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An international study designed to answer reliably whether, for women who have hormone sensitive early breast cancer (the most common type of breast cancer), 10 years of adjuvant tamoxifen (a hormone treatment) confers more benefit than just 5 years in terms of reducing the risk of relapse and improving overall, long-term survival: Adjuvant Tamoxifen - Longer Against Shorter (ATLAS)

Submission date 12/10/2012	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 18/10/2012	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 29/06/2015	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol

Background and study aims

We know from previous studies of many thousands of women with breast cancer that taking tamoxifen each day, for at least the first few years after surgery, reduces the risk of the breast cancer returning. Tamoxifen does this by interfering with the effect of the natural female hormones on the growth of any traces of breast cancer that may have remained. What is not known, though, is exactly how long women should carry on taking tamoxifen. Most women nowadays receive treatment for about five years, but it might be that 10 years of tamoxifen could be even better. This is why we are doing this study, called ATLAS, to help find out reliably which treatment duration is best in terms of reducing the risk of the breast cancer coming back, and improving long-term survival.

Who can participate?

Any woman with breast cancer (where the cancer has been removed by surgery) and who has been taking tamoxifen for some time, and where the woman and her doctor are uncertain whether she should keep on taking it for a few more years, or whether she should now stop.

What does the study involve?

The ATLAS collaboration aims to randomly allocate many thousands of women to one of two

groups: one group stopping tamoxifen after some years of treatment and one group continuing for at least 5 extra years. Several hundred hospitals in many countries world-wide were invited to participate in ATLAS. After discussing the study with her doctor (and family/friends) a woman must sign an information and consent leaflet. Half of the women will be asked to continue taking tamoxifen for at least another five years (unless, later on, new evidence or some reason emerges why they should stop), and the other half will be asked to stop tamoxifen now and to stay off it (unless, later on, new evidence or some reason emerges why they should restart). No special tests or investigations are required to join the study and the woman's own doctor always remains responsible for her wellbeing. There is just a short annual follow-up form which asks for one line of information on the current status of each woman in the study. All information is treated in strict confidence and stored securely at the central study office in Oxford. No individual woman is identified in the study results.

What are the possible benefits and risks of participating?
We very much hope that taking tamoxifen for longer than a few years will provide extra protection against the breast cancer returning and as a result will save many extra lives, and that there will be enough extra benefit to outweigh any side-effects. We know that there is a small risk that tamoxifen will cause cancer of the lining of the womb (endometrium) - which, if caught early, can be successfully treated by hysterectomy. We also know, though, that a few years of tamoxifen has, so far, prevented many more breast cancers coming back than the few womb cancers it has caused. Tamoxifen might also increase the risk of an internal blood clot (thromboembolism), but this may well be counterbalanced by a reduction in the risk of having a heart attack because of the cholesterol-lowering effect of tamoxifen. It is only through studies like ATLAS that we will be able to estimate reliably the balance of benefits and risks of 10 years of tamoxifen compared with just 5 years, so that doctors can then ensure that they give their patients the optimal treatment as well as knowledgeably explaining how the benefits and risks balance out.

Where is the study run from?
ATLAS is coordinated by the University of Oxford's Clinical Trial Service Unit & Epidemiological Studies Unit, which has a very long history in conducting large international trials like this.

When is the study starting and how long is it expected to run for?
ATLAS started in 1995, completed recruitment of 15 262 women in March 2005, and all women had completed their 5 year trial treatment period by March 2010. Follow-up in ATLAS will continue until 2015 by which time, there should be clear answers on the main question being addressed.

Who is funding the study?
The study has received funding from Cancer Research UK, the UK Medical Research Council, the US Army Breast Cancer Research Program and the EU (Biomed Programme).

Who is the main contact?
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Study website
http://www.ctsu.ox.ac.uk/research/mega-trials/atlas/atlas-website

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2004-000735-29

IRAS number

ClinicalTrials.gov number
NCT00003016

Secondary identifying numbers
MHRA CTA: 21584/0002/001; EudraCT number: 2004-000735-29

Study information

Scientific Title
An international randomised trial, involving tens of thousands of women, of 10 versus 5 years of adjuvant tamoxifen in the treatment of oestrogen receptor positive breast cancer, to assess the effects on relapse free and overall survival

Acronym
ATLAS

Study objectives
The worldwide randomised evidence now shows that 5 years of adjuvant tamoxifen, following the initial management of early breast cancer, greatly reduces the risk of relapse and improves long-term survival. Tamoxifen is now used by about 1 million women worldwide, avoiding about 20,000 deaths from breast cancer annually. However, there is substantial uncertainty as to whether more than 5 years of hormonal treatment produces even greater benefit. The fundamental aim of ATLAS is to assess reliably the benefits and risks (in terms of recurrence of the disease and long-term survival) of prolonging adjuvant tamoxifen by an extra 5 years in breast cancer patients who have already had about 5 years of treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxford Tropical Research Ethics Committee, 06/01/2003, ref: 035-02

Study design
International multicentre randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Screening

Participant information sheet
Patient information sheet can be found at http://www.ctsu.ox.ac.uk/research/mega-trials/atlas/atlas-protocol (see pages 11-14)

Health condition(s) or problem(s) studied
Operable, oestrogen receptor positive breast cancer already trated with ~5 years of adjuvant tamoxifen

Interventions
Random allocation was either to stop tamoxifen immediately, using no placebo tablets and restarting endocrine therapy only if a definite indication was thought to have emerged, or to continue tamoxifen for another 5 years (total 10 years), stopping before then, or changing to another endocrine therapy, only if a definite contra-indication was thought to have emerged. The tamoxifen regimen used both before and during the trial treatment period was almost always 20 mg/day oral Nolvadex. (In countries where continuing up to or beyond 5 years was not affordable for many patients, ATLAS supplied free Nolvadex to enable a woman to receive 5 years of tamoxifen prior to enrolment in ATLAS and for the full 5-year post-randomisation period.) All other aspects of patient management were at the doctor's discretion.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tamoxifen

Primary outcome measure

1. Recurrence (loco-regional, contralateral or distant)
2. Breast cancer mortality

Secondary outcome measures
1. Overall mortality
2. Various first events before recurrence:
2.1. Cancer incidence (particularly uterine, including endometrial)
2.2. Hospital admissions for particular reasons (particularly uterine or vascular)
2.3. Cause-specific mortality

Overall study start date
01/03/1995

Completion date
01/12/2015

Eligibility

Key inclusion criteria
Women were eligible for randomisation if:
1. They had had early breast cancer (in which, by definition, all detected disease could be removed surgically)
2. They had subsequently been on adjuvant tamoxifen for several years and were still on it (or had stopped only recently, and could therefore resume treatment without much interruption)
3. They still appeared clinically free of disease (with any local recurrence removed and no distant recurrence ever detected)
4. Long-term follow-up appeared practicable; and, fundamentally,
5. Substantial uncertainty was shared by the woman and her doctor about whether to stop tamoxifen or to continue for several more years, so compliance with random allocation to stop or to continue both seemed likely. There were no restrictions on age, type of initial surgery or histology, hormone receptor status, nodal status or what other treatments had also been given.

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
10,000-20,000: 15, 262 women were randomised in ATLAS in total

Key exclusion criteria
Any perceived contraindications to continuing tamoxifen precluded entry. These were specified not by the ATLAS protocol but by the judgment of the responsible clinician. However, the protocol suggested as possible contraindications to tamoxifen continuation (and hence to trial entry):
1. Intended or actual pregnancy or breast feeding

2. Retinopathy
3. Need for coagulation therapy
4. Significant endometrial hyperplasia
5. Any other serious toxicity thought to be due to tamoxifen
6. Negligibly low risk of breast cancer death
7. Presence of another major life-threatening disease

Date of first enrolment
01/03/1995

Date of final enrolment
01/03/2005

Locations

Countries of recruitment
Argentina

Australia

Belarus

Belgium

Brazil

Chile

China

Colombia

Croatia

Cuba

Czech Republic

Egypt

England

Estonia

France

Greece

Hong Kong

India

Iran

Ireland

Israel

Italy

Japan

Latvia

Lithuania

Mexico

Netherlands

New Zealand

Oman

Paraguay

Poland

Portugal

Russian Federation

South Africa

Spain

Taiwan

Tunisia

Türkiye

United Kingdom

United States of America

Study participating centre

Clinical Trial Service Unit and Epidemiological Studies Unit
Oxford
United Kingdom
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Sponsor information

Organisation
University of Oxford (UK)

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Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Medical Research Council (UK)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
AstraZeneca* (UK)

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Funder Name
US Army Breast Cancer Research Program (USA)

Funder Name
EU-Biomed (EU)

Funder Name
*AstraZeneca had no involvement in the scientific design or management of ATLAS, which is sponsored by the University of Oxford, the host organisation of the Clinical Trial Service Unit and Epidemiological Studies Unit (the international coordinating centre of ATLAS).

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	09/03/2013		Yes	No