SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ARIMIDEX™ 1 mg tablet

ACTIVE INGREDIENT: Anastrozole

Trial title (number): A Randomised, Double-blind Trial to assess Quality of Life with ARIMIDEX™ Alone, NOLVADEX™ Alone, or ARIMIDEX and NOLVADEX in Combination, when used as Adjuvant Treatment for Breast Cancer in Postmenopausal Women (1033IE/0029)

Clinical phase: IIIb

First patient recruited: 28 April 1998
Last patient recruited: 28 April 1999
Data cut-off date: 29 June 2001
AstraZeneca approval date: 8 February 2002

Principal investigator and location (centre number): (Centre 001), (Centre 0002)

Publications: Baum M. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in post-menopausal women: Baseline patient and tumor characteristics. European Journal of Cancer 2000;36(Suppl 5):S69 (Abstract 139).
Baum M. The ATAC breast cancer adjuvant trial in postmenopausal women. The Breast 2001;10(1):S32 (Abstract P63).
Baum M, Houghton J, Study Group. ATAC adjuvant trial in post-menopausal breast cancer. European Journal of Cancer 1998;34(Suppl):S39 (Abstract P99).
Dowsett M, on behalf of the ATAC Trialists' Group. Pharmacokinetics of 'Arimidex' and tamoxifen alone and in combination in the ATAC adjuvant breast cancer trial. Breast Cancer Research and Treatment 2000;64(1):64 (Abstract 236).

Houghton J, Baum M, on behalf of the ATAC Steering Committee and Investigators. Arimidex, tamoxifen alone or in combination (ATAC) adjuvant trial in post-menopausal breast cancer. European Journal of Cancer 1998;34(Suppl 5):S83 (Abstract 385).
Howell A, on behalf of the ATAC Trialists' Group. The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) adjuvant breast cancer trial in post-menopausal women: Regional variation in knowledge of hormone receptor status prior to randomisation into the trial. Annals of Oncology 2000;11(Suppl 4):20 (Abstract 76P).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists Group (Endometrial Sub-Protocol). The ATAC (arimidex, tamoxifen, alone or in combination) adjuvant breast cancer trial in post-menopausal women: Baseline endometrial sub-protocol data. European Journal of Cancer 2000;36(Suppl 5):S69 (Abstract 140).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists Group (Endometrial Sub-Protocol). The ATAC ('Arimidex', tamoxifen, alone or in combination) trial: transvaginal ultrasound scan findings overestimate observed pathological findings in postmenopausal gynaecologically asymptomatic women before treatment. Breast Cancer Research and Treatment 2000;64(1):64 (Abstract 233).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists Group. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) Trial: transvaginal ultrasound scan findings overestimate observed pathological findings in postmenopausal gynaecologically asymptomatic women before treatment. The Breast 2001;10(1):S30 (Abstract P55).
Jackson TL, Duffy SRG, on behalf of the ATAC Trialists Group (Endometrial Sub-Protocol). The ATAC ('Arimidex', Tamoxifen, alone or in combination) trial: the effectiveness of transvaginal ultrasonography and diagnostic hysteroscopy in the prediction of endometrial abnormalities in asymptomatic postmenopausal women. Breast Cancer Research and Treatment 2000;64(1):63 (Abstract 232).
Jackson TL, Duffy SRG, of behalf of the ATAC Trialists Group. The ATAC Trial: the effectiveness of transvaginal ultrasonography and hysteroscopy in the prediction of endometrial abnormalities in asymptomatic menopausal women. The Breast 2001;10(1):S30 (Abstract P56).
Sainsbury R, on behalf of the ATAC Trialists' Group. The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) adjuvant breast cancer trial in post-menopausal women: Regional variations in surgical practice in patients recruited into the trial. Annals of Oncology 2000;11(Suppl 4):20 (Abstract 78P).
Stroner P, Gallagher J, Houghton J. Managing ATAC - the largest adjuvant breast cancer trial ever conducted. Controlled Clinical Trials 2000;21(2)(Suppl):60S (Abstract 35).

OBJECTIVES

The primary objectives of this trial were to compare QOL between the anastrozole (1 mg) group, the tamoxifen (20 mg) group, and the anastrozole (1 mg) plus tamoxifen (20 mg) combination group during the first 2 years of treatment. Specifically, this trial will:

- compare the difference in QOL between the anastrozole group and the tamoxifen group, and

- compare QOL in the anastrozole plus tamoxifen combination group with the tamoxifen group for non-inferiority. If non-inferiority was concluded, then the difference in QOL between these 2 groups was assessed.

The secondary objectives of this trial were: to compare the incidence of specific endocrine symptoms between the 3 treatment groups; to compare the Emotional Well Being (EWB) and Social Well Being (SWB) values between the 3 treatment groups at each scheduled visit; to determine the patients' most bothersome endocrine symptoms in each of the 3 treatment groups; and to provide information about QOL 28-days post recurrence.

METHODS

Design: This was a randomised, double-blind, parallel-group, multicentre, collaborative trial designed in conjunction with the Cancer Research Campaign, United Kingdom. This subprotocol assessed the QOL of a subset of patients from the main Arimidex, Tamoxifen Alone or in Combination (ATAC) trial (protocol number 1033IL/0029). These patients are to receive their randomised treatment within the main ATAC trial until completion of the study (5 years), or until disease recurrence was confirmed or continued treatment was refused. Assessments within this QOL subprotocol occurred over the first 2 years of treatment, plus assessments at disease recurrence and 28-day post-recurrence, should this occur within the 5-year trial period. The trial was led by a Steering Committee (consisting of the principal investigator, other trial investigators and scientists, an independent statistician, and representatives from the various collaborative groups plus clinical and Statistical personnel from AstraZeneca) supported by an Independent Data Monitoring Committee (IDMC).

Population: Postmenopausal women undergoing treatment for invasive primary breast cancer. This trial was designed to recruit approximately 1000 patients from the main ATAC trial.

Dosage: Patients received treatment as allocated within the main ATAC trial. They were given once-daily oral doses of anastrozole (1 mg) (formulation F011292, 11292) and tamoxifen placebo (formulation F011003, 12062); tamoxifen (20 mg) (formulation F006293, 12061) and anastrozole placebo (formulation F011314; 11314); or anastrozole (1 mg) plus tamoxifen (20 mg). Trial treatment continued until disease recurrence, or until the patient withdrew from treatment for any other reason, or until the end of the subprotocol.

Key assessments:

Quality of life: Data were collected using the Functional Assessment of Cancer Therapy - Breast (FACT-B) questionnaire with an Endocrine Subscale (ES) questionnaire. The primary endpoint was the Trial Outcome Index (TOI) of the FACT-B. The TOI was assessed using the Physical Well Being (PWB), Functional Well Being (FWB), and Breast Cancer Subscale (BCS) components of the patient questionnaire. The secondary endpoints were: specific endocrine symptom response; ES; EWB and SWB; QOL 28 days post-recurrence; and most bothersome endocrine symptoms. The questionnaires were completed at baseline, before trial treatment was administered, and at each scheduled visit within the first 2 years of the main ATAC trial (months 0, 3, 6, 12, 18, and 24), prior to seeing the investigator. Follow-up data will be collected every 6 months for up to 5 years, or until disease recurrence if this occurred within the 5 year trial period. In addition, the questionnaires were completed at unscheduled visits, any visit associated with suspected recurrence of disease, and 28 days after confirmed recurrence.

Safety: The incidence of adverse events are summarised in the clinical study report for the main ATAC trial (1033IL/0029). An Independent Data Monitoring Committee (IDMC) was established to evaluate data from this trial and to consider the results of the formal interim analysis; the IDMC comprised 3 independent experts (2 clinicians and 1 statistician). The IDMC reviewed blinded safety data on a regular basis and subsequently advised the Steering Committee.

RESULTS

Demography: In total, 1105 patients (from 114 centres in 10 countries worldwide) previously randomised to treatment in the main ATAC trial, were recruited into the QOL trial between 28 April 1998 and 28 April 1999. A total of 1021 were included in the primary analysis population. Patient population and disposition is presented in Table A.

Table A Patient population and disposition

	Anastrozole 1 mg	Tamoxifen 20 mg	Anastrozole 1 mg plus tamoxifen 20 mg
Population			
Mean age (range) (years)[a]	62.8 (43.4 to 86.4) (N = 335)	63.7 (45.5 to 90.7) (N = 347)	64.2 (45.2 to 89.5) (N = 339)
Body weight (range) (kg)	71.5 (41.3 to 120.2) (N = 332)	71.1 (36.2 to 127.0) (N = 343)	71.9 (38.0 to 145.3) (N = 335)
Caucasian (n [%])	331 (98.8)	342 (98.6)	331 (97.6)
Disposition			
Discontinued (n [%])	49 (7.3)	67 (9.7)	66 (9.7)

[a] There was a period from the initiation of the trial until 01 September 1997 (date of protocol amendment) where patients <45 years of age were permitted to enter the trial.

Age distribution was similar across the 3 groups, with a fairly even distribution of patients in the under 60 years and ≥60 to ≤70 years. Breast cancer history and baseline characteristics of breast cancer status were also similar for the 3 treatment groups.

Quality of life:

Quality of life for patients treated with either anastrozole alone or the combination of anastrozole plus tamoxifen was similar to the quality of life for patients treated with tamoxifen alone, as shown by the results of the primary endpoint of TOI. The primary statistical analysis of the mean TOI scores is presented in Table B.

Table B Longitudinal analysis of trial outcome index (TOI)

Treatment comparison	Difference in TOI[a]	2-sided 95% CI	Lower limit of 1-sided 95% CI	p-value
Anastrozole 1 mg versus tamoxifen 20 mg	-0.75	-1.98 to 0.47	NA	0.227
Anastrozole 1 mg plus tamoxifen 20 mg versus tamoxifen 20 mg[b]	-0.10	-1.32 to 1.12	-1.12	0.871

[a] TOI Trial outcome index, defined as the sum of physical well being, emotional well being, and breast cancer subscale scores.
[b] If the lower limit of the 2-sided 95% confidence interval is

Analysis of the secondary endpoints of specific endocrine symptom response, endocrine subscale score, emotional well-being and social well-being, QOL 28-day post-recurrence provided no evidence of differences between the treatment groups. The secondary and per-protocol analyses showed results consistent with the primary analysis.
Some differences were evident in the numbers of patients who classified a particular endocrine system event as “most bothersome.” The clinical importance of these findings for this secondary endpoint is unclear.
Safety: Safety data collected on patients in this trial are presented in the main ATAC clinical trial report (CTR) (1033IL/0029).