

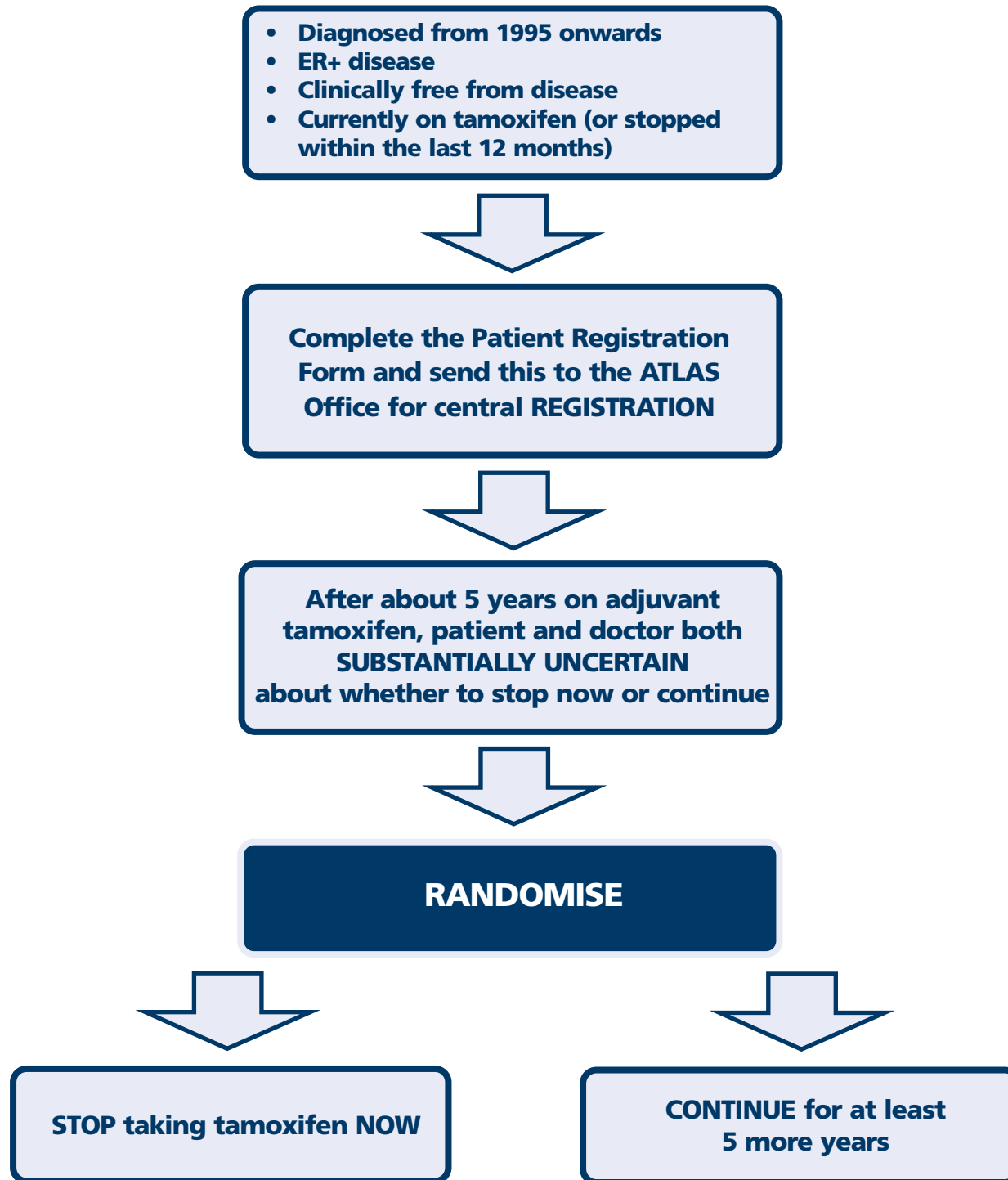
ATLAS: New emphasis, same protocol

A trial of 10 versus 5 years of adjuvant tamoxifen in women with ER+ disease



Newsletter No. 8

June/July 2001



US National Institutes of Health report endorses the need for trials like ATLAS

The US National Institutes of Health organised a Consensus Development Conference on 1-3 November 2000 on the adjuvant treatment of breast cancer. The first research priority they listed was that “trials should be conducted to better define the risks and benefits of continuing tamoxifen beyond 5 years”.

An independent expert panel took evidence from international clinicians and scientists, and then prepared a “Consensus Statement”. Many of the Panel’s main conclusions were based on the latest world-wide randomised evidence as brought together by the Early Breast Cancer Trialists’ Collaborative Group. This NIH Consensus Statement will have a major impact on the management of breast cancer, not only in the US, but world-wide. Among the Panel’s main conclusions concerning the standard treatment of early breast cancer were:

- **Radiotherapy:** If the woman has had a mastectomy, then radiotherapy is recommended only if she had at least 4 (four) positive axillary lymph nodes. If she has had conservative surgery, radiotherapy to the conserved breast is also recommended.
- **Chemotherapy:** If the woman is less than 70 years of age, 4-6 cycles of an anthracycline-based regimen are recommended UNLESS the tumour is ≤ 1 cm with no nodal involvement.
- **Tamoxifen:** 5 years of tamoxifen should be standard adjuvant hormone therapy in women with ER+ disease. Although tamoxifen is associated with a slight but definite risk of endometrial cancer and venous thromboembolism, the benefits of tamoxifen far outweigh the risks.
- **Trials should be conducted to better define the risks and benefits of continuing tamoxifen for more than 5 years. This was the first research priority identified by the Panel.**

A full copy of the Consensus Statement is enclosed with this Newsletter or is available at http://odp.od.nih.gov/consensus/cons/114/114_statement.htm

Update on the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meeting, September 2000

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) was established in 1984 and meets every 5 years to bring together all of the researchers world-wide who have undertaken randomised trials that have assessed any aspect of the treatment of early breast cancer where survival is a primary end-point. In September 2000, the EBCTCG considered data from more than 300 trials involving about 200 000 women. Some of the main results are described in this Newsletter.

ATLAS Trial Office, CTSU, Radcliffe Infirmary, Oxford OX2 6HE, UK
Tel: +44 1865 404844 Fax: +44 1865 404845 E-mail: atlas@ctsu.ox.ac.uk

EBCTCG 2000: Key results

Tamoxifen

The evidence is now clear that about 5 years of adjuvant tamoxifen produces greater benefit than just 1 or 2 years. The 2000 EBCTCG overview showed that among women with hormone-sensitive breast cancer (that is, women with oestrogen receptor positive [ER+] disease), 5 years of tamoxifen produces a 13% (standard error [SE] 1.4) absolute reduction in recurrence at 15 years, and a 9% (SE 1.4) reduction in death from breast cancer (so, 13% fewer recurrences and 9% fewer deaths from breast cancer among women receiving tamoxifen than among those not) - see figures 1 and 2. This kind of benefit of tamoxifen is seen in ALL women with oestrogen receptor positive (ER+) disease independent of age, nodal status or whether chemotherapy was used (see Table 1).

Tamoxifen 5 yrs vs Not in ER+ disease (8000 women)

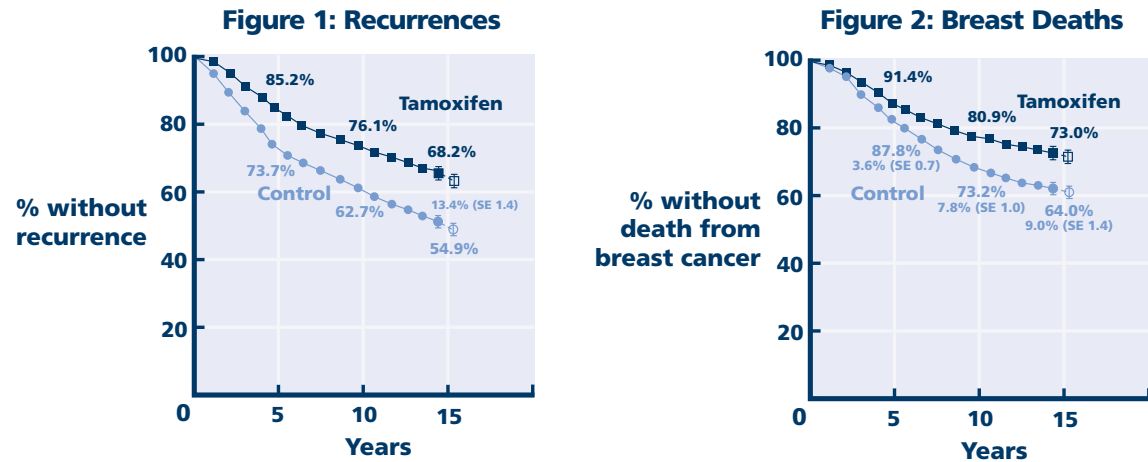


Table 1: Effects of Tamoxifen in women with ER+ disease randomised in trials of five years of adjuvant Tamoxifen vs no Tamoxifen

Category of woman	No. randomised	Absolute reduction (and standard error) in recurrence with tamoxifen 10 years after randomisation
< 50 years	3000	10% (SE 2.0)
> 50 years	5000	15% (SE 1.3)
Node negative	5000	12% (SE 1.2)
Node positive	3000	13% (SE 2.3)
In the presence of chemotherapy	3000	9% (SE 2.2)
In the absence of chemotherapy	5000	15% (SE 1.3)

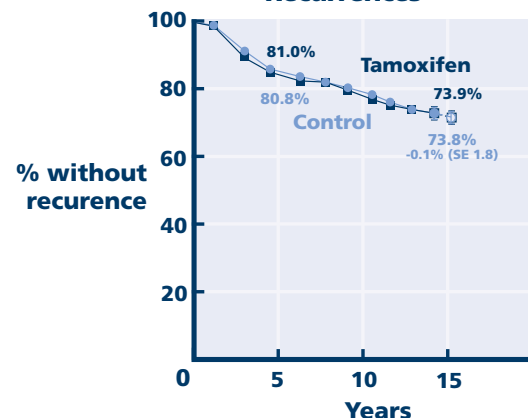
EBCTCG, 2000

There are ~1 million women world-wide currently on tamoxifen. If these women are treated for about 5 years with the drug, then over a period of 10-15 years this will avoid about 90 000 deaths from the disease.

Tamoxifen in ER negative disease

There was NO definite evidence in the Overview of any benefit of tamoxifen among women who did not have oestrogen receptors measurable on the original tumour, that is, those with reliably measured ER negative [ER-] tumours.

Figure 3: Effects of Tamoxifen 5 yrs vs. Not in 4000 women with ER poor disease Recurrences



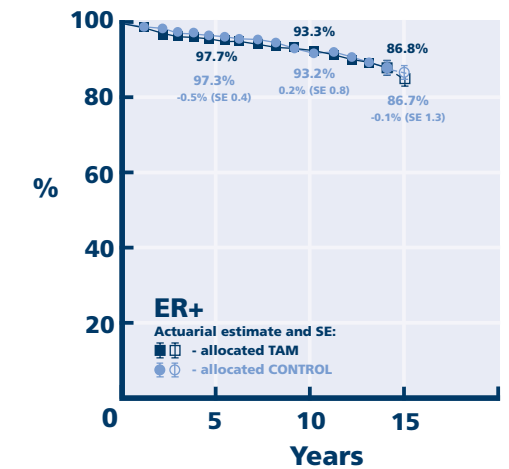
Side-effects of tamoxifen

There are three life-or-death side-effects, two adverse and one beneficial. Tamoxifen causes an **increase** in deaths from **pulmonary embolus (PE)**, and from **endometrial cancer**, but in contrast, tamoxifen approximately **halves** the risk of developing a new cancer in the opposite breast. For every 1000 women treated with about 5 years of tamoxifen, there will be an additional 2-3 deaths from PE and endometrial cancer in the first 10-15 years. However, this excess hazard is outweighed by the definite and substantial benefits on second breast cancer and, of course, is greatly outweighed by the reduction in the risk of recurrence of and death from, the primary cancer.

Table 2:

10-year mortality among 1000 women receiving about 5 years of tamoxifen	
Breast Cancer	~80 per 1000 FEWER deaths
Endometrial cancer	~2 per 1000 MORE deaths
All other cancers	NO DIFFERENCE
Pulmonary embolus	~1 per 1000 MORE deaths
Other causes of death	NO DIFFERENCE

Figure 4: Tamoxifen 5 yrs vs. Not Non-Breast Deaths



Tamoxifen duration: 10 years vs. 5 years unanswered

There is now large-scale randomised evidence confirming that 5 years of adjuvant tamoxifen provides more benefit than 1 or 2 years, but so far, there is not enough randomised data to answer reliably the question of whether prolonging tamoxifen for an extra 5 years (10 years in total) is even better. For, the effective size of a trial of tamoxifen duration depends chiefly on the number of recurrences, (which, by definition, here includes contralateral breast cancer) and thus far there is only one tenth as many recurrences in the trials of 10 versus 5 years as in the trials of ~5 versus fewer years of adjuvant tamoxifen.

Table 3:

Number of recurrences and main conclusions from trials of longer versus shorter adjuvant tamoxifen

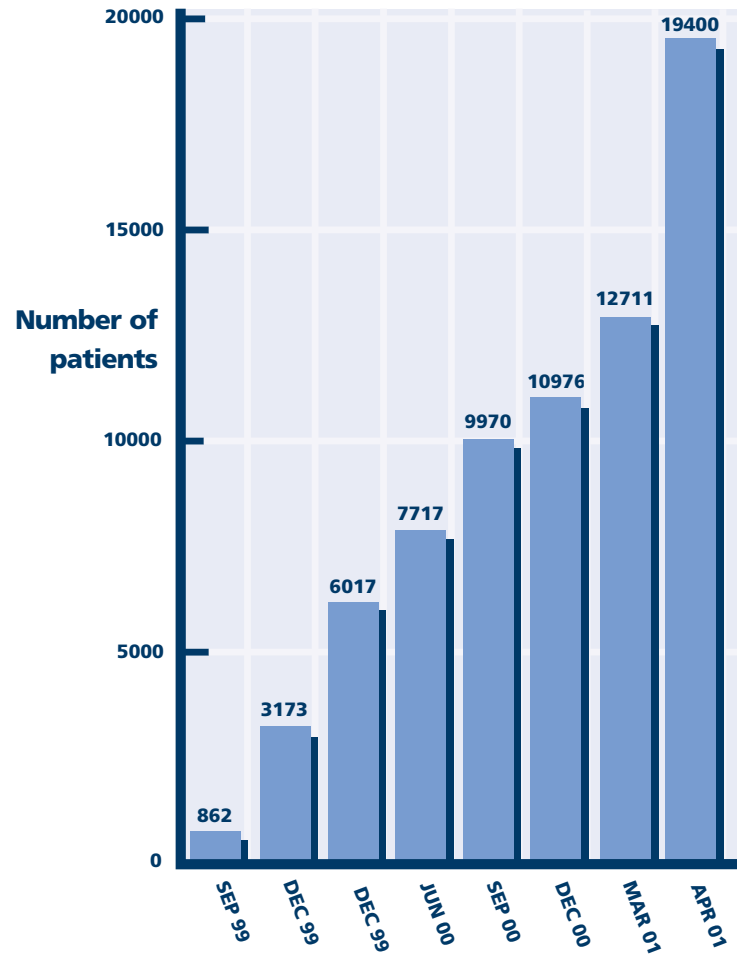
Duration comparison	Number of recurrences in the trials	Result
~5 years vs 1-2 years	4 200	Definite: 5 years better than 1-2 years
10 years vs 5 years	450	Still uncertain: much more randomised data required

Apart from ATLAS and aTTom (the UK counterpart to ATLAS), which have randomised too recently for the long-term effects yet to be apparent, there are only 3 trials of 10 versus 5 years, none of which involved large numbers of recurrences (B-14 trial [64 vs 54 recurrences], the Scottish trial [49 vs 38 recurrences] and the ECOG trial [17 vs 29 recurrences]). Although these B-14 and Scottish results were not published until 2001 (JNCI 2001;93:684-690 and JNCI 2001;93:456-462, respectively), they (together with the results from the ECOG trial and the blinded results from ATLAS and aTTom) were fully available in September 2000 to the EBCTCG and to the NIH Consensus Conference in November 2000. The EBCTCG review of these recurrences found no net benefit or hazard in the first 5 years after randomisation (years 5-9 after diagnosis), but found that the few recurrences thereafter (33 longer vs 45 shorter, not significant) suggested the possibility that large-scale evidence from ATLAS and aTTom would eventually reveal some benefit of longer treatment in the second decade after diagnosis. The NIH Consensus Conference likewise concluded that one of the main research questions that still needed answering properly about the treatment of early breast cancer was whether 10 years of adjuvant tamoxifen would, in the long term, be better than just 5.

Find out the oestrogen receptor status of all registered and randomised women

10 years of adjuvant tamoxifen may well produce better survival than just 5 years **only** in women whose original tumour is ER+. If so, then knowing the ER status of large numbers of the women in ATLAS would help the study to get a more strikingly positive result, and might (even more importantly) protect it against a false negative result that could be disastrous for hundreds of thousands of women. **Please help us by providing the ER status at the time of registration or at randomisation.** If you randomise a patient now without an ER result, we will write to you to ask for this. We want to determine the ER status of as many as possible of women in ATLAS for whom no ER assay was available at the time of registration or randomisation. ATLAS will help cover the costs of this if necessary.

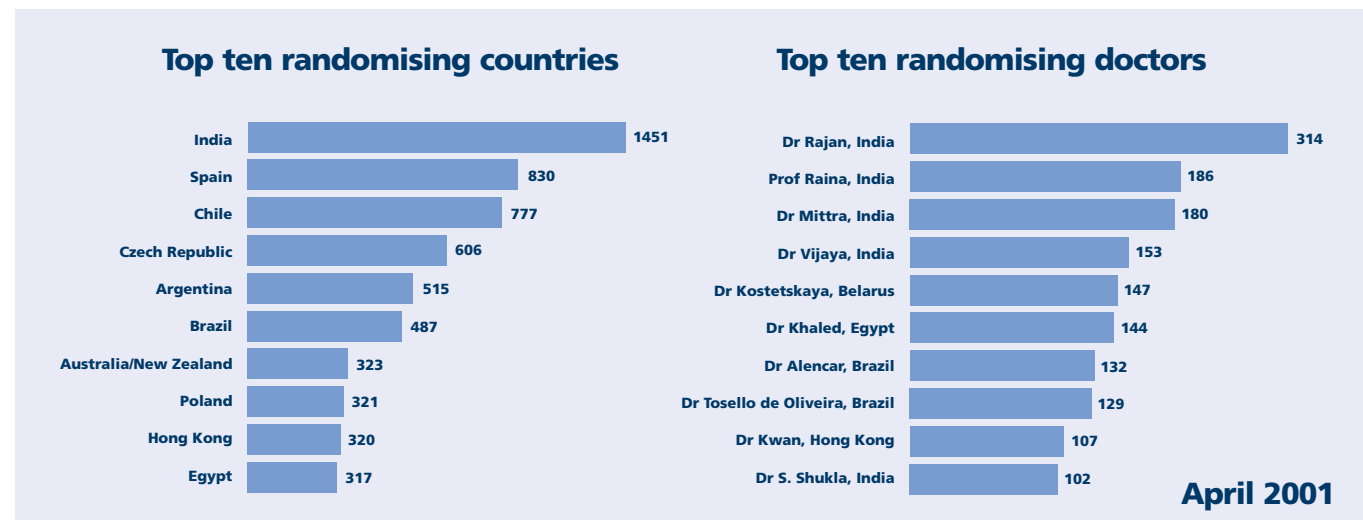
Figure 7: ATLAS Patient Registration: Cumulative Accrual to 30th April 2001



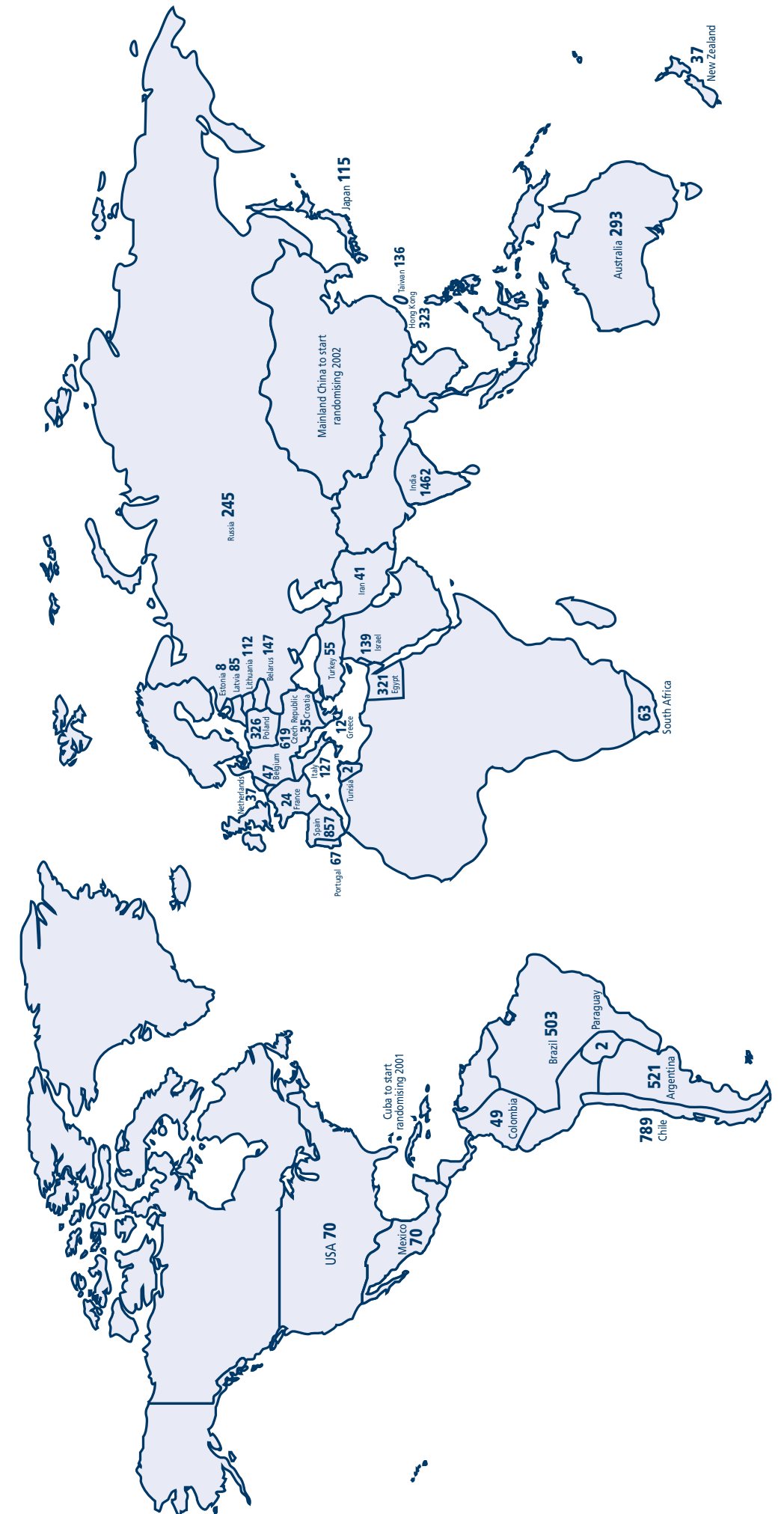
Between March and April 2001, mainland China registered more than 5000 women with ER+ disease.

Progress in ATLAS

ATLAS is now ongoing in more than 30 countries world-wide, both developed and developing. Already about 8000 women have been randomised in ATLAS. The target is at least 15 000 women with ER+ disease randomised after 5 years of tamoxifen. The USA, Uruguay, Cuba and mainland China have now joined the trial, and Sweden and Denmark are currently considering whether to collaborate.



Number of patients randomised into ATLAS world-wide



Total: 7739, 30th April 2001