PHASE III RANDOMIZED ADJUVANT STUDY OF TAMOXIFEN ALONE VERSUS SEQUENTIAL TAMOXIFEN AND ANASTROZOLE IN HORMONE-RESPONSIVE POSTMENOPAUSAL BREAST CANCER PATIENTS (NATIONAL SURGICAL ADJUVANT STUDY OF BREAST CANCER [NSAS BC] 03)

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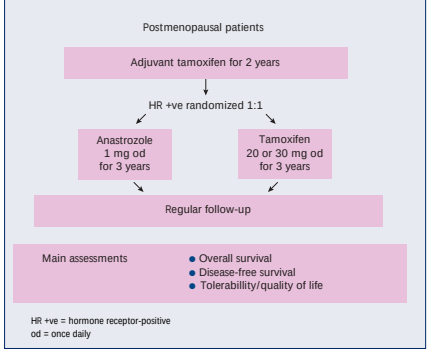
INTRODUCTION

- Tamoxifen, a non-steroidal antioestrogen, was the 'gold standard' endocrine treatment for breast cancer for more than 25 years. In patients with oestrogen receptor-positive tumours, adjuvant treatment of early breast cancer with tamoxifen is associated with a reduction in mortality of 26% compared with controls[1]
- In recent years the aromatase inhibitor, anastrozole, has shown superior efficacy compared with existing standards in the treatment of hormone-sensitive advanced breast cancer, both versus tamoxifen as a first-line therapy[2–5] and versus megestrol acetate as a second-line therapy[6–8]
- Furthermore, first results from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial have shown that anastrozole is superior to tamoxifen for the adjuvant treatment of early breast cancer in postmenopausal women, showing a relative risk reduction in favour of anastrozole of 22% for disease-free survival (hazard ratio = 0.78; p = 0.005) in hormone receptor-positive patients at a median follow-up of 33.3 months[9]
  - This benefit remained significant following the recent updated analysis, based on a median follow-up of 47 months, with the absolute benefit between treatments continuing to increase over time[10]
- In the ATAC trial, anastrozole also demonstrated a number of important tolerability benefits compared with tamoxifen[9]
- ATAC is one trial amongst a large programme of ongoing clinical trials involving aromatase inhibitors currently underway across the whole of the breast cancer disease spectrum
  - However, ATAC does not address the sequencing of anastrozole and tamoxifen as adjuvant therapy; this is being explored in a number of other trials
- Here we outline the ongoing studies being conducted in postmenopausal women with early breast cancer, and present trial NSAS BC 03 – an adjuvant sequencing trial being carried out in Japanese women
- Each of the trials discussed compares tamoxifen with the sequence of tamoxifen followed by anastrozole, to ascertain whether or not patients who are currently receiving adjuvant tamoxifen can gain any benefit by switching to anastrozole

ADJUVANT SEQUENCING TRIALS

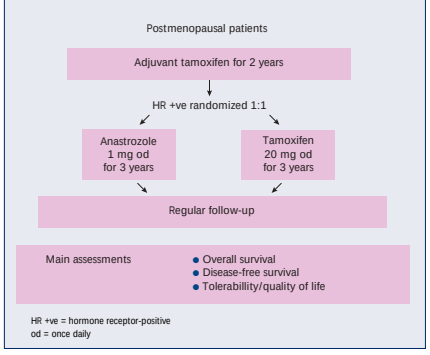
- A number of sequencing trials with anastrozole are ongoing (ARNO, ABCSG 8, Italian, ABCSG 6a, NSAS BC 03)
- All of these trials involve patients with hormone receptor-positive tumours
- The main endpoints for these trials are disease-free survival, overall survival and tolerability
- The trial designs for the studies involving postmenopausal patients are shown in Figures 1–4

Figure 1: ARNO ('Arimidex' – 'Nolvadex') (German) trial design



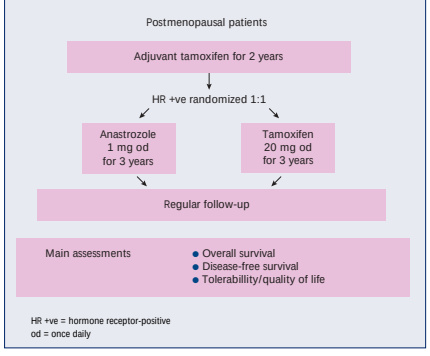
- Started 1996, closed to patient entry end of August 2002 with 1056 patients recruited

Figure 2: ABCSG 8 (Austrian Breast Cancer Study Group Trial 8) trial design



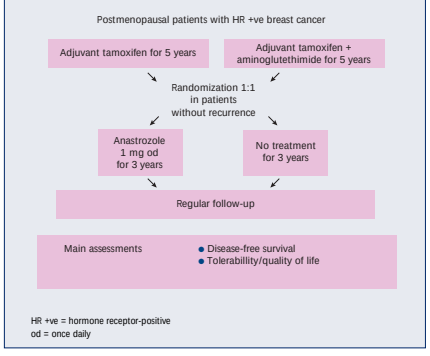
- Started 1996, recruited 2500 patients (target accrual 3500 patients)

Figure 3: Italian study design



- Started 1998, recruited 427 patients (target accrual 1000 patients)

Figure 4: ABCSG 6a trial design



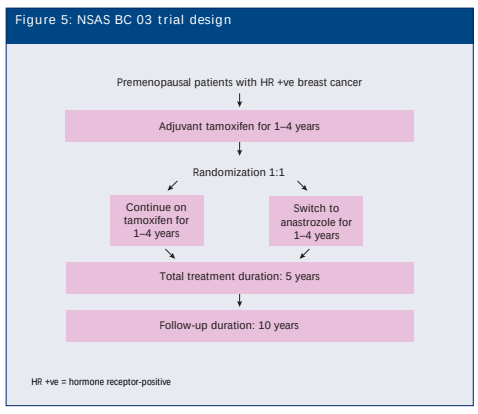
- Started 1996, recruited a total of 823 patients

NATIONAL SURGICAL ADJUVANT STUDY OF BREAST CANCER (NSAS BC) 03

- NSAS BC 03 is the first trial of adjuvant anastrozole to be initiated in Japanese women
- This ongoing study compares the efficacy and safety of 5 years' adjuvant tamoxifen with 5 years' sequential treatment with tamoxifen followed by anastrozole in postmenopausal Japanese women with hormone-responsive early breast cancer
- NSAS BC 03 is a randomized, open-label, multicentre trial, which aims to recruit a total of 2500 patients who have received adjuvant tamoxifen for 1–4 years
- Once recruited, patients are randomized 1:1 to either continue receiving tamoxifen for 1–4 years, or to switch to anastrozole for 1–4 years, resulting in a total treatment duration of 5 years in all patients
- Follow-up is planned for 10 years from final recruitment
- The design of trial NSAS BC 03 is shown in Figure 5

- The eligibility criteria for this trial are as follows:
  - Postmenopausal women
  - <75 years
  - Breast cancer stage I–IIIB
  - Performance status 0–1
  - Oestrogen and/or progesterone receptor-positive tumours
  - Prior treatment = surgery ± chemotherapy ± radiation therapy
  - Receiving tamoxifen for 1–4 years just prior to entering the trial

Figure 5: NSAS BC 03 trial design



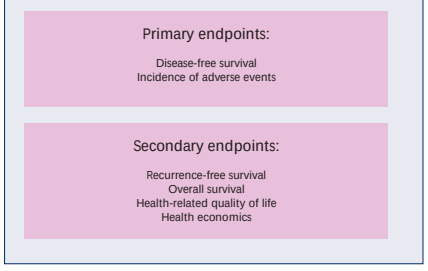
- The randomization adjustment factors for this trial are shown in Table 1
- The trial endpoints are shown in Figure 6

Table 1: NSAS BC 03 randomization adjustment factors

Factor	Classification
Age	<59/>60 years
Clinical stage	I, IIA, IIB/IIIA/IIIB
Number of lymph nodes	0/1–3/≥4
HER/neu	Unknown/0, 1+, 2+/3+
Tumour size	<3 cm/≥3 cm
Surgery	Breast conservation surgery/ mastectomy
Chemotherapy	Yes/No
Tamoxifen treatment duration	1–2 years/2–4 years
Hormone receptor status	ER+ and PgR+/ER+ and PgR–/ ER– and PgR+

HER/neu = Herceptin; ER+ = oestrogen receptor-positive; PgR+ = progesterone receptor-positive; ER– = oestrogen receptor-negative; PgR– = progesterone receptor-negative

Figure 6: NSAS BC 03 trial endpoints



SUMMARY

- The benefits of adjuvant treatment with anastrozole compared with tamoxifen in early breast cancer are now becoming apparent as emerging data from the ATAC trial mature
- As a result, for the first time, anastrozole is confirmed as a valid first-choice treatment in the adjuvant setting for postmenopausal women with hormone-sensitive early breast cancer
- The ongoing adjuvant trial programme will determine whether or not switching from tamoxifen to anastrozole confers additional benefit compared with continued tamoxifen therapy
- The NSAS BC 03 trial is the first large adjuvant trial of anastrozole in postmenopausal Japanese breast cancer patients

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