

Endocrine and Targeted Manipulation of Breast Cancer:  
Proceedings of the Sixth Cambridge Conference

*Supplement to Cancer*

## Endocrine and Targeted Manipulation of Breast Cancer: Summary Statement for the Sixth Cambridge Conference

**Steven E. Come, MD<sup>1</sup>**  
**Aman U. Buzdar, MD<sup>2</sup>**  
**James N. Ingle, MD<sup>3</sup>**  
**Stephen R. D. Johnston, MD, PhD, FRCP<sup>4</sup>**  
**Angela M. Brodie, PhD<sup>5</sup>**  
**R. Charles Coombes, MD<sup>6</sup>**  
**William R. Miller, PhD, DSc<sup>7</sup>**  
**Kathleen I. Pritchard, MD<sup>8</sup>**  
**Eric P. Winer, MD<sup>9</sup>**  
**Jo Anne Zujewski, MD<sup>10</sup>**  
**Paul E. Goss, MD, PhD, FRCP, FRCP<sup>11</sup>**

<sup>1</sup> Breast Cancer Program, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

<sup>2</sup> Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

<sup>3</sup> Division of Medical Oncology, The Mayo Clinic, Rochester, Minnesota.

<sup>4</sup> Department of Medicine, Royal Marsden Hospital, London, United Kingdom.

<sup>5</sup> Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, Maryland.

<sup>6</sup> Department of Medicine, Breast Unit, Imperial College School of Medicine, London, United Kingdom.

<sup>7</sup> Breast Research Group, University of Edinburgh, Edinburgh, United Kingdom.

<sup>8</sup> Clinical Trials and Epidemiology, University of Toronto at Toronto Sunnybrook Regional Cancer Centre, Toronto, Ontario, Canada.

<sup>9</sup> Breast Oncology Center, Dana-Farber Cancer Institute, Boston, Massachusetts.

<sup>10</sup> Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland.

The Sixth Cambridge Conference on Endocrine and Targeted Manipulation of Breast Cancer was convened in Cambridge, Massachusetts on April 30 and May 1, 2007. The purpose of this multidisciplinary meeting of leaders in clinical and

<sup>11</sup> Breast Cancer Research, Massachusetts General Cancer Center, Boston, Massachusetts.

The symposium and educational proceedings publications were supported by educational grants provided by AstraZeneca Pharmaceuticals, Pfizer Inc, and Novartis Pharmaceuticals. Program management and Continuing Medical Education Sponsorship were provided by InforMEDical Communications, Inc, Carlisle, Massachusetts.

Dr. Come has acted as a consultant and member of the Speakers' Bureau and has received research support from AstraZeneca. He has also acted as a member of the Speakers' Bureau for Novartis and Pfizer.

Dr. Buzdar has received research funding from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Pfizer, and Taiho.

Dr. Ingle has acted as a consultant for Novartis.

Dr. Johnston has received research funding from AstraZeneca and GlaxoSmithKline, and has been a member of the Speakers' Bureau for GlaxoSmithKline.

Dr. Brodie is a member of the Advisory Board for AstraZeneca and Pfizer, and has received research support from AstraZeneca and Novartis.

Dr. Coombes has received research support from AstraZeneca and has received honoraria and research support from Pfizer.

Dr. Miller has received honoraria and is a member of the Speakers' Bureau for AstraZeneca, Novartis, and Pfizer.

Dr. Pritchard has acted on the advisory committee and received honoraria from Aefera; received research funding from Amgen; acted on the advisory

board, acted as a consultant, provided expert testimony, and received honoraria and research funding from AstraZeneca; acted as a consultant for Biomira; received research funding from Bristol-Myers Squibb; acted on the advisory committee, acted as a consultant, and received honoraria from Hoffmann-La Roche; received research funding from the National Cancer Institute of Canada; acted on the advisory board, acted as a consultant, and received honoraria and research funding from Novartis; acted on the advisory board, acted as a consultant, and received research funding from Ortho-Biotech; acted on the advisory committee, acted as a consultant, and received honoraria and research funding from Pfizer; acted on the advisory committee, acted as a consultant, provided expert testimony, and received honoraria and research funding from Sanofi-Aventis; and acted on the advisory committee, acted as a consultant, and received honoraria and research funding from YM Biosciences.

Dr. Winer is a member of the advisory board for AstraZeneca and Pfizer.

Dr. Goss is a member of the advisory board and Speakers' Bureau for AstraZeneca, GlaxoSmithKline, Pfizer, and Novartis.

Presented at Endocrine and Targeted Manipulation of Breast Cancer: Proceedings of the Sixth Cambridge Conference, Cambridge, Massachusetts, April 30–May 1, 2007.

Address for reprints: Steven E. Come, MD, Breast Cancer Program, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Room CC-913, Boston, MA 02215; Fax: (617) 667-9919; E-mail: scome@caregroup.harvard.edu

Received August 24, 2007; revision received October 8, 2007; accepted October 11, 2007.

basic research and patient treatment was to assess the most recent data in the field, articulate current best practices, and identify the next steps to advance both patient care and research. Topics included a review of data from major recent and ongoing trials of endocrine treatment in patients with early breast cancer and from studies combining endocrine therapy with other treatment. The current status of breast cancer prevention efforts was examined. Preclinical models of response and resistance, initial efforts to profile tumor response and resistance during endocrine therapy in patients, and new developments in pharmacogenomics were also highlighted. In this article, a synopsis of the key issues discussed, conclusions, and recommendations are summarized; these are presented at greater length in the individual articles and accompanying Open Discussions that comprise the full conference proceedings. In the 2 years since the Fifth Conference, we have gained valuable follow-up data from key trials in early breast cancer, which have helped to clarify both the efficacy and safety and tolerability of the available strategies for endocrine therapy. Observations using endocrine agents in combination with other treatment have been similarly extended. More detailed analysis of preclinical models has improved our understanding of resistance to endocrine therapy, and efforts to explore these and other mechanisms in the clinic are now underway. All of this has and continues to contribute to a growing understanding of how to optimize the use of endocrine agents in both treating and preventing breast cancer. *Cancer* 2008;112(3 suppl):673-78. © 2007 American Cancer Society.

**KEYWORDS:** endocrine therapy, breast cancer, estrogen, aromatase inhibitors, tamoxifen.

## **CLINICAL UPDATE**

### **Adjuvant Endocrine Therapy in Postmenopausal Women**

Hormone receptor-positive disease in postmenopausal women is the most common presentation of early breast cancer. Trials of adjuvant endocrine therapy comparing tamoxifen with aromatase inhibitors (AIs) or comparing 5 years of tamoxifen treatment with 2 to 3 years of initial tamoxifen followed by a switch to an AI to complete 5 years of total therapy have completed accrual and continue to accumulate follow-up data.

For the 2 trials—Arimidex [anastrozole], Tamoxifen, Alone or in Combination (ATAC) and Breast International Group (BIG) 1-98—that directly compare monotherapy with tamoxifen with an AI, there is an absolute improvement in disease-free survival of approximately 3% for women receiving the AI. However, there has been no difference noted with regard to overall survival in either trial to date, with a median follow-up of >90 months for ATAC and >51 months for BIG 1-98. The previously observed, statistically significant advantage in distant disease-free survival for letrozole versus tamoxifen in the BIG 1-98 trial was not present in the most recent analysis, which has additional follow-up but includes only women in the 2 monotherapy arms.

The trials that compare 5 years of tamoxifen treatment with tamoxifen given for 2 to 3 years fol-

lowed by an AI to complete 5 years of therapy—the Intergroup Exemestane Study (IES), the Austrian Breast Cancer Study Group 8 trial (ABCSCG 8), the Arimidex [anastrozole]-Nolvadex [tamoxifen] 95 study (ARNO 95), and the Italian Tamoxifen Anastrozole trial (ITA)—also demonstrate a reduction in disease recurrence of approximately 3% to 4% in the AI-containing treatment arms. A borderline overall survival advantage for the AI arm was observed in the IES trial if only the patients with hormone receptor-positive disease and unknown hormone receptor status (>98% of the total enrollment) were analyzed, and for the 3 smaller trials using anastrozole (ABCSCG8, ARNO95, and ITA) when the results were combined in a meta-analysis. Thus, at this point, a best approach for initial adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive tumors has not emerged. There has been a slight overall reduction in early disease recurrence for those women beginning treatment with an AI, but in the ATAC study, for example, this represents only 5 fewer distant recurrences per 1000 women during the first 2.5 years of treatment. Because there has been no overall survival advantage to date and little data regarding late recurrences, it is unclear whether the long-term outcome data will favor the initial use of an AI or some initial tamoxifen before conversion to an AI. The first

report on the 2 sequential arms of the BIG 1-98 trial will likely occur in 2008 and will be compared with the 2 monotherapy arms. However, the sequential arms are relatively small, and may be underpowered to resolve this issue. Currently, either monotherapy with an AI or initial tamoxifen followed by an AI is an acceptable strategy as is 5 years of tamoxifen therapy for those women who have tolerance or financial issues that might preclude the use of an AI. The initial use of an AI for the subset of women at the highest risk of early disease recurrence (those with larger tumors, positive lymph nodes, and possibly those who are HER-2/*neu* positive) could be considered pending additional data.

### **Extended Adjuvant Endocrine Therapy in Postmenopausal Women**

Women with hormone receptor-positive breast cancer face a prolonged risk of disease recurrence; the Oxford overview demonstrates that greater than half of the recurrences in this population occur >5 years after diagnosis.<sup>1</sup> The majority of these events are distant metastases. The National Cancer Institute of Canada (NCIC) MA.17 trial comparing 5 years of letrozole therapy with placebo in postmenopausal women who had completed 5 years of tamoxifen treatment reported a 4.6% absolute reduction in recurrence in the AI arm.<sup>2</sup> A significant improvement for overall survival was observed for lymph node-positive patients. This trial continues to yield important data with ongoing follow-up. The hazards ratio for disease recurrence with letrozole versus placebo declines progressively over time. By the fourth year of letrozole therapy, there is an 81% reduction in the rate of disease recurrence compared with the placebo arm. A new analysis has also demonstrated that introducing an AI several years after tamoxifen therapy has been completed can still significantly lower the risk of disease recurrence. The tolerability of extended adjuvant endocrine therapy among patients participating in the trial was good, although there is likely a selection bias because women who had the most difficulty with endocrine treatment during the initial 5 years might be less likely to pursue extended treatment. The NCIC MA.17 trial has set the precedent for longer endocrine therapy and spawned the design and initiation of multiple trials to evaluate the use of endocrine therapy for >5 years.

### **Adjuvant Endocrine Therapy in Premenopausal Women**

Tamoxifen remains the standard of care for adjuvant endocrine treatment in premenopausal women. However, there are 2 ongoing National Cancer Institute (NCI)-Cancer Therapy Evaluation Program

(CTEP)-sponsored trials that have been designed to evaluate the comparative efficacy of AIs and tamoxifen in this population: 1) a phase 3 trial with 3 treatment arms that compares tamoxifen alone with tamoxifen combined with ovarian function suppression and with exemestane combined with ovarian function suppression (the Suppression of Ovarian Function Trial [SOFT trial]) and 2) a phase 3 trial of 2 treatment arms that compares tamoxifen plus ovarian function suppression with exemestane plus ovarian function suppression (the Tamoxifen and Exemestane trial [TEXT trial]).

### **Safety of AIs in the Adjuvant Setting**

Further follow-up in the adjuvant endocrine trials in postmenopausal women and their substudies also has provided some reassurance with regard to the safety of AIs. Although excess bone loss and/or an increased risk of fracture have been reported with AI use in each of the adjuvant trials, it appears that the greatest bone loss occurs primarily within the first few years after the initiation of AI therapy. In the ATAC trial, fracture risk curves separate initially but converge during continuation of therapy and appear to overlap after the discontinuation of anastrozole. In the bone substudy of this trial, none of the 81 women who had a normal bone mineral density (BMD) scan at baseline and received anastrozole became osteoporotic during the 5 years of AI therapy. In the IES trial, BMD declined 4% in the first 6 months of exemestane treatment (and after tamoxifen discontinuation) and then approximately 1% per year thereafter. The net bone density loss at 60 months was approximately 2% for the sequence of tamoxifen followed by exemestane, which is comparable to the expected normal postmenopausal bone loss of approximately 2% to 3% over 5 years. Further data are available from the placebo-controlled NCIC MA.17 bone substudy, in which 226 patients (122 of whom received letrozole and 104 of whom received placebo) were enrolled. Patients' baseline characteristics and the median length of follow-up were similar in the 2 treatment groups. At 24 months, patients being treated with letrozole had a significant decrease from baseline in total hip BMD (-3.6% vs -0.71%;  $P = .044$ ) and lumbar spine BMD (-5.35% vs -0.70%;  $P = .008$ ). Letrozole was found to increase the urine N-telopeptide at 6 months, 12 months, and 24 months ( $P = .054$ ;  $P < .001$ ; and  $P = .016$ , respectively). No patient went below the threshold for osteoporosis in total hip BMD after baseline, but more women became osteoporotic based on BMD in the lumbar spine while receiving letrozole compared with placebo (4.1% vs 0%;  $P = .064$ ). It is interesting

to note that bisphosphonate use at the discretion of the treating physician occurred more frequently in the placebo arm compared with patients treated with letrozole (10.6% vs 4.1%, respectively;  $P = .07$ ).

Based on these data, women receiving an AI alone or tamoxifen followed by an AI should have a baseline BMD scan at the time an AI is initiated. If the patient's BMD is normal, it should be repeated approximately every 2 years while the patient receives treatment. Women with osteopenia or osteoporosis should be followed annually with BMD and receive appropriate therapy for bone loss. The presence of osteopenia or even osteoporosis is not an absolute contraindication to AI use.

AIs have no estrogen agonist effect and therefore do not stimulate the endometrium. Thus, in the randomized trials, tamoxifen, when compared with an AI, is associated with an increase in vaginal discharge, vaginal bleeding, endometrial thickness, and uterine cancer. An increase in the rate of hysterectomy has also been observed in women receiving tamoxifen, although the indications for the excess procedures cannot be discerned from the trials. Vaginal dryness as a result of estrogen depletion is common in women using AIs. Vaginal estrogens, which are often administered to treat this side effect, are absorbed systemically to some extent, although it is unclear whether this occurs at a level that could interfere with the efficacy of treatment.

There has been a nonsignificant increase in cardiovascular events observed in AI users in several trials. However, the event rate is extremely low overall. Lipid substudies have revealed a protective effect of tamoxifen on serum lipids, with relatively flat cholesterol levels during AI therapy. In the NCIC MA.17 lipid substudy, women who had normal serum lipid levels upon entering the trial maintained normal levels during 36 months of treatment with letrozole.

Although these data support the safety of AI therapy, these agents often prove more difficult symptomatically for patients than is captured in the initial clinical trial reports. Arthralgias and stiffness are common and are usually easily managed with reassurance or mild analgesia. However, some patients experience intolerable joint symptoms leading to the discontinuation of therapy.

### **Combining Endocrine Therapy with Other Standard Treatments**

Results of the Breast Intergroup 0100 trial suggest that endocrine therapy, in this case tamoxifen, should not be given concurrently with chemotherapy. However, this conclusion remains tentative, and to our knowledge no other trials to date have directly

addressed the issue of concurrent versus sequential use of endocrine and chemotherapies. Furthermore, there is no comparable data available with regard to the optimal schedule for combining AIs with chemotherapy. It is also unknown whether AIs should be given concurrently with or after primary breast cancer radiation therapy.

### **Prevention**

Several completed randomized trials have compared endocrine agents versus placebo for breast cancer prevention. Ten-year data from the International Breast Cancer Intervention Study (IBIS)-1 trial, which, unlike the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 prevention study was not unblinded, demonstrated a "carry over" effect for tamoxifen. There is in fact a greater benefit observed at 10 years than at the 5-year analysis. In the NSABP P-2 (STAR) trial, raloxifene was found to be equal to tamoxifen with regard to the reduction in invasive cancers but was less effective in preventing noninvasive cancers. There were fewer uterine cancers noted with the use of raloxifene than tamoxifen but the difference was not found to be significant. Prevention studies have established a very favorable therapeutic index for tamoxifen in women aged <50 years at the time of the initiation of treatment. To our knowledge, to date, raloxifene has not been studied in a randomized clinical trial for breast cancer prevention in premenopausal women.

Each of the adjuvant endocrine trials in postmenopausal women demonstrates that AIs are more effective than tamoxifen in reducing contralateral cancers. The planned NSABP P-4 prevention trial of letrozole versus raloxifene has not been approved by the U.S. National Cancer Institute (NCI). The NCIC MAP3 and IBIS-2 trials compare exemestane and anastrozole, respectively, with placebo; importantly, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MAP3 trial allows women who have received prior selective estrogen receptor modulator (SERM) therapy to be enrolled in this trial based on the observation of substantial contralateral breast cancer prevention in the NCIC MA.17 trial in women receiving letrozole after 5 years of tamoxifen therapy.

### **THE BIOLOGY OF RESPONSE AND RESISTANCE Preclinical Xenograft Studies**

Human breast cancer cells expressing estrogen receptor (ER) and engineered to express aromatase (MCF-7CA) grown as tumors in nude mice have demonstrated early up-regulation of HER-2/*neu* signaling during letrozole therapy. This is considered an

important mechanism of resistance to endocrine therapy; trastuzumab can reverse this acquired resistance due to long-term letrozole treatment. The scheduling of trastuzumab therapy is important in the xenograft model. Trastuzumab was found to be very effective in resistant tumors when introduced at the time of the development of resistance and given in addition to letrozole rather than instead of letrozole. This may have important implications for clinical trial design.

Cross talk between the estrogen and growth factor pathways with up-regulation of HER-2/*neu* and phosphorylation of mitogen-activated protein (MAP) kinase in the MCF-7 xenograft model can be prevented if the ER- $\alpha$  is targeted with fulvestrant simultaneous to the initiation of letrozole therapy. This preclinical observation is currently being evaluated in 2 ongoing clinical trials, which will be discussed.

### Combining Endocrine Therapy with Other Targeted Treatment

A variety of clinical trials have been and are being conducted to explore combinations of therapeutic agents in an effort to abrogate resistance to endocrine therapy. Based on MCF-7 xenograft and cell line data, the Fulvestrant and Anastrozole Clinical Trial (FACT) and the Southwest Oncology Group (SWOG) S0226 trials are evaluating the use of fulvestrant in combination with an AI in the first-line metastatic setting. The Study of Fulvestrant, Exemestane, and Anastrozole (SoFEA) trial is addressing the role of fulvestrant in combination with or without continued estrogen suppression at the time of disease progression during nonsteroidal AI therapy. Combinations of AIs with trastuzumab and with lapatinib are addressing the association between the up-regulation of HER-2/*neu* and endocrine resistance. Furthermore, there is the preliminary evidence that ER might be expressed in some women with ER-negative, HER-2/*neu* amplified breast cancer after treatment with trastuzumab, indicating the possibility that endocrine therapy could be a previously unrecognized option for these patients. This potentially important observation also is supported by preclinical data.

To our knowledge to date, trials combining tyrosine kinase inhibitors (TKIs), farnesyl transferase inhibitors (FTIs), or mammalian target of rapamycin (mTOR) inhibitors with endocrine therapy have been disappointing. Issues of target and patient selection and of trial design complicate the assessment of these strategies and results. Furthermore, there is a great deal of redundancy in many of these pathways. Thus, even an approach with appropriate target and

patient selection might fail if the targeted pathway is not completely inhibited by treatment.

### Profiling Response and Resistance to AIs in Women with Early Breast Cancer

The analysis of serial core needle biopsy specimens from women with early breast cancer is enabling the further investigation of preclinical findings and is providing important new insights. Gene expression arrays performed on tumor biopsies taken at baseline and after 2 weeks of exposure in women receiving neoadjuvant letrozole have revealed that numerous genes are altered during this brief interval. Tumors that ultimately manifest clinical resistance display heterogeneous profile patterns, suggesting that resistance in human breast cancer many involve a variety of mechanisms. Furthermore, gene expression changes that separate responding and nonresponding tumors do not appear to be those characteristically associated with estrogen dependence or with proliferation in these preliminary studies.

### Pharmacogenomics

Tamoxifen is converted to its active metabolite endoxifen by the enzyme cytochrome P450 (CYP) 2D6. Recent investigation has revealed significant genotypic variation in this enzyme, with variations noted among races and among individuals. Prospective analysis of a retrospective trial has revealed significant differences in outcome between extensive and poor metabolizers of tamoxifen. In addition, many commonly used medications including the selective serotonin reuptake inhibitors (SSRIs) paroxetine, fluoxetine, sertraline, and citalopram interfere with this enzyme, as does celecoxib. This is of particular concern because SSRIs are frequently prescribed to counter the menopausal symptoms associated with endocrine therapy. Potent and moderate CYP2D6 inhibitors should be avoided during tamoxifen therapy.

AIs act on the aromatase enzyme CYP19. Initial trials are underway to evaluate AI pharmacogenomics. Although pharmacogenomics is an area of investigation in endocrine therapy that is just beginning, it may contribute toward the better understanding of previously conducted trials. For example, it is possible that differences in outcomes between tamoxifen and AIs noted in early adjuvant trials might reflect the proportion of tamoxifen recipients who are poor metabolizers of that agent rather than an absolute slight superiority of AIs as a therapeutic class. Consideration must now be given to profiling not only the tumor but also the patient.

**UNRESOLVED ISSUES AND PRIORITIES FOR FUTURE RESEARCH**

Endocrine therapy has provided meaningful advances in breast cancer treatment and prevention, but some patients continue to develop recurrence and die of the disease. In the short term, more effort is needed to optimize what we have already achieved by reducing early attrition from endocrine therapy and by applying the demonstrated benefits of extended endocrine therapy to a greater proportion of patients. The long duration of risk of disease recurrence in patients with hormone receptor-positive breast cancer is increasingly recognized, but the side effects and complications of the endocrine therapy given to address this risk are also real. Thus, a mechanism to determine, with increased precision, which patients might be spared endocrine therapy altogether and those who should receive prolonged endocrine therapy would be of great value. This is true not only in the management of early breast cancer but even more so in the prevention setting, in which the “number needed to treat” is much greater. Sorting out these issues may be more important than choosing between available agents because data from existing trials suggest very similar levels of benefit.

More data are needed for premenopausal women and for the integration of endocrine therapy with other standard treatments as well as targeted biologic

agents. To properly assess targeted therapy, greater emphasis must be placed on the selection of the target, confirming that the patient population to be studied has a tumor that expresses the target, and on verification that the targeted pathway is effectively inhibited by the treatment. The complexity of breast cancer dictates a paradigm shift from empiricism toward translational research to identify the best designs for the next generation of clinical trials. Although cell lines and xenograft models have been extremely useful to date, an increasing emphasis on sampling human tumors is needed to better understand the apparent heterogeneity of hormone receptor-positive human breast cancer and mechanisms of resistance. Paired specimens prior to and after exposure to endocrine agents in neoadjuvant and preoperative non-therapeutic trials are of high value, as are biopsy specimens from tumors that continue to progress during endocrine therapy in the metastatic setting.

**REFERENCES**

1. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. *Lancet* 2005;365:1687-1717.
2. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* 2005;97:1262-1271.