Randomized Trial of Tamoxifen Versus Tamoxifen Plus Aminoglutethimide as Adjuvant Treatment in Postmenopausal Breast Cancer Patients With Hormone Receptor-Positive Disease: Austrian Breast and Colorectal Cancer Study Group Trial 6

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Purpose: To determine whether the addition of aminoglutethimide to tamoxifen is able to improve the outcome in postmenopausal patients with hormone receptor-positive, early-stage breast cancer.

Patients and Methods: A total of 2,021 postmenopausal women were randomly assigned to receive either tamoxifen for 5 years alone or tamoxifen in combination with aminoglutethimide (500 mg/d) for the first 2 years of treatment. Tamoxifen was administered at 40 mg/d for the first 2 years and at 20 mg/d for 3 years.

Results: All randomized and eligible patients were included in the analysis according to the intention-to-treat principle. After a median follow-up of 5.3 years, the 5-year disease-free survival in the aminoglutethimide plus tamoxifen group was 83.6% versus 83.7% in the monotherapy group (P = .89). The corresponding data for overall survival at 5 years were 91.4% and 91.2%, respectively (P = .74). More patients failed to complete combination treatment (13.7%) because of side effects as compared to tamoxifen alone (5.2%; P = .0001).

Conclusion: Aminoglutethimide given for 2 years in addition to tamoxifen for 5 years does not improve the prognosis of postmenopausal patients with receptor-positive, lymph node-negative or lymph node-positive breast cancer.


The crucial value of adjuvant endocrine treatment in early breast cancer has been illustrated most extensively with the antiestrogen tamoxifen. The first clinical trials for adjuvant therapy with tamoxifen were started as early as the late 1970s. The first investigation to demonstrate a definite survival advantage with adjuvant tamoxifen versus no adjuvant treatment was the Nolvadex Adjuvant Trial Organization study. Subsequently, the benefit of adjuvant tamoxifen was confirmed by the results of additional large, randomized trials, especially in patients presenting with strongly estrogen receptor (ER)-positive tumors. Thus, treatment with tamoxifen became standard care in postmenopausal hormone-responsive breast cancer. However, it has been hypothesized that the results of adjuvant tamoxifen may be improved by addition of other endocrine drugs. Not only may the antiestrogen fail to target tamoxifen-resistant cell clones, but the partially agonist action shown by this agent also raised certain concerns, particularly after its effect on the endometrium was disclosed some 10 years ago. The focus on tamoxifen in recent years has therefore been to understand its toxicity, to identify patients more likely to benefit from the drug, and to optimize duration of use.

For these reasons, addition of other antiestrogenic agents is now of interest in the search for a meaningful complement to, or perhaps substitution for, tamoxifen in the adjuvant treatment of breast cancer. By virtue of their peripheral mode of action, aromatase inhibitors are considered a particularly attractive class of drugs. They have been shown to effectively inhibit estrogen synthesis in such peripheral tissues as muscle, fat, and skin; normal breast stromal tissue; and breast tumor tissue.

Aminoglutethimide was one of the first aromatase inhibitors to become available for clinical use. It has been proven to effectively block estrogen production in the adrenal cortex, extraglandular peripheral tissues containing aromatase, and breast carcinoma tissue. Moreover, this first-generation agent has been proven to be effective in the treatment of postmenopausal women with advanced breast cancer. Approximately 30% of patients respond to aminoglutethimide treatment, a response rate similar to that obtained using tamoxifen. ER status was shown to be useful in predicting response to this form of treatment in metastatic disease.

On the basis of promising preliminary reports, the Austrian Breast and Colorectal Cancer Study Group (ABCSD) initiated a prospective, randomized clinical study (ABCSD Trial 6) in 1990 for postmenopausal patients with hormone receptor-positive breast cancer, comparing adjuvant tamoxifen plus aminoglutethimide.
thimide with tamoxifen alone to determine the relative efficacy of the combined approach.

PATIENTS AND METHODS

Study Design

After receiving approval by the relevant institutional review boards and ethics committees, the central data center in Vienna coordinated patients’ random assignment by telephone. In total, 52 departments and hospitals participated in this trial. Data collection, protocol review, data monitoring, and quality control were performed centrally.

Inclusion criteria were stage I or II breast cancer, postmenopausal status, ER and/or progesterone receptor (PgR) positivity, confirmed either by biochemical or immunohistochemical analyses. Patients were stratified by age (50 to 60, 61 to 70, and 71 to 80 years), tumor stage (≤ 2 to 2.1 to 3, and ≥ 5.1 cm), nodal involvement (none, 1 to 3, 4 to 10, and ≥ 11), histological tumor grading,16 surgical procedure used (breast-conserving treatment [BCT] or modified radical mastectomy [MRM], with or without radiotherapy), hormone receptor status (ER-positive/PgR-positive, ER-positive/PgR-negative, ER-negative/PgR-positive), and participating center. Adaptive randomization was applied according to Pocock and Simon.17

When patients’ written informed consent was obtained, trial participants were randomly assigned with equal probability to receive either tamoxifen alone for 5 years or aminoglutethimide (125 mg twice daily for the first week, 125 mg in the morning and 250 mg in the evening for the second week, and 250 mg twice daily thereafter) for the first 2 years of therapy in addition to tamoxifen for 5 years. For the first 2 years, tamoxifen was given twice daily at 20 mg. Increased tamoxifen dosage was chosen after reports that simultaneous administration with aromatase inhibitors may impair its level of bioavailability,18 with the objective of avoiding undertreatment in the combination arm. Tamoxifen administration was reduced to 20 mg/d after 2 years, taking into account a potentially increased risk for endometrial cancer.9,10

Patients

Postmenopausal patients with histologically confirmed primary unilateral breast cancer (pT1 to pT3a) with negative or positive axillary nodes (pT1a exclusively in the presence of positive ipsilateral axillary nodes) were enrolled on Trial 6. Patients were classified as postmenopausal following at least a 1-year interval since the last menstrual period. Otherwise, if the menopausal status was not clearly determinable, gonadotropins, follicle-stimulating hormone, and luteinizing hormone had to be in the postmenopausal range. Surgical treatment consisted either of BCT or MRM with obligatory negative margins plus complete axillary clearance, which included complete level I and II dissection. Patients were required to present a minimum of six axillary nodes on histology, whereas our recommendation was to histologically investigate at least 10 nodes. ER and/or PgR levels had to be ≥ 10 fmol/mg cytosol protein when performed biochemically or positive (+ or ++) when performed immunohistochemically.

Ineligibility criteria included evidence of distant metastases, premenopausal status, preoperative antineoplastic treatment and irradiation, previous malignancy (except cured squamous cell carcinoma of the skin or early cervical cancer), negative or unknown hormone receptor status, bilateral oophorectomy or radiation castration, and serious medical or emotional problems. Patients were required to begin treatment within 6 weeks after surgery.

Most patients undergoing BCT were treated with radiotherapy, which was optional in mastectomized patients and left to the discretion of the individual investigator.

All trial subjects received follow-up examinations every 3 months for the first 3 years and at 6-month intervals thereafter. Routine evaluation of patients included clinical examination and laboratory analyses (including carcinoembryonic antigen and cancer antigen 15-3 tests). Chest x-rays and liver ultrasound examinations were performed every 6 months, and mammography was performed annually, or more frequently if clinically indicated. Patients’ first relapse (locoregional, distant, or combined) and death served as primary end points for disease-free survival (DFS) and overall survival (OS), respectively. A local or regional relapse had to be confirmed histologically whenever possible.

Statistical Methods

All patient data were collected at the ABCSG Trial Center and processed and analyzed applying SAS software (SAS Institute Inc., Cary, NC).

When the required trial size was prospectively calculated, OS was estimated to be 70% for these patients on the basis of available data at that time. To detect a 5-year survival difference of 10% (65% to 75%) 5 years after termination of recruitment, with a two-sided test of significance of .05 and a power of 80%, we initially planned to recruit 666 trial participants over a period of 4 years. Because interim analyses revealed that overall prognosis was markedly better than expected in these patients, and thus that maintaining the initially planned trial size would yield an insufficient number of events, we subsequently increased target accrual three-fold.

OS was expressed as the number of months from the date of randomization until death. DFS was defined as the interval between the day of surgery and the first evidence of recurrent breast cancer. Patients who died because of confirmed reasons other than breast disease, without having experienced breast cancer recurrence, were considered as censored for all analyses. Time to first relapse or death was estimated and graphically presented according to the method of Kaplan and Meier.19 Differences between curves were assessed by Mantel’s log-rank test20 for censored survival data.

Furthermore, interactions were investigated between treatment and prognostic variables. The Cox proportional hazards model21 was applied in a univariate and multivariate manner to model the prognostic value of treatment, tumor grade, tumor stage, lymph node status, age, ER, PgR, surgical procedures, and radiotherapy on time to first relapse and survival time. Interactions of treatment with prognostic variables were investigated by including the product of individual hazards into the model. The proportional hazards assumptions were checked by integrating a time-dependent factor. All given P values are from two-sided analyses.

Toxicity was analyzed by comparing the patients’ highest grades of side effects experienced in each group within the first 2 years and the remaining 3 years of therapy.

All randomized and eligible patients with checklists were included in the analyses according to the intention-to-treat principle. The date of final analysis was March 30, 2000.

RESULTS

Patient Characteristics

From December 1990 to December 1995, a total of 2,021 patients were randomly assigned to ABCSG Trial 6. Nine were subsequently found to be ineligible after central source data verification by the Trial Center and were excluded from all analyses. The reasons for exclusion were the presence of distant metastases (two patients), presence of a second malignancy (one patient), and missing evaluation of hormone receptor content (two patients). Although premenopausal status was the reason for two exclusions, another particularly young patient was withdrawn from our study despite having undergone bilateral salpingo-oophorectomy and, thus, induction of postmenopausality. Finally, one woman was excluded because of decreased prothrombin time. Six of these ineligible patients had been randomly assigned to receive tamoxifen plus aminoglutethimide, and three had been assigned to receive tamoxifen alone. Of the remaining 2,012 patients, 1,008 were randomly assigned to receive tamoxifen plus aminoglutethimide, and 1,004 were randomly assigned to tamoxifen monotherapy. No follow-up results were available for 26 of 2,012 patients (1.3%). These patients were excluded from the analyses. Detailed radiotherapy documentation was available for 1,929 patients.

Population characteristics, such as age, tumor size, and primary treatment (type of surgery, radiotherapy), were well balanced between the two treatment arms (Table 1). In
particular, no significant differences were identified between
the groups for the number of pathological lymph nodes and
ER and/or PgR status. The median duration of follow-up was
5.3 years for all patients.

**DFS**

Among the 1,986 evaluated patients, 330 (16.6%) relapses
occurred during the observation period, 165 in each of the
treatment groups (Table 2). No significant difference in the
probability of recurrence was found between the two groups

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T (n = 996)</th>
<th>T+AG (n = 990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>24 (2.4)</td>
<td>22 (2.2)</td>
</tr>
<tr>
<td>51-60</td>
<td>291 (29.2)</td>
<td>302 (30.5)</td>
</tr>
<tr>
<td>61-70</td>
<td>411 (41.3)</td>
<td>395 (40.0)</td>
</tr>
<tr>
<td>71-80</td>
<td>270 (27.1)</td>
<td>271 (27.4)</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>576 (57.8)</td>
<td>578 (58.4)</td>
</tr>
<tr>
<td>&gt; 2 ≤ 5</td>
<td>391 (39.3)</td>
<td>381 (38.5)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>29 (2.9)</td>
<td>31 (3.1)</td>
</tr>
<tr>
<td>No. of nodes involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>620 (62.2)</td>
<td>615 (62.1)</td>
</tr>
<tr>
<td>1-3</td>
<td>252 (25.3)</td>
<td>261 (26.4)</td>
</tr>
<tr>
<td>4-10</td>
<td>92 (9.2)</td>
<td>85 (8.6)</td>
</tr>
<tr>
<td>≥ 11</td>
<td>32 (3.2)</td>
<td>29 (2.9)</td>
</tr>
<tr>
<td>Estrogen receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>801 (80.5)</td>
<td>818 (82.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>194 (19.5)</td>
<td>171 (17.3)</td>
</tr>
<tr>
<td>Progesterone receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>801 (80.5)</td>
<td>818 (82.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>194 (19.5)</td>
<td>171 (17.3)</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1, 2, or unknown</td>
<td>779 (78.2)</td>
<td>773 (78.1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>217 (21.8)</td>
<td>217 (21.9)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast conservation</td>
<td>545 (54.7)</td>
<td>538 (54.3)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>451 (45.3)</td>
<td>452 (45.7)</td>
</tr>
</tbody>
</table>

**Prognostic Factors**

Cox multiple regression analysis showed that the size of
the tumor, PgR status, and axillary node status represented
signiﬁcant prognostic factors for DFS and OS (data not shown).
Grading was an independent signiﬁcant prognostic factor for
DFS only. The relative risk of recurrence was reduced in patients
with grade 3 tumors treated with combination therapy as com-
pared with tamoxifen alone. If we take the relative risk for
tamoxifen plus aminoglutethimide as 1, the relative risk in
the tamoxifen-alone group was 1.36 for grade 3 tumors and 0.85 for
grades 1, 2, and unknown. These ﬁndings are statistically
signiﬁcant (P = .04).

**Second Primary Tumors and Side Effects**

Forty-four secondary cancers (4.4%) occurred in the group
treated with tamoxifen and aminoglutethimide, and 51 (5.1%) in
the group treated with tamoxifen alone. Various types were
found in both arms, with a similar distribution and a prevalence
of colon and contralateral breast disease (Table 2). Similarly, no
significant difference of endometrial cancer was found between
the study groups.

There were no treatment-related deaths. Forty-nine patients
(5.0%) in the tamoxifen plus aminoglutethimide group experi-
ced major grade 3 and 4 side effects, as compared with 21
(2.2%) in the group treated with tamoxifen alone (Table 3; P = .0008).
As expected, major side effects occurred more frequently
in the group given combination endocrine treatment than in
the group treated exclusively with tamoxifen, and more frequently
in both groups during the first 2 years of treatment compared with
the following 3 years.

In contrast, hot flashes, headache, and depressive discharges
were experienced more often in patients treated with tamoxifen
alone than in those undergoing combination treatment. Side
effects were the reason for withdrawal from treatment in 136
patients (14.0%) of the tamoxifen plus aminoglutethimide group

### Table 2. Number of First Recurrences, Second Primary Tumors, and Deaths

<table>
<thead>
<tr>
<th>Recurrence (locoregional and/or distant metastases)</th>
<th>T (n = 996)</th>
<th>T+AG (n = 990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional recurrence</td>
<td>31 (3.1)</td>
<td>35 (3.5)</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>100 (10.0)</td>
<td>98 (9.9)</td>
</tr>
<tr>
<td>Lymph nodes supraclavicular</td>
<td>14 (1.4)</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Bone</td>
<td>34 (3.4)</td>
<td>47 (4.7)</td>
</tr>
<tr>
<td>Liver</td>
<td>24 (2.4)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>Lung</td>
<td>18 (1.8)</td>
<td>20 (2.0)</td>
</tr>
<tr>
<td>Others</td>
<td>10 (1.0)</td>
<td>8 (0.8)</td>
</tr>
<tr>
<td>Other malignant diseases</td>
<td>51 (5.1)</td>
<td>44 (4.4)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>13 (1.3)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>15 (1.5)</td>
<td>12 (1.2)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>8 (0.8)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Others</td>
<td>15 (1.5)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>Death</td>
<td>94 (9.4)</td>
<td>100 (10.1)</td>
</tr>
<tr>
<td>Breast cancer-related</td>
<td>89 (8.9)</td>
<td>93 (9.4)</td>
</tr>
<tr>
<td>Breast cancer-unrelated</td>
<td>5 (0.5)</td>
<td>7 (0.7)</td>
</tr>
</tbody>
</table>

Abbreviations: T, tamoxifen; T+AG, tamoxifen plus aminoglutethimide.
and in 51 patients (5.2%) of the tamoxifen group ($P = .0001$; Table 3).

**DISCUSSION**

The objective of this randomized trial was to evaluate the efficacy of the nonselective aromatase inhibitor aminoglutethimide combined with tamoxifen as compared with exclusive standard tamoxifen administration. Trial 6 investigated these adjuvant therapy modalities and showed that combination endocrine treatment is not superior to tamoxifen in postmenopausal patients with primary, hormone receptor–positive breast cancer. The foremost rationale for implementing combination endocrine treatment was our hypothesis that reduction of peripheral serum estradiol by the agency of an aromatase inhibitor should increase the efficacy of tamoxifen. Our results clearly fail to support this idea and, rather, indicate conclusively that the reduction of peripheral serum estradiol in postmenopausal patients does not enhance the efficacy of tamoxifen.

Adjuvant tamoxifen given for 5 years currently represents the standard of care for postmenopausal patients with endocrine-responsive breast cancer. The most recent update of results emerging from the Scottish Adjuvant Tamoxifen Trial after a median follow-up of 15 years confirms that if adjuvant tamoxifen is given to women with operable breast cancer, it need not be for more than 5 years. 22 One explanation for the limited efficacy is that breast cancer cells, at least in an experimental design, develop to depend on tamoxifen, and that the late failure of, or the de novo resistance to, adjuvant tamoxifen may theoretically be related to these observations. 23,24 Several theoretical approaches have been established to improve treatment results in this group of patients, encompassing the majority of primary breast cancer patients. First, increasing the tamoxifen dose has been investigated. In terms of both recurrence and mortality, the benefits associated with tamoxifen 20 mg/d were seen to be as large as with 30 to 40 mg/d. Unfortunately, high-dose regimens have resulted in some additional toxicity and side effects and have been abandoned in most centers worldwide after the effect of tamoxifen on the endometrium was established. 9,10,25 Second, the duration of tamoxifen treatment can also be increased. Although more data have become available in recent years, the optimum duration of drug administration is still undetermined. The results of randomized trials 26-28 indicate that the optimum duration of tamoxifen treatment is at least 5 years. Its fair level of tolerability is well recognized, with a rare incidence of serious adverse events and a drug-related treatment withdrawal rate of less than.
5%.

Conversely, the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated that 10 years of tamoxifen does not improve survival compared with 5 years, whereas it significantly increases the risk of endometrial hyperplasia and cancer.

The use of tamoxifen with other drugs therefore promises to be a rewarding approach. The addition of cytotoxic chemotherapy to adjuvant tamoxifen has been suggested, and data have been presented to argue that this combination may be superior to tamoxifen alone, at least in the intermediate-risk group of postmenopausal patients. Recently presented data from the Breast Cancer Group for Clinical Research, that applied a lower dose of aminoglutethimide (250 to 500 mg/d) potentially suppress circulating estrogens to the same levels as full doses without compromising treatment efficacy and do not require hydrocortisone substitution. Conceptualized approximately the same time as Trial 6, two investigations comparing 500 and 1,000 mg daily in the metastatic setting showed no significant difference in response rates or survival.

A prospective trial, carried out by the Italian Oncology Group for Clinical Research, that applied a lower dose of aminoglutethimide than our own revealed no difference in outcome or side effects between monotherapy and a combination with hydrocortisone as first-line endocrine treatment for advanced breast cancer.

In the mid-1980s, 2-year courses of adjuvant aminoglutethimide administration, alone or in combination, were regarded as feasible and effective duration of adjuvant antiaromatase therapy. Ten years ago, Jones et al reported on a double-blind, placebo-controlled investigation, with 8 years of follow-up and application of adjuvant aminoglutethimide in 354 patients with lymph node-positive disease. Their data were consistent with previously published interim analyses showing significant, yet merely transient, improvements in event-free survival and OS for patients receiving longer-term drug. Results of the Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group 04B study have recently become available; the trial explored sequential endocrine therapy and accrued 380 women from 1992 to 1998. Switching patients from tamoxifen to aminoglutethimide...
resulted in comparable event-free survival but longer OS time in those switched to the aromatase inhibitor.

In our trial, toxicity was observed to be much higher in the combination endocrine treatment group than in that given tamoxifen monotherapy. Side effects obviously induced by aminogluthethimide were seen less frequently than previously reported in the literature.\textsuperscript{13,45,46} Along with a lack of survival superiority, this fact led to the conclusion that the addition of aminogluthethimide to tamoxifen fails to bring about the treatment improvement we had hoped for.

Although the overall results of Trial 6 did not show a benefit for combination endocrine therapy, an interesting significant treatment interaction was observed with grading. Patients with grade 3 tumors have been observed to experience a superior outcome after addition of aminogluthethimide compared with tamoxifen alone. Given the limitations of retrospective subgroup analyses, it will be necessary to test this finding in prospective randomized studies and to investigate newer aromatase inhibitors in combination with tamoxifen.

It remains to be determined whether this negative result holds true for other aromatase inhibitors, such as letrozole or anastrozole. Preclinical and early clinical trials have shown these third-generation aromatase inhibitors to be superior to aminogluthethimide.\textsuperscript{47-49} Nonsteroidal inhibitors show well-defined mechanisms of action, a greater specificity and potency\textsuperscript{50} than earlier agents, and a superior tolerability profile.\textsuperscript{47,51,52} Several ongoing clinical investigations apply tamoxifen for 5 years followed by aromatase inhibitors for a total duration of adjuvant hormones exceeding 7 years. With a target of 4,800 participants, the United States–Canadian MA.17 intergroup trial is currently randomizing postmenopausal patients who are disease-free after standard tamoxifen administration to an additional 5 years of letrozole or placebo. Similarly designed, National Surgical Adjuvant Breast and Bowel Project B-33 is assigning this patient population to 2 years of the steroidal aromatase inactivator exemestane or placebo after the standard 5 years of tamoxifen treatment.\textsuperscript{53}

Preliminary results of the Anastrozole, Tamoxifen Alone or in Combination (ATAC) Trial have more recently been presented.\textsuperscript{54} A benefit was identified for anastrozole (1 mg/d) alone over tamoxifen (20 mg/d) alone, yet the combination of the two agents did not yield results superior to tamoxifen monotherapy. Although this is consistent with our findings for the combination of tamoxifen with aminogluthethimide, the precise reasons remain to be elucidated. It has been suggested that aromatase inhibitors reduce estrogen levels and lead to a subsequent hypersensitivity by receptor upregulation in tumor cells, which counteracts the tamoxifen effect. An alternative interpretation of the presented results of Trial 6 may also be formulated with respect to the deficiencies shown by the tamoxifen-aminogluthethimide combination: First, the concept of peripheral inhibition of aromatase action may simply not apply in the presence of tamoxifen. This is suggested by reports of in vitro differences between different-generation aromatase inhibitors with regard to in vivo aromatase inhibition. Then, decrease of serum estradiol levels might be irrelevant for a clinically notable effect. If new-generation aromatase inhibitors show similar or superior efficacy in early breast cancer, sequential use following tamoxifen may prove more effective. The Italian Cooperative Group, for example, recently published preliminary results of a study investigating possible survival benefits to arise from tamoxifen sequenced with aminogluthethimide treatment.\textsuperscript{55} The Arimidex-Nolvadex Trial examined anastrozole treatment after initial tamoxifen administration. Finally, the ABCSG is currently comparing 5 years of tamoxifen with 2 years of tamoxifen followed by 3 years of the third-generation, nonsteroidal inhibitor. With the establishment of large-scale multicenter collaborative groups, the clinical efficacy, tolerability, and patients’ acceptance of newer-generation aromatase inhibitors will eventually be conclusively evaluated, thus serving to clarify the role of these agents in the adjuvant treatment of early breast cancer in postmenopausal patients.

**ACKNOWLEDGMENT**

We are grateful to Irene Agstner, Martina Mittlböck, Prof. Richard Pötter, Prof. Michael Schemper, and Karl Thomanek, Vienna University, for their biometrical and editorial expertise, and to all patients for participating in ABCSG Trial 6.

**APPENDIX**

The appendix is available online at www.jco.org.

**REFERENCES**


