SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ARIMIDEX™ 1 mg tablet

ACTIVE INGREDIENT: Anastrozole

Trial title (number): Randomised, Double-blind Trials to Compare the Efficacy and Safety of ARIMIDEX™ (Anastrozole 1 mg Daily) with Tamoxifen (20 mg Daily) as First-line Therapy for Advanced Breast Cancer in Postmenopausal Women: Safety and Survival Update 2001 (1033IL/0030 and 1033IL/0027)

Clinical phase: IIIb

Trial 1033IL/0030

First patient recruited:	26 February 1996
Last patient recruited:	09 July 1998
Data cut-off:	31 May 2001

Trial 1033IL/0027

First patient recruited:	21 August 1995
Last patient recruited:	01 July 1998
Data cut-off:	31 May 2001

Principal investigator and location (centre number): (Centre 0001)

Publications: Bonneterre J, Thürlimann BJK, Robertson JFR on behalf of the 'Arimidex' Study Group. Preliminary results of a large comparative multi-centre clinical trial comparing the efficacy and tolerability of Arimidex™ (anastrozole) and tamoxifen (TAM) in postmenopausal women with advanced breast cancer (ABC). Eur J Cancer 1999;35(Suppl 4):S313 (Abstract 1257).

Bonneterre J, Thürlimann B, Robertson JFR, Krzakowski M, Mauriac L, Koralewski P, et al for the Arimidex Study Group. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18(22):3748-57.
Buzdar A, Bonneterre J, Nabholtz JM, Robertson JFR, Thürlimann B, von Euler M, et al on behalf of the Anastrozole Study Group. Anastrozole (AN) versus tamoxifen (TAM) as first-line therapy for advanced breast cancer (ABC) in post-menopausal (PM) women: Findings highlight the importance of receptor status assessment prior to treatment initiation. Ann Oncol 2000;11(Suppl 4):25 (Abstract 99O).
Nabholtz JM, Bonneterre J, Buzdar AU, Thuerlimann BJK, Robertson JFR, Webster A, et al on behalf of the 'Arimidex' Study Group. Preliminary results of two multi-center trials comparing the efficacy and tolerability of Arimidex™ (anastrozole) and tamoxifen (TAM) in postmenopausal (PM) women with advanced breast cancer (ABC). Breast Cancer Res Treat 1999;57(1):31 (Abstract 27).
Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, et al for the Arimidex Study Group. 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(22):3758-67.
Robertson J, Buzdar A, Nabholtz J, Thürlimann B, Bonneterre J, von Euler M, et al. Anastrozole (Arimidex™) versus tamoxifen as first-line therapy for advanced breast cancer (ABC) in post-menopausal (PM) women - Prospective combined analysis from two international trials. Eur J Cancer 2000;36(Suppl 5):S88 (Abstract 219).
Robertson JFR on behalf of the Arimidex 1st-Line study group. Anastrozole (Arimidex™) versus tamoxifen as 1st-line therapy for advanced breast cancer (ABC) in post-menopausal (PM) women - combined analysis from two identically designed multicenter trials. Br J Cancer 2000;83(Suppl 1):39 (Abstract P43).
Thuerlimann BJK, Nabholtz JM, Bonneterre J, Buzdar AU, Robertson JFR, Webster A, et al on behalf of the 'Arimidex' Study Group. Preliminary results of two comparative multi-centre clinical trials comparing the efficacy and tolerability of Arimidex™ (anastrozole) and tamoxifen (TAM) in postmenopausal women with advanced breast cancer (ABC). The Breast 1999;8(4):214 (Abstract 004).
Thurlimann BJ, Bonneterre J, Buzdar A, Nabholtz J, Robertson JF, Sahmoud T. First line endocrine therapy in postmenopausal patients with advanced breast cancer and visceral metastases: anastrozole (Arimidex) versus tamoxifen. Proceedings of the American Society of Clinical Oncology 2001;20:22b (Abstract 1835).

OBJECTIVES

The objective of these analyses was to use updated data (as of 31 May 2001, the data cut-off date) to compare anastrozole 1 mg with tamoxifen 20 mg in terms of time to death (survival) for Trials 0030 and 0027, both individually and for the 2 trials combined, and to provide an update on the safety data from the combined trial population.

METHODS

Design: Trials 0030 and 0027 were randomised, double-blind, double-dummy, multicentre studies comparing the efficacy and safety of anastrozole 1 mg daily with tamoxifen 20 mg daily as first-line therapy for advanced breast cancer in postmenopausal women. Patients were administered their randomised treatment until, in the opinion of the investigator, there was sufficient evidence of disease progression to stop treatment.

Population: A total of 1021 postmenopausal women (1033IL/0030: 353 patients; 1033IL/0027: 668 patients) with advanced breast cancer entered these trials.

Statistical considerations: The primary statistical analysis for time to death (survival) was performed on an intention-to-treat (ITT) basis. Secondary analyses based upon a per-protocol (PP) population (ie, excluding patients with significant protocol violations and/or deviations) were also performed to assess the robustness of the conclusions. Secondary subgroup analyses were also undertaken by hormone-receptor status.

Time to death (survival) was summarised by randomised treatment using Kaplan-Meier methodology. Kaplan-Meier estimates of median times to event were also presented for each treatment. For the treatment comparison, a Cox's regression model was used to assess whether anastrozole was non-inferior to tamoxifen.

No formal statistical analyses were performed on the safety data.

RESULTS

Demography: A total of 1021 postmenopausal women, 353 from 97 centres in the United States and Canada (Trial 0030) and 668 from 83 centres in Europe, Central and South America, Australia, New Zealand, and South Africa (Trial 0027), were randomised to treatment. Of these patients, 511 were randomised to receive anastrozole 1 mg od and 510 to treatment with tamoxifen 20 mg od. A total of 1009 patients began their randomised treatment. Ninety per cent of the patients were Caucasian. The mean age was 67 years (range 30 to 92 years).

Ninety-two patients (anastrozole 1 mg: 50; tamoxifen 20 mg: 42) were still receiving trial treatment at the time of the data cut-off (31 May 2001) for this updated safety and survival analysis.

Efficacy: Table A summarises the survival status for all randomised patients in Trials 0030 and 0027, separately and combined, by trial treatment and Table B presents the results of the statistical analyses for the ITT population.

Table A Survival status for all patients in Trials 0030 and 0027, separately and combined

Survival status	Number (%) of patients [a]					
	Trial 0030		Trial 0027		Combined data	
	Anastrozole 1 mg (n = 171)	Tamoxifen 20 mg (n = 182)	Anastrozole 1 mg (n = 340)	Tamoxifen 20 mg (n = 328)	Anastrozole 1 mg (n = 511)	Tamoxifen 20 mg (n = 510)
Alive	75 (43.9)	76 (41.8)	150 (44.1)	148 (45.1)	225 (44.0)	224 (43.9)
Dead	96 (56.1)	106 (58.2)	190 (55.9)	180 (54.9)	286 (56.0)	286 (56.1)

[a] Data for these patients were censored at the last known observation.

Table B Time to death (survival): statistical analysis - ITT population

Treatment comparison: tamoxifen 20 mg versus anastrozole 1 mg	Hazard ratio [a]	Lower 95% confidence limit
Trial 0030 [b]	1.02	0.81
Trial 0027 [b]	0.94	0.79
Combined data [b]	0.97	0.84

[a] Hazard ratios >1.00 indicate that anastrozole is associated with a longer time to death (survival) than tamoxifen.
[b] Unadjusted Cox regression model (including treatment factor only).

Anastrozole 1 mg was shown to be similar to tamoxifen 20 mg with regard to the endpoint of time to death (survival); anastrozole 1 mg met the prespecified criteria for non-inferiority to tamoxifen 20 mg for the combined dataset. Anastrozole 1 mg is therefore at least as efficacious as tamoxifen 20 mg in terms of overall survival. Results from both the secondary (adjusted) analyses and the PP population also met the criteria for non-inferiority.
Data from Trial 0030 were consistent with the combined data with anastrozole 1 mg demonstrating non-inferiority to tamoxifen 20 mg; however, non-inferiority could not be concluded in Trial 0027 alone.
In the subset of patients known to have hormone-receptor positive tumours, anastrozole 1 mg was shown to be at least as effective as tamoxifen 20 mg in terms of overall survival.
Safety: Table C presents an overview of the various categories of adverse events reported.

Table C Overview of patients with adverse events (combined data)

Category [a]	Number (%) of patients			
	Data cut-off for 4MSU 09 September 1999		**Data cut-off of 31 May 2001**	
	Anastrozole (n = 506)	Tamoxifen (n = 511)	Anastrozole (n = 506)	Tamoxifen (n = 511)
Any adverse event	**415 (82.0)**	**429 (84.0)**	**422 (83.4)**	**432 (84.5)**
Drug related	209 (41.3)	207 (40.5)	211 (41.7)	212 (41.5)
Serious adverse event	**96 (19.0)**	**111 (21.7)**	**111 (21.9)**	**116 (22.7)**
Drug related	13 (2.6)	23 (4.5)	13 (2.6)	23 (4.5)
Withdrawal	**387 (76.5)**	**414 (81.0)**	**457 (90.3)**	**468 (91.6)**
Due to adverse event	24 (4.7)	28 (5.5)	27 (5.3)	28 (5.5)
Due to drug-related adverse event	10 (2.0)	13 (2.5)	10 (2.0)	13 (2.5)
Due to serious adverse event	15 (3.0)	20 (3.9)	17 (3.4)	20 (3.9)
Drug related	4 (0.8)	8 (1.6)	4 (0.8)	8 (1.6)
Death	**164 (32.4)**	**152 (29.7)**	**285 [c] (56.3)**	**287 (56.2)**
During treatment [b]	22 (4.3)	17 (3.3)	26 (5.1)	19 (3.7)
Due to adverse event	10 (2.0)	7 [d] (1.4)	13 (2.6)	7 [d] (1.4)
After treatment	142 (28.1)	135 (26.4)	259 (51.2)	268 (52.4)
Unrelated to breast cancer	25 (4.9)	11 (2.2)	39 (7.7)	25 (4.9)

[a] Patients may fall into more than 1 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; this explains the apparent discrepancy between Tables A and C in terms of the numbers of deaths reported on each treatment.
[d] An additional patient (Patient 0030/0001/0007) treated with tamoxifen died as a result of breast cancer following an adverse event ('heart failure').
4MSU 4-month Safety Update.
n Number of patients treated.

The most frequently reported adverse event for both treatment groups was hot flushes (COSTART term: vasodilatation). Other commonly reported adverse events included nausea, asthenia, and various types of pain. Overall, the most commonly reported drug-related adverse events were hot flushes and nausea. These adverse events were reported with similar frequencies in the anastrozole second-line programme and in the registration package for the first-line submission, and were not unexpected given the known safety profile of the drug.

The proportion of patients who died by the time of the data cut-off (31 May 2001) because of an adverse event either during treatment or within 14 days of the end of treatment was low (20 patients [2.0%]). A further 64 patients (6.3%) died after treatment from causes unrelated to breast cancer. These deaths are more likely to be related to concomitant disease or subsequent therapy than to first-line trial treatment. Of the deaths reported, the majority of patients (448 [44.1%]) died as a result of breast cancer after treatment. In cases where adverse events led to death, none of the primary causes was attributable to trial treatment.

The incidence of adverse events leading to withdrawal was also low (5.4%) and was similar for both treatment groups. No notable differences were evident between the groups in terms of specific adverse events leading to withdrawal.

The overall incidence of serious adverse events was similar for the 2 treatment groups. The most frequently reported serious adverse events (experienced by ≥10 patients from the combined dataset) were pathological fracture, nausea, dyspnoea, pneumonia, cerebrovascular accident, and vomiting. The majority of these events were not related to trial treatment.