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Worldwide, more than 1 million women with early breast cancer take adjuvant tamoxifen. However, there is uncertainty about the optimal duration of treatment. ATLAS is a major international trial which will help to assess this optimal duration reliably. If ATLAS demonstrates an additional advantage from longer treatment, then several thousands of deaths could be avoided each year if women are treated accordingly. The ATLAS collaboration continues to achieve its interim and overall objectives. Since 1 October 1995, the infrastructure for the trial has been established in several hundred hospitals in more than 20 countries worldwide; collaborators' meetings have been organized in most countries; free tamoxifen has been negotiated, funding for its supply and distribution secured, and 2 cycles of tamoxifen have already been distributed; by 1/10/97 232 hospitals had ethical approval, with the remaining hospitals in the process of obtaining approval; randomization had started in 146 hospitals, with about 1600 patients already randomized. The first annual follow-up took place in January 1997 on all patients randomized in the study. The independent Data Monitoring Committee had its second meeting in March 1997 and endorsed the continuing importance of ATLAS, including its design and implementation. The first meeting of the Steering Committee was held in Oxford in September 1997, and ATLAS continues to have a high profile at important international breast cancer meetings.

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FOREWORD

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Richard Peto 10/10/97

PI - Signature Date

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A. INTRODUCTION

The scientific rationale for ATLAS, its philosophy and design, have been described in detail in the original application for support and in the first 2 annual reports. They are reviewed in this report, an important part of which is the draft manuscript by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) concerning the 1995 overview of randomised tamoxifen trials which is shortly to be submitted for publication (**Appendix 1**).

1. Background

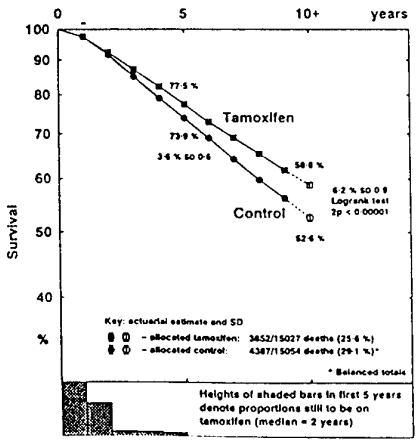
ATLAS concerns the use of tamoxifen in early breast cancer and, in particular, is designed to assess reliably the balance of benefits and risks of prolonging adjuvant tamoxifen by an extra 5 years in women who have already had a few years of treatment and for whom there is uncertainty about whether they should stop their tamoxifen, or continue for longer.

1.1 The randomised evidence on adjuvant tamoxifen

Breast cancer is common; more than 800 000 new cases will be diagnosed worldwide in 1997 alone, making breast cancer the leading cause of female neoplastic death in developed societies. In developing societies, breast cancer is only second to cervical cancer in cancer deaths. The reliable demonstration that a practicable and widely available treatment for such a common disease produces a moderate improvement in long-term survival (e.g. improving survival by a few per cent from, say, 50% to 52 or 53%) could lead to some hundreds of thousands of women being treated accordingly each year, and the avoidance or delay of several thousand deaths worldwide. This would be a worthwhile benefit to establish.

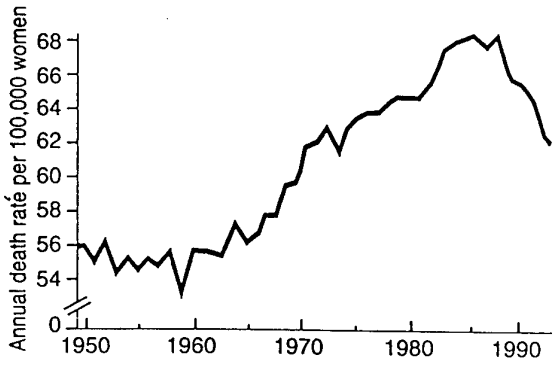
The EBCTCG overview of randomised trials of adjuvant tamoxifen vs. no tamoxifen demonstrated a highly significant improvement in 10-year survival corresponding to an average of about 5 or 6 fewer deaths per 100 women treated with *a few years* of tamoxifen (Figure 1)[1]. This was confirmed by an updated overview in 1995[4] **(Appendix 1).** Following the demonstration by the EBCTCG overview in the mid-1980s that tamoxifen confers definite survival benefits, there was a substantial increase in the use of tamoxifen. Indeed, more than one million women worldwide are currently prescribed tamoxifen, making it one of the most widely used and effective forms of medical oncology which exists. It now prevents tens of thousands of breast cancer deaths each year worldwide.

Figure 1: Mortality (all ages/nodal/oestrogen receptor status (ER)) in 30 000 women in trials of tamoxifen vs. no tamoxifen



Before the EBCTCG results emerged, there had been little evidence of any decrease in breast cancer death rates over the previous half-century. But now, a sudden decrease in breast cancer mortality during the early 1990s is being observed which can be attributed largely to the benefits of improved treatment, particularly with tamoxifen[2-3] (Figure 2).

Figure 2: Breast cancer mortality in England and Wales, 1950-93 [3]



This beneficial effect of tamoxifen is seen with a few years of treatment: on average in the EBCTCG overview of trials of tamoxifen vs. control, women had received ~2 years of tamoxifen. However, there is substantial uncertainty regarding the optimal duration of treatment in the adjuvant setting and this uncertainty has lead to variation in clinical practice.

1.2 The relevance of the duration of tamoxifen treatment

Most trials of tamoxifen have involved 1, 2 or 5 years of tamoxifen vs. no tamoxifen. Within this range, indirect randomised comparisons suggest that more prolonged tamoxifen may be more effective at preventing or delaying recurrent disease and improving survival compared with shorter regimens. In addition, tamoxifen reduces the incidence of contralateral breast cancer and this effect appears to be more marked with longer treatment[1,4]. Although no other long-term beneficial side-effects have yet been reliably demonstrated, long-term (but not short-term) use of tamoxifen may also have a beneficial effect on coronary heart disease through its cholesterol-lowering effect[5-8]. The oestrogenic effects of prolonged tamoxifen may confer other benefits[9-11] (e.g. reduction of osteoporosis in post-menopausal women). Further randomised evidence is needed to confirm or refute whether such benefits exist. Whilst the benefits of tamoxifen are greater with more prolonged therapy, the reliably established adverse long-term side-effects may also be affected by the length of treatment. Specifically, the risk of tamoxifen-induced endometrial cancer appears to be increased with more prolonged therapy[1,4,12-15]. There is an interest in other potential long-term effects of tamoxifen[16-21], but no other major life-threatening or life-prolonging side-effects have been **reliably** demonstrated[4].

1.3 The balance of beneficial and adverse effects with longer tamoxifen regimens

Whilst an increase in endometrial cancer attributable to tamoxifen - mediated through tamoxifen's oestrogen-like activities in this hormone-sensitive tissue - is definite, this is smaller than the definite decrease in contralateral breast cancer. Moreover, the increase in the number of endometrial cancer deaths is much smaller than the absolute decrease in all-cause mortality. In the EBCTCG overview, for every 1000 women treated with ~2 years of tamoxifen, about 3 additional cases of endometrial cancer (and only one death) were seen (compared with 50-60 deaths **avoided** overall). Hence, the available randomised evidence when considered in its entirety supports the continued use of tamoxifen in the adjuvant setting[22].

However, both adverse and beneficial effects may increase if tamoxifen is taken for many years and any assessment of the effects of tamoxifen must address the overall balance of risks and benefits. It is quite possible that additional benefits could be obtained by prolonging tamoxifen by a few extra years. However, if any such survival advantage exists, then it is likely to be modest. As tamoxifen is so widely practicable, such differences would be well worth knowing about, and might avoid or delay several thousand deaths worldwide. But, for this is to be convincingly established - so as to influence clinical practice - requires reliable large-scale direct randomised comparisons of different durations of tamoxifen. **So far, the net effect of tamoxifen when used for longer than 5 years has not been properly studied**[23,24] either through indirect comparisons of duration between trials of tamoxifen versus

no tamoxifen, or through direct comparisons in trials which compare within the same study, 5 years of tamoxifen versus longer treatment.

2. The need for direct randomised comparisons of longer versus shorter tamoxifen

Whilst comparisons between trials of different durations of tamoxifen vs. no tamoxifen **suggest** that longer treatment may be better, such comparisons are indirect and evidence is needed from direct randomised comparisons of different duration regimens.

A second generation of trials comparing 2 years vs., generally, about 5 years of tamoxifen has been started, and it seems probable that these trials will eventually be able to provide reliable evidence on the relative effects of a few extra years of treatment. Indeed, preliminary results from direct randomised comparisons of 2 years vs. 5 years support the indirect evidence from the EBCTCG overview that, at least for recurrence, longer treatment is more effective[25-26]. A recently reported trial conducted in France comparing 2 years of tamoxifen with about 7 years produced the same finding, with patients who had received longer treatment having significantly reduced rates of recurrent disease[27]. However, it will take many years for these relatively small trials to provide a reliable answer in particular with respect to overall survival, and further randomisation will produce an answer more rapidly. Thus, in the interim, it remains appropriate to supplement these preliminary data with evidence from other ongoing trials, including ATLAS, addressing the question of duration.

For the comparison of 5 years vs. 10 years of tamoxifen, the current trials are of insufficient size - even in combination and with prolonged follow-up - to detect the type of moderately-sized difference that might exist[12,28-29]. Hence, as was concluded by the independent ATLAS Data Monitoring Committee, which reviewed the totality of the available data from these trials (see page 13), the need for ATLAS has been corroborated by the early results of all of these trials and the recent stoppage of one of the trials may well, in time, be shown to have been premature[23-24,30].

3. The need for large-scale randomised evidence and long-term follow-up

The reliable demonstration, or refutation, of any plausibly moderate-sized additional advantage that might be produced from longer treatment requires large-scale randomised comparisons. Small-scale randomised evidence carries the substantial risk of undue weight being given to favourable or unfavourable random fluctuations based on few events — particularly if interim analyses are carried out repeatedly and any extreme "zigs" or "zags" produced by chance unduly emphasized[30]. Long follow-up among a large number of randomised patients is required before sufficient numbers of recurrences and deaths will have occurred to allow reliable comparisons.

But, there is another reason why comparisons of different tamoxifen durations require long follow-up. It is evident from the EBCTCG overview that there is a substantial "carry-over" benefit from tamoxifen lasting beyond the treatment period. A few years of adjuvant tamoxifen produces a reduction in the annual recurrence rate and in the annual death rate not only **during** treatment, but also for a few years **after** treatment has stopped[4,32]. This persistent benefit **enhanced** the absolute difference in 10-year survival observed in trials of tamoxifen vs. no tamoxifen. However, in trials comparing stopping after a few years versus continuing for longer, this carry-over benefit amongst patients stopping their tamoxifen may mean that, for the first few years of additional treatment, there is little apparent additional benefit from continuing tamoxifen — **even if, later on, a worthwhile benefit from longer treatment emerges.** Consequently, it is imperative that follow-up in such trials is sufficiently long to allow any late survival benefit from continuing tamoxifen to emerge (see table 1).

Table 1: Example of the numbers of deaths that might be observed in various periods after randomisation of 20 000 women between **stop** and **continue** tamoxifen after an initial 5 years of tamoxifen

Years since randomisation	**SHORTER** (e.g. stop after ~ 5 years of tamoxifen): **10 000 women**	**LONGER** (e.g. continue for 5 extra years after 5 years of tamoxifen): **10 000 women**	Stat. significance of such a result NS = not significant
0-3 years	**~1000**	**~1000**	**NS**
0-6 years	**~2000**	**~1900**	**NS**
0-10 years	**~3000**	**~2750**	**P<0.0001**

In summary, the major deficiency in research evidence and hence, the main uncertainty in clinical practice, lies in the assessment effects of prolonging adjuvant tamoxifen beyond 5 years. On the basis of existing evidence, there are already strong reasons to hope for greater benefits with more prolonged treatment and that, for example, there may well be a net additional survival benefit, albeit modest in size, when treatment is prolonged by an extra 5 years amongst women who have already had some years of tamoxifen. But, although modest, reliable demonstration of such survival improvements from longer treatment could lead to the avoidance of several thousand deaths worldwide each year, if women are treated accordingly. This was the fundamental rationale for the ATLAS trial at the time of the original funding application, and it remains appropriate now: for, ATLAS may be the only trial which is large enough to address this question reliably.

4. Primary objective of ATLAS

To answer reliably the question of whether 5 extra years of tamoxifen is worthwhile requires the further randomisation and prolonged follow-up of some tens of thousands of women. The primary objective of ATLAS is to assess reliably the balance of benefits and risks of prolonging tamoxifen in women who have already had a few years of treatment, and who, along with their doctors, are uncertain whether to stop, or continue for longer. About 20 000 eligible women are to be randomised either to stopping their tamoxifen, or continuing it for 5 more years and then followed for at least 10 years to allow sufficient time for the overall balance of benefits and hazards to emerge. The principal analysis will be an analysis by allocated treatment group of all-cause mortality, supplemented by analyses of (i) deaths from specific causes, (ii) other primary cancers, (iii) vascular deaths, and (iv) other major events requiring hospitalization. Subgroup analyses will be conducted with respect to the prior duration of tamoxifen, age, ER status, nodal status and other prognostic factors recorded at randomisation.

B. BODY OF THE REPORT

1. Review of statement of work

The initial funding from the US Army has successfully established the infrastructure for this international collaboration, and supported the early stages of the trial's implementation. The first stage of ATLAS — that is, the development of a widescale collaborative group and the establishment of the materials and procedures needed for the smooth conduct of the trial — has now mainly been completed by the international coordinating centre in Oxford under the direction of Dr Christina Davies, the trial coordinator.

Both the first and second annual reports to the US Army covering the periods 1 October 1994 - 30 September 1995, and 1 October 1995 - 30 September 1996, respectively, have been accepted by the US Army. Both reviewers of the second report reconfirmed the importance of ATLAS, the appropriateness of the study design and the need now to concentrate on the recruitment phase of the trial in accordance with the revised statement of work provided in the second report which was endorsed by the US Army. See below.

Statement of Work

October 1994	Finalisation of trial protocol
August 1995	Clinical Coordinator appointed
August 1995-	Identification of national coordinators
October 1996	Establish national network of centres
	Arrange practicalities of organising the trial in different countries
	Develop trial materials for local use
	Launch meetings in different countries
Mid-1996-1999	Recruitment period
1 January 1997-2005	Ascertain current status of all women randomised annually.
Spring (annually)	Interim report to Data Monitoring Committee
Autumn (annually)	ATLAS Steering Committee meeting

Note: Following the randomisation of about 20,000 women, it is clear that they will need to be **followed for many years** (i.e. at least until 2005 and preferably until 2010). Additional funding has been applied for such follow-up from the US Army Breast Cancer Research Program.

2. ATLAS: A trial of longer versus shorter *hormonal* treatment

The collaboration, which is larger than originally anticipated, is continuing to grow as clinicians worldwide recognise the relevance of the study question. Furthermore, clinicians now realise that ATLAS not only addresses the question of the duration of tamoxifen, and whether "longer" tamoxifen is more beneficial than "shorter", but also addresses the broader question of the appropriate duration of hormonal therapy as a category of treatment. The relevance of this becomes more clear when considering the newer hormonal agents which are emerging and which may, eventually, because of their supposed fewer adverse side-effects, replace tamoxifen. However, the relevance of ATLAS is only increased by their development since if longer tamoxifen is shown to be of greater benefit than shorter treatment, then this is likely to be relevant to these newer agents.

3. Shift in clinical practice regarding tamoxifen duration: Uncertainty still remains

Randomisation is increasing steadily, with over 1600 patients randomised (figure 2). These patients have been entered into the trial at varying points in terms of their prior duration of adjuvant tamoxifen according to the point at which they and their doctors became uncertain about whether to stop or

continue their tamoxifen (which is the main eligibility criterion for ATLAS). However, as discussed in the introduction to the present report, recent evidence favouring 5 years of tamoxifen compared with shorter regimens may produce a lag period as clinicians hitherto prescribing shorter regimens shift to using 5 years. A few years ago, although there was still uncertainty about the appropriate length of tamoxifen, the majority of doctors would probably have been expected to prescribe about 2 years of tamoxifen routinely. Now, with the reliable evidence (primarily from the EBCTCG and to a lesser extent from the early results from various tamoxifen duration trials) suggesting that, at least for recurrence, longer regimens of about 5 years are more beneficial than shorter treatment periods, the situation is changing. There is a general shift in clinical practice towards the use of longer tamoxifen regimens.

As a result, accrual to ATLAS may take longer than originally anticipated since some clinicians may not become uncertain about the continuation or stoppage of tamoxifen until later, after their patients have received about 5 years of tamoxifen. However, the use of the uncertainty principle as the main eligibility criterion in ATLAS **embraces** this shift in clinical opinion, allows ATLAS to remain pertinent to the residual uncertainty about tamoxifen, and allows clinicians to address their "updated" uncertainties by offering randomisation for those patients for whom there is uncertainty about stopping or continuing **whenever that uncertainty may arise**.

4. Results of an international survey of tamoxifen prescribing practice

Dr Paul McGale, the senior computer programmer for ATLAS, and Dr Davies have conducted a large survey of worldwide tamoxifen prescribing practice as a means of establishing the level of uncertainty about the optimal use of tamoxifen.

More than 3000 clinicians worldwide were sent a postal questionnaire which they were asked to return to Oxford. The questionnaire asked very simple information about the length of treatment with tamoxifen that the clinician prescribed on a routine basis for different categories of patients with early breast cancer. The survey showed major variation in the way clinicians use tamoxifen. Age and nodal status were found to be key factors influencing treatment with tamoxifen or not. The 1995 EBCTCG overview demonstrated that amongst ER positive women, about 5 years of tamoxifen produced similar benefits regardless of age or nodal status. However, in the survey, whilst 92% of clinicians used tamoxifen in post-menopausal women, only 46% chose to do so in younger women. Regardless of age, node negative women were less likely to receive tamoxifen. The ER status played an important role in whether clinicians used tamoxifen: 60% of clinicians would not use tamoxifen in younger women (i.e. pre-menopausal) with ER-negative tumours, whereas only 20% would not do so in a post-menopausal woman with ER-negative disease. Whilst there was substantial variation in the length of tamoxifen prescribed amongst clinicians, about 60% of clinicians would regularly prescribe tamoxifen for about 5 years.

4.1 Interpretation of survey findings

ER status	Age & nodes: Missed benefit	Duration
Previous trials have shown substantially less benefit if the ER-status of the primary tumour has been carefully tested and is completely negative. But, tamoxifen produces substantial benefit for women with even weakly positive ER measurements (and for those whose ER status has not been measured). Hence, some clinicians would not use tamoxifen if a definitely negative ER measurement was available.	Among women with a positive ER measurement, the previous trials find that a tamoxifen regimen of about 5 years produces substantial benefits, regardless of age or nodal status. However, while 92% of the surveyed clinicians would use tamoxifen routinely for post-menopausal women, only half would do so for pre-menopausal women. If half do so and half do not, they cannot all be right in their policies - and, the trials show that tamoxifen can help young women. Likewise, although tamoxifen is widely used for women with node positive disease, it is only routinely used by some but not all clinicians for node-negative disease, despite the trial results.	Where tamoxifen is used, the usual duration depended little on ER status, age or nodal status of the patient. However, it did depend on the doctor: over 60% would usually give tamoxifen for about 5 years, but some would usually give it for a shorter time, and some for a longer time, underlining the need for reliable information on the optimal duration.

4.2 Implications of the survey findings for ATLAS

First and foremost, the survey has confirmed the major variation in clinical practice, and hence the level of uncertainty which must exist amongst clinicians, concerning the use of tamoxifen as an adjuvant. The survey confirms that clinicians are uncertain about ***who*** benefits from tamoxifen as well as about the ***optimal duration*** of treatment. The need for and appropriateness of the design of ATLAS are confirmed by the survey: clearly, more information is required regarding the effects of long-term tamoxifen to guide clinicians and to reduce the level of uncertainty which presently exists. The use of the ***"Uncertainty Principle"*** as the key eligibility criterion both with respect to prior tamoxifen duration and age/nodal/ER status of woman responds to clinicians differing levels of certainty about whom to treat and for how long, and allows these varying levels to be embraced and addressed. As a result, within ATLAS a **heterogeneous** patient population will be recruited and therefore, the trial has major potential to inform treatment of most women, according to their prognosis. If additional funding can be obtained, it is intended to repeat this survey to establish the impact of the 1995 EBCTCG findings since, when these are published and disseminated, there is expected to be treatment of a broader group of patients, in recognition of the wide group of patients that can potentially gain some benefit from tamoxifen.

5. Current status of the ATLAS collaboration

Overall, there has been an extremely enthusiastic response to the ATLAS trial worldwide and the prospect of international collaboration on a massive scale is now a reality. The importance of the question being addressed in ATLAS is widely recognised by collaborators and the pragmatic design of the trial — with emphasis on streamlined procedures and minimal workload for collaborators — makes large-scale participation practicable for busy clinicians, and has helped considerably to overcome the difficulties in organising this international collaboration.

In the last annual summary to the US Army, we reported that 99 centres had ethics approval and 34 of these were entering patients into the trial. 382 patients had been randomised. One year later, major progress has been made so that the number of centres with ethics approval has more than doubled so that now, 232 centres have ethics approval. No local ethics committee has declined to approve ATLAS

and it is anticipated that several hundred hospitals should eventually participate. 146 of these 232 centres are actively randomising patients into ATLAS with the remainder about to start. Some centres have required a free supply of tamoxifen before being able to accrue patients, whilst others are in the process of implementing the trial locally. In particular, the systematic identification of potentially eligible patients who might be invited to join ATLAS can be time-consuming at the outset of the trial, although once this process is started, it becomes easier and is a more organised approach to accessing the potential pool of patients. 1600 patients have been randomised and, as additional centres join the collaboration, and as committed centres steadily accrue patients, randomisation is expected to continue to increase rapidly.

Those countries which are expected to make a major contribution to ATLAS in terms of patient accrual, notably, Spain, Argentina and Italy, have had hitherto some difficulties relating to regulatory authority approval of the trial, importation of free tamoxifen etc. These problems which could not have been anticipated at the outset of the study have now been largely overcome and so again, accrual rates are expected to rise. Since the last annual report, new countries have joined the ATLAS collaboration (Colombia, Croatia, Egypt, South Africa, Greece, Taiwan) and additional countries are still expected to join. Discussions are ongoing with leading clinicians in North America regarding the possible implementation of the trial there. Regardless of the involvement of additional countries, ATLAS is now on target to achieve its accrual of about 20 000 patients. Expansion of the collaboration remains appropriate, however, since the larger the collaboration, the more rapid the recruitment target will be reached.

Dr Davies has been approached by the UK-based parallel tamoxifen duration study - aTTom which is coordinated by a separate trials unit based at the University of Birmingham and is recruiting solely within the UK. ATLAS and aTTom, whilst similar in concept and primary objective, are separate trials, with independent management and administration. However, the two trial teams are necessarily in frequent and close contact to ensure complementarity. aTTom has been proceeding slowly relative to ATLAS and Dr Davies was therefore approached to help to coordinate the trial in a more systematic way, so as to recruit UK-based patients. It is anticipated that the involvement of the Oxford group will enable the randomised evidence to be obtained more rapidly, so that this question of the optimal duration of treatment can be answered more quickly. The two trials will remain separate, but with Dr Davies playing a leading role in their overall coordination.

More than a doubling of centres with ethics approval and quadrupling of patient accrual in the last 12 months

Figure 3: Cumulative accrual to ATLAS (global)

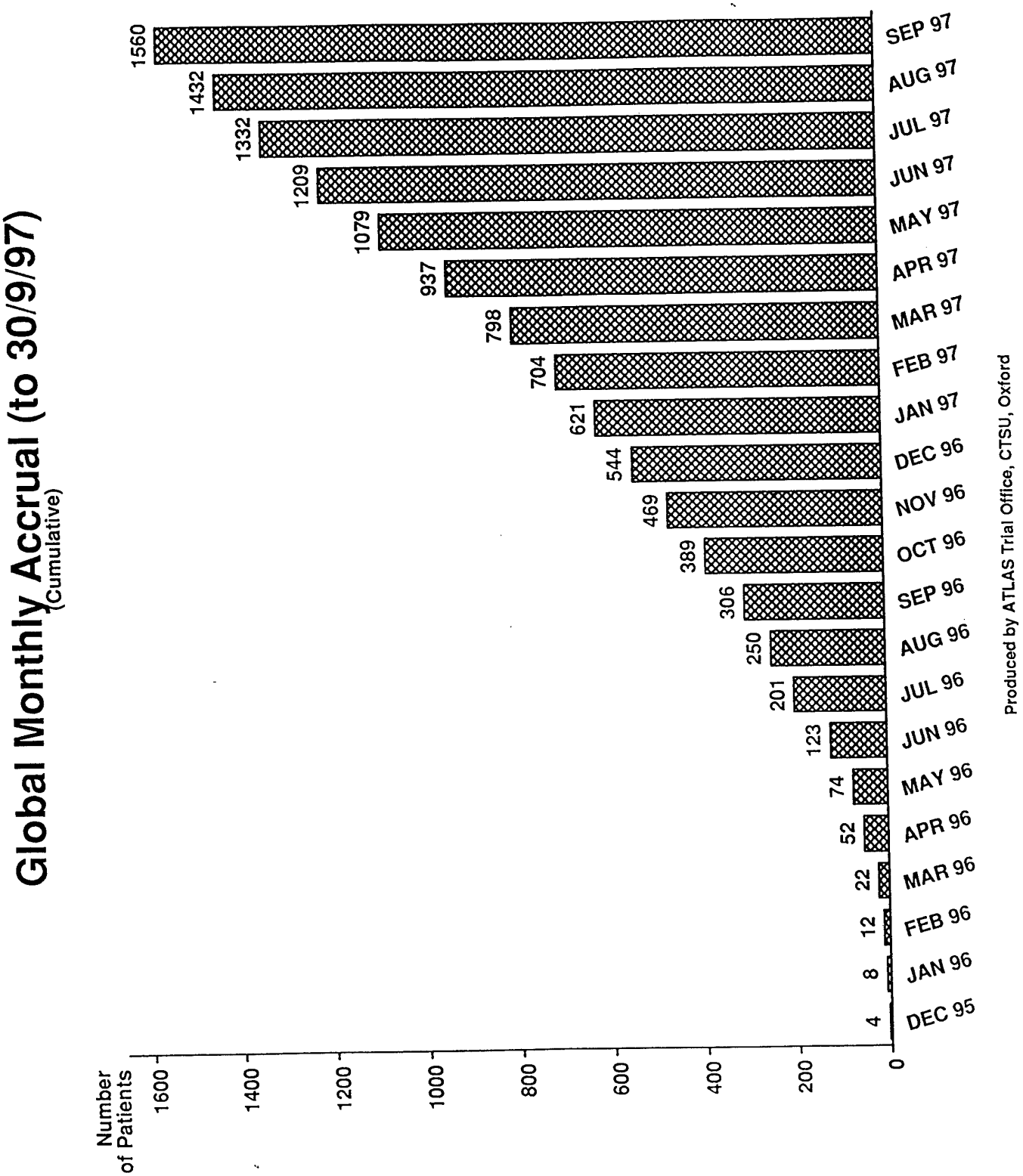


Table 2: Status of the ATLAS collaboration

ATLAS PROGRESS 13 October 1997															
	National Coordinator Identified (Y/N)	No of potential centres	Centres with Ethics	No of Centres Randomising	No of Patients Randomised	Regulatory authority/ Ministry of Health Approval required (Y/N/U)	1st Collaborators' Meeting (Y/N/date)	Local Coordinator identified in all centres	Free Tamoxifen required	National Tamoxifen distributor identified	Tamoxifen distribution organised	Trial materials translated	Trial materials printed (Target Date)	Trial materials distributed for ethics approval	No of Breast Cancers diagnosed each yr (Approx)
TOTALS			**232**	**146**	**1605**										320500
						HIGH									
AUSTRALIA/ NEW ZEALAND	Professor J Forbes/Dr V Harvey	50	15	11	58	N	10-13/4/96	Y	Y	ICI	Y	Y	Y	Y- 30/3/96	8000
ARGENTINA	Dr R Chacon/Dr M Abraham	80	63	22	98	Y obtained	11-12/4/96	Y	Y	Maria-Ines Genisans	Y	Y	Y	Y -1/4/96	9000
CHILE	Dr R Arriagada/Dr O Peralta	60	34	21	206	N	09/04/96	Y	Y	Sra Agosin CONAC	Y	Y	Y	Y - 20/6/96	2400
CZECH	Dr L Petruzelka	27	15	11	177	N	08/03/96	Y	N	n/a	n/a	Y	Y	Y - 10/5/96	3700
HONG KONG	Dr W Kwan	5	5	4	200	N	1-5/7/96	Y	N	n/a	n/a	Y	Y	Y- 2/96	-
INDIA	Dr I Mittra	16	10	9	326	N	05/02/96	Y	Y	Dr Rajan	Y	Y	Y	Y -17/8/96	63000
ISRAEL	Dr N Ben-Baruch	15	4	3	19	N	26/01/96	Y	N	n/a	n/a	Y	Y	Y-10/5/96	1600
ITALY	Dr A Nicolucci	50	18	13	59	Y obtained	27/03/96	Y	Y (not all centres)	Dr Nicolucci	Y	Y	Y	Y - 1/4/96	25000
JAPAN	Dr Y Ohashi/Dr Y Nomura	42	14	13	43	N	28-29/6/96		N	Y	Y	Y	Y	Y	21000
POLAND	Dr T Pienkowski	33	14	7	46	Y obtained	07/09/96	Y	N	n/a	n/a	Y	Y	Y - 17/7/96	8000
SPAIN	Dr Xavier Bonfil	40	1	1	5	Y obtained	N	N	Y	Dr Bonfil	Y	Y	Y	Y - 9/97	12600
						MEDIUM									
BELARUS	Dr T Kostetskaya	1	1	1	62	N	N	Y	Y	Dr Kostetskaya	Y	Y	Y	Y - 23/5/96	-
BRAZIL	Dr H Salvador Silva	21	5	5	73	N	12/11/96	Y	Y	Dr Salvador/Dr Reis	Y	Y	Y	Y - 31/7/96	39000
COLOMBIA	Dr Carlos J Castro	1	1	1	5	N	N	Y	Y	Dr Carlos Castro	Y	Y	Y	Y	
CROATIA	Dr Damir Vrbanec	1	1	1	5	U	N	Y	N	n/a	n/a	Y	Y	Y	-
EGYPT	Dr Khaled	1	1	1	31	U	N	Y	Y	Dr Khaled	Y	Y	Y	Y	-

ATLAS Progress

LATVIA	Dr Berzins	1	1	1	23	U	N	Y	Y	Dr Berzins	Y	Y	Y	Y	-
LITHUANIA	Prof K Valuckas	5	5	3	52	Y obtained	28/02/96	Y	Y	Prof Valuckas/Dr Aizenas	Y	Y	Y	Y - 3/96	-
MEXICO	Dr J Zinser	15	2	2	10	N	03/04/96	Y	Y	Dr Zinser	Y	Y	Y	Y	9000
NETHERLANDS	Dr E Rutgers	30	1	1	6	N	N	N	U	N	N	Y	Y	Y	8300
RUSSIA	Prof V Semiglazov	5	3	3	48	Y obtained	N	Y	Y	Dr Kostetskaya	Y	Y	Y	Y -11/95	-
S AFRICA	Prof W Bezwoda	?	4	2	7	N	N	Y	Y	Dr Anne Gudgeon	Y	Y	Y	-	5000
TAIWAN	Dr Z Hou	1	1	1	18	U	N	Y	N	n/a	n/a	Y	Y	-	-
TURKEY	Prof C Topuzlu	7	6	6	23	N	10/05/96	Y	Y	Prof Topuzlu/Dr Dincer	Y	Y	Y	Y	11000
							LOW								
AUSTRIA	N	?	0	0	0	U	N	U	U	U	N	N	N	N	4100
BELGIUM	Dr M Piccart	?	2	1	3	U	N	N	U	N	N	Y	Y	Y	5700
DENMARK	N	?	0	0	0	U	N	N	U	N	N	N	N	N	2900
ESTONIA	Prov V Ratsep	2	1	1	1	N	01/03/96	Y	Y	Prof V Ratsep	Y	Y	Y	Y - 3/96	-
FINLAND	Dr K Holli	6	0	0	0	U	N	N	U	N	N	N	N	N	2200
FRANCE	N	?	0	0	0	U	N	N	U	N	N	Y	Y	N	25000
GREECE	Dr E Razis	?	2	1	1	U	N	N	U	N	N	Y	Y	N	
HUNGARY	Dr E Juhos	5	0	0	0	N	24/05/96	N	N	n/a	n/a	N	N	N	3000
LUXEMBOURG	N	?	0	0	0	U	N	N	U	N	N	N	N	N	200
MOLDOVA	Dr A Cucierol	1	1	0	0	U	N	Y	U	U	U	Y	Y	Y	-
PORTUGAL	Dr C Silva	?	0	0	0	U	N	N	U	N	N	N	N	N	3500
SLOVAKIA	N	?	0	0	0	U	N	N	U	N	N	N	N	N	1300
SWEDEN	Lars Rutqvist	?	0	0	0	Y obtained	N	N	U	N	N	N	N	N	5000
TUNISIA	Dr Khaled	1	1	0	0	U	N	Y	Y	Y	N	Y	Y	Y	N/K

6. Organisation of the supply and distribution of free tamoxifen

As described in previous reports to the US Army, it has been necessary to provide free supplies of tamoxifen in some countries for those patients randomised in ATLAS to continue treatment for the next 5 years. Zeneca Pharmaceuticals plc have provided sufficient Nolvadex, the most commonly used form of tamoxifen. The coordination of the packaging, labelling and distribution of appropriate amounts of tamoxifen to collaborating centres has been a major initiative managed by the coordinating centre in Oxford. Special computer programmes have been required to calculate the amount of tamoxifen needed on a per centre basis, and to ensure that centres always have sufficient supplies. Records of the batch of tablets distributed to particular centres are required, in case, for any reason, a particular batch needs to be recalled. Different countries have different regulations for packaging and importation of free drug supplies, and it has been necessary to fulfil the varying requirements. In each country, a tamoxifen coordinator has been appointed - usually the national coordinator for ATLAS within that country. Sufficient tamoxifen is sent for the entire country to the tamoxifen coordinator on a 6-monthly basis, and the coordinator is then responsible for distribution to individual hospitals within that country according to instructions from Oxford. Shipments are sent in January and July of each year, and it is anticipated that the free provision of drug will allow rapid randomisation in particular countries. Overcoming some of the difficulties surrounding tamoxifen provision has been extraordinarily time-consuming and has often required the involvement of the UK Foreign Office and the Ambassadors in particular countries. However, these difficulties have now been overcome and 2 cycles of tamoxifen provision have now been despatched successfully.

N.B. The design and management of ATLAS will remain entirely independent of the pharmaceutical company involvement to ensure that no suggestion of lack of objectivity of the findings can be made.

7. First annual follow-up

In ATLAS, long-term follow-up of all randomised patients is fundamental. In view of the varying health care systems, and management patterns and the availability (or not, as the case may be) of national cancer registration/mortality statistics records in collaborating countries, it has been essential to ensure that appropriate mechanisms are in place for long-term follow-up of women randomised in the different countries. The first annual follow-up took place in January 1997 when simple data were requested on all patients randomised. Follow-up information was obtained for more than 96% of patients. The remaining patients are not lost to follow-up but many of them only attend follow-up clinics annually and had not, at the time of the annual follow-up in ATLAS attended their regular visit. Doctors are requested to provide the information as soon as possible - because of the simplicity of the data request and the mechanisms in place to ensure follow-up in all patients in all countries, it is anticipated that there will be minimal loss to follow-up. It would be premature to report the data so far, but one very reassuring feature at follow-up was the good compliance with the allocated treatment by women randomised in ATLAS. This will be closely monitored through annual follow-up.

8. First ATLAS Steering Committee meeting

The first phase of the implementation of ATLAS involved establishing contacts with reputable and scientifically rigorous clinicians worldwide who could work with the international coordinating centre in Oxford to establish a network of clinicians nationally, which would then participate in ATLAS. The major effort has been undertaken by Richard Peto and Christina Davies who have travelled worldwide to establish such contacts (the ATLAS National Coordinators) and to raise the profile of the trial at breast cancer meetings. Many of the countries in which ATLAS is taking place did not have an existing trial network that could be readily exploited, although where these were available (for example, in Italy and Australia) ATLAS has been integrated into them. Furthermore, although there tended to be an established trial coordinating office with which to work in those countries where there was already a

network, in other countries it has been necessary — after establishing a network — to develop mechanisms for coordination of this newly-developed network.

Once this initial step had been taken, the next phase in the trial was, and is, to maintain, strengthen and extend the collaboration within each country, and to ensure active participation in ATLAS. In view of the scale of the collaboration, this has been achieved mainly through close collaboration between Oxford and each of the national coordinators, who are then responsible for coordinating the clinical network in each of their respective countries. The international coordinating centre still undertakes the bulk of the administrative workload and has overall responsibility for coordination and management of the trial. However, Oxford is dependent on the support of the various national coordinators, each of whom is a member of the ATLAS Steering Committee. Dr Davies has been successful in obtaining additional funding through the EC Biomed Programme to provide dedicated support for national coordinating centres in 5 European countries (Spain, Italy, Czech Republic, Poland and Israel), and this should enhance the success of the collaborative networks in each of these countries.

The ATLAS Steering Committee had its first meeting in Oxford on 14/15 September 1997, when representatives from all around the world discussed progress. The formal terms of reference of the Committee are as follows:

1. To review and advise on progress of ATLAS towards its interim and overall objectives
2. To consider the recommendations of the Data Monitoring Committee

The specific aims of the Steering Committee meeting were as follows:

1. To review the randomised evidence on tamoxifen
2. To review current tamoxifen prescribing practice
3. To review progress of ATLAS: Globally, nationally and locally
4. To consider ways to strengthen the collaboration & maximize accrual

The meeting was very successful and forms the basis of the 3rd ATLAS Newsletter (**Appendix 2**) which aims to provide direct advice to collaborators on particular aspects of the trial, notably, the identification of potentially eligible patients and also the process of informed consent. Following the Steering Committee meeting in Oxford, national coordinators worldwide are now ready to work more closely with clinicians in their country and it is anticipated that there will now be a further major increase in accrual worldwide.

The Steering Committee plans to meet on an annual basis and it is anticipated that the next meeting will be held in Florence to coincide with the 1st European Breast Cancer Conference at which many of the ATLAS National Coordinators will be present.

9. Second meeting of the ATLAS independent Data Monitoring Committee

The Data Monitoring Committee met in March 1997 and reviewed the progress of the study and the data from other studies of the effects of different durations of adjuvant treatment with tamoxifen for women who have had breast cancer, including those relating to the main side-effects that might be anticipated. The Committee was satisfied with the progress of the trial, noting the steady increase in ethics approval and patient accrual. The Committee unanimously approved the continuation of the trial with the present protocol and information sheet. The Committee will have a teleconference call in April 1998 to review progress.

C. CONCLUSIONS

Overall, there has been an extremely enthusiastic response to the ATLAS trial worldwide and, with several hundred hospitals in more than 20 countries participating, and with more committed to joining, the possibility of international collaboration on a massive scale is now a reality. The success of the collaboration has been achieved primarily by addressing an important clinical question which is relevant to clinicians worldwide and which is relevant to the management of several hundreds of thousands of women globally.

By adopting a scientifically rigorous but pragmatic trial design within ATLAS, widespread collaboration has been facilitated because clinicians can integrate the trial into their routine practice with little or no disruption. The first stage of ATLAS — that is, the development of a wide-scale collaborative group and the establishment of the materials and procedures needed for the smooth conduct of the trial — has now been completed although all of the time, the collaboration is expanding. 232 centres now have ethics approval and this is expected to increase in coming months. The target is to help the majority of potential collaborating centres to obtain ethics approval by the next annual review by the US Army. 146 of these 232 centres are randomising patients - the remainder are well on the way now to starting accrual. 1600 patients have already been entered into the trial a four-fold increase in last year's total. As many of the centres in those countries which are likely to make an important contribution to the trial are about to start randomising, then accrual is likely to increase very rapidly now. As a result, ATLAS should now be successful in obtaining large-scale randomisation and long-term follow-up and thus realise its objectives of making a major contribution to the reliable assessment of the effects of prolonged tamoxifen in women with early breast cancer. An application for additional funding has been submitted to the US Army Breast Cancer Program and it is hopeful that this will be successful to ensure that the main objective of the trial is fulfilled and the scientific returns on the initial investment realized.

This successful collaboration, because of its strong foundations, will exist not only for the duration of ATLAS but will also provide a "ready-made" international network for future cancer treatment trials. Thus ATLAS can help to establish more widely large-scale streamlined randomised trials that can rapidly provide reliable evidence on questions of public health importance, and promote the adoption of research-based clinical practice globally.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. Lancet 1992; 339: 1-15 and 71-85.
2. Chu KC, Tarone RE, Kessler LG, et al. Recent trends in US breast cancer incidence, survival and mortality rates. J Natl. Cancer Inst. 1996; 88:1571-1580.
3. Beral V, Hermon C, Reeves G, Peto R. Sudden fall in breast cancer death rates in England & Wales. Lancet 1995; 345: 1642-43.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1997 (Submitted for publication)
5. Rutqvist LE, Mattsson A. Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. J Natl. Cancer Inst. 1993; 85: 1398-1406.
6. Love RR, Wiebe DA, Newcomb PA, et al. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. Ann Intern Med 1991; 115: 860-64.
7. McDonald CC, Stewart HJ, for the Scottish Breast Cancer Committee. Fatal myocardial infarction in the Scottish Adjuvant Tamoxifen Trial. Br Med J 1991; 303: 435-37.
8. Guetta V, Lush RM, Figg WD, et al. Effects of the antioestrogen Tamoxifen on low density lipoprotein concentrations and oxidation in post-menopausal women. Am J Cardiol 1995; 76: 1072-73.
9. Powles T, Tickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual energy x-ray absorptiometry in healthy premenopausal and post-menopausal women. J Clin Oncol 1996; 14: 78-84.
10. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. New Engl J Med 1992; 326: 852-56.
11. Kristensen B, Ejlersten B, Dalgaard P, et al. Tamoxifen and bone metabolism in post-menopausal low risk breast cancer patients. A randomized study. J Clin Oncol 1994; 12: 992-97.2.
12. Fisher BV, Dignam J, Bryant J et al. The worth of 5 versus more than 5 years of tamoxifen therapy for breast cancer patients with negative nodes and estrogen-receptor positive tumors: an update of NSABP B-14. J Natl. Cancer Inst. 1996 ;88:1529-1543
13. Fornander T, Hellstrom AC, Moberger B. Descriptive clinicopathological study of 17 patients with endometrial cancer during or after adjuvant tamoxifen in early breast cancer. J Natl. Cancer Inst. 1993; 85: 1850-55.
14. Andersson M, Storm H, Mouridsen H. Carcinogenic effects of adjuvant tamoxifen treatment and radiotherapy for early breast cancer. Acta Oncologica 1992; 31: 259-63
15. Fisher B, Constantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel projects (NSABP) B-14. J Natl. Cancer Inst. 1994; 86: 527-37
16. Nayfield SG, Karp SE, Ford LG et al. Potential role of tamoxifen in prevention of breast cancer. J Natl. Cancer Inst. 1991; 83: 1450-1459
17. Williams GM, Iatropoulos MJ, Djordjevic MV, et al. The triphenylethylene drug tamoxifen is a strong liver carcinogen in the rat. Carcinogenesis 1993; 7.:315-317
18. Fornander T, Rutqvist LE, Cedermark B, et al. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. Lancet 1989; 1: 117-20.
19. Pavlidis M, Petris C, Briassoulis E. Clear evidence that long-term, low-dose tamoxifen treatment can induce ocular toxicity. Cancer 1992; 69: 2961-2964.
20. Nayfield SG, Gonn MB. Tamoxifen-associated eye disease. A review. J Clin Oncol 1996; 14: 1018-1026.
21. Jones SE, Cathcat C, Pumray S, et al. Frequency, severity, and management of tamoxifen-induced depression in women with node-negative breast cancer. Proc ASCO 1993; 12: 78 (abstract 112).
22. WHO IARC Press Release. IARC Evaluates the Carcinogenic risk associated with Tamoxifen. Feb 1996

23. Swedish Breast Cancer Co-operative Group. Randomized trial of 2 versus 5 years of adjuvant tamoxifen in postmenopausal early-stage breast cancer. J Natl. Cancer Inst. 1996 ;88: 1543-1550
24. Current Trials Working Party of the Cancer Research Campaign Breast Cancer Trials Group. Preliminary results from the Cancer Research Campaign trial evaluating tamoxifen duration in women aged fifty years or older with breast cancer. J Natl Cancer Inst. 1996; 88: 1834-1839.
25. Tormey DC, Gray R, Falkson HC (for the Eastern Co-operative Oncology Group). Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. J Natl. Cancer Inst. 1996;88:1828-1833.
26. Stewart HJ, Forrest AP, Everington D et al. Randomised comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer. Br J Cancer 1996; 74: 297-299.
27. Delozier T, Spielmann J, Mace-Lesec'h M, Janvier M et al. Short-term versus lifelong adjuvant tamoxifen in early breast cancer: a randomized trial (TAM-O1). Proceedings of the American Society of Clinical Oncology 1997; Abstract (451)
28. Swain S. Editorial: Tamoxifen: the Long and Short of It. J Natl. Cancer Inst. 1996; 88:1510-1513
29. Peto R. Editorial: Five years of tamoxifen - or more?. J Natl. Cancer Inst. 1996; 88: 1791-1793
30. Collins R, Peto R, Gray R, Parish S. Large scale randomised evidence: trials and overviews. In: Oxford Textbook of Medicine (3rd edition, 1996) edited by Weatherall DJ, Ledingham JGG, Warrell DA. Oxford: Oxford University Press.
31. National Cancer Institute Clinical Announcement. Adjuvant therapy of breast cancer: tamoxifen update, November 30 1995
32. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. J Natl. Cancer Inst. 1988; 319: 1681-92

Tamoxifen for early breast cancer: an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group
(Collaborators are listed at the end of the report)

SUMMARY

Background: Among women with early breast cancer, there have been several dozen randomised trials of adjuvant tamoxifen, and a systematic overview of their results is presented.

Methods: In 1995, information was sought on each woman in any unconfounded randomised trial of adjuvant tamoxifen versus no adjuvant tamoxifen that began before 1990. Information was obtained and analysed centrally on each of 36,689 women in 55 such trials, comprising about 87% of the worldwide evidence.

Findings: One-fifth of the women had low, or zero, levels of the oestrogen receptor protein (ER) measured in their primary tumour. Among these women with "ER-poor" tumours, the effect of tamoxifen was uncertain and they are excluded from the subsequent analyses of recurrence and total mortality. Almost 30,000 women remain, 18,000 with definitely "ER-positive" tumours plus 12,000 with untested tumours (of which an estimated 8000 would have been ER-positive). Dividing the trials into those of 1 year, 2 years and about 5 years of adjuvant tamoxifen, the proportional recurrence reductions produced during about 10 years of follow-up were 21% SD 3, 29% SD 2 and 47% SD 3 respectively, with a highly significant trend towards greater effect with more prolonged treatment ($\chi^2_1 = 52.0$, $2P<0.00001$). The corresponding proportional mortality reductions were 12% SD 3, 17% SD 3 and 26% SD 4 respectively, among which the test for trend was again significant ($\chi^2_1 = 8.8$, $2P=0.003$). The absolute improvement in survival grew steadily wider throughout the first 10 years. Although the proportional mortality reductions were similar for women with node-positive and for those with node-negative disease, the absolute mortality reductions were not. In the trials of about 5 years of adjuvant tamoxifen the absolute improvements in 10-year survival were 10.9% SD 2.5 for node-positive ($2P<0.00001$) and 5.6% SD 1.3 for node-negative ($2P<0.00001$), with the apparent benefit largely irrespective of age, menopausal status, daily tamoxifen dose (which was generally 20 mg) and of whether chemotherapy had been given to both groups. Allowance for the effects of non-compliance with the allocated treatment would slightly increase the estimated absolute improvement in 10-year survival (e.g. to about 12% for node-positive and 6% for node-

negative), but the absolute benefit for very-good-prognosis patients with screen-detected node-negative disease might be substantially less than 6%.

In terms of other outcomes, the proportional reductions in contralateral breast cancer were 13% SD 13, 26% SD 9 and 47% SD 9 in the trials of 1, 2 or about 5 years of adjuvant tamoxifen, but endometrial cancer was increased. The absolute decrease in contralateral breast cancer was about twice as large as the absolute increase in the incidence of endometrial cancer. Tamoxifen had no apparent effect on the incidence of colorectal cancer or, after exclusion of deaths from breast or endometrial cancer, on any of the other main categories of cause of death (total 1866 such deaths: overall relative risk 0.99 SD 0.05).

Interpretation: A few years of adjuvant tamoxifen substantially improves the 10-year survival of women with ER-positive tumours, and of women whose tumours are of unknown ER status, with the proportional reductions in breast cancer mortality being largely unaffected by other patient characteristics or treatments.

INTRODUCTION

In women with "early" breast cancer all detectable cancer is, by definition, restricted to the breast (and, in the case of "node-positive" patients, the local lymph nodes) and can be removed surgically. But, undetected micrometastatic deposits of the disease may remain that, perhaps after a delay of several years, develop into a clinically detectable recurrence that eventually causes death. It has been shown previously that the use of adjuvant tamoxifen significantly improves the 10-year survival for such women[1-3], but uncertainty has remained about whom to treat and for how long treatment should usually continue. Many randomised trials have assessed the effects of one or two years of adjuvant tamoxifen, and others have assessed the effects of about five years of treatment. More recently, some have directly compared five years with either shorter or longer durations, but results from these are generally not yet available (or, where available, are not yet sufficiently mature). The present overview is therefore restricted just to the trials of adjuvant tamoxifen versus no adjuvant tamoxifen ("control"). Many of these trials allowed or encouraged the use of tamoxifen for any women in the control group who relapsed. So, although they provide a direct assessment of the effects of adjuvant tamoxifen on recurrence rates, for mortality they involve the comparison of adjuvant tamoxifen versus no tamoxifen until relapse (i.e. they are trials that compare the effects on survival of two different ways of using tamoxifen).

METHODS

At five-yearly intervals since 1984/85, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has undertaken systematic overviews (meta-analyses) of all randomised trials of any aspect of the treatment of early breast cancer[1-5]. This paper is based on data collected and finalised in 1995/96.

Trial identification and data checking procedures have been described previously[1-3]. For the analyses presented here, data were sought for all randomised trials that began before 1990 and compared adjuvant tamoxifen for any duration versus no such treatment for women with early breast cancer. As in previous reports, the trials were divided into three categories on the basis of their average intended duration of adjuvant tamoxifen: about one year, two years, or more than two years[3]. As the median duration in the latter category of trials was five years, these are generally described as trials of "about five years" of adjuvant tamoxifen.

Data on each individual patient

Information was sought for each woman on her age and menopausal status at randomisation, on whether or not there had been evidence of tumour spread to the axillary or other local lymph nodes ("node-positive" or "node-negative" disease) and on the results of any oestrogen receptor (ER) or progesterone receptor (PR) measurements on the primary tumour. In the present report, node-positive also includes the few women with unrecorded nodal status or with only clinical evidence of nodal involvement, as their prognosis was like that of women with definite nodal involvement. Node-negative includes those who had an axillary dissection and those who had only axillary sampling, as both had a similar prognosis, and also includes the few women with only clinical evidence of lack of nodal involvement.

Three categories of ER status at entry are defined[3]. ER-positive (which, where quantitative measurements were available, was defined as at least 10 femtomoles of ER per mg cytosol protein, but was otherwise accepted as reported), ER-poor (all others whose ER status was supplied) and unrecorded ER status. For PR status, the same three definitions were used. In general, women with unrecorded ER status also have unrecorded PR status, but the converse is not necessarily true.

Information was also sought on the date of randomisation, the allocated treatment, and the dates of first subsequent occurrence of any contralateral breast cancer, other second primary cancer, local recurrence, distant recurrence and death, ideally with follow-up to 1995. (To avoid the "tie-breaking bias"[6], event times were calculated in completed years.) The cause of death was requested only for those who died without any record of distant recurrence.

The data were checked for internal consistency and were amended or updated as necessary through correspondence with the responsible trialists. Before being finalised, the overview analyses were presented and discussed at a meeting in September 1995 of those who had conducted the trials. In addition, this manuscript was circulated to them, and to other members of the EBCTCG, and revised in the light of their comments.

Statistical methods

The statistical methods are described in detail elsewhere[1-3], and use the intention-to-treat principle. First each trial is analysed separately, and then the resulting "log-rank" statistics, one per trial, are combined to give an overall estimate of the effect of tamoxifen. When information from different trials is combined in this way, women in one trial are compared directly only with other women in that same trial, and never with women in another trial. The combination of evidence from different trials yields, as an overall estimate of the effect of treatment in those trials, a weighted average of the apparent effect of treatment in each separate trial: it does not, however, implicitly assume that the true effect of treatment is the same in each trial.

The principal events analysed are "recurrence" and death. Recurrence is defined as the first reappearance of breast cancer at any site (local, contralateral or distant). The few women who were recorded as having died of breast cancer (or from an unknown cause) without any record of recurrence were analysed as having had a recurrence just before they died. Women who died from other causes without a recorded recurrence are "censored" at the date of death in the analyses of recurrence as first event. Deaths from an unknown cause are included with deaths from breast cancer, unless it was specifically stated that breast cancer was not the cause. In analyses of breast cancer deaths, the statistical conventions used to avoid bias are as in the EBCTCG overviews of radiotherapy[4] and ovarian ablation[5], and involve log-rank subtraction. Tests for trend with respect to tamoxifen duration relate the median number of years of tamoxifen (1, 2 or 5) in the three categories of trial to the corresponding logrank "O-E" values. (If w is the weighted average of these three tamoxifen durations, with weights proportional to the variances of the three logrank values, then the test for trend determines whether $(w-1)(O_1-E_1)+(w-2)(O_2-E_2)+(w-5)(O_5-E_5)$ differs significantly from zero.)

Two-sided significance tests are used not only for overview results but also for any chi-squared tests that are on only 1 degree of freedom (so, $\chi^2_1 = 3.84$ would be described not as P=0.05 but as 2P=0.05). SD denotes standard deviation, which is used interchangeably with standard error (so, 25 SD 2 would denote a value of 25 with standard error 2). 2P>0.1 is sometimes denoted "Not Significant" (NS), even though some results with 2P<0.1 could also arise by chance.

Proportional benefits (odds reductions) and absolute benefits

Throughout this report, the effects of treatment are described either as **proportional** benefits (e.g. as a 25% reduction in the death rate*) or as **absolute** benefits. For a given proportional reduction in the death rate, the absolute improvement in 10-year survival is bigger for women with node-positive than for those with node-negative disease. A rough rule for these particular trials is that the ratio of the absolute to the proportional mortality reduction during the first 10 years will be about two-fifths for

* Terminology: a proportional reduction of one-quarter in the annual odds of death might equivalently be described as an odds ratio of 0.75, a hazard function of 0.75, an odds reduction of 25% or a 25% reduction in the death rate.

node-positive patients and one-fifth for node-negative patients. Thus, for example, a 25% reduction in the death rate might produce an absolute benefit of about 10% for patients with node-positive disease (e.g. improving the 10-year survival from 50% to about 60%), but only about a 5% absolute benefit for those with node-negative disease (e.g. improving the 10-year survival from 75% to about 80%).

MATERIALS

63 randomised controlled trials of adjuvant tamoxifen versus no adjuvant tamoxifen that began before 1990 were identified, involving a total of more than 42,000 women (Table 1). This is substantially more than in the previous cycle of this collaboration[3], as some trials were then still recruiting, some were unavailable, and those that began in 1985-9 were not eligible. Of the 63 trials, some scheduled no adjuvant chemotherapy for either group, but others randomised tamoxifen plus concurrent chemotherapy versus the same chemotherapy alone. 55 of these trials are available for the present analyses, and 8 are not. Three of these 8 are large trials of prolonged tamoxifen (CRC under 50s, SWOG 8897 and ECOG 5188) that began shortly before 1990 and have as yet made no results available. But, although these three trials involve a total of more than 4000 women, they would by 1995 have collected information on only a limited number of deaths, most of which would have been during the first few years after randomisation (when there is already much evidence from other trials about the effects of tamoxifen). Information from the trials of 1 or 2 years of tamoxifen is 95% complete. So, overall, the amount of missing data is probably too small to affect the analyses that follow in any important way.

Individual patient data were provided for 36,689 women in the 55 trials available, with 14,140 first recurrences and 13,268 deaths during an average of about 10 years of follow-up. 88% (32,422) of the women were in trials that reported contralateral breast cancer separately, and in these trials 6% (839) of the first recurrences involved a new primary cancer in the opposite breast. 90% (32,947) of the women were in trials that distinguished between deaths from breast cancer and from other causes, and in these trials 15% (1872) of the deaths were specified as being due to causes other than breast cancer and were not preceded by any record of breast cancer recurrence. Only these are defined in the present analyses as being "non-breast-cancer deaths".

In the previous cycle of this overview, the adjuvant tamoxifen versus no adjuvant tamoxifen analyses involved 11,095 first recurrences and 8219 deaths among 29,892 women[3]. The main increases since then are in the amount of evidence from trials of about 5 years of tamoxifen, which has increased from 1038 deaths among 6398 women[3] to 2300 among 8349, and in the amount of evidence on events occurring more than five years after randomisation. These extra data increase the statistical stability of the effects in trials of about five years of tamoxifen, of the effects in later time periods and of the effects in particular subgroups of women.

RESULTS

General structure of Figures

In each Figure, the left-hand side describes recurrence rates and the right-hand side describes mortality rates. Also, in each Figure the upper, middle and lower parts describe respectively the trials of 1 year, 2 years and about 5 years of adjuvant tamoxifen. The first two Figures (and the Tables) include all women with relevant data, while later Figures exclude women with ER-poor tumours.

Combination of separate trial results

Figure 1 shows the results from each of the 55 trials, irrespective of duration of follow-up, with subtotals for the trials of 1 year, 2 years and about 5 years of adjuvant tamoxifen. Each trial result is denoted by a black square indicating the ratio (for tamoxifen versus control) of the recurrence rates or of the death rates, together with the 99% confidence interval. The solid vertical line indicates a ratio of 1.0 (i.e., no difference between treatment and control), and results to the left of it favour tamoxifen. For each category of trials from which the results are combined, the overall ratio and its 95% confidence interval are shown by a broken vertical line together with a small diamond-shaped symbol, next to which is the corresponding proportional reduction (% and SD).

Overall findings

The totals at the bottom of Figure 1 show that, both for recurrence as a first event and for mortality, allocation to tamoxifen produces statistically definite (2P<0.00001) benefits after about 10 years of follow-up. But, the subtotals suggest that the proportional risk reductions depend on the scheduled duration of tamoxifen.

For recurrence, the proportional reductions in the trials of 1 year, 2 years and about 5 years of tamoxifen, together with their standard deviations, were 18% SD 3, 25% SD 2 and 42% SD 3 respectively, which are all highly significantly different from zero (each 2P<0.00001: left side of Figure 1). The heterogeneity between these three recurrence reductions is statistically definite ($\chi^2_2 = 48.4$, P<0.00001), as is the test for trend with respect to tamoxifen duration ($\chi^2_1 = 48.4$; 2P<0.00001). By contrast, when trials of similar tamoxifen durations are compared with each other, no significant heterogeneity remains between the recurrence reductions ($\chi^2_{52} = 60.0$, NS). These and other results relate to the overall findings after about 10 years of follow-up, without separation of the events during and after the first 5 years.

For mortality, the proportional reductions in the death rates in the trials of 1 year, 2 years and about 5 years of tamoxifen were 10% SD 3, 15% SD 2 and 22% SD 4, all

three of which are highly significantly different from zero (two with 2P<0.00001: right side of Figure 1). Although the heterogeneity between them is only moderately significant (χ^2_2 = 6.3, P=0.04), the test for trend between them provides somewhat clearer evidence of there being a greater mortality reduction in the trials of more prolonged adjuvant treatment (χ^2_1 = 6.2, 2P=0.013). Again, however, when trials of similar tamoxifen durations are compared with each other, no significant heterogeneity remains between the mortality reductions (χ^2_{52} = 49.7, NS).

Some of the apparent differences between the effects of treatment in the subtotals for trials of different durations of tamoxifen may be due to systematic differences in the types of patient or in the trial design. For example, in the trials of shorter tamoxifen durations a smaller proportion of the women had ER-positive tumours and the duration of follow-up was longer. These factors will now be investigated.

Hormone receptors

Figure 2 subdivides the overall results by what is known about the ER status of the primary cancer. The black squares relate to the effects of treatment among women whose primary tumour was of known ER status (i.e., ER-positive or ER-poor), and the white squares relate to those among women whose tumours were of unknown ER status. For each tamoxifen duration the proportional reduction in recurrence (left side of Figure 2) appears to be greater for patients with ER-positive tumours than for patients with ER-poor tumours, and this heterogeneity in therapeutic effect is most definite in the trials of about 5 years of tamoxifen (χ^2_1 for heterogeneity = 26.5, 2P<0.00001). Likewise, for each tamoxifen duration the proportional reduction in mortality (right side of Figure 2) appears to be greater for patients with ER-positive tumours than for patients with ER-poor tumours, and again this heterogeneity in therapeutic effect is most definite in the trials of about 5 years of tamoxifen (χ^2_1 for heterogeneity = 8.0, 2P=0.005).

Results among women with ER-positive tumours: Among the 18,000 women with ER-positive tumours, the proportional reductions in the recurrence rates in the trials of 1 year, 2 years and about 5 years of tamoxifen were 21% SD 5, 28% SD 3 and 50% SD 4 respectively (left side of Figure 2). These recurrence reductions are all highly significant (each 2P<0.00001), as is the trend between them (χ^2_1 = 45.5, 2P<0.00001). The respective proportional mortality reductions among women with ER-positive tumours are 14% SD 5, 18% SD 4 and 28% SD 5 in the trials of 1, 2 and about 5 years of tamoxifen (right side of Figure 2). Each of these three mortality reductions is also statistically significant, as is the trend between them (χ^2_1 = 5.6, 2P=0.02).

In these women with ER-positive tumours, the progesterone receptor (PR) measurements did not seem to help predict the response to tamoxifen. Thus, among the 2000 women with ER-positive, PR-poor tumours, the recurrence reduction produced by tamoxifen was 32% SD 6 (2P<0.00001) and the mortality reduction was 18% SD 7 (2P=0.01), which are not materially different from the corresponding reductions of 37% SD 3 (2P<0.00001) and 16% SD 4 (2P<0.00001) among the 7000 women with ER-positive, PR-positive tumours. If attention is restricted just to the trials of about 5 years of tamoxifen then there is again good evidence of benefit in the women with ER-positive, PR-poor tumours: recurrence reduction 46% SD 9 (2P<0.00001), mortality reduction 28% SD 11 (2P=0.01).

Results among women with ER-poor tumours: Among the 8000 women with ER-poor tumours, the benefits of treatment were less clear. Overall, irrespective of the duration of tamoxifen that was tested, the proportional recurrence reduction was 10% SD 4 (2P=0.007), with a 95% confidence interval that runs from a 2% to a 17% recurrence reduction. But, although this result is statistically significant, the apparent benefit is small, and the lower confidence limit is close to zero. (Moreover, if contralateral recurrences — the receptor status of which may be largely unrelated to that of the original primary — are ignored then the overall proportional recurrence reduction becomes 9% SD 4 [2P=0.02], with 95% CI running from 1% to 16%.) The proportional recurrence reductions in the trials of 1 year, 2 years and about 5 years of tamoxifen were 6% SD 8 (NS), 13% SD 5 (2P=0.01) and 6% SD 11 (NS) respectively, with no evidence of any positive trend towards greater benefit with longer tamoxifen treatment.

The mortality reductions among the women with ER-poor tumours appeared even less promising than the foregoing recurrence reductions. Overall, irrespective of tamoxifen duration, the mortality reduction was only 6% SD 4 (NS). In the trials of 1, 2 and about 5 years of tamoxifen, the mortality reductions were 6% SD 8 (NS), 7% SD 5 (NS) and -3% SD 11 (NS); again, there is no suggestion of a positive trend towards greater benefit with more prolonged treatment.

It is difficult to know whether these recurrence and mortality results indicate a small but real benefit in some women whose tumours would, even by the best current ER assay methods, still be wholly ER-negative, or whether they reflect benefit only among those who, although their tumour was classified as "ER-poor" in these trials, would have had some ER protein detected in it by more sensitive assay methods (see Discussion).

In women with ER-poor tumours, there was not enough evidence to determine whether PR measurements could help predict the response to tamoxifen. Among the 2000 women with ER-poor, PR-poor tumours, tamoxifen had no apparent effect on recurrence or mortality rates (the odds reduction being 1% SD 7 in both cases), while among the 602 women with ER-poor, PR-positive tumours, the recurrence reduction was 23% SD 12 (2P=0.05) and the mortality reduction was 9% SD 14 (NS). These numbers of women are not large, so these analyses are unstable. Hence, the existence of at least some real benefit cannot be excluded for those whose tumours were ER-poor, PR-poor, and cannot be assumed for those whose tumours were ER-poor, PR-positive.

Results among women with unrecorded ER status: About half of the tumours in women aged under 50 and about three-quarters of those in women aged over 50 would have been classified as ER-positive by the assays available some years ago[7]. Hence, it can be estimated that about two-thirds of the women whose tumours were of unrecorded ER status in these trials would, if measured, have had ER-positive tumours. If so, then the observed effects of tamoxifen among the women with tumours of unrecorded ER status should be at least two-thirds of the effects observed in those known to have ER-positive tumours. The highly significant benefits among the 12,000 women with tumours of unrecorded ER status in Figure 2 support this, illustrating that even if an ER measurement on the primary tumour is not available, adjuvant tamoxifen can still produce substantial benefit. (99% of the tumours with unrecorded ER status also had unrecorded PR status.)

Effects on recurrence and mortality after excluding women with ER-poor tumours

Tamoxifen can interfere with breast cancer cells by interacting with the ER protein, but this is impossible if the protein is wholly absent throughout the cancer. Hence, even though other mechanisms of action are possible, and even though there may be some small benefit among those classified as having ER-poor tumours, the subsequent analyses of recurrence or of total mortality include only the 18,000 women with confirmed ER-positive tumours and the 12,000 women with tumours of unrecorded ER status, of which about 8000 might also have been ER-positive. (Analyses of other outcomes, however, will still involve all women, irrespective of their hormone receptor status.) Figure 2 shows that further restriction to those with tumours that were known to be ER-positive would not have materially affected the apparent sizes of the effects of treatment on recurrence or on mortality.

Because Figures 3 to 7 exclude women with ER-poor tumours, the proportion with ER-positive tumours is larger and the risk reductions are slightly more extreme than in Figure 1, as are the trends towards greater benefit with longer tamoxifen duration (trend tests in Figure 3: recurrence, $\chi^2_1 = 52.0$, 2P<0.00001; mortality, $\chi^2_1 = 8.8$, 2P=0.003). The estimated proportions with ER-positive tumours still differ slightly between the trials of 1 year, 2 years and about 5 years of tamoxifen, being 82%, 87% and 94% respectively, but this can account for only a small part of the trend in efficacy.

Nodal status: Figure 3 shows that, both for recurrence and for mortality, the proportional risk reductions within each category of tamoxifen duration appear to be about the same for women with node-positive disease as for women with node-negative disease. (In confirmation, all six of the chi-squared tests for heterogeneity between the proportional risk reductions produced by tamoxifen in women with node-positive and those with node-negative disease are non-significant.) At least in terms of 10-year outcome, the same proportional benefit for node-positive as for node-negative disease would generally imply a greater absolute benefit for those with node-positive disease. These absolute benefits are illustrated in Figure 4 for the effects of 1, 2 and about 5 years of adjuvant tamoxifen.

The left side of Figure 4 provides analyses of recurrence as a first event, describing the proportions who would, in the absence of other causes of death, still be alive and free of any recurrence (local, distant or contralateral) of breast cancer. For the trials of 1 or 2 years of tamoxifen, the absolute improvements in this 10-year recurrence risk appear larger for women with node-positive disease than for those with node-negative disease. In the trials of about 5 years of tamoxifen, however, the absolute improvement in this 10-year recurrence risk appears to be about as great for women with node-negative disease (absolute improvement 14.9% SD 1.4) as for those with node-positive disease (absolute improvement 15.2% SD 2.5). This could well be because the play of chance has led to slight over-estimation of the effects of 5 years of tamoxifen in those with node-negative disease or to slight under-estimation of the effects in those with node-positive disease, but still in both cases the real benefits must be substantial. (Note: As some women die of unrelated causes, an absolute improvement in the 10-year recurrence risk of 15% would correspond to an absolute difference of only about 14% in the 10-year recurrence-free survival.)

The right side of Figure 4 describes all-cause mortality by means of standard Kaplan-Meier survival curves. The absolute improvements in 10-year survival appear greater for those with node-positive disease than for those with node-negative

disease in each category of tamoxifen duration. For patients with node-negative disease in the trials of 1, 2 and about 5 years of tamoxifen the absolute improvements in 10-year survival are 3.4% SD 2.1 (2P=0.09), 2.3% SD 1.3 (2P=0.06) and 5.6% SD 1.3 (2P<0.00001) respectively, whereas for those with node-positive disease the absolute improvements are 4.5% SD 1.4 (2P=0.001), 7.2% SD 1.2 (2P<0.00001) and 10.9% SD 2.5 (2P<0.00001). The mortality in Figure 4 is not all due to breast cancer: indeed, analyses of the deaths before recurrence indicate that even in the absence of breast cancer only about 92% of these women would have survived 10 years from randomisation. As tamoxifen has little effect on the aggregate of all other causes of death (see below), restriction to breast cancer deaths would make little difference to the estimated absolute benefits, but would slightly increase the proportional mortality reductions, especially for women with node-negative disease (data not shown).

Background risk during the first 5 years (0-4), and later (years 5+): The recurrence rate among control-allocated women was about twice as great during the first five years as during the next five years (left side of Figure 4). This was true both for women with node-positive and for those with node-negative disease. Thus, the probability of recurrence during the first five years was about 1/2 for node-positive controls and 1/4 for node-negative controls, but, among those who were still free of recurrence five years after randomisation, the probability of recurrence during the next five years was only about 1/4 for node-positive controls and 1/8 for node-negative controls.

The death rate among control-allocated women was, however, no greater during the first five years than during the next five years (right side of Figure 4). The death rate in year 0 was low, as women had had to be free of detectable disease when randomised, but throughout years 1-9 the annual death rate stayed fairly constant. (Hence, if a "log" scale had been used in Figure 4 then the survival curves would have been approximately straight in years 1-9 for each of the 6 control groups — and, in fact, for each of the 6 tamoxifen groups, though with shallower slopes: see below.)

Benefits during the first 5 years, and later: The main divergence between the recurrence graphs for tamoxifen takes place during the first five years, with a substantial benefit already apparent during the first year after randomisation (left side of Figure 4). For mortality, however (right side of Figure 4), there is no apparent benefit during the first year after randomisation (perhaps because many control-allocated women whose disease recurred early then received tamoxifen), but during

the next four years there was a significant difference in the probability of survival. Thus, five years after randomisation there was a significant difference in survival, and during the next five years this grew significantly larger. Figure 5 provides separate analyses of the effects of treatment on the proportional risk reductions during years 0-4 and later (years 5+).

For recurrence (left side of Figure 5), the proportional reductions during years 0-4 were 22% SD 4, 34% SD 3 and 51% SD 4 in the trials of 1, 2 and about 5 years of tamoxifen (each 2P<0.00001), with a significant trend (2P<0.00001) towards greater effect with longer treatment. Among those still free of recurrence five years after randomisation, those who had originally been allocated tamoxifen still had a somewhat better prognosis than those who had not: the proportional reductions in the rate of recurrence after years 0-4 were 14% SD 7, 5% SD 6 and 33% SD 7 respectively. Again there is a significant trend towards a greater effect with longer treatment ($\chi^2_1 = 7.2$; 2P = 0.007) but, considered separately, only the last of these additional benefits is clearly significantly different from zero (2P<0.00001). Thus, in the trials of about 5 years of adjuvant tamoxifen, the recurrence rate was reduced by about half during years 0-4 and by about one-third during the next few years. This occurred despite the fact that by the end of the first five years the tamoxifen group included substantial numbers of women who would, in the absence of tamoxifen, already have relapsed, while the control group did not. Of the recurrences after the first five years in tamoxifen-allocated women, one-third involved women who had been re-randomised to continue tamoxifen during years 5-9, but two-thirds involved women who had been allocated to stop taking tamoxifen by the end of year 4. If most of them did so, then part of the reduction in the recurrence rate after the first five years represents a "carry-over" effect, whereby adjuvant tamoxifen reduces the recurrence rate not only while treatment continues but also for some years after.

For mortality (right side of Figure 5), an unexpected[3] feature of these results is that the proportional risk reductions during the period after the first five years were remarkably similar to those during years 0-4. The proportional mortality reductions during years 0-4 were 11% SD 4 (2P=0.02), 17% SD 4 (2P<0.00001) and 28% SD 6 (2P<0.00001) in the trials of 1, 2 or about 5 years of tamoxifen. The corresponding proportional mortality reductions during years 5+ were similar, being 13% SD 5 (2P=0.009), 15% SD 4 (2P=0.0003) and 24% SD 6 (2P=0.00005) respectively. Hence, a few years of tamoxifen significantly improves the proportion surviving for 5 years and, in addition, having previously had such treatment significantly improves the subsequent prognosis of those who have already survived 5 years.

Different treatment regimens: The apparent relevance of tamoxifen duration has already been extensively discussed. The daily dose of tamoxifen was 20 mg in about half the trials, and 30-40 mg in the other trials. In terms both of recurrence and of mortality, the benefits appeared to be about as big in the trials of 20 mg/day as in the trials of 30-40 mg/day (Figure 6). No major trial, however, has involved a directly randomised comparison between different daily doses of tamoxifen.

Some of the trials were of adjuvant tamoxifen versus no systemic adjuvant therapy, with no adjuvant chemotherapy scheduled for either group (Tam vs nil in Figure 6), while others were of adjuvant tamoxifen plus chemotherapy versus the same chemotherapy alone (Tam + C vs C in Figure 6). For recurrence (left side of Figure 6), the proportional reductions were significant both in the trials of tamoxifen versus nil and in the trials of tamoxifen plus chemotherapy versus the same chemotherapy alone. In the trials of only 1 or 2 years of tamoxifen, the recurrence reductions were significantly larger in the absence of chemotherapy than in its presence. But, in the trials of about 5 years of adjuvant tamoxifen the recurrence reductions seemed equally large in the absence and the presence of chemotherapy. In all cases, however, irrespective of whether or not chemotherapy was to be used, tamoxifen was of additional benefit in delaying recurrence. The same appears to be true for mortality (right side of Figure 6): indeed, the mortality reduction appears, perhaps chiefly by chance, to be particularly great in the trials of 5 years of tamoxifen plus chemotherapy versus the same chemotherapy alone.

Age and menopausal status: In the trials of 1 or of 2 years of tamoxifen there are significant trends towards greater recurrence reductions in older than in younger women (left side of Figure 7), but no such trend is apparent in the trials of about 5 years of tamoxifen. As the trials of 1 or 2 years of tamoxifen suggest less benefit in younger than in older women, this apparent lack of any such trend in trials of about 5 years of tamoxifen may be misleading. But, the recurrence reductions produced by about 5 years of tamoxifen are substantial and highly significant both in women aged under 40 when randomised (54% SD 13 reduction) and in those aged 40-49 (41% SD 10 reduction). Therefore, much of this apparent benefit in women aged under 50 must be real.

For mortality (right side of Figure 7) the patterns are similar, but less stable. In the trials of 1 or 2 years of tamoxifen there are slight trends towards greater mortality reductions at older ages, but these trends are not clearly significant, and no such trend is apparent in the trials of about 5 years of tamoxifen. Among those who were over 70 when randomised, many of the deaths over the next 10 years will have been from

causes unrelated to the original breast cancer, and this may have diluted any trends in the effects of treatment on all-cause mortality.

Women aged 40-49 and those aged 50-59 were further subdivided by their menopausal status when randomised. In neither case, however, did this subdivision significantly affect the age-specific results (data not shown).

Finer subdivision of the evidence: After the effects of tamoxifen have been subdivided by treatment duration, further subdivision by just one other factor (as in various Figures) may be somewhat unreliable and further subdivision by two other factors may be very unreliable. For example, although there is no apparent heterogeneity of benefit when the effects of 5 years of tamoxifen are subdivided both by age and by concurrent chemotherapy (data not shown), this is not statistically reliable evidence of homogeneity of benefit. Even such a large data set cannot reliably support excessively fine subdivisions of the available evidence.

Effects of tamoxifen on other outcomes

Table 2 describes the effects of tamoxifen on various other outcomes: contralateral breast cancer (which has already been included in all previous analyses of recurrences, accounting for 6% of them), colorectal and endometrial cancer incidence (including both fatal and non-fatal cases, as long as there had been no previous recurrence of breast cancer), and death from endometrial cancer or from a cause other than breast or endometrial cancer (among women with no previous recurrence of breast cancer recorded). As the hormone receptor status of the original breast cancer may have little relevance to the effects of tamoxifen on these other outcomes, women with ER-poor disease are not excluded, although their exclusion would not materially alter the findings in the Tables. Most trials provided data on all of these other outcomes, but a few reported on only some of them (see Materials), introducing slight differences between the denominators in different sections of Table 2.

For these analyses of other outcomes, the period at risk involves only the time before any breast cancer recurrence, which, as adjuvant tamoxifen delays recurrence, is about 10% longer for those allocated tamoxifen than for those not (6% longer in the trials of 1 year of tamoxifen, 14% longer in the trials of about 5 years of tamoxifen). This means that the crude proportions of tamoxifen-allocated and of control-allocated women suffering these other outcomes cannot be compared directly, so the first two columns of data in Table 2 relate the outcomes to the numbers of woman-years at risk rather than the numbers randomised. More exact allowance can be made by proper "logrank"

analyses and "survival curve" calculations, and these are presented in the remaining columns of Table 2.

Contralateral breast cancer incidence: In the trials of 1, 2 or about 5 years of tamoxifen, the proportional reductions in the incidence rate of contralateral breast cancer among women allocated tamoxifen were, respectively, 13% SD 13 (NS), 26% SD 9 (2P=0.004) and 47% SD 9 (2P<0.00001). This tendency for the trials of longer tamoxifen duration to involve larger reductions in the incidence of new primary cancer in the opposite breast is significant (trend test: $\chi^2_1 = 7.3$, 2P=0.008), and these analyses indicate that about 5 years of tamoxifen approximately halves the annual incidence rate of contralateral breast cancer.

For contralateral breast cancer, the proportional risk reductions were approximately independent of age, as was the absolute annual incidence among the control-allocated women (which, taking all ages together was 5 per 1000 [based on 485 cases in 95.3 thousand years of follow-up]: Table 2). A quarter of the women in these trials are from Japan, where the national breast cancer rates are lower than in North America or Western Europe, and the annual incidence of contralateral breast cancer in the control-allocated women was 2 per 1000 in Japan and 6 per 1000 elsewhere. Hence, if the incidence of contralateral breast cancer really can be halved by about 5 years of tamoxifen, then the absolute annual benefit would be about 1 per 1000 in Japan and 3 per 1000 elsewhere, both for younger and for older patients. (These control rates in women with only one breast still at risk are about 3 times the respective rates in Japan and Europe during the mid-1980s[8] in women with two breasts at risk and no prior disease.) The proportional reduction in contralateral breast cancer appeared to be about the same size in women with ER-poor tumours (29% SD 15; 2P=0.06) as in other women (30% SD 6).

Colorectal cancer incidence: Overall, there was a slight and non-significant excess of colorectal cancer among those allocated tamoxifen (ratio of incidence rates = 1.11 SD 0.15; NS). The apparent excess was larger (though still not significant) in the trials of 1 year of tamoxifen (ratio 1.33 SD 0.28, NS), and there was no apparent excess in the trials of 2 years (ratio 1.05 SD 0.24, NS) or about 5 years (ratio 0.98 SD 0.25, NS) of tamoxifen. None of these results is statistically significant, and as the apparent excess was almost entirely confined to the trials of only one year of treatment, the randomised evidence, taken as a whole, does not indicate that tamoxifen produces any increase in colorectal cancer.

Endometrial cancer incidence: By contrast, the overall increase in the incidence of endometrial cancer was highly statistically significant (ratio of incidence rates = 2.58 SD 0.35; 2P<0.00001). As this is based on a total of only 32 cases among control-allocated women, the separate odds ratios for the trials of 1, 2 and about 5 years of tamoxifen cannot be estimated reliably. So, although the respective odds ratios of 2.2, 1.8 and 4.2 in these three groups of trials suggest that 1-2 years of tamoxifen approximately doubles the incidence of endometrial cancer and that 5 years approximately quadruples it, these ratios are not significantly different from each other. The relative risks appeared to be similar in the Japanese trials and in the other trials, but the absolute risks in the control-allocated patients did not, being 0.1 and 0.4 per 1000 per annum respectively. In the general population, the annual incidence rates of endometrial cancer during the mid-1980s at ages 55-84 were 0.1 per 1000 in Japan but 1 per 1000 in the US "SEER" areas, with the rates in Europe about half those in the US[8]. Hence, if the relative risk associated with tamoxifen is about the same in different populations, then the absolute risks will differ substantially.

Even in the trials of about 5 years of tamoxifen, the absolute increase in endometrial cancer was only about half as big as the absolute decrease in contralateral breast cancer. The three largest such trials, all of which were in Europe or North America, provided data on the incidence of both contralateral breast cancer and endometrial cancer, and their results are summarised in Table 3. In them, allocation to about 5 years of tamoxifen was associated with 33 more cases of endometrial cancer, but 66 fewer cases of contralateral breast cancer.

Endometrial cancer mortality: Of 124 women who developed endometrial cancer, 18 died with breast cancer recurrence reported and 40 died without it (29 with death attributed to endometrial cancer, 3 probably due to the disease, and 8 not due to breast or endometrial cancer). Overall, there were 27 endometrial cancer deaths (including the 3 "probable" such deaths) among women allocated tamoxifen and 5 among those not (2P=0.0008). This does not include any of the 18 deaths after recurrence of breast cancer had been reported, as such deaths are likely to be due to breast cancer. (The mortality analyses in Figures 1-7, however, include all deaths, irrespective of their cause.)

The absolute excess of deaths from endometrial cancer during the whole decade after randomisation was, in each of the 3 tamoxifen duration categories, about 1 or 2 per 1000 (corresponding to an annual excess of about 0.2 per 1000). There was a non-significant tendency for the excess of endometrial cancer deaths to be greater in

the trials of more prolonged tamoxifen. But, although this trend may well be real, the absolute excess was not large. Among 3673 women allocated about 5 years of tamoxifen in trials that provided cause-of-death information, there were 7 endometrial cancer deaths during 26.4 thousand woman-years of follow-up during the period before any recurrence of breast cancer, and the cumulative risk during the whole of the first decade was about 2 deaths from endometrial cancer per 1000 (with 95% confidence limits that range from about 0 to 4 per 1000).

Causes of death other than breast or endometrial cancer: The underlying causes of those deaths that were specified not to be due to breast cancer (and that had not been preceded by any recorded recurrence of breast cancer) were subdivided into nine categories: endometrial cancer, and other neoplastic, cardiac, cerebrovascular, other vascular, respiratory, infective, other medical, and non-medical causes. The difference in non-breast-cancer mortality between tamoxifen and control was significant only for endometrial cancer (Table 2) and not for any of the other eight categories separately (each 2P>0.1), for the aggregate of all cardiac or vascular deaths (2P>0.1), or for the aggregate of all non-breast, non-endometrial cancer deaths (death rate ratio 0.99 SD 0.05, 2P=1.0; Table 2).

Among women allocated tamoxifen there were non-significantly fewer deaths attributed to non-neoplastic diseases of the liver (9 tamoxifen vs 12 control) or to primary liver cancer (3 vs 7). Based on 1990 West European or North American death rates[10], the number of deaths that would have been expected to have been attributed to liver cancer in the control group is about 4, less whatever fraction would be expected to be misdiagnosed as hepatic metastases. One-quarter of the patients were from Japan, where the national death rates from liver cancer are high, but neither in Japan (0 tamoxifen vs 3 control) nor elsewhere (3 vs 4) was any excess of liver cancer deaths recorded in the tamoxifen-allocated women in these trials.

DISCUSSION

This collaboration has now continued for over 10 years, accumulating more randomised evidence on tamoxifen than is available on any other anti-cancer drug. What is new in these updated results is the growing importance of the hormone receptor measurement as a determinant of the response to treatment, the widening range of patients for whom adjuvant tamoxifen is now known to be protective (including those aged under 50), the strength of the indirect evidence that about 5 years of adjuvant tamoxifen is (particularly after long follow-up) more effective than shorter durations of treatment, the definiteness of the evidence on endometrial cancer, and the evidence of safety with respect to other causes of death. Among

patients with ER-positive tumours (or those for whom no receptor measurement is available), a few years of adjuvant tamoxifen is of net benefit not only for women with node-positive but also for women with node-negative disease (Figures 3 & 4), and, if any cytotoxic therapy is to be given, then cytotoxic therapy plus a few years of adjuvant tamoxifen is better than cytotoxic therapy alone (Figure 6). Finally, adjuvant tamoxifen can produce substantial benefit not only for those aged 50-69 and those aged 70+ but, in contrast with earlier reports[1-3], for those aged under 50 (Figure 7). These new conclusions are discussed further below.

A slight weakness is the unavailability of three large trials of prolonged tamoxifen that began just before 1990 and have not yet been published (Table 1). But, by 1995 those trials would have contributed appreciably only to the first few years after randomisation, and since there is so much data from other trials on the effects of treatment during this early period, the unavailability of these three studies should make no material difference to the findings.

Hormone receptors

ER-positive (or ER status unknown): The apparent benefits of tamoxifen for women whose tumours were classified as "ER-positive" are still about as great as in the previous cycle of this collaboration[3]. Figure 2 shows that, taking all tamoxifen durations together, the recurrence reduction among women with known ER-positive tumours is now 34% SD 3 (compared with 32% SD 3 previously[3]), and the mortality reduction is now 20% SD 3 (compared with 21% SD 3 previously[3]). There was no evidence in these trials that a negative progesterone receptor assay could identify a non-responsive subset of women with ER-positive tumours. Moreover, even if an ER receptor assay has not been done (or the assay result is uncertain: see below), it may be best to act as if the patient had an ER-positive tumour, since the benefits of tamoxifen were about three-quarters as great for those with untested receptor status ("ER unknown" in Figure 2) as for women with known ER-positive tumours.

ER-poor tumours: By contrast, however, there is now less evidence of benefit in women whose tumours were classified as ER-poor: Figure 2 shows that, taking all tamoxifen durations together, the proportional recurrence reduction among them is now only 10% SD 4 (compared with 13% SD 4 previously[3]), which would be 9% SD 4 if contralateral recurrences were ignored, and the proportional mortality reduction is now only 5% SD 3 (compared with 11% SD 5 previously[3]). Moreover, even if consideration is restricted to the trials of about 5 years of tamoxifen, which appeared to be a particularly effective regimen for women with ER-positive tumours, there was no apparent effect on recurrence or mortality among women with ER-poor tumours

(Figure 2), especially if contralateral recurrences are ignored. There was some suggestion that a positive progesterone receptor assay might identify a tamoxifen-responsive subset of those with ER-poor tumours, but the number of women studied was far too small for this to be trustworthy.

The present results suggest that a reliably negative ER measurement might identify women for whom even prolonged hormonal therapy would offer no material protection against their original breast cancer. For, although allocation to tamoxifen may have produced a slight reduction in the non-contralateral breast cancer recurrence rates among women whose original tumour was classified many years ago as "ER-poor", these women must have included some whose tumour would, if re-tested by more sensitive methods, have been correctly classified as ER-positive. If these women could be identified and removed from the present ER-poor category, it is likely that no significant evidence would remain in this overview of protection of truly ER-negative women against the spread of their original tumour. The chief benefit to be expected among them would then be a reduction in the incidence of contralateral breast cancer (or, following partial mastectomy, in new ipsilateral breast cancer), and in absolute terms this is not large. Thus, whereas the overall benefits of a few years of adjuvant tamoxifen for women with ER-positive disease are substantial and definite, those for women with disease that has been reliably shown to be completely without any functional hormone receptor are not, and remain a matter for research. If there are some smaller, but still real, benefits among women whose tumours were reliably shown to be ER-negative, this would be of both practical and theoretical importance.

Dangers of false-negative ER assays: For women with ER-positive disease, a few years of adjuvant tamoxifen can substantially improve the 10-year survival. So, whereas a false positive ER assay is unlikely to be dangerous (especially since a few years of tamoxifen appears to produce a reduction in the risk of contralateral breast cancer that is bigger than any increase in the risk of endometrial cancer), a false negative ER assay that led to tamoxifen being withheld could be fatal. Apparently negative ER assay results should therefore be considered extremely carefully, and perhaps repeated, either by the same or by a different method[11], as even values of only a few femtomoles of ER protein per mg of cytosol protein might indicate a tumour that would have at least some response to adjuvant tamoxifen.

Duration of adjuvant tamoxifen

5 years versus shorter: After exclusion of women with ER-poor tumours, the difference between the recurrence reductions associated with 5 years and with only

one or two years of adjuvant tamoxifen is large, and cannot be accounted for by differences in nodal status, tamoxifen dose, concurrent chemotherapy, age or menopausal status (Figures 3, 6, 7). So, it provides strong evidence that about 5 years of adjuvant tamoxifen produces a substantially greater delay of recurrence than is produced by just one or two years of treatment. Further support for this conclusion is provided by the two directly randomised comparisons of five years versus two years of adjuvant tamoxifen that have recently been published[12,13], in which longer treatment yielded a 21% SD 7 further reduction in recurrences during the first few years after randomisation (373 [11.6%] recurrences among 3211 allocated 5 years vs 469 [14.3%] among 3271 allocated 2 years; 2P<0.001).

For mortality, there is also a significant trend (2P=0.003) towards a greater benefit with longer tamoxifen treatment among women who were not classified as ER-poor (Figure 3). But, the difference in the sizes of the proportional risk reductions is less extreme for mortality than for recurrence, and in the published trials of 5 versus 2 years of tamoxifen[12,13], the difference is less extreme for breast cancer deaths (6.9% vs 8.5%, 2P=0.02) than for breast cancer recurrence. Judgements may differ as to how strong the evidence now is as to whether 5 years of adjuvant tamoxifen produces a greater survival advantage than shorter regimens, especially if those who relapse then get tamoxifen. Substantially larger amounts of evidence from directly randomised comparisons of 5 years versus shorter durations of adjuvant tamoxifen should, however, become available for central review in about the year 2000.

5 years versus longer: The present review has not addressed the question of whether giving adjuvant tamoxifen for more than 5 years would produce any worthwhile additional benefits, and it may well take at least another decade for this question to be answered reliably[9]. Both the adverse and the protective long-term side-effects are likely to be greater with, for example, 10 years than with 5 years of adjuvant tamoxifen. Trials among women who have already completed 5 years of adjuvant tamoxifen of the effects of continuing for another 5 years might well involve twofold further differences (Table 2) in the incidence of endometrial cancer and of contralateral breast cancer. In Europe or North America, this would be expected to yield an absolute increase of about 1% in endometrial cancer and an absolute decrease of about 1% in contralateral breast cancer. If so, then the balance of risk and benefit would then be determined chiefly by the effect of the additional treatment on the long-term recurrence rate of the original breast cancer. One potential difficulty for such trials is the possible "carry-over" benefit of adjuvant tamoxifen, whereby 5 years of adjuvant tamoxifen produces a substantial protective effect not only while it is being taken but also during the next 5 years (Figure 5). Hence, even if 10 years of

adjuvant tamoxifen is importantly better than 5 years of adjuvant tamoxifen, this advantage may not become substantial until well after year 10. Results to about year 10 have recently been reported from three such trials[14-16], finding no evidence of early benefit[7]. So far, however, these three trials have involved a total of only about 100 breast cancer deaths among 1700 women (mostly with node-negative disease). Although follow-up continues, these plus the further such trials that are now trying to recruit much larger numbers of women will probably not yield clear results before the year 2010.

Thus, the currently available trial results indicate that about 5 years of adjuvant tamoxifen is at least as effective as any other widely tested duration, but still leave substantial uncertainty as to how long such treatment should routinely continue[9]. This is entirely consistent with the statement in the summary of the 1995 NCI clinical announcement that "While we eagerly await the results [of trials of 5 years versus longer], all available evidence indicates that 5 years of tamoxifen is a reasonable standard for the adjuvant setting"[17].

Age

There is now good evidence, particularly for the more prolonged regimens, that adjuvant tamoxifen is of substantial value not only in older women but also in those aged under 50 (Figure 7), unless they have an ER-negative tumour. The apparent lack of benefit among younger women suggested by the previous overviews[1-3] may have been partly due to the play of chance (which, particularly in trials of only one or two years of treatment, could obscure any real benefits) and partly due to the higher prevalence of ER-negative disease in younger women. With the larger numbers now available, however, it is clear that about 5 years of adjuvant tamoxifen has a substantial effect both on recurrence and on long-term survival not only in older women but also in younger women (irrespective of whether the benefit is exactly as great among younger as among older women). Moreover, the substantial benefits of adjuvant ovarian ablation on long-term survival in women under the age of 50 that have recently been demonstrated[5] provide further evidence of the importance of adjuvant hormonal therapy for many premenopausal breast cancer patients. Hence, neither youth nor age should be a barrier to the use of tamoxifen in women with ER-positive tumours, or with no ER measurement available.

Concurrent, or consecutive, chemo-endocrine therapy

Many forms of chemotherapy or radiotherapy might be more effective in the absence of a drug such as tamoxifen that selectively slows the division of the very cancer cells that they would otherwise have attacked. If so, it might be better to delay the

start of any hormonal treatment until after any radiotherapy or chemotherapy have been completed, especially if these treatments last only a few months. But, irrespective of whether — in comparison with the trials of tamoxifen alone — there are greater or lesser treatment effects in the trials of tamoxifen plus chemotherapy versus chemotherapy alone, the addition of tamoxifen to chemotherapy certainly produces some additional benefits. In particular, chemotherapy plus about 5 years of tamoxifen is substantially better than the same chemotherapy alone. This highly significant additional benefit provides strong evidence that the long-term survival of women with ER-positive tumours (or with tumours of unknown ER status) would generally be improved by also giving some years of adjuvant tamoxifen (although, unfortunately, no large directly randomised comparisons of concurrent versus consecutive chemo-endocrine therapy are yet available). Hence, even definite plans to give certain such women radiotherapy and/or chemotherapy without concurrent tamoxifen should not preclude the subsequent use of adjuvant tamoxifen.

Conclusions

The present results indicate that the fundamental question to ask when assessing the proportional risk reduction that a woman with early breast cancer can expect from a few years of adjuvant tamoxifen is whether her tumour is definitely ER-negative (and not whether she is young or old, with or without nodal involvement, or receiving chemotherapy). If it is reliably measured to be ER-negative, then although adjuvant tamoxifen might produce a small net benefit (Figure 2), this still requires further research. If, however, her tumour has detectable estrogen receptors, then adjuvant tamoxifen, perhaps for about 5 years, should generally produce benefits about as great as in the lower part of Figure 4, largely irrespective of age, prior chemotherapy or menopausal status — and, even if hormone receptor measurements are not available, or yielded uncertain results, then a substantial fraction of these benefits can still be expected.

Indeed, even Figure 4 may slightly under-estimate the real benefits. For, a few per cent of the women did not have ER-positive tumours, and in many trials there is some non-compliance (with a few of those allocated adjuvant tamoxifen not receiving it as scheduled and a few of those allocated control actually receiving some adjuvant tamoxifen). If, for example, only 90% of the full benefit is seen in the trials, then the improvement in 10-year survival that could be achieved in women with functional hormone receptors actually taking 5 years of adjuvant tamoxifen would be about 6% and 12% respectively for women with node-negative and with node-positive disease. These benefits are bigger than those reported previously[3], partly because attention is chiefly being restricted to women with ER-positive tumours and partly because the

effects of prolonged treatment can now be assessed reliably. The absolute benefits at 10 years would, however, be substantially smaller for women with an extremely good prognosis, such as those with small localised tumours of good histological grade, which can nowadays be found by screening programmes.

Trials of ovarian ablation began half a century ago[5] and trials of tamoxifen began a quarter of a century ago, yet in the early 1980s hormonal adjuvant therapy was still greatly under-valued. Since then, receptor assays have improved, treatments have become more prolonged and there have been substantial increases in the total numbers of randomised women, in the duration of follow-up of the trials and, through the present collaboration, in the public availability of the randomised evidence. It is now clear that, at least for women whose primary tumours had functional oestrogen receptors, effective hormonal treatment is of substantial value. This report makes no recommendations as to who should or should not be treated, for treatment decisions involve not only survival and cancer recurrence but also symptomatic side-effects, costs, and other factors that have not been reviewed. (To avoid misleading claims, symptomatic side-effects should be assessed in large trials that are not only randomised but also involve placebo tablets[18].) But, for survival and recurrence the balance of the known long-term benefits and risks strongly favours adjuvant tamoxifen for many women.

FIGURE LEGENDS

Figure 1: Separate results from all 55 tamoxifen trials, subdivided by scheduled duration of adjuvant tamoxifen. Left: recurrence as a first event (including contralateral breast cancer, and censoring at the time of death from another cause without any recurrence); Right: all-cause mortality. Each trial is described by one line of data, giving the year that randomisation began, an abbreviated trial name, and the adjuvant tamoxifen schedule (mg/day and duration in years, with † indicating randomisation of tamoxifen plus chemotherapy versus the same chemotherapy alone), followed by the recurrence and mortality analyses. The area of each black square is proportional to the amount of information contributed by the trial it describes, so larger squares are associated with shorter confidence intervals (i.e. with more informative results). Subtotals for the trials of 1, 2 and about 5 years of tamoxifen are provided, as are the χ^2 tests for heterogeneity between these subtotals. Tests for trend with respect to the median tamoxifen duration (1, 2 or 5 years) yield $\chi^2_1 = 48.4$ for recurrence (2P<0.00001) and $\chi^2_1 = 6.2$ for mortality (2P=0.013). (* For balance, the 410 control patients in the only 3-way trial count twice in the "adjusted control" totals; all the other trials were approximately evenly randomised.)

Figure 2: Proportional risk reductions, subdivided by tamoxifen duration and by ER status. Left: recurrence; Right: mortality. Each line describes a subtotal, combining the results from particular types of women in particular categories of trial. Here and in later Figures, where some

women have tumours of unknown ER status an estimate is given of the proportion who, if they had been tested, would have had ER-positive tumours (estimated as half the women aged under 50, and three-quarters of the others[7]). Within each tamoxifen duration category, the tests for heterogeneity relate to differences between the results for ER-poor, ER unknown and ER-positive. For the 18,000 women with ER-positive disease, the trend test for increasing benefit with increasing tamoxifen duration yields $\chi^2_1 = 45.5$ (2P<0.00001) for recurrence and $\chi^2_1 = 5.6$ (2P=0.018) for mortality. For the 8000 women with ER-poor disease, the trend test yields $\chi^2_1 = 0.02$ (NS) for recurrence and $\chi^2_1 = 0.53$ (NS) for mortality.

Figure 3: Proportional risk reductions, subdivided by tamoxifen duration and by nodal status (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. Although women with ER-poor disease have been excluded, the ER status was unreported for more than one-third of those that remain, and an estimate of the overall proportion who would, if tested, have had ER-positive disease is given for each line of analyses. Overall, the estimated proportions with ER-positive disease are about 82%, 87% and 94% respectively in the trials of 1, 2 or about 5 years of tamoxifen. The tests for trend between the effects of 1, 2 and about 5 years of tamoxifen in these predominantly ER-positive women yield $\chi^2_1 = 52.0$ for recurrence (2P<0.00001) and $\chi^2_1 = 8.8$ for mortality (2P=0.003).

Figure 4: Absolute risk reductions during the first 10 years, subdivided by tamoxifen duration and by nodal status (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. The values for the tamoxifen and control patients at 5 and at 10 years, and the absolute differences in 10-year outcome, are given beside each pair of lines. For women with node-negative disease, the annual event rates during years 0-4, 5-9 and 10+ after randomisation are given at the foot of each box, together with their standard deviations (SD) and the numbers of events (and "woman-years" at risk) on which they are based.

Figure 5: Proportional risk reductions during the first five years (0-4) and later, subdivided by tamoxifen duration (after excluding women with ER-poor disease). Left: recurrence; Right: mortality.

Figure 6: Proportional risk reductions, subdivided by tamoxifen duration and either by daily tamoxifen dose or by whether women were all to avoid chemotherapy or all to receive it (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. "Tam vs nil" denotes trials where neither group was scheduled to receive adjuvant chemotherapy, and "Tam+C vs C" denotes trials of tamoxifen plus adjuvant chemotherapy versus the same chemotherapy alone.

Figure 7: Proportional risk reductions, subdivided by tamoxifen duration and by age when randomised (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. Tests for trend with respect to age are provided.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomised trials among 28,896 women. N Engl J Med 1988; 319: 1681-92.
2. Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer, vol 1: worldwide evidence 1985-1990. Oxford: Oxford University Press, 1990.
3. Early Breast Cancer Trialists' Collaborative Group. Systematic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992; 339: 1-15, 71-85.
4. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomised trials. N Engl J Med 1995; 333: 1444-55.
5. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. Lancet 1996; 348: 1189-96.
6. Peto R. A statistical detail: the tie-breaking bias. Pages 379-381 in: Symington T, Williams AE, McVie JG (editors). Cancer: Assessment and Monitoring. London: Churchill Livingstone, 1980.
7. Elwood JM, Godolphin W. Oestrogen receptors in breast tumours: associations with age, menopausal status and epidemiological and clinical features in 735 patients. Brit J Cancer 1980; 42: 635-44.
8. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J (editors). Cancer Incidence in Five Continents, volume VI. International Agency for Research on Cancer, Lyon, 1992.
9. Peto R. Five years of tamoxifen — or more? (editorial). J Natl Cancer Inst 1996; 88: 1791-3.
10. Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr. Mortality from Smoking in Developed Countries 1950-2000: Indirect Estimates from National Vital Statistics. Oxford University Press, 1994
11. Clark GM, Harvey JM, Osborne CK, Allred DC. Estrogen receptor status determined by immuno-histochemistry is superior to biochemical ligand-binding assay for evaluating breast cancer patients (abstract). Proc ASCO 1997 (in press).
12. Swedish Breast Cancer Cooperative Group. Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. J Natl Cancer Inst 1996; 88: 1543-9.
13. Current Trials Working Party of the Cancer Research Campaign Breast Cancer Trials Group. Preliminary results from the Cancer Research Campaign Trial

evaluating tamoxifen duration in women aged fifty years or older with breast cancer. J Natl Cancer Inst 1996; 88: 1834-9.

14. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N et al. The worth of five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 1996; 88: 1529-42.
15. Stewart HJ, Forrest AP, Everington D, McDonald CC, Dewar JA, Hawkins RA et al. Randomised comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer. The Scottish Cancer Trials Breast Group. Br J Cancer 1996; 74: 297-9.
16. Tormey DC, Gray R, Falkson HC (for the Eastern Cooperative Oncology Group). Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. J Natl Cancer Inst 1996; 88: 1828-33.
17. Anonymous. National Cancer Institute Clinical Announcement: Adjuvant therapy of breast cancer — tamoxifen update. November 30, 1995. Bethesda (MD): National Institutes of Health, 1995
18. Cuzick J. Chemoprevention of breast cancer with tamoxifen. Pp.95-109 in: Hakama M, Beral V, Buiatti E, Faivre J, Parkin DM (eds). Chemoprevention in Cancer Control, IARC Scientific Publication No. 136. IARC, Lyon, 1996

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Table 1: Availability of data from randomised trials that began before 1990 of adjuvant tamoxifen versus no adjuvant tamoxifen

Mean scheduled duration of adjuvant tamoxifen treatment	Nos. of trials* and of women				
	Available		Not yet available		
1 year or less	14	9,128	1	100	(1%)
2 years	32	19,212**	4	1,400	(7%)
3 or more (median: 5) years	9	8,349	3	4,200	(33%)
Any duration	55	36,689**	8	5,700	(13%)

* ACETBC-1 counts as 2 trials, as does Stockholm B.

** The Amsterdam C8209 trial randomised women evenly between 1 year, 3 years and control; to achieve balanced numbers, some totals elsewhere count these 410 control patients twice.

Table 2: Effects of treatment allocation on selected outcomes

(Includes all women, irrespective of ER status, in those trials with data on the relevant outcome)

Scheduled tamoxifen duration	Events / 1000 years† Allocated tamoxifen	Adjusted control	Tamoxifen Obs. – Exp.	Variance of O-E	Ratio of rates & SD	2-sided P-value (or NS)	10-year risk per 1000†† Tam-oxifen	Con-trol	Difference & SD
Contralateral breast cancer incidence*									
1 year	101/29.0	106/27.2	-6.9	50.8	0.87 SD 0.13	NS	23	26	3 SD 4
2 years	175/53.5	220/47.2	-27.7	91.4	0.74 SD 0.09	0.004	21	28	7 SD 3
~5 years	93/23.6	159/21.0	-39.1	62.0	0.53 SD 0.09	<0.00001	26	47	21 SD 5
Total	369/106.1	485/95.3	-73.6	204.2	0.70 SD 0.06	<0.00001	23	32	9 SD 2
Colorectal cancer incidence*									
1 year	42/29.0	27/27.2	4.8	16.8	1.33 SD 0.28	NS	9	7	-2 SD 2
2 years	42/53.5	38/47.2	0.8	17.6	1.05 SD 0.24	NS	5	5	0 SD 1
~5 years	34/23.6	30/21.0	-0.3	15.7	0.98 SD 0.25	NS	9	9	0 SD 2
Total	118/106.1	95/95.3	5.3	50.1	1.11 SD 0.15	NS	7	7	0 SD 1
Endometrial cancer incidence*									
1 year	23/28.9	10/27.2	5.7	8.2	2.2**	0.05	5	2	-3 SD 1
2 years	26/55.4	13/48.9	4.9	9.5	1.8**	0.11	4	2	-2 SD 1
~5 years	43/26.9	9/23.6	15.0	12.8	4.2**	<0.0001	11	3	-9 SD 2
Total	92/111.2	32/99.6	25.6	30.5	2.58 SD 0.35**	<0.00001	6	2	-4 SD 1
Endometrial cancer mortality*									
1 year	11/27.2	4/25.7	2.8	3.7	**	NS	2	1	-1 SD 1.0
2 years	9/56.1	1/49.5	3.5	2.4	**	0.03	1	0	-1 SD 0.4
~5 years	7/26.4	0/23.2	3.0	1.7	**	0.02	2	0	-2 SD 0.8
Total	27/109.7	5/98.4	9.4	7.8	**	0.0008	1.7	0.4	-1 SD 0.4
Death from a cause other than breast or endometrial cancer*									
1 year	339/27.2	279/25.7	11.3	148.2	1.08 SD 0.09	NS	77	73	-4 SD 6
2 years	423/56.1	414/49.5	-15.7	190.9	0.92 SD 0.07	NS	49	52	3 SD 4
~5 years	228/26.4	193/23.2	1.4	101.7	1.01 SD 0.10	NS	59	58	-1 SD 6
Total	990/109.7 (9.0)	886/98.4 (9.0)	-3.1	440.8	0.99 SD 0.05	NS	59	59	0 SD 3

† Tamoxifen delays recurrence, increasing the number of thousands of woman-years at risk; reduction of tamoxifen-allocated events by about 10% would approximately correct for this. (The statistical analyses in columns 4-10, however, exactly correct for it.)

†† As patients spend about two-thirds of the first 10 years alive and without recurrence, these 10-year risks are estimated as two-thirds of the Kaplan-Meier calculations of the 10-year risks if no other events had occurred. Note: Comparisons between the odds ratios in trials of different tamoxifen durations may be useful, but comparisons between the absolute risks may not be, as they are not standardised for age (or other risk factors).

* With no prior recurrence of breast cancer recorded. The trend in odds ratio with respect to tamoxifen duration is significant for contralateral breast cancer ($\chi^2_1 = 7.3$, $P<0.01$), but NS ($P>0.1$) for the other endpoints.

** Odds ratio not statistically stable (and so, just for endometrial cancer, estimated from events/1000 years).

Table 3: Side-effects in the 3 trials of prolonged* tamoxifen that reported both contralateral breast cancer and endometrial cancer

Trial name country and year began	Stockholm B Sweden 1976		Scottish Scotland 1978		NSABP B-14 USA 1981		All 3 trials (median tam. duration = 5 years)	
	Tam	Nil	Tam	Nil	Tam	Placebo	Tam	Control
No. of women	1104	1096	666	657	1439	1453	3209	3206
Woman-years (thousands)	8.2	7.4	5.4	4.3	10.4	9.4	24.0	21.2
CANCER INCIDENCE								
Contralateral breast cancer**								
Observed in trial	26	51	17	29	48	77	91 (66 fewer)	157
National expected	9.8	8.9	5.6	4.5	15.0	13.5	30.4	26.9
Endometrial cancer incidence**								
Observed in trial	15	5	10	3	17	1	42 (33 more)	9
National expected	5.0	4.5	1.7	1.3	7.7	6.9	14.4	12.7
MORTALITY								
Endometrial cancer deaths**								
Observed in trial	1	0	2	0	4	0	7 (7 more)	0
All deaths, from any cause								
Observed in trial	263	300	305	354	248	278	816 (116 fewer)	932

* Overall, the median adjuvant tamoxifen duration was 5 years, but within each trial it has two possible values. Each trial initially randomised adjuvant tamoxifen (Tam) versus no adjuvant tamoxifen until relapse (Nil), and later re-randomised some of the tamoxifen-allocated women who had not yet relapsed between two different durations of adjuvant tamoxifen (2 vs 5 years in Sweden, 5 vs 10+ years in Scotland, and 5 vs 10 years in the US). The present report ignores the results of the re-randomisation, which are reviewed elsewhere[9], and compares only Tam vs Nil.

** Only events without prior breast cancer recurrence are analysed. National expected numbers multiply the age-specific woman-years at risk before first breast cancer recurrence by the endometrial cancer incidence rates and by **half** the breast cancer incidence rates during 1983-87 for Sweden, Scotland and the US (0.1 black + 0.9 white rates in the US "SEER" areas)[8].

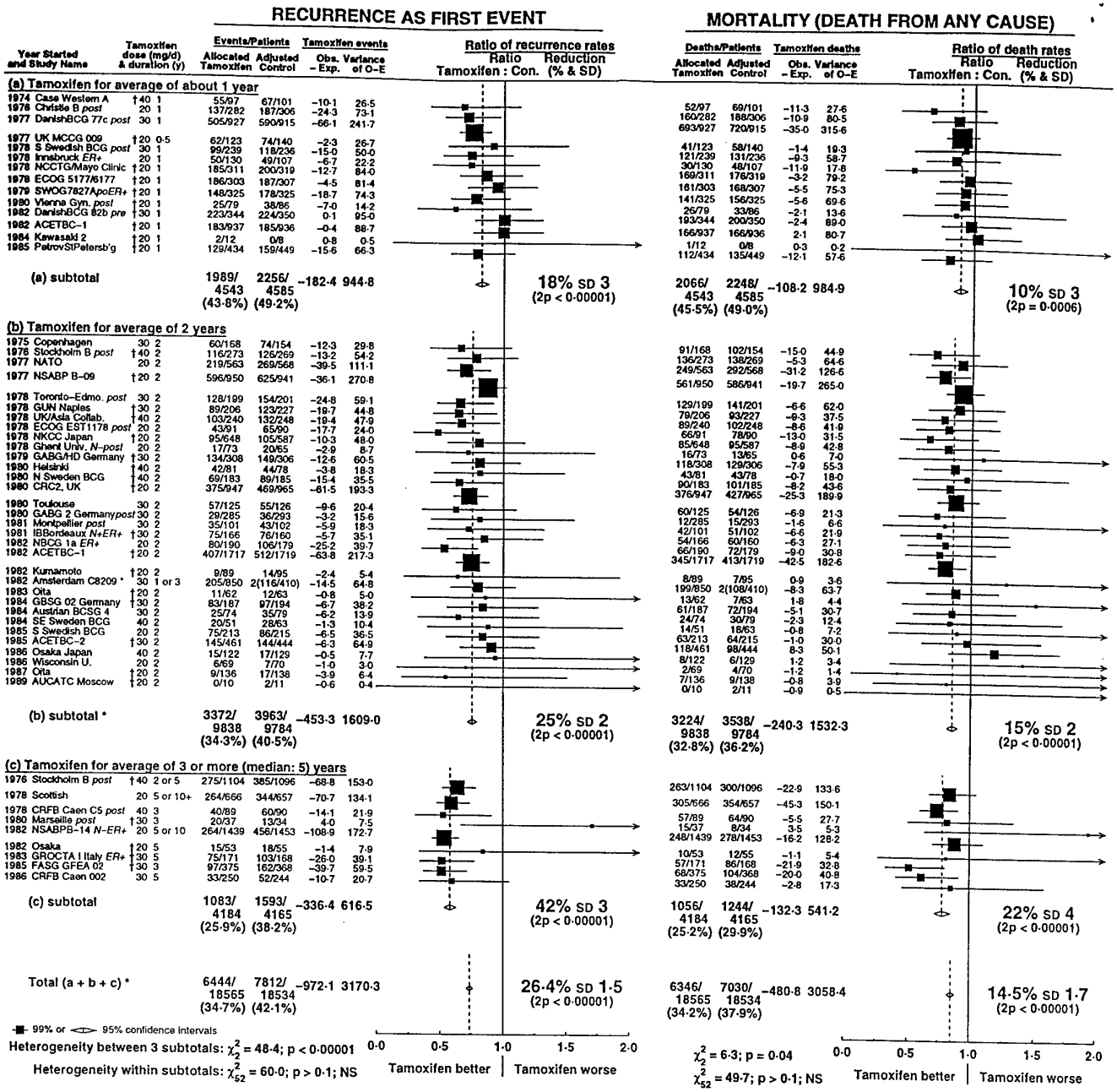


Figure 1: Separate results from all 55 tamoxifen trials, subdivided by scheduled duration of adjuvant tamoxifen. Left: recurrence as a first event (including contralateral breast cancer, and censoring at the time of death from another cause without any recurrence); Right: all-cause mortality. Each trial is described by one line of data, giving the year that randomisation began, an abbreviated trial name, and the adjuvant tamoxifen schedule (mg/day and duration in years, with † indicating randomisation of tamoxifen plus chemotherapy versus the same chemotherapy alone), followed by the recurrence and mortality analyses. The area of each black square is proportional to the amount of information contributed by the trial it describes, so larger squares are associated with shorter confidence intervals (i.e. with more informative results). Subtotals for the trials of 1, 2 and about 5 years of tamoxifen are provided, as are the χ^2 tests for heterogeneity between these subtotals. Tests for trend with respect to the median tamoxifen duration (1, 2 or 5 years) yield χ^2_1 = 48.4 for recurrence (2P<0.00001) and χ^2_1 = 6.2 for mortality (2P=0.013). (* For balance, the 410 control patients in the only 3-way trial count twice in the "adjusted control" totals; all the other trials were approximately evenly randomised.)

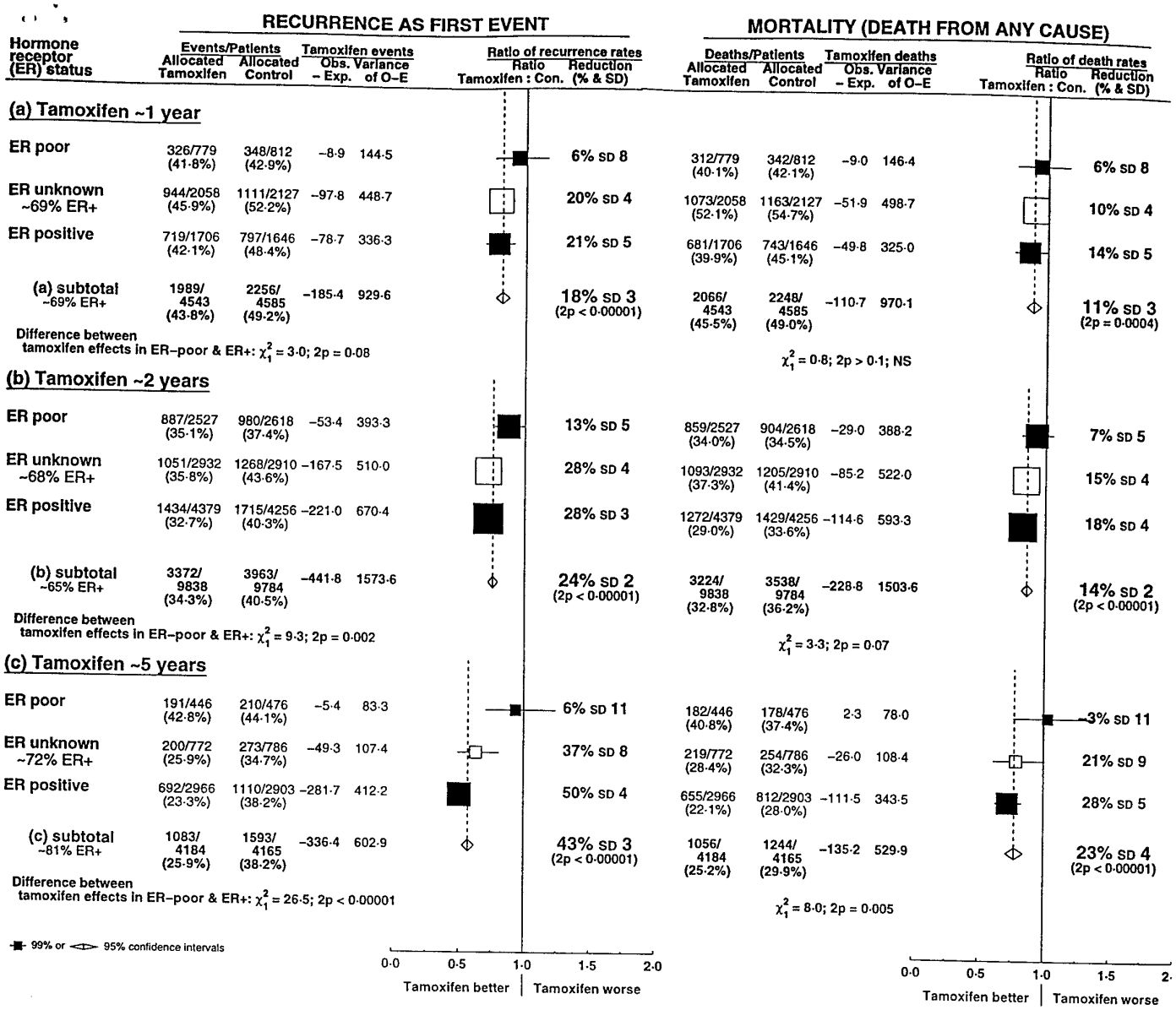


Figure 2: Proportional risk reductions, subdivided by tamoxifen duration and by ER status. Left: recurrence; Right: mortality. Each line describes a subtotal, combining the results from particular types of women in particular categories of trial. Here and in later Figures, where some women have tumours of unknown ER status an estimate is given of the proportion who, if they had been tested, would have had ER positive tumours (estimated as half the women aged under 50, and three-quarters of the others[7]). Within each tamoxifen duration category, the tests for heterogeneity relate to differences between the results for ER-poor, ER unknown and ER positive. For the 18,000 women with ER positive disease, the trend test for increasing benefit with increasing tamoxifen duration yields χ^2_1 = 45.5 (2P<0.00001) for recurrence and χ^2_1 = 5.6 (2P=0.018) for mortality. For the 8000 women with ER-poor disease, the trend test yields χ^2_1 = 0.02 (NS) for recurrence and χ^2_1 = 0.53 (NS) for mortality.

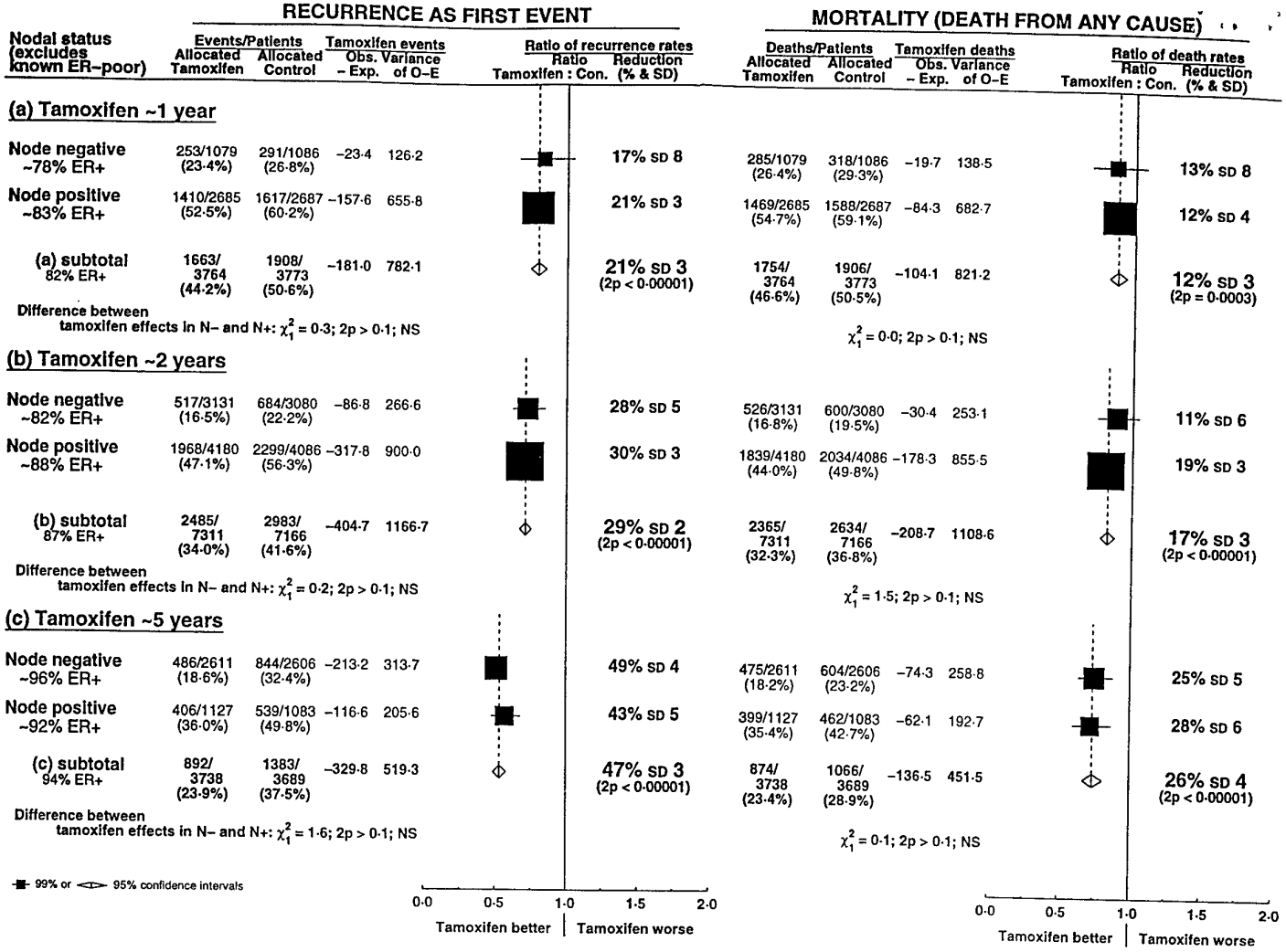


Figure 3: Proportional risk reductions, subdivided by tamoxifen duration and by nodal status (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. Although women with ER-poor disease have been excluded, the ER status was unreported for more than one-third of those that remain, and an estimate of the overall proportion who would, if tested, have had ER positive disease is given for each line of analyses. Overall, the estimated proportions with ER positive disease are about 82%, 87% and 94% respectively in the trials of 1, 2 or about 5 years of tamoxifen. The tests for trend between the effects of 1, 2 and about 5 years of tamoxifen in these predominantly ER positive women yield $\chi^2_1 = 52.0$ for recurrence (2P<0.00001) and $\chi^2_1 = 8.8$ for mortality (2P=0.003).

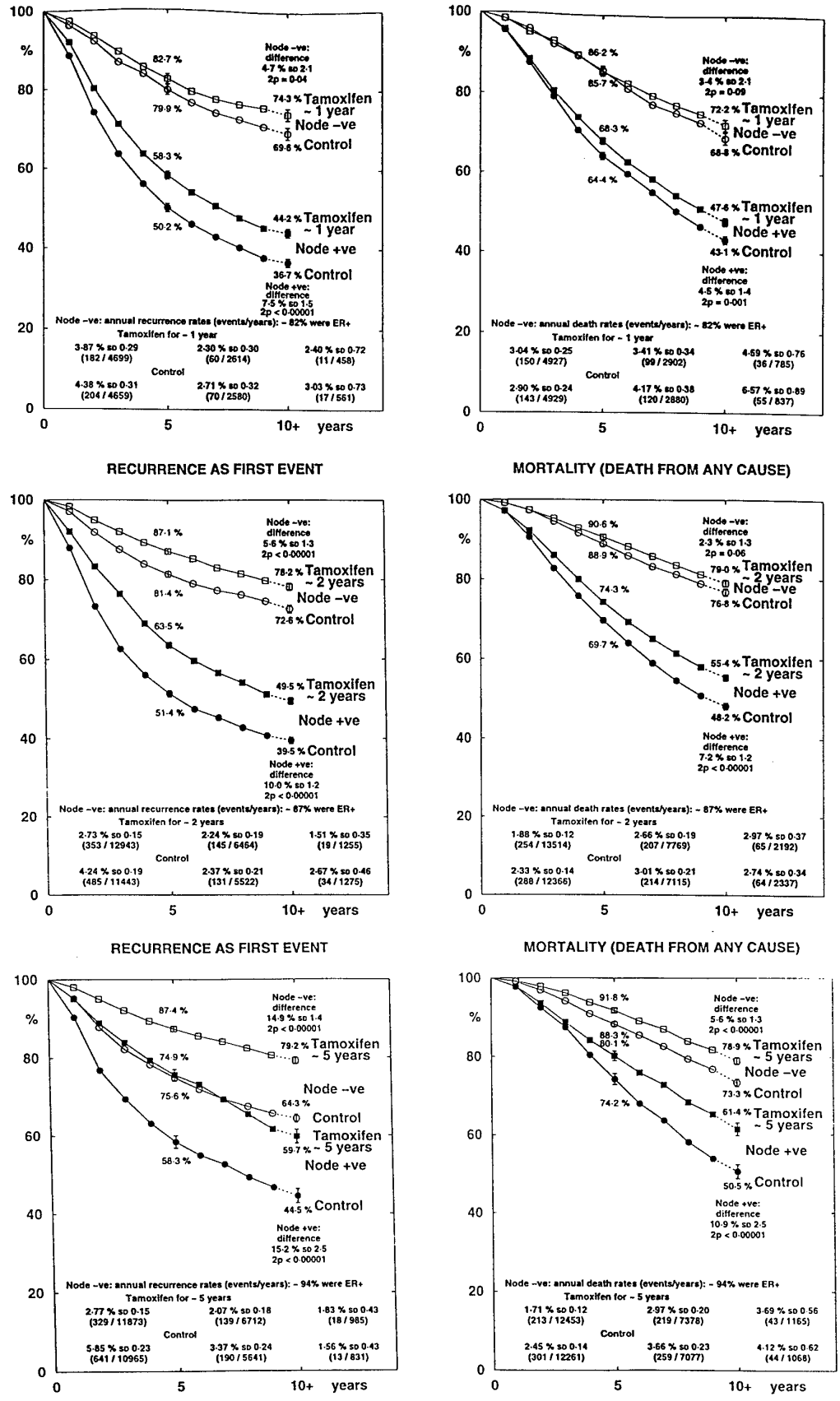


Figure 4: Absolute risk reductions during the first 10 years, subdivided by tamoxifen duration and by nodal status (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. The values for the tamoxifen and control patients at 5 and at 10 years, and the absolute differences in 10-year outcome, are given beside each pair of lines. For women with node-negative disease, the annual event rates during years 0-4, 5-9 and 10+ after randomisation are given at the foot of each box, together with their standard deviations (SD) and the numbers of events (and "woman-years" at risk) on which they are based.

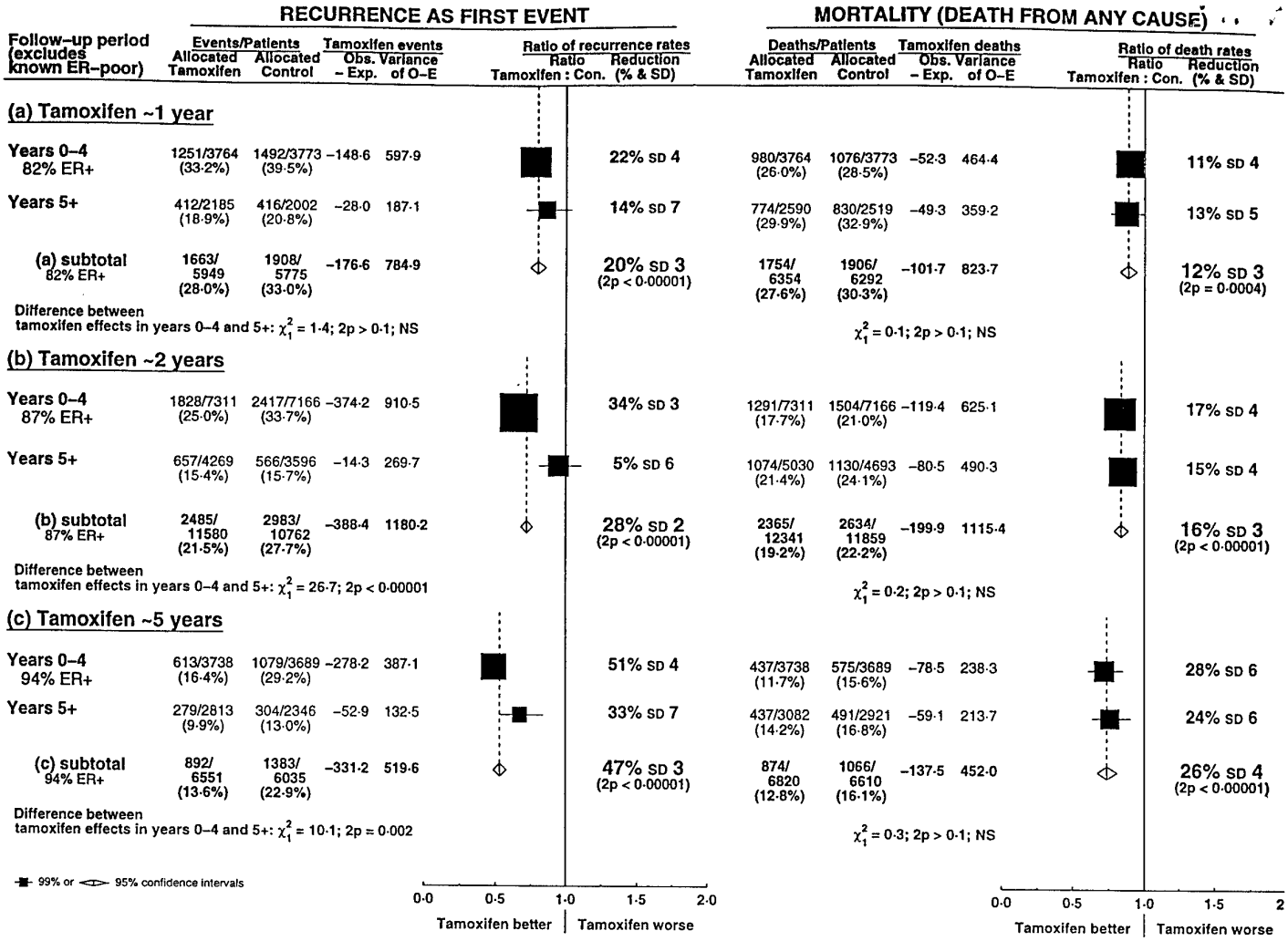


Figure 5: Proportional risk reductions during the first five years (0-4) and later, subdivided by tamoxifen duration (after excluding women with ER-poor disease). Left: recurrence; Right: mortality.

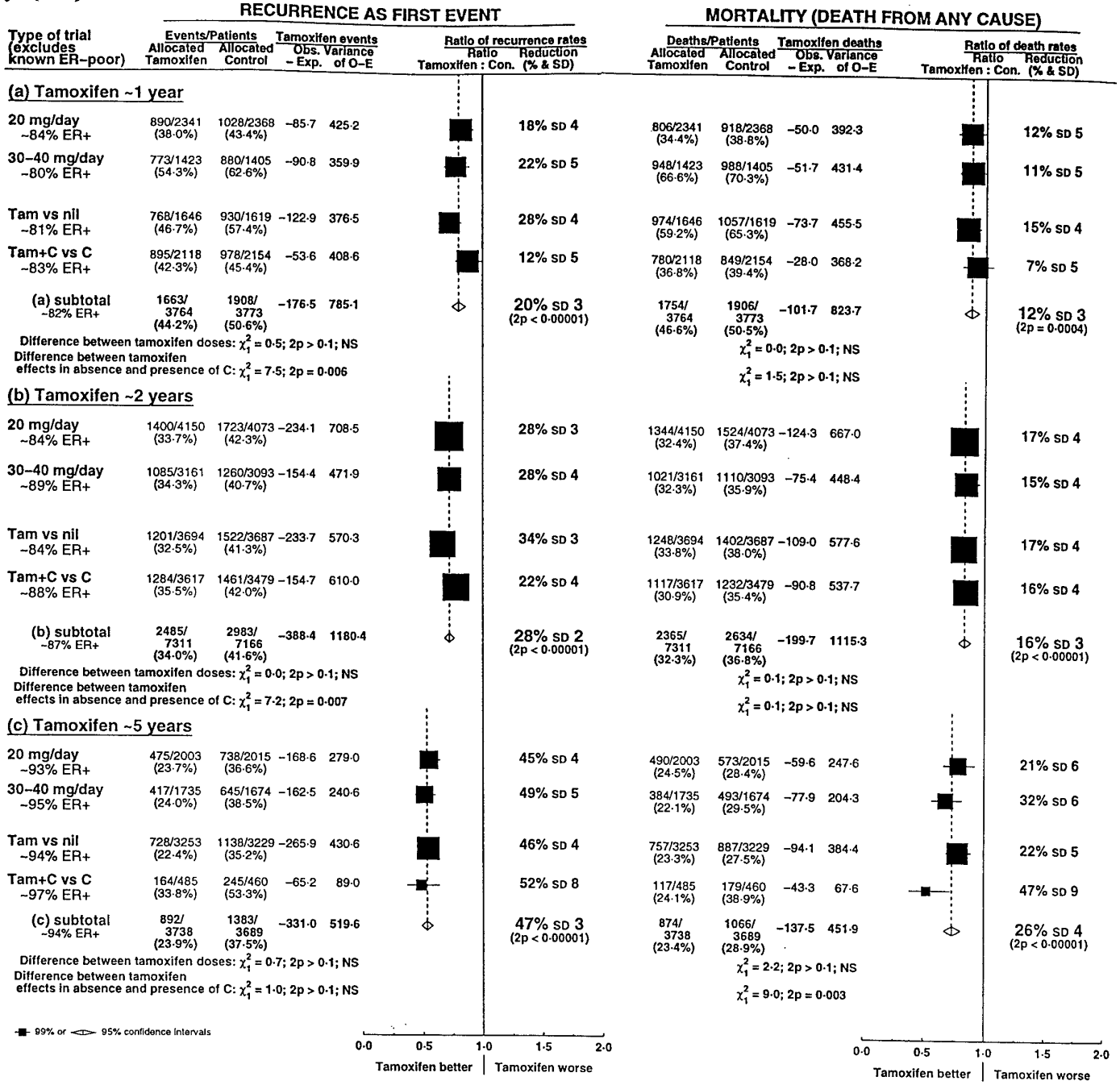


Figure 6: Proportional risk reductions, subdivided by tamoxifen duration and either by daily tamoxifen dose or by whether women were all to avoid chemotherapy or all to receive it (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. "Tam vs nil" denotes trials where neither group was scheduled to receive adjuvant chemotherapy, and "Tam+C vs C" denotes trials of tamoxifen plus adjuvant chemotherapy versus the same chemotherapy alone.

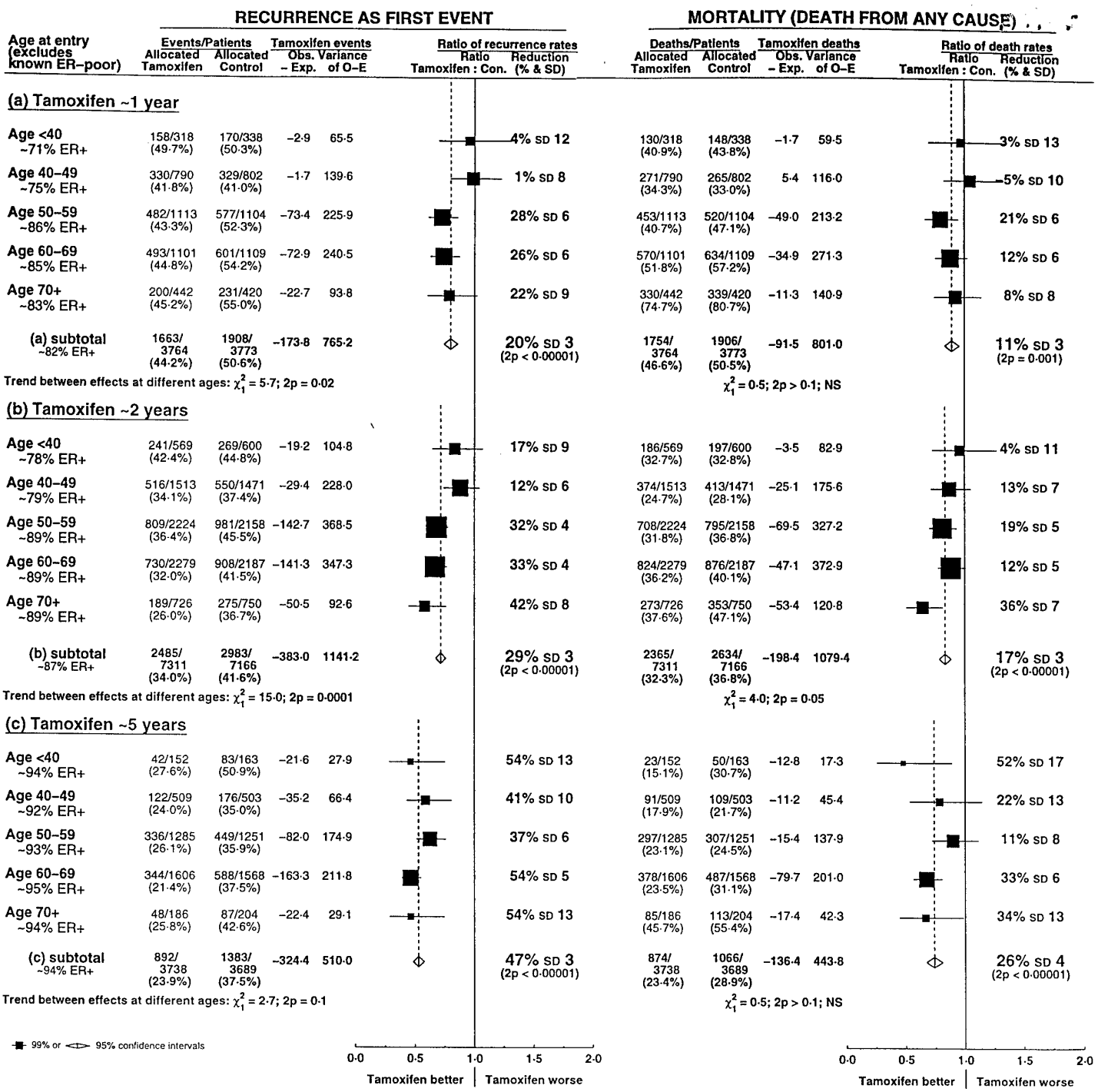


Figure 7: Proportional risk reductions, subdivided by tamoxifen duration and by age when randomised (after excluding women with ER-poor disease). Left: recurrence; Right: mortality. Tests for trend with respect to age are provided.

ADJUVANT TAMOXIFEN – LONGER AGAINST SHORTER

Newsletter No.3 November 1997

5 years of tamoxifen definitely produces lower recurrence rates than just 2 years, and may produce better survival

"5 years of adjuvant tamoxifen treatment is more promising than just 2 years, although even for this comparison, a definitive conclusion about long-term survival may not be possible until at least the year 2000."

Richard Peto JNCI (Dec 1996) 88, 1791-3

AIM: Randomise about **20,000** women to assess reliably the benefits and risks of **5 extra years** of adjuvant tamoxifen in early breast cancer

Woman on tamoxifen for some time, and UNCERTAIN whether to STOP NOW or CONTINUE

R A N D O M I S E

STOP	**CONTINUE**
TAMOXIFEN NOW	5 MORE YEARS

To be RELIABLE, the study must be LARGE — to be LARGE, it must be SIMPLE

5 years versus longer tamoxifen

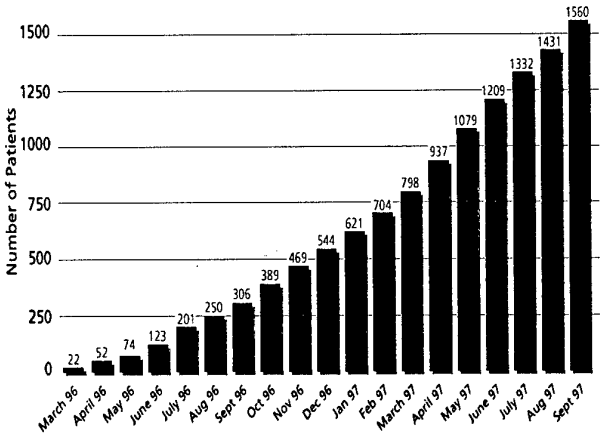
"But, neither direct nor indirect randomised comparisons can yet address the question of whether substantially more than 5 years of adjuvant tamoxifen treatment will yield better long-term survival. The continuing disagreement as to whether longer treatment is promising....will probably be resolved only by long-term follow-up of substantially larger numbers of patients than those in the existing trials. If the trials of different tamoxifen durations that are currently randomising new patients can achieve really large-scale recruitment before the year 2000, then they will yield preliminary findings in 2005 and reliable findings in 2010"

Richard Peto JNCI (Dec 1996) 88, 1791-3

Making ATLAS work: keep it SIMPLE!

SIMPLE PATIENT ENTRY
NO EXTRA TESTS
FREE TAMOXIFEN
SIMPLE ANNUAL FOLLOW-UP

Worldwide accrual in ATLAS



1500+ and increasing fast!

"Prolonging tamoxifen beyond 5 years could provide additional benefit - but we don't know yet. The answer will be relevant not just to tamoxifen, but hormonal therapy in general. With more than 1 million women already on tamoxifen, it is an important question to answer and it should be possible to randomise 10 or 20 thousand women into ATLAS."

Dr Christina Davies
ATLAS Coordinator

Helen Monaghan,
ATLAS Administrator

"If you have not yet requested ethics approval, **please** send the protocol to your local committee. Obtaining ethics approval is usually easy. After entering the first few patients, doctors find ATLAS easy and it provides a solution to their uncertainty about tamoxifen duration....."

If you might like to join ATLAS or if you need help or advice, then contact

ATLAS Office
Clinical Trial Service Unit
Radcliffe Infirmary
Oxford, OX2 6HE England
tel: +44 1865 794569
fax: +44 1865 316116
e-mail: atlas@ctsu.ox.ac.uk

To take part in ATLAS:

Contact ATLAS office for trial materials

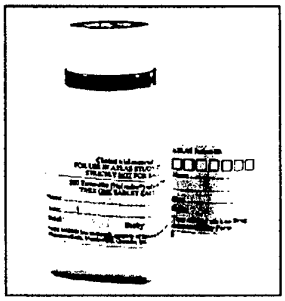
Obtain local ethics approval

Identify eligible patients

Randomise
(by telephone, fax, mail or e-mail)

Annual follow-up only

Randomise your first few patients, then it's easy!



FREE tamoxifen

Free tamoxifen is available for all patients in ATLAS randomised to CONTINUE treatment for 5 years. **Please contact the ATLAS office in Oxford to obtain your extra free supply.**

Identifying potential ATLAS patients
Xavier Bonfill, National Coordinator, Spain

Dr Xaviar Bonfill
National Coordinator
SPAIN

Identifying patients for ATLAS is not complicated: the main eligibility criterion is UNCERTAINTY about whether, after a few years on tamoxifen, a woman should stop, or continue her tamoxifen for a few years longer. As long as there is uncertainty, and the woman is currently free from any clinical evidence of disease, she is eligible. There are different ways to find patients depending on the resources available. **The main aim is to maximise the number randomised.**

Required features for eligibility
• currently on tamoxifen • uncertain whether to STOP tamoxifen or CONTINUE for a few extra years • currently disease free of breast cancer

Category	Eligible ?
• Any type of breast cancer	✓
• Pre-menopausal	✓
• Post-menopausal	✓
• Node negative	✓
• Node positive	✓
• ER+	✓
• ER poor	
• ER untested/unknown	✓
• Any type of initial surgery	✓
• Any other previous adjuvant therapy	✓

TIPS for identifying potentially eligible patients

- Whenever a woman on tamoxifen attends follow-up, consider her for ATLAS
- Flag potentially eligible patients' notes and either invite to attend clinic or consider them for the trial when they attend routine follow-up
- If possible, make a list of women on tamoxifen - a **"Tamoxifen Register"**- through established data sources (e.g. hospital register, pharmacy register, breast cancer clinic, surgical files etc.) and update it regularly
- Discuss ATLAS with other doctors in your hospital caring for women on tamoxifen and display information about ATLAS in the hospital, waiting rooms, etc.

Informed consent: A few tips

John Forbes, National Coordinator, Australia/New Zealand

In ATLAS, patients give written consent before joining (see figure 1). The concerns which different doctors and patients have about the trial and about informed consent will be different - both need help in understanding the process. However, irrespective of the trial, doctors should always act in the best interests of the patients, and should routinely discuss the various options for management including stopping or continuing tamoxifen: ATLAS provides a framework for this.

Informed consent is made easier in ATLAS because the trial is asking a question that is obviously relevant to a large, well-defined group of women. Moreover, this question of longer versus shorter hormonal therapy - not just longer versus shorter tamoxifen - will be of persisting relevance. Both treatment arms in ATLAS are standard forms of care and tamoxifen is known to be relatively non-toxic. There should be no increased costs for the patient: tamoxifen can be provided free of charge patients in both arms are followed up without extra tests, or follow-up visits beyond those in routine practice.

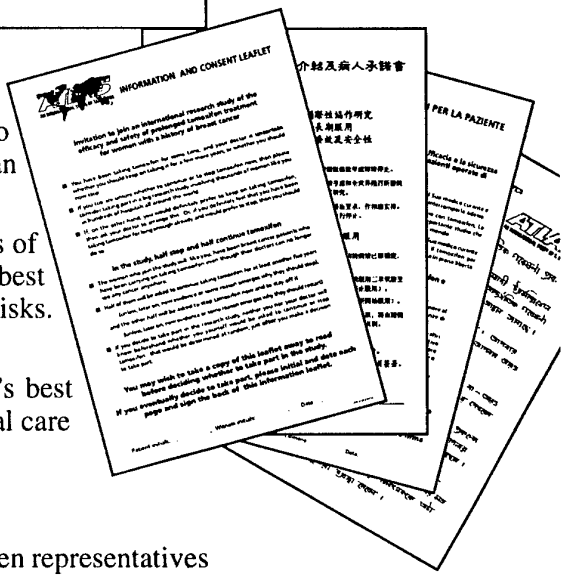
Typical questions from a potentially eligible woman

- Which do **you** think is better for me: STOPPING or CONTINUING?
- Will my breast cancer come back if I don't join the study?
- Will I get endometrial cancer if I stay on tamoxifen?

Dr John Forbes
National Coordinator
Australia/New Zealand

TIPS for getting consent

- Whenever possible, provide **advance information** to patients about the trial so that they have time to consider whether to join or not. Where possible, use **nurse counsellors** who can discuss the trial with the woman before and after joining
- Explain that **uncertainty** exists about the risks and benefits of both stopping **and** continuing tamoxifen: either might be best for the woman and both options will have benefits and risks. ATLAS is trying to find the overall balance
- Being in a study like ATLAS **is** in the individual woman's best interests: both stopping or continuing may represent optimal care



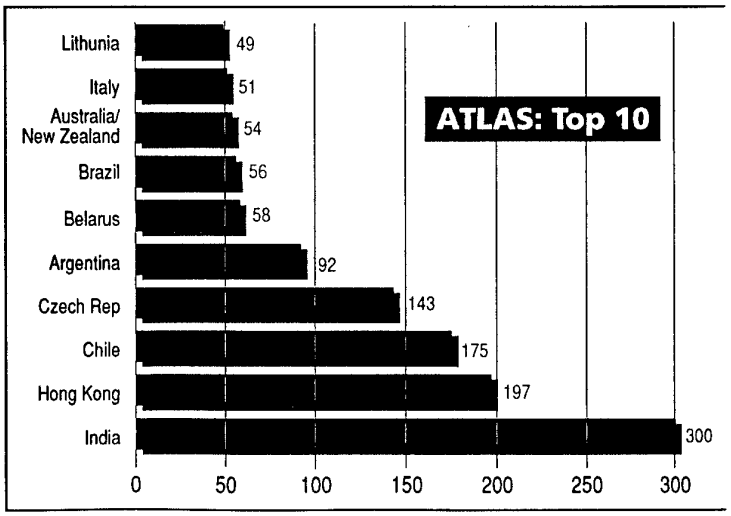
ATLAS Steering Committee meet in Oxford

The ATLAS Steering Committee met in Oxford in September, when representatives from all around the world discussed progress. The Committee reviewed the evidence on tamoxifen duration, including the preliminary results from various trials of longer versus shorter tamoxifen. **They concluded that it is only through large-scale randomised evidence in a study like ATLAS that a reliable answer will emerge about the optimal duration of tamoxifen and, in particular, about the effects of prolonging tamoxifen beyond 5 years.**

Message from Chris Williams, Chairman of the ATLAS Steering Committee

"Already 230 centres have ethics approval and more than 1600 women have been randomised. We know there are difficulties in organising research studies, but because ATLAS is simple and involves almost no extra work, doctors have been willing to join. ATLAS will help establish a framework for future studies that can answer important clinical questions about the management of breast cancer."

CONGRATULATIONS! Doctors in India have randomised more than 300 patients with the Regional Cancer Centre in Trivandrum entering 152 patients.



Survey of worldwide tamoxifen prescribing practice suggests wide variation in use, and confirms the need for ATLAS

A large survey (undertaken by the ATLAS Office) of tamoxifen prescribing practice showed major variation in the way clinicians use tamoxifen. Age and nodal status were found to be key factors influencing treatment with tamoxifen or not. The 1995 EBCTCG overview demonstrated that amongst ER positive women, about 5 years of tamoxifen produced similar benefits regardless of age or nodal status. However, in the survey, whilst 92% of clinicians used tamoxifen in post-menopausal women, only 46% chose to do so in younger women. Regardless of age, node negative women were less likely to receive tamoxifen. The ER status played an important role in whether clinicians used tamoxifen: 60% of clinicians would not use tamoxifen in younger women (ie pre-menopausal) with ER-negative tumours, whereas only 20% would not do so in a post-menopasual woman with ER-negative disease. Whilst there was substantial variation in the length of tamoxifen prescribed amongst clinicians, about 60% of clinicians would regularly prescribe tamoxifen for about 5 years.

KEY FINDINGS

- There is ***wide variation*** in tamoxifen prescribing practice and significant ***missed potential benefit***
- ER status and age are major determinants of tamoxifen use
- Nodal status also influences use
- Significant ***variation*** in length of tamoxifen used but ***> 60%*** clinicians use ***~ 5 yrs***

ER status

Previous trials have shown substantially less benefit if the ER-status of the primary tumour has been carefully tested and is completely negative. But, tamoxifen produces substantial benefit for women with even weakly positive ER measurements (and for those whose ER status has not been measured). Hence, some clinicians would not use tamoxifen if a definitely negative ER measurement was available.

Age & nodes: Missed benefit

Among women with a positive ER measurement, the previous trials find that a tamoxifen regimen of about 5 years produces substantial benefits, regardless of age or nodal status. However, while 92% of the surveyed clinicians would use tamoxifen routinely for post-menopausal women, only half would do so for pre-menopausal women. If half do so and half do not, they cannot all be right in their policies - and, the trials show that tamoxifen can help young women. Likewise, although tamoxifen is widely used for women with node positive disease, it is only routinely used by some but not all clinicians for node-negative disease, despite the trial results.

Duration

Where tamoxifen is used, the usual duration depended little on ER status, age or nodal status of the patient. However, it did depend on the doctor: over 60% would usually give tamoxifen for about 5 years, but some would usually give it for a shorter time, and some for a longer time, underlining the need for reliable information on the optimal duration.

How do you decide whether to use tamoxifen?
Are you uncertain about the optimal length of use?

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