

Genesis and Outcome of a Breast Cancer Trial to Develop the Aromatase Inhibitor Anastrozole

Anthony Howell^{1*}

Featured Article: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, ATAC Trialists' Group. *Lancet* 2005;365:60–2.²

Aromatase inhibitors block the enzyme aromatase, which is responsible for conversion of the adrenal derived precursor, androstenedione, to estrogen in tissues such as fat, muscle, and in the breast in postmenopausal women. Estrogens drive the proliferation and metastasis of estrogen receptor positive breast cancer (about 70% of the total). In the mid 20th century bilateral adrenalectomy was used to reduce postmenopausal estrogens but this major operation was replaced by use of the adrenal steroid hormone synthesis inhibitor, aminoglutethimide, although corticosteroid replacement had to be used. Aromatase inhibitors were the real advance, and the introduction of a simple once per day pill in the 1990s (1) lead the way to evaluation of their value, first in advanced breast cancer against standard therapy of tamoxifen or megestrol acetate (2) and then, quite rapidly, to the initiation of trials of therapy given after surgery to prevent relapse (adjuvant therapy).

In the mid-1990s tamoxifen was the standard adjuvant endocrine therapy and was of major importance to public health because it reduced deaths from breast cancer by about one third. Michael Baum, a well-known innovative breast surgeon, then at the Royal Marsden Hospital in London (who had performed the first adjuvant tamoxifen trial), with close colleagues decided to compare tamoxifen with anastrozole and with both drugs together in a three arm trial that we called ATAC (Arimadex, Tamoxifen Alone or in Combination). As is often the case the first design was written on the back of an envelope. Discussions with staff at AstraZeneca were met with enthusiasm and a protocol

was written with statistical input from Professor Jack Cuzick, who had been involved as statistician in a number of other breast cancer trials. The protocol was submitted to the appropriate Ethics Committee and our problems began. Because tamoxifen was so effective, the Ethics Committee dismissed the use of anastrozole alone saying that tamoxifen was so successful that women's lives could not be put at risk by omitting tamoxifen in any arm. They demanded that a two arm trial design of tamoxifen vs tamoxifen and anastrozole should be pursued. Thankfully they were persuaded to change their minds and the three arm trial was initiated with the first patient (of over 9000 worldwide) being randomized in Manchester (UK) in June 1996. The first planned statistical analysis was performed in 2002 and the results were reported by Michael Baum, the first Chairman of the Trial Steering Committee, at the San Antonio Breast Cancer Symposium in December 2002, indicating a significant reduction in the number of relapses in women taking anastrozole (treatment duration 5 years) compared with tamoxifen. The data indicated that, if anything, the combination was inferior to tamoxifen and thus, if we had not persuaded the Ethics Committee to change its mind, we would have a null result and anastrozole would not be the widespread preferred treatment for early breast cancer that it is today.

I had the privilege, as the second Chairman of the Trial Steering Committee, of presenting the more mature results of the ATAC Trial at the 2005 San Antonio Breast Cancer Symposium. The *Lancet* agreed to publish the paper, which subsequently became a citation classic, on the same day as my presentation. Publication resulted in a sea change in the adjuvant treatment of breast cancer and the drug was called a "blockbuster" by the company because of its international widespread use (and sales!). At that time we reported that there was a reduction of 23% in breast cancer relapse and a reduction of 42% in contralateral breast cancer in women taking anastrozole compared with those taking tamoxifen. Such reductions were subsequently confirmed in trials testing the other two potent aromatase inhibitors, letrozole and exemestane.

As befits a major trial (and a Citation Classic!) the trial has produced a series of important additional observations. For example, we showed no decrement in quality of life using anastrozole (3), a reduction in

¹ Manchester Breast Centre, The Christie NHS Foundation Trust, University of Manchester, Manchester, UK.

* Address correspondence to the author at: Manchester Breast Centre, The Christie NHS Foundation Trust, University of Manchester, Wilmslow Rd., Manchester M20 4BX, UK. E-mail anthony.howell@christie.nhs.uk.

Received January 13, 2012; accepted January 18, 2012.

Previously published online at DOI: 10.1373/clinchem.2011.181206

² This article has been cited more than 975 times since publication.

tamoxifen-associated gynecological problems (4), and new analyses that help predict who should be treated (5). Patients (to whom we owe enormous thanks), remain blinded to their therapy and follow-up continues to determine the long-term effectiveness and toxicity of anastrozole up to at least 20 years from randomization.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

References

1. Plourde PV, Dyroff M, Dukes M. Arimidex: a potent and selective fourth-generation aromatase inhibitor. *Breast Cancer Res Treat* 1994;30:103–11.
2. Jonat W, Howell A, Blomqvist C, Eiermann W, Winblad G, Tyrrell C, et al. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. *Eur J Cancer* 1996;32A:404–12.
3. Fallowfield L, Cella D, Cuzick J, Francis S, Locker G, Howell A. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol* 2004;22:4261–71.
4. Duffy S, Jackson TL, Lansdown M, Philips K, Wells M, Clack G, et al. The ATAC adjuvant breast-cancer trial: six-year results of the endometrial subprotocol. *J Obstet Gynaecol* 2010;30:596–604.
5. Cuzick J, Dowsett M, Pineda S, Wale C, Salter J, Quinn E, et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. *J Clin Oncol* 2011;29:4273–8.