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Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women

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Abstract

Anastrozole ('Arimidex') is indicated for the treatment of advanced breast cancer in postmenopausal women. Combined analysis of two international randomised, double-blind trials ($n=1021$) showed that in patients with hormone receptor-positive tumours, first-line treatment with anastrozole significantly prolonged the time to progression (TTP) compared with tamoxifen (median TTP: 10.7 versus 6.4 months, respectively; $P=0.022$). Second-line tamoxifen following anastrozole, or *vice versa*, in this trial population was unblinded. The treatments were crossed over and then efficacy was assessed using a questionnaire. Of 511 patients randomised to anastrozole, 137 (26.8%) received second-line tamoxifen. Questionnaire data were available for 119 patients; 58 (48.7%) gained clinical benefit (CB = complete + partial response (CR + PR) + (stable disease (SD) $\geqslant$ 24 weeks)), while 12 (10.1%) had an objective response (OR = CR + PR). Of 510 patients randomised to tamoxifen, 134 (26.3%) received second-line anastrozole. Questionnaire data from 95 patients showed that 54 (56.8%) gained CB and 7 of the patients gaining CB (7.4%) had an OR. Previous studies showed anastrozole is effective after first-line tamoxifen. These data show that the sequential administration of first-line anastrozole followed by tamoxifen provides effective use of these drugs in the treatment of postmenopausal women with advanced breast cancer.

Keywords: Anastrozole; Tamoxifen; Sequencing; Postmenopausal; Advanced breast cancer; First-line; Second-line

1. Introduction

Approximately two-thirds of all breast cancers are oestrogen receptor (ER)-positive [1], of which 60–70% will respond to hormone therapies, including oestrogen deprivation strategies. Consequently, reducing the level of oestrogen remains a valuable target for breast cancer treatment in both pre- and postmenopausal women. This is achieved either by agents that block oestrogen at the receptor level, for example tamoxifen, or by inhibitors of oestrogen biosynthesis, such as the aromatase inhibitors (AI), in postmenopausal patients.

The use of available classes of endocrine agents in the optimal sequence to prolong survival, maintain quality of life and provide maximal palliation is the goal of treatment for advanced breast cancer. Traditionally, tamoxifen has been used as the first-line therapy for advanced breast cancer, with AIs being used as second-line treatment when tamoxifen fails. As second-line treatment, AIs have efficacy and tolerability benefits over megestrol acetate and have been established as the agents of choice in this setting [2,3], relegating megestrol acetate to third- or fourth-line use.

Results from two recent studies, the North American and the TARGET (Tamoxifen or 'Arimidex' Randomised

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Group Efficacy and Tolerability) trials, indicate that anastrozole should now be considered as an alternative first-line therapy to tamoxifen in postmenopausal women with advanced breast cancer [4–6]. The North American study, in which approximately 90% of patients had confirmed oestrogen- and/or progesterone-receptor (ER/PgR)-positive tumours, reported a significant improvement in time to disease progression (TTP) and percentage of patients gaining clinical benefit (CB) with anastrozole compared with tamoxifen (median TTP: anastrozole 11.1 months, tamoxifen 5.6 months, $P = 0.005$; CB: anastrozole 59%; tamoxifen 46%, $P = 0.0098$) [5]. The TARGET study, in which only 45% of patients had confirmed ER/PgR-positive tumours, found that median TTP and CB rates were similar for both anastrozole and tamoxifen [4]. These two studies were designed and prospectively planned for combined analysis. Subgroup analysis of patients with ER/PgR-positive tumours using the combined data from the two studies also showed a significant improvement in TTP in the anastrozole arm compared with the tamoxifen arm (median TTP: anastrozole 10.7 months, tamoxifen 6.4 months, $P = 0.022$) [6]. Indeed, anastrozole was the first endocrine agent to show significant benefit over tamoxifen with respect to TTP in patients with hormone-sensitive tumours.

When making the decision to use anastrozole first-line, it is important that clinicians are confident that the change in sequence of administration of endocrine agents from tamoxifen followed by anastrozole to anastrozole followed by tamoxifen does not impact on the overall benefit to patients provided by the two drugs. Thus, we carried out a retrospective collection of data from the TARGET and North American first-line trials to determine whether or not tamoxifen was effective as a second-line endocrine therapy in patients progressing on anastrozole treatment. A further aim was to investigate whether or not there was any detrimental impact on overall benefit to patients when tamoxifen was given after anastrozole compared with tamoxifen followed by anastrozole.

We present the findings from this retrospective analysis with respect to objective response (OR) and CB for the overall population, and separately consider the influence of hormone receptor status and visceral spread.

2. Patients and methods

A total of 1021 patients in the North American ($n = 353$) [5] and TARGET ($n = 668$) [4] trials were randomised 1:1 to receive either anastrozole 1 mg once daily (od) or tamoxifen 20 mg od. Randomised double-blind, double-dummy treatment was continued until objective disease progression; patients could then receive further therapy on an open-label basis, including cross-over to anastrozole or tamoxifen as second-line therapy. Details of patients receiving intervening therapies before crossing over to tamoxifen or anastrozole, and types of therapy received, were documented. Patients were followed-up until death (combined median duration of follow-up = 18.2 months) [6]. The methods have been described in more detail elsewhere [4–6]. Written informed consent was obtained from all patients, and the studies were approved by the appropriate institutional review board at each site.

The efficacy of the cross-over from anastrozole to tamoxifen and *vice versa* was assessed retrospectively using questionnaires for data collection and by evaluation of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Objective response was calculated as CR + PR, and CB was calculated as CR + PR + (SD $\geqslant$ 24 weeks).

The completed case report forms from the two studies were used to identify patients (and their treating clinicians) who had received treatment with anastrozole followed by tamoxifen on relapse and also those patients who had received tamoxifen followed by anastrozole. Questionnaires designed to ascertain the OR and CB to each of the treatments received were sent to these investigators for completion (Fig. 1 shows the questionnaire). These questionnaires were not part of the original study protocol and were returned at the investigators' discretion.

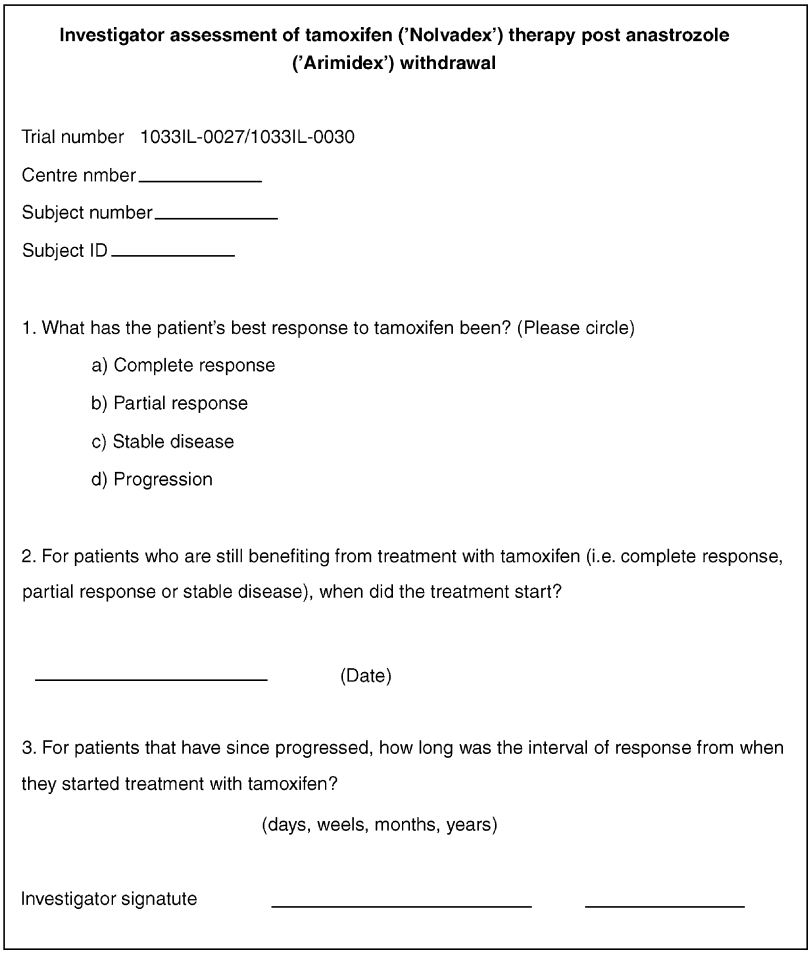
3. Results

3.1. Patients' characteristics

Patients' characteristics were similar between the anastrozole and tamoxifen groups (Table 1). In both groups, there was a higher proportion of patients with early breast cancer and with unknown hormone receptor status tumours in the sub-group that did not cross over versus the sub-group that crossed over to the alternative therapy.

3.2. Patients crossed over from anastrozole to tamoxifen

Of the 511 patients who were initially randomised to anastrozole, 137 (26.8%) received tamoxifen as second-line therapy (Fig. 2). 40 patients who crossed over from anastrozole to tamoxifen had intervening chemotherapy, other hormonal therapy or a combination of other hormonal therapy and chemotherapy (Table 2). Of these patients, 4 (2.9%) received intervening hormonal therapy and 7 (5.1%) received combined hormonal and chemotherapy; therefore, use of tamoxifen in these patients should be considered third-line. One patient was subsequently found to have stayed on anastrozole



Investigator assessment of tamoxifen ('Nolvadex') therapy post anastrozole ('Arimidex') withdrawal

Trial number 1033IL-0027/1033IL-0030

Centre nmber _____

Subject number _____

Subject ID _____

1. What has the patient's best response to tamoxifen been? (Please circle)

a) Complete response

b) Partial response

c) Stable disease

d) Progression

2. For patients who are still benefiting from treatment with tamoxifen (i.e. complete response, partial response or stable disease), when did the treatment start?

_____ (Date)

3. For patients that have since progressed, how long was the interval of response from when they started treatment with tamoxifen?

(days, weels, months, years)

Investigator signatute _____ _____

Fig. 1. Assessment questionnaire for patients who crossed over to receive tamoxifen following anastrozole treatment.

Table 1
Patients' characteristics for those crossing over and not crossing over from anastrozole to tamoxifen or from tamoxifen to anastrozole

	Anastrozole		Tamoxifen	
	Crossed to tamoxifen ($n=98$)	Did not cross over ($n=413$)	Crossed to anastrozole ($n=105$)	Did not cross over ($n=405$)
Age (years)				
Median (range)	69 (31–90)	67 (30–91)	67 (41–92)	66 (40–92)
Weight (kg)[a]				
Median (range)	67 (40–121)	69 (40–121)	65 (44–127)	68 (36–140)
Disease status at first diagnosis (n (%))				
Advanced	49 (50.0)	166 (40.2)	53 (50.5)	176 (43.5)
Early	49 (50.0)	245 (59.3)	52 (49.5)	228 (56.3)
Unknown	0	2 (0.5)	0	1 (0.2)
Hormone receptor status[b] (n (%))				
+ve	70 (71.4)	235 (56.9)	78 (74.3)	228 (56.3)
−ve	1 (1.0)	1 (0.2)	0	1 (0.2)
Unknown	27 (27.6)	177 (42.9)	27 (25.7)	176 (43.5)

[a] Weight was recorded for 97 patients in the anastrozole group that crossed to tamoxifen and 404 that did not cross over, and 102 patients in the tamoxifen group that crossed to anastrozole and 394 that did not cross over.

[b] Data for most recent hormone receptor status. Hormone receptor-positive status includes patients with tumours that are oestrogen receptor- and/or progesterone receptor-positive.

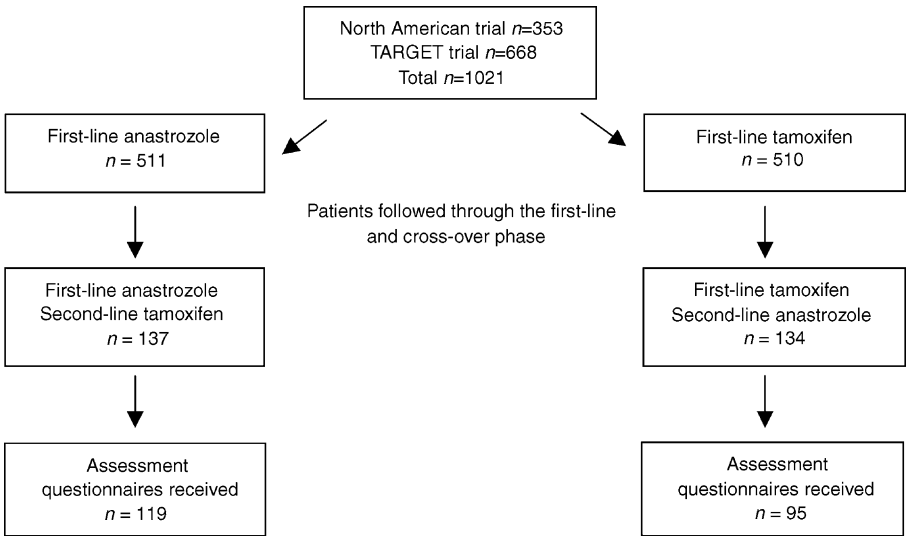


Fig. 2. Trial profile.

and had not received tamoxifen as second-line therapy. The remaining 374 (73.2%) patients who did not cross over to tamoxifen received alternative second-line therapies (Table 3).

Overall, replies to the assessment questionnaires were received for 119 patients (85 of these patients received no intervening chemotherapy, other hormonal therapy or combined chemotherapy and hormonal therapy), the results of which are shown in Table 4. For the overall population, 10.1% (12/119) of patients had an OR and 48.7% (58/119) achieved CB. Results for patients crossing directly to tamoxifen, without intervening therapy, were similar to those for all patients (Table 4).

In the sub-group of patients with confirmed ER/PgR-positive tumours, OR was reported in 8.1% (6/74) of patients and CB in 47.3% (35/74) of patients (Fig. 3). For those patients with visceral metastases (±tumours at other sites), OR and CB rates were 13.3% (6/45) and 48.9% (22/45), respectively, compared with OR and CB rates of 8.2% (6/73) and 49.3% (36/73), respectively, in patients without visceral metastases (Fig. 4).

3.3. Patients crossed over from tamoxifen to anastrozole

Of the 510 patients initially randomised to tamoxifen, 134 (26.3%) were recorded as having received anastrozole as second-line therapy (Fig. 2). 27 patients who crossed over from tamoxifen to anastrozole had intervening chemotherapy, other hormonal therapy, or combined hormonal therapy and chemotherapy (Table 2). Of these patients, 6 (4.5%) received intervening hormonal therapy and 3 (2.2%) received a combination of hormonal and chemotherapy; therefore, the use of anastrozole in these patients should be considered third-line. The remaining 376 (73.7%) patients who did not cross over to anastrozole received alternative second-line therapies (Table 3).

Overall, replies to the assessment questionnaires were received for 95 patients (74 of these patients received no intervening chemotherapy, other hormonal therapy, or combined chemotherapy and hormonal therapy), the

Table 2
Patients crossing over from anastrozole to tamoxifen or tamoxifen to anastrozole who received intervening therapies

Intervention therapy	Tamoxifen following anastrozole ($n=137$)	Anastrozole following tamoxifen ($n=134$)
Hormonal therapy	4	6
Combination of hormonal and chemotherapy	7	3
CMF	11	2
FEC	2	5
Other cytotoxic agent	16	11
Total	40	27

CMF, cyclophosphamide, methotrexate and fluorouracil; FEC, fluorouracil, epirubicin and cyclophosphamide.

Table 3
Patients who did not receive anastrozole or tamoxifen as second-line treatment

Second-line therapy[a]	First-line therapy	
	Anastrozole ($n=511$)	Tamoxifen ($n=510$)
Radiotherapy, *n* (%)	106 (20.7)	115 (22.5)
Chemotherapy, *n* (%)	138 (27.0)	154 (30.2)
Further hormonal therapy, *n* (%)	161 (31.5)	198 (38.8)
Other therapies, *n* (%)	98 (19.2)	95 (18.6)
No further treatment, *n* (%)	126 (24.7)	115 (22.5)

[a] Some patients received more than one therapy.

results of which are shown in Table 5. In the overall population, 7.4% (7/95) of patients and 56.8% (54/95) of patients showed OR and CB, respectively. Results for patients crossing directly to tamoxifen, without intervening therapy, were similar to those for all patients (Table 5).

In the sub-group of patients with confirmed ER/PgR-positive tumours, OR was reported in 4.5% (3/66) of patients and CB in 59.1% (39/66) of patients (Fig. 3). For those patients with visceral metastases, OR and CB were 7.5% (3/40) and 52.5% (21/40), respectively, compared with an OR and CB of 7.3% (4/55) and 60.0% (33/55), respectively, in those patients without visceral metastases (Fig. 4).

Table 4
Efficacy data following cross-over treatment from anastrozole to tamoxifen

	All patients receiving tamoxifen following anastrozole	Patients crossing directly to tamoxifen[a]	Patients receiving intervening therapy
Questionnaire	137	96	41
Replies	119	85	34
OR (no./total (%))	12/119 (10.1)	8/85 (9.4)	4/34 (11.8)
SD (no./total (%))	63/119 (52.9)	48/85 (56.5)	15/34 (44.1)
SD ⩾24 weeks	46/119 (38.7)	35/85 (41.2)	11/34 (32.4)
SD <24 weeks	13/119 (10.9)	10/85 (11.8)	3/34 (8.8)
SD duration unknown	4/119 (3.4)	3/85 (3.5)	1/34 (2.9)
CB (no./total (%))	58/119 (48.7)	43/85 (50.6)	15/34 (44.1)
PD (no./total (%))	31/119 (26.1)	24/85 (28.2)	7/34 (20.6)
Not evaluable (missing)	13	5	8

OR, objective response (complete and partial responses); SD, stable disease; CB, clinical benefit (complete and partial responses + (stable disease ⩾24 weeks)); PD, progressive disease.

[a] Direct cross-over: no intervening chemotherapy, hormonal therapy or a combination of both.

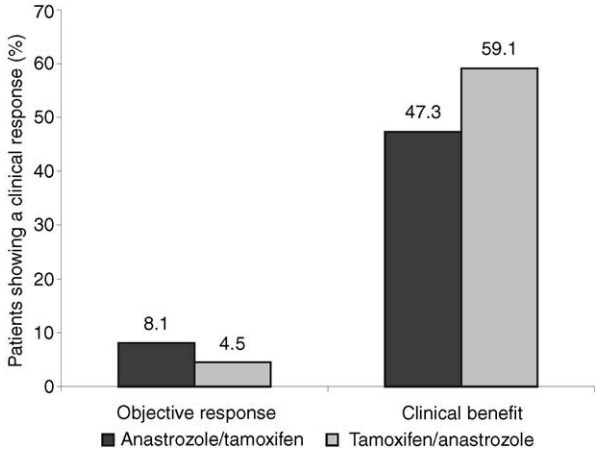


Fig. 3. Objective response and clinical benefit following cross-over treatment with anastrozole and tamoxifen for patients with oestrogen and/or progesterone receptor-positive status.

4. Discussion

These data, obtained with a similar cross-over rate for both sequences, show good and similar activity for tamoxifen following anastrozole treatment compared with anastrozole following tamoxifen treatment, and thus indicate that tamoxifen is effective as second-line therapy in patients progressing on first-line anastrozole. The results for each treatment sequence were similar in all patient groups, with no difference seen between patients in the overall population and those with ER/PgR-positive tumours or for patients with or without visceral metastases. Clinical benefit and OR for the different patient groups were also similar between the treatment sequences.

Furthermore, our results suggest that the sensitivity to second-line endocrine treatment is maintained in patients receiving an intervening therapy after failure of first-line hormonal therapy with tamoxifen or anastrozole (Tables 4 and 5). A total of 8% of patients receiving tamoxifen following anastrozole and 6.7% of patients receiving anastrozole following tamoxifen received

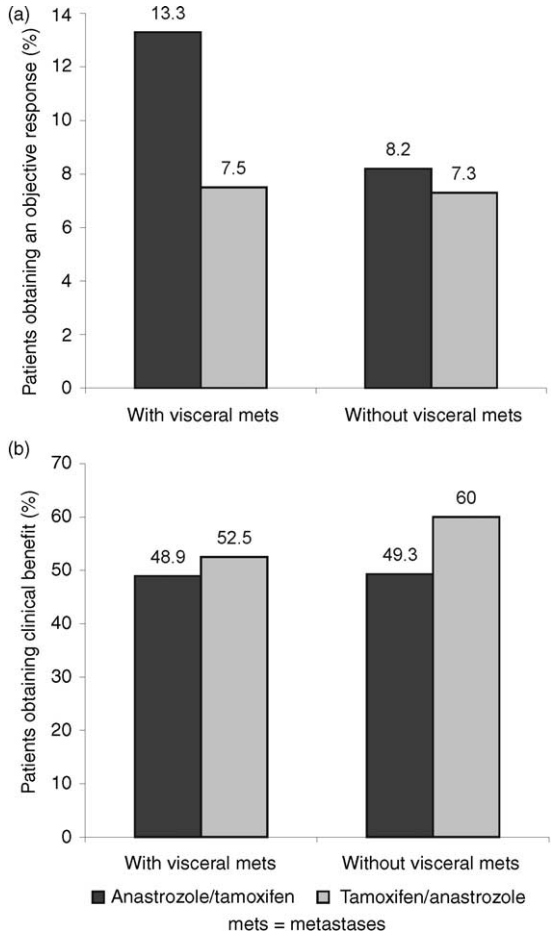


Fig. 4. (a) Objective response and (b) clinical benefit following cross-over treatment with anastrozole and tamoxifen for patients with and without visceral metastases.

Table 5
Efficacy data following cross-over treatment from tamoxifen to anastrozole

	All patients receiving anastrozole following tamoxifen	Patients crossing directly to anastrozole[a]	Patients receiving intervening therapy
Questionnaire	134	107	27
Replies	95	74	21
OR (no./total (%))	7/95 (7.4)	6/74 (8.1)	1/21 (4.8)
SD (no./total (%))	55/95 (57.9)	45/74 (60.8)	10/21 (47.6)
SD ⩾24 weeks	47/95 (49.5)	39/74 (52.7)	8/21 (38.1)
SD <24 weeks	7/95 (7.4)	5/74 (6.8)	2/21 (9.5)
SD duration unknown	1/95 (1.1)	1/74 (1.4)	0
CB (no./total (%))	54/95 (56.8)	45/74 (60.8)	9/21 (42.9)
PD (no./total (%))	21/95 (22.1)	15/74 (20.3)	6/21 (28.6)
Not evaluable (missing)	12	8	4

OR, objective response (complete and partial responses); SD, stable disease; CB, clinical benefit (complete and partial responses + (stable disease ⩾24 weeks)); PD, progressive disease.
[a] Direct cross-over: no intervening chemotherapy, hormonal therapy or a combination of both.

intervening hormonal therapy or a combination of hormonal and chemotherapy; for these patients, the following therapy is to be considered third-line, rather than second-line, endocrine therapy.

This retrospective analysis was not part of the study protocol and some investigators did not respond. However, the proportion of questionnaires returned was high and similar for the anastrozole/tamoxifen (87%) and tamoxifen/anastrozole (71%) treatment groups. In addition, cross-over to the alternative treatment was not part of the study protocol. Further treatment was at the investigators' discretion, and some investigators may have deemed certain patients unsuitable for further endocrine therapy or preferred alternative endocrine agents. Again, a similar proportion of patients in each arm crossed over to the alternative treatment (26.8% in the anastrozole arm and 26.3% in the tamoxifen arm).

A sub-analysis of the cross-over data in terms of survival has not been performed. However, in the initial survival analysis of the combined data [7], the median time to death (TTD) was comparable between the two treatment arms (39.2 months versus 40.1 months, for tamoxifen versus anastrozole, respectively, in the overall population, hazard ratio (HR) = 0.97, lower 95% confidence limit (CL) = 0.84; 40.8 months versus 41.3 months, respectively, in the ER/PgR-positive subgroup, HR = 1.00, lower 95% CL = 0.83).

Although previous trials have shown that third-generation AIs, anastrozole, letrozole and exemestane are effective in postmenopausal women with advanced breast cancer who have progressed on tamoxifen [2,3,8], there are no comparable cross-over data for third-generation AIs other than anastrozole (letrozole and exemestane) versus tamoxifen in the treatment of advanced breast cancer. A trial comparing letrozole with tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer included a cross-over design [9], but no results on sequencing of treatments from this trial have been published to date. However, cross-over data for the second-generation AI fadrozole and tamoxifen show similar results to those presented here. Fadrozole 1 mg twice daily ($n = 105$) was compared with tamoxifen 20 mg od ($n = 107$) in postmenopausal women with advanced disease [10]. Of these, 148 (70%) crossed over to the alternative treatment when the initial treatment failed: 82 to tamoxifen and 66 to fadrozole. The objective response rate was 29% in patients switching from fadrozole to tamoxifen and 9% in patients switching from tamoxifen to fadrozole; CB rates were 59 and 55%, respectively. Overall survival (OS) for the crossed-over patients was not presented; however, OS for all 212 randomised patients receiving the first treatment was similar in the two arms ($P = 0.90$), with more than 25% of patients surviving for 5 years.

Since AIs have a different mechanism of action to tamoxifen they might be expected to produce a further response in patients progressing on tamoxifen. Several studies have also found that an alternative AI is effective after treatment with a previous AI has failed. Both formestane and exemestane have been shown to be effective in patients who have progressed on aminoglutethimide [11,12], while anastrozole was effective in patients who progressed on formestane [13]. Exemestane has also shown efficacy in patients who progressed on aminoglutethimide, anastrozole, letrozole or vorozole [14]. These studies indicate that complete cross-resistance does not occur between AIs and that sequencing of treatments prolongs the beneficial effect of endocrine therapy. The successful strategy of sequential

endocrine treatment in advanced breast cancer is currently being investigated in the adjuvant setting to extend the benefit of this approach to all breast cancer patients [15–18].

Further to previous reports from the North American and TARGET trials [4–6] and from a more recent, independent trial [19], the current data support the use of anastrozole as first-line treatment in postmenopausal women with hormone receptor-positive advanced breast cancer. Additional data to confirm the best treatment sequence for advanced breast cancer will be derived from the Swiss Group for Clinical Cancer Research (SAKK) cross-over trial, which is a sub-trial of the larger TARGET trial. This sub-trial is investigating cross-over responses in a double-blind manner following first-line anastrozole and tamoxifen in a formalised, randomised way [20].

Until recently, tamoxifen was the preferred treatment for advanced breast cancer in postmenopausal women who had not received prior adjuvant endocrine therapy. The data presented here confirm that first-line anastrozole followed by tamoxifen is an effective treatment sequence, and that changing over therapy to this sequence should not impact on the overall benefit of these drugs. Since anastrozole is a more effective and better tolerated first-line agent compared with tamoxifen for postmenopausal women with hormone receptor-positive advanced breast cancer, anastrozole followed by tamoxifen may be considered the better treatment strategy for treating these patients.

5. Conflict of interest statement

Dr B. Thürlimann has served as an adviser for and has received fees from AstraZeneca.

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References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998, **351**, 1451–1467.
2. Buzdar AU, Jonat W, Howell A, *et al*. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. *Cancer* 1998, **83**, 1142–1152.
3. Dombernowsky P, Smith I, Falkson G, *et al*. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomised trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998, **16**, 453–461.
4. Bonneterre J, Thürlimann B, Robertson JFR, *et al*. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women—results of the TARGET (Tamoxifen or Arimidex™ Randomised Group Efficacy and Tolerability) study. *J Clin Oncol* 2000, **18**, 3748–3757.
5. Nabholtz JM, Buzdar A, Pollak M, *et al*. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000, **18**, 3758–3776.
6. Bonneterre J, Buzdar A, Nabholtz JM, *et al*. Anastrozole (Arimidex) is superior to tamoxifen as first-line therapy in hormone receptor-positive advanced breast cancer: results of two randomized trials designed for combined analysis. *Cancer* 2001, **92**, 2247–2258.
7. Nabholtz JM, Bonneterre J, Buzdar A, Robertson JFR, Thürlimann B. Anastrozole (Arimidex™) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. *Eur J Cancer* 2003, **39**, 1684–1689.
8. Kaufmann M, Bajetta E, Dirix L-Y, *et al*. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. *J Clin Oncol* 2000, **18**, 1399–1411.
9. Mourisden H, Gershanovich M, Sun Y, *et al*. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001, **19**, 2596–2606.
10. Thürlimann B, Beretta K, Bacchi M, *et al*. First-line fadrozole HCI (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer. Prospective randomised trial of the Swiss Group for Clinical Cancer Research SAKK 20/88. *Ann Oncol* 1996, **7**, 471–479.
11. Murray R, Pitt P. Aromatase inhibition with 4-OH-androstenedione after prior aromatase inhibition with aminoglutethimide in women with advanced breast cancer. *Breast Cancer Res Treat* 1995, **35**, 249–253.
12. Thürlimann B, Paridaens R, Serin D, *et al*. Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer progressing on aminoglutethimide: a phase II multicentre multinational study. *Eur J Cancer* 1997, **33**, 1767–1773.
13. Harper-Wynne C, Coombes RC. Anastrozole shows evidence of activity in postmenopausal patients who have responded or stabilised on formestane therapy. *Eur J Cancer* 1999, **35**, 744–746.
14. Lonning PE, Bajetta E, Murray R, *et al*. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol* 2000, **18**, 2234–2244.
15. Boccardo F, Rubagotti A, Amoroso D, *et al*. Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: results of an Italian cooperative study. *J Clin Oncol* 2001, **19**, 4209–4215.
16. Goss PE. Preliminary data from ongoing adjuvant aromatase inhibitor trials. *Clin Cancer Res* 2001, **7**(Suppl. 12), 4397s–4401s. [discussion 4411s-4412s].
17. Coombes RC, Bliss JM, Gibson LJ, *et al*. The Intergroup Exemestane Study (IES)—design and characteristics. *Proc ASCO* 2002, **21**, 44b (abstr 1986).
18. International Breast Cancer Study Group IBCSG 18-98. Adjuvant therapy for postmenopausal patients with operable breast cancer who have estrogen receptor or progesteron receptor positive tumors. Tamoxifen vs letrozole vs tamoxifen followed by letrozole. Available from: http://www.ibcsg.org/pub_trials_open.shtml

19. Milla-Santos A, Milla L, Portella J, *et al*. Anastrozole vs tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer: a double-blind, prospective, randomized, phase III study. *Am J Clin Oncol* 2003, 26, 317–322.
20. Thürlimann B, Hess D, Koeberle D, *et al*. Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind crossover SAKK trial 21/95—a sub-study of Anastrozole Trial 0027. *Proc 25th Annual SABCS*, *Breast Cancer Res Treat* 2002, **76**(Suppl. 1) (abstr 255). Available from: http://www.abstracts-on-line.com/abstracts/BCS/ [accessed January 2003].