

December 2005

No. 2 Winter 2005-2006

Special points of interest:

- Progress so far
- Letter from Professor Dowsett
- The TA/01 team
- Meetings and events

Letter from Chief Investigator

Dear colleagues

All aromatase inhibitor (AI) trials published to date have indicated a prolonged disease-free survival rate for patients treated with AIs. One of the main aims of TA/01 is to build a tissue resource of tumours from ATAC patients and use them to study the molecular mechanisms of response to therapy in an attempt to guide future treatment decisions.

I'd like to say thank you to all who have contributed to this important project so far. We have collected a substantial number of blocks for the tissue resource and it

would not have been possible without the help of centre staff and of course the Principal Investigators and pathologists.

If you are a Principal Investigator whose centre is not currently involved in TA/01 and you would like to par-

ticipate, it is not too late to be part of the study. All you have to do is contact Jill Knox, Clinical Project Manager (contact details on back page).

With best wishes

Mitch Dowsett



Methodology

TA/01 (also known as TransATAC) is an accompanying translational research study to the ATAC trial which has demonstrated the superiority of anastrozole over tamoxifen as adjuvant therapy in early breast cancer at 33 months (The Lancet 2002, 359: 2131), 47 months (Breast Cancer Res Treat 2003, 77: 295) and 68 months (The Lancet 2005, 365: 60-2) follow-up.

Tissue microarray (TMA) technology is used to build the TransATAC tissue resource.

This allows very small amounts of tissue to be removed from the paraffin blocks that were prepared by pathologists to make the diagnosis of breast cancer.

Initial plans are to build the tissue resource and use it in preliminary studies to evaluate certain proteins by immunohistochemistry (IHC)

which have been suggested to be important in response to hormonal therapy (e.g., HER-2, EGFr, AIB1, AKT-phos and IGFR-1). Several hundred slides can be cut from TMAs so they will be available to support additional IHC studies of potential new biomarkers.

Inside this issue:

Study Progress	2
Response to TA/01	2
Publications	3
RNA Analyses	3
The TA/01 Team	4
FAQs	4

TA/01 Patient Population (RoW)

	N
Total patients in ATAC RoW	6504
Excluded:	
Patients randomised to combination arm & monotherapy ER/PgR negative patients	<u>-2532</u>
Eligible TA/01 RoW patient population	3972

December 2005

Study Progress

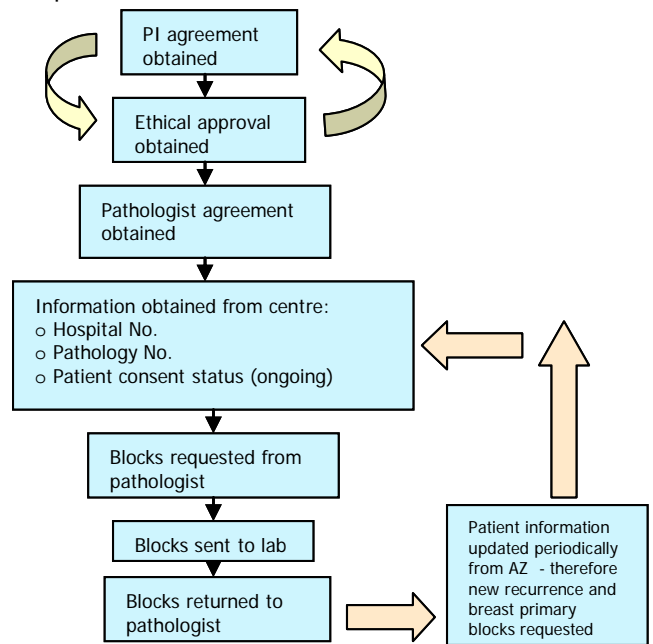
As the N American centres are co-ordinated separately by Prof D Craig Allred in Houston, Texas, USA, the figures presented are for the rest of the world (RoW).

Since TA/01 Update No 1 was issued in June 2004, the methodology of the study has changed slightly. Owing to the results from the ATAC trial, which showed no clinical benefit from the combination arm, we are no longer collecting primary tumour blocks from these patients.

To date, we have collected 1465 (37%) primary tumour blocks for eligible patients. Of these over 1300 blocks

have been arrayed in the laboratory at the Royal Marsden Hospital in London. This flow-

chart shows the steps that have to be taken to enable tumour block collection.



Area for invasion is marked

So far, primary tumour blocks from 1465 eligible patients have been collected

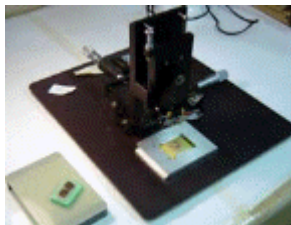
Response from Principal Investigators

Patients from the UK make up the majority of those eligible for TA/01. There are 1918 eligible patients from British centres and the response from Principal Investigators (PIs) has been excellent. PIs have agreed to provide tumour samples for 97% of UK patients.

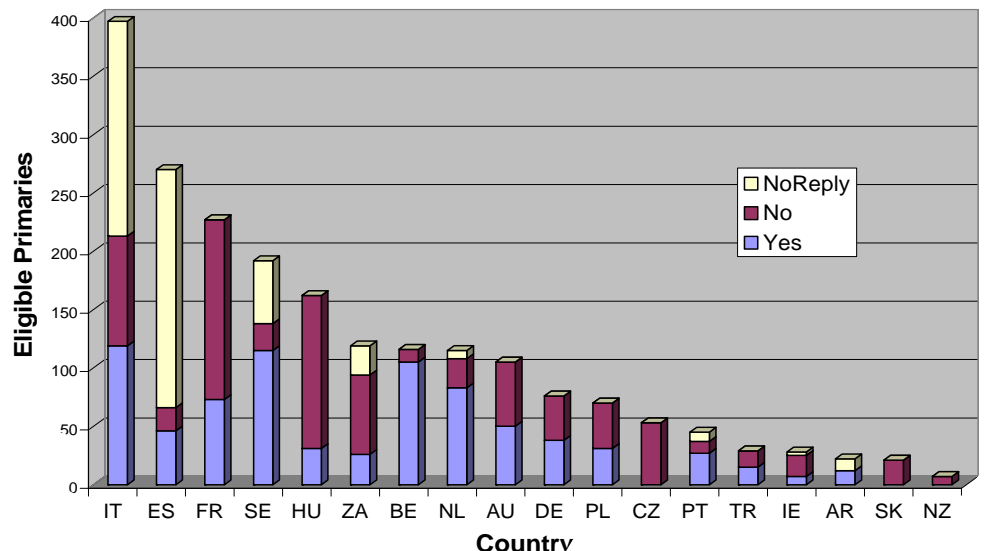
Possible reasons for this high

participation rate are that ethical approval for all UK centres was obtained before all other countries, ATAC monitors (who took communication to investigators by hand and were able to answer questions) for many UK centres work in the same unit as the TA/01 project manager and logistically dealing with UK centres is easier in terms

of language, geography and professional networks. The graph below shows the response from PIs from other countries.



Tissue arrayer prepares to identify area to take micro core sample from



ATAC Trial Publication



Mitch Dowsett and colleagues from the ATAC trial have recently published results from some exploratory analysis from the ATAC trial.

The idea for the paper was stimulated by the finding that anastrozole was superior to tamoxifen (in terms of disease-free survival and time to recurrence) but was restricted to patients with hormone-receptor positive dis-

ease. This led these researchers to retrospectively hypothesise that this benefit might differ according to PgR status.

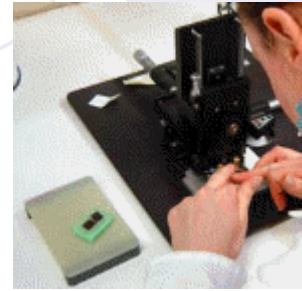
They found that time to recurrence was longer for patients on anastrozole than those treated with tamoxifen in both ER+/PgR+ and ER+PgR- subgroups but the benefit was substantially greater in the PgR- subgroup.

The authors point out that as this was an exploratory analyses, this effect should be considered as hypothesis generat-

ing and assessed prospectively in other trials comparing the adjuvant use of an aromatase inhibitor with tamoxifen.

Read the full article:

Dowsett, M et al; Retrospective Analysis of Time to Recurrence in the ATAC Trial According to Hormone Receptor Status: an Hypothesis-Generating Study. J of Clin Oncol 23: 7512-7517, 2005.



Micro core taken from recipient block for donor block

RNA Protocol Amendment Approved

Recent work by Soon Paik (who is a member of the ATAC Pathology Subcommittee) and his colleagues has demonstrated that we can predict the prognosis (in terms of recurrence) of tamoxifen-treated, node-negative breast cancer patients.

This exciting data inspired the idea for developing a protocol amendment for TA/01 in an attempt to predict prognosis

for patients treated with anastrozole.

In June 2005, we received ethical approval for the UK centres to take four sections of 10 micron thickness from each block for RNA analyses. Molecular profiles will be developed based on RT-PCR.

Ethical approval is underway for some other countries to be involved in these analyses too.

This will give us the opportunity to answer key questions about the response to hormone therapy in women which immuno-histochemistry (IHC) cannot identify.

Read more:

(Paik, S et al. A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. The New N Engl J Med 2004; 351; 27; 2817-2826).

Update:

RNA analyses to be carried out

Meetings and Events

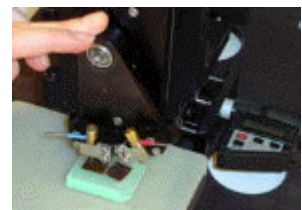
The TA/01 team meet every 2-3 months in London to discuss day-to-day issues of running the study. The ATAC Pathology Sub-committee meet every 6 months and last met in June 2005 in London. They will meet next to discuss analyses at the San Antonio Breast Cancer Symposium in December.

A poster entitled "Evaluation of Participation in TransA-

TAC, a Companion International Research Study to ATAC" was displayed at the Nottingham Breast Cancer Conference in September. The poster highlighted difficulties of retrospectively obtaining tumour blocks. It charted the responses to invitations to Principal Investigators for participation from Jan 2003-Feb 2005.

Several difficulties, such as

changes in legislation, lack of staff and time were noted and it was concluded that tumour blocks should be collected prospectively rather than retrospectively wherever possible.



0.6 mm micro samples are taken from the donor block

For all TA/01 queries, please contact

Jill Knox
Clinical Project Manager
Clinical Trials Group
University College London
Charles Bell House
67-73 Riding House Street
London W1W 7EJ

Phone: +44 (0)20 7679 9699
Fax: +44 (0)20 7679 9691
Email: j.knox@ctg.ucl.ac.uk
www.ctg.ucl.ac.uk/tao1

The study is co-ordinated by the Clinical Trials Group of the Department of Surgery at University College London (UCL). This experienced centre runs large multi-centre phase III randomised cancer clinical trials. Joan Houghton is the Director of the Clinical Trials Group and TA/01 is managed by Jill Knox. Norman Williams, Trial Co-ordinator for the ATAC trial, is also based there.

The laboratory work is carried out at the Department of Academic Biochemistry at the Royal Marsden Hospital (RMH) in London. Mitch Dowsett (Chief Investigator of TA/01) heads this department

and Janine Salter and Emma Quinn are responsible for arraying the tumour blocks.

The Royal Marsden is a leader in the field of cancer, with a successful record of innovation in nursing care, pioneering new treatments and the development of new anti-cancer drugs. The hospital's unique relationship with The Institute of Cancer Research brings new advances from the laboratory to ensure all patients can benefit from the latest treatments.

The Tissue Resource is under the guidance of ATAC Steering Committee who are advised by the ATAC Pathology Sub-committee. The Sub-

committee members are: Mitch Dowsett (chair), Craig Allred, Hugh Bishop, Jo Diver, Jack Cuzick, Ian Ellis, Joan Houghton, Denis Larsimont, Liz Mallon, Soon Paik, Francisco Sapunar, Hironobu Sasano and Norman Williams.



Janine and Emma from the Lab at RMH

Frequently Asked Questions

Q: What am I being asked to do?

A: We hope that you and your local pathology colleagues will join us in this project by providing tissue blocks from the ATAC patients under your care, which we can use to construct tissue microarrays before returning the blocks to your pathologist.

Q: Do pathologists receive payment?

A: The equivalent of £20 sterling per patient will be paid to Pathology Depts.

Q: What about future use of the tissue sample?

A: The use of the tissues for molecular analysis is subject to approval by the Pathology

Sub-Committee (with ratification from the ATAC Steering Committee) according to agreed guidelines. Investigators and other groups are welcome to submit proposals with priority being given to investigators who have supported the tissue collection.

Q: Will I be informed of results?

A: We will of course communicate results from this work to participating investigators prior to publication. In addition, results for individual patients may be sent to investigators on request, although these will not be for diagnostic use and are for research purposes only.

Main Objectives of TA/01

- assess biomarkers including HER-2 overexpression and EGF receptor (EGFr) status in excision biopsies
- identify differences in phenotypes of tumours at local relapse according to treatment
- identify differences in phenotypes of new primary breast tumours presenting in patients according to randomised treatment

AstraZeneca
INTERNATIONAL

breakthrough
breast cancer

TA/01 is supported by grants from AstraZeneca and Breakthrough Breast Cancer (a UK based charity)