causality	
	Anastrozole 1 mg ($n=506$)		Tamoxifen 20 mg ($n=511$)	
	n	(%)	*n*	(%)
Depression	30	(5.9)	36	(7.0)
Tumour flare	15	(3.0)	18	(3.5)
Thromboembolic disease	27	(5.3)	46	(9.0)
Gastrointestinal disturbance	184	(36.4)	207	(40.5)
Hot flushes	139	(27.5)	123	(24.1)
Vaginal dryness	16	(3.2)	11	(2.2)
Lethargy	6	(1.2)	17	(3.3)
Vaginal bleeding	5	(1.0)	13	(2.5)
Weight gain	12	(2.4)	8	(1.6)

4. Discussion

Based on this latest analysis, we can now report that anastrozole was non-inferior to tamoxifen in terms of survival (lower 95% CI >0.8) in both the overall population and the ER+/PR+ subgroup. Furthermore, median survival was longer than 3 years with both anastrozole and tamoxifen, suggesting the high level of benefit received by adequately selected patients in both treatment arms in this trial. Interestingly, the median overall survival of patients in both treatment groups in this study was longer than that of patients in a study of letrozole versus tamoxifen in the advanced setting at a median follow-up of 32 months (34 and 30 months for letrozole and tamoxifen, respectively, $P=0.53$ by log rank, $P=0.079$ by Wilcoxon) [7]. The patient populations for the two studies were similar with respect to age, hormone receptor-positive status and prior adjuvant endocrine therapy [6,8].

The first-line study comparing letrozole with tamoxifen also showed no significant survival advantage for letrozole. The authors of that study concluded that this might be due to a large proportion (51%) of patients crossing over to the alternative treatment following disease progression [7]. The data from both this study and the present study indicate a lack of a survival advantage over tamoxifen. This is not an entirely unexpected finding as a substantial number of patients in both trials that crossed over to the other therapy because they failed on their first therapy or received alternative treatment at the discretion of the investigator.

Anastrozole continued to be generally well tolerated and confirmed the established safety profile for the drug; adverse events were typically mild-to-moderate in intensity with only a limited number of withdrawals considered to be drug-related. Furthermore, as was seen at the initial analysis [6], vaginal bleeding and thromboembolic events remained lower in the anastrozole group compared with the tamoxifen group. Hot flushes and vaginal dryness were reported marginally less in the tamoxifen group compared with the anastrozole group.

It is of interest that, in this study, most patients received anastrozole or tamoxifen only and did not cross over to the alternative treatment. Approximately 25% of patients in each arm who progressed on tamoxifen were crossed over to anastrozole and vice versa and the remaining patients received different treatments including chemotherapy, radiotherapy and other endocrine agents. As the median survival was similar in both treatment arms, this suggests that the sequence of 'anastrozole followed by tamoxifen' was of similar efficacy as the sequence 'tamoxifen followed by anastrozole'. The choice of treatment sequence should then take other factors such as quality of life and tolerability into consideration. A longer time to progression at an earlier stage of treatment is likely to have a beneficial effect on the psychological well being and quality of life of the patient. Thus, although there was no difference in survival between the two groups, the improved tolerability profile and the superior TTP seen with anastrozole support the use of anastrozole before tamoxifen.

5. Conclusions

These results show that both the proportion of patients who died and the median TTD were similar with anastro-

zole and tamoxifen. Together with the superior TTP and improved tolerability profile, these data confirm the place of anastrozole as first-line treatment for postmenopausal women with advanced breast cancer.

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