# Anastrozole Is Superior to Tamoxifen as First-Line Therapy in Hormone Receptor Positive Advanced Breast Carcinoma

## *Results of Two Randomized Trials Designed for Combined Analysis*

**Jacques Bonneterre, M.D., Ph.D.**[1]
**Aman Buzdar, M.D.**[2]
**Jean-Marc A. Nabholtz, M.D., M.Sc.**[3]
**John F. R. Robertson, M.D.**[4]
**Bert Thürlimann, M.D.**[5]
**Mikael von Euler, M.D.**[6]
**Tarek Sahmoud, M.D.**[6]
**Alan Webster, M.Sc.**[6]
**Mark Steinberg, M.D.**[7]
**for the Arimidex Writing Committee on behalf of the Investigators Committee Members**

[1] Centre Oscar Lambret, Lille, France.

[2] Anderson Cancer Center, Houston, Texas.

[3] University of California at Los Angeles, Los Angeles, California.

[4] Nottingham City Hospital, Nottingham, United Kingdom.

[5] Swiss Group for Clinical Cancer Research, Bern, Switzerland.

[6] AstraZeneca, Alderley Park, United Kingdom.

[7] AstraZeneca, Wilmington, Delaware.

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The following investigators were involved in these studies: Prof. Dr. F. Gago, Francisco CEAM (Centro de Estudio de Afecciones Mamarias), Mendoza, Argentina; Dr. C. Maañon, Claudio Hospital San Bernardo, Salta, Argentina; Prof. Dr. A. Nuñez de Pierro, Anibal Hospital J. Fernandez, Buenos Aires, Argentina; Prof. Dr. R. Tozzini, Roberto Hospital del Centenario-Ginecología, Rosario, Santa Fe, Argentina; Dr. J. Beith, Royal Prince Alfred Hospital, Camperdown, NSW, Australia; Dr. M. Byrne, Sir Charles Gairdner Hospital, Nedlands, Australia; Dr. M. Green, Royal Melbourne Hospital, Parkville, Australia; Dr. J. Ph. Janssens, Salvatorziekenhuis, Hasselt, Belgium; Prof. Dr. S. Van Belle, Dienst Oncologie, Gent, Belgium; Dr. G. De Wasch, Henri Serruys Ziekenhuis, Oostende, Belgium; Dr. A. L.

**BACKGROUND.** Two randomized, double-blind trials have compared tamoxifen 20 mg daily and the selective, nonsteroidal aromatase inhibitor anastrozole 1 mg daily as first-line therapy for advanced breast carcinoma (ABC) in postmenopausal women. The trials were prospectively designed to allow for combined data analyses.

**METHODS.** The combined study population included 1021 postmenopausal women (median age, 67 years [range, 30–92]) with ABC whose tumors were either estrogen and/or progesterone receptor positive or of unknown receptor status. Primary endpoints were time to progression (TTP), objective response, and tolerability.

**RESULTS.** At a median duration of follow-up of 18.2 months, anastrozole was at least equivalent to tamoxifen in terms of median TTP (8.5 and 7.0 months, respectively; estimated hazard ratio [tamoxifen relative to anastrozole], 1.13 [lower 95% confidence level, 1.00]). In a retrospective subgroup analysis, anastrozole was superior to tamoxifen with respect to TTP (median values of 10.7 and 6.4 months for anastrozole and tamoxifen, respectively, two-sided $P = 0.022$) in patients with estrogen and/or progesterone receptor positive tumors (60% of combined trial population). In terms of objective response, 29.0% of anastrozole and 27.1% of tamoxifen patients achieved either a complete response (CR) or a partial response (PR). Clinical benefit (CR + PR + stabilization of $\geq$ 24 weeks) rates were 57.1% and 52.0% for anastrozole and tamoxifen, respectively. Both anastrozole and tamoxifen were well tolerated. Anastrozole led to significantly fewer venous thromboembolic ($P = 0.043$; not adjusted for multiple comparisons) events, and vaginal bleeding was reported in fewer patients treated with anastrozole than with tamoxifen.

**CONCLUSIONS.** In postmenopausal women with hormonally sensitive ABC, anastrozole should be considered as the new standard first-line treatment. ***Cancer* 2001;92:2247–58.** *© 2001 American Cancer Society.*

**KEYWORDS: postmenopausal, breast carcinoma, tamoxifen, anastrozole, hormone receptor, aromatase inhibitor.**

Endocrine therapy is widely accepted for the adjuvant treatment of breast carcinoma, primarily directed at reducing the synthesis of estrogen or blocking estrogen receptors in tumors that are hormone dependent.

In postmenopausal women with breast carcinoma whose disease has progressed after treatment with the endocrine therapy tamoxifen, a second-line endocrine agent such as an aromatase inhibitor frequently is prescribed to provide maximum palliative benefit with minimum toxicity. The new generation nonsteroidal aromatase inhibitor anastrozole (Arimidex™; AstraZeneca Pharmaceuticals LP, Wilmington, DE) is both potent and selective and is given orally once

daily. Because it is selective, it is well tolerated, while providing near maximal estrogen suppression, both in the peripheral circulation and within the tumor itself.[1,2] Based on a prospective combined analysis of two trials, anastrozole has shown a significant survival advantage over megestrol acetate in postmenopausal patients with advanced breast carcinoma progressing on previous tamoxifen treatment.[3]

To confirm the suitability of anastrozole as a first-line treatment, two identical randomized trials compared anastrozole and tamoxifen as first-line treatment for advanced breast carcinoma in postmenopausal women. Including 1021 women in total, these are the largest studies that have been performed to date in this group of patients to our knowledge. One trial was conducted in the United States and Canada (the North American trial)[4] and the other in Europe, Australia, New Zealand, South America, and South Africa (the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability [TARGET] trial).[5] Each of the trials individually identified that anastrozole is at least as effective as tamoxifen for the first-line treatment of advanced breast carcinoma in postmenopausal women in terms of time to disease progression (TTP). In addition, the results from the North American trial showed a significant improvement in TTP with anastrozole compared with tamoxifen ($P = 0.005$), this being the first observation of a single endocrine agent to show a significant efficacy benefit over tamoxifen to our knowledge.

An important observation from these trials was that the proportion of patients with tumors known to be estrogen receptor (ER) and/or progesterone receptor (PgR) positive (ER+ and/or PgR+) differed markedly between the North American trial (in which approximately 90% of patients were known to be ER+

Frasson, Catholique University (PUC), Porto Alegre, Brazil; Dr. A. Malzyner, Sao Paulo, Brazil; Dr. S. Moraes, Womans Reference Centre, Sao Paulo, Brazil; Dr. C. Tosello de Oliveira, Brazilian Institute for Combat to Cancer, Sao Paulo, Brazil; Andrew Arnold, M.D., Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada; David Bowman, M.D., Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada; Susan Dent, M.D., Ontario Cancer Treatment and Research Foundation, Thunder Bay Regional Cancer Centre, Thunder Bay, Ontario, Canada; Pradip Ganguly, M.D., Department of Radiation Oncology, H. Bliss Murphy Cancer Centre, St. John's, Newfoundland, Canada; David Holland, M.D., Lethbridge Cancer Clinic, Lethbridge, Alberta, Canada; Paul Klimo, M.D., Department of Oncology, Lion's Gate Oncology Clinic, North Vancouver, British Columbia, Canada; Jean Latreille, M.D., Division of Hematology & Medical Oncology, Montreal, Quebec, Canada; Robert Myers, M.D., Credit Valley Professional Bldg., Mississauga, Ontario, Canada; Jean Robert, M.D., CHA Pavillon St.-Sacrement, Quebec, Canada; Eva Tomiak, M.D., Ottawa Regional Cancer Centre, Ottawa Civic Division, Ottawa, Ontario, Canada; Maria Rosalia B. Tria Tirona, M.D., Allan Blair Cancer Centre, Pasqua Hospital, Saskatchewan, Canada; Maureen Trudeau, M.D., Women's College Hospital, Department of Oncology, Toronto, Ontario, Canada; Shailendra Verma, M.D., Ottawa Regional Cancer Centre, Ottawa General Hospital Division, Ottawa, Ontario, Canada; Robyn Young, M.D., Scott & White Clinic, Temple, TX; Labib Zibdawi, M.D., Community Cancer Clinic, York County Hospital, Newmarket, Ontario, Canada; Dr. O. Bednarik, Istav, Brno, Czech Republic; Dr. J. Fischer, Nemocnice v Ceskych Budejovicich, Ceske Budejovice, Czech Republic; Dr. B. Konopasek, Onkologicka klinika, University Karlovy, Onkologicke oddeleni, Prague, Czech Republic; Dr. J. Machacek, Onkologicka klinika, Fakultni nemocnice Olomouc, Czech Republic; Dr. P. Vodvarka, Radioterapeuticka klinika, Ostrava-Poruba, Czech Republic; Prof. F. Given, University College Hospital, Galway, Ireland; Dr. Achille, Cabinet Medical, Strasbourg, France; Dr. P. Chollet, Centre Jean Perrin, Clermont Ferrard, France; Dr. D. Langlois, Centre St. Michel, La Rochelle, France; Dr. M. Rios, Centre Alexis Vautrin, Vandoeuvre les Nancy, France; Prof. M. Tubiana-Hulin, Centre Rene Higuenin, Saint Cloud, France; Dr. Veyret, Centre Henri Becquerel, Rouen, France; Dr. E. Vuillemin, Centre St. Yves, Vannes, France; Prof. Dr. W. Eiermann, Frauenklinik vom Roten Kreuz, Munich, Germany; Prof. J. Hilfrich, Henriettenstiftung, Hannover, Germany; Dr. E. Kettner, Staedtishes klinikum, Madgeburg, Germany; Dr. Med. K. Kuhndel, Univ. Frauenklinik Leipzig, Leipzig, Germany; Dr. E. Merkle, Olgohospital, Frauenklinik Berg, Stuttgart, Germany; Dr. J. Erfan, Josa A County Hospital, Nyiregyhaza, Hungary; Dr. T. Nagykalnai, Uzsoki u Hospital, Budapest, Hungary; Dr. T. Pinter, Petz Aladar County Hospital, Gyor, Hungary; Dr. I. Szakolczai, National Institute of Oncology, Budapest, Hungary; Dr. J. Szanto, BAZ County Hospital, Miskolc, Hungary; Prof. F. Boccardo, Instituto Nazionale per la Ricerca sul Cancro, Genoa, Italy; Dr. G. Brignone, Ospedale M Ascoli, Palermo, Italy; Prof. C. Bumma, Ospedale S Giovanni, Turin, Italy; Dr. Alberto Scanni, Ospedale Fatebenefratelli, Milan, Italy; Dr. J. De La Garza, Instituto Nacional de Cancerologia, Mexico; Dr. J. L. Gonzales-Vela, Centro Medico Darox, Monterrey, Mexico; Dr. G. Morgan-Villela, Centro Medico Nacional de Occidente IMMS, Guadalajara, Mexico; Dr. S. Allan, Palmerston North Hospital, Palmerston North, New Zealand; Dr. B. Karczmarek-Borowska, Regional Oncology Centre, Lublin, Poland; Dr. J. Zaluski, Maria Sklodowska-Curie Memorial Institute, Poznan, Poland; Dr. B. da Costa, Hospital de Santa Maria, Lisbon, Portugal; Dr. J. Gouveia, Hospital de Santo Antonio dos Capuchos, Lisbon, Portugal; Dr. A. Monteiro, Hospital de Santo Antonio dos Capuchos, Lisbon, Portugal; Dr. R. da Luz, Hospital de Santa Maria, Klinika Radioterapie a Onkologie Fakultna Nemocnica L, Lisbon, Portugal; Dr. L. Bohunicky, National Cancer Institute, Bratislava, Slovakia; Dr. M. Wagnerova, Radiotherapie a Onkologie Fakultna Nemocnica L Pasteura, Kosice, Slovakia; Dr. G. Landers, Medical Mews 7, Overport, South Africa; Prof. P. E. Jonsson, Kirurgiska kliniken, Lasarettet, Helsingborg, Sweden; Prof. G. Westman, Onkologiska kliniken Regionsjukhuset, Orebro, Sweden; P.D. Dr. M. Castiglione, Onkologische Abteilung Inselspital, Bern, Switzerland; Dr. D. Hess, Medizinische Klinik C Kantonsspital, St. Gallen, Switzerland; Dr. L. Perey, Centre Pluridisciplinaire d'Oncologie, Lausanne, Switzerland; P. D. Dr. Ch. Rochlitz, Onkologie Kantonsspital, Basel, Switzerland; Dr. C. Sessa, Ospedale San Giovanni, Bellinzona, Switzerland; Dr. N. Güler, Hacettepe University, Ankara, Turkey; Prof. Dr. N. Molinas Mandel, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey; Prof. Dr. A. Ober, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey; Prof. Dr. D. Firat, Hacettepe University, Ankara, Turkey; Prof. Dr. S. Okkan, Istanbul University, Istanbul, Turkey; Prof. Dr. S. Serdengecti, Istanbul University, Istanbul, Turkey; Dr. W. P. Abram, The Belvior Park Hospital, Belfast, Northern Ireland; Mr. L. C. Barr, Withington Hospital, Manchester, U.K.; Prof. R. W. Blamey, City Hospital, Nottingham, U.K.; Dr. D. J. Dodwell, Cookridge Hospital, Leeds, U.K.; Mr. S. R. Ebbs, Mayday University Hospital, Surrey, U.K.; Mr. C. D. M. Griffith, Royal Victoria Hospital, Newcastle-Upon-Tyne, U.K.; Mr. R. Hall, York District Hospital, York, U.K.; Mr. C. Humphrey, Birch Hill Hospital, Littleborough, U.K.; Dr. C. Keen, Maidstone Hospital, Maidstone, U.K.; Mr. M. Kissin, Royal Surrey County Hospital, Guildford, U.K.; Prof. S. J. Leinster, Royal Liverpool University Hospital, Liverpool, U.K.; Dr. T. W. J. Lennard, Department of Surgery, University of Newcastle, Newcastle-Upon-Tyne, U.K.; Dr. R. C. F. Leonard, Western General Hospital, Edinburgh, U.K.; Prof. M. B. McIlmurray, Royal Lancaster Infirmary, Lancaster, U.K.; Dr. A. Stewart, Christie Hospital & Holt Radium Institute, Manchester, U.K.; Dr. J. Waxman, Hammersmith Hospital, London, U.K.; Mr. A. Wilson, Whittington Hospital, London, U.K.; Rafat H. Ansari, M.D., Michiana Hematology-Oncology, PC, South Bend,

and/or PgR+) and the TARGET trial (in which approximately 45% of patients were known to be ER+ and/or PgR+). An assessment of subgroup data based on the patient demography at baseline did not reveal any factor other than receptor status that may have accounted for the differences in TTP observed between the two trials. This finding raises important public health issues and highlights that, in various regions of the world, there are marked differences in the approach to the routine management of breast carcinoma, which ultimately may affect the outcome of treatment.

The North American and the TARGET trials were designed similarly and prospectively intended for combined analysis. The findings of this combined analysis are presented here, and the differences between these trials in terms of the known receptor status of tumors are reported and discussed.

## MATERIALS AND METHODS

### Study Design

The two trials were double-blind, randomized, multicenter studies comparing the efficacy and tolerability of anastrozole 1 mg once daily with tamoxifen 20 mg once daily as first-line therapy for advanced breast carcinoma in postmenopausal women. One trial was conducted at 97 sites in the United States and Canada (North American trial), and the other at 83 sites in Europe, Australia, New Zealand, South America, and South Africa (TARGET trial).

The primary objectives of both trials were to compare the two drugs with respect to TTP, objective response (OR) rate, and tolerability in similar patient types. The secondary objectives were to compare treatment groups with respect to time to treatment failure (TTF), response duration, and clinical benefit duration. All patients were to be observed until objec-

IN; Rita A Blanchard, M.D., Boston Medical Center, Boston, MA; Peter Bushunow, M.D., Rochester General Hospital, Department of Pharmacy, Rochester, NY; Peter D Byeff, M.D., Hematology/Oncology, Southington, CT; Ray H Clark, M.D., Hematology/Oncology Associates, Jackson, MI; Gary I Cohen, M.D., Greater Baltimore Medical Center, Baltimore, MD; Steven E. Come, M.D., Beth Israel Deaconess Medical Center, Boston, MA; H. Peter DeGreen, M.D., Lancaster Cancer Center, Ltd, Lancaster, PA; Margaret A. Deutsch, M.D., Raleigh Internal Medicine, Raleigh, NC; Robert O. Dillman, M.D., Hoag Cancer Center, Newport Beach, CA; Nikolay V Dimitrov, M.D., Professor of Medicine, Dept. of Medicine, Michigan State University, East Lansing, MI; William R Edwards, M.D., Rockford Clinic, Rockford, IL; Michael Entmacher, M.D., Fox Chase Cancer Center, Memorial Hospital of Burlington County, Mt. Holly, NJ; Frederick Ey, M.D., HealthFirst Medical Group, Portland, OR; M. Francisco Gonzalez, M.D., Center for Cancer Treatment and Research, Columbia, SC; Judie R. Goodman, D.O., Providence Cancer Center, Southfield, MI; Generosa Grana, M.D., Cooper Cancer Institute, Voorhees, NJ; Robert Granatir, M.D., Office of Drs. Granatir & Jacquin, Salem, OR; Allan M Grossman, M.D., Knoxville Hematology & Oncology Associates, Knoxville, TN; Lyndsay Harris, M.D., Duke University Medical Center, Durham, NC; C. Eric Hartz, M.D., Cancer Care of Maine, Bangor, ME; David L Headley, D.O., The Oncology Clinic, PC, Colorado Springs, CO; Robert Hirsch, M.D., Comprehensive Cancer Research Group, Inc., Comprehensive Cancer Center, North Miami Beach, FL; Karen Hoelzer, M.D., Springfield Clinic, St. John's Pavilion, Springfield, IL; Jeremy K. Hon, M.D., Huntsville Hospital, Huntsville, AL; John Horton, M.B., Ch.B., Moffitt Cancer Center & Research Institute, Tampa, FL; Fred Kass, M.D., Cancer Foundation of Santa Barbara, Santa Barbara, CA; L. Wayne Keiser, M.D., Redwood Regional Medical Group, Santa Rosa, CA; Robert O. Kerr, M.D., Southwest Regional Cancer Center, Austin, TX; Rayna Kneuper-Hall, M.D., Medical University of South Carolina, Charleston, SC; Richard Kosierowski, M.D., North Penn Hospital, Lansdale, PA; Leslie R. Laufman, M.D., Columbus Community Clinical Oncology Program, Columbus, OH; Barry C. Lembersky, M.D., Allegheny General Hospital, Pittsburgh, PA; Eric P. Lester, M.D., Lakeland Medical Center, St. Joseph, MI; Ellis Levine, M.D., Roswell Park Cancer Center, Buffalo, NY; Deborah Lindquist, M.D., Cancer Center at Sedona, Sedona, AZ; Gershon Y. Locker, M.D., The Evanston Hospital, Kellogg Cancer Care Center, Evanston, IL; Ivan S. Lowenthal, M.D., Northwestern Connecticut Oncology and Hematology Associates, Torrington, CT; Alan P. Lyss, M.D., Missouri Baptist Cancer Center, St. Louis, MO; Stefan Madajewicz, M.D., Medical Oncology HSCT-17, Stony Brook, NY; Harish K. Malhotra, M.D., North Shore Hematology/Oncology Assoc., PC, East Setauket, NY; Robert J. Meister, M.D., Arlington-Fairfax Hematology-Oncology, PC, Arlington, VA; Michael Meshad, M.D., Providence Cancer Center, Mobile, AL; Gerald P. Miletello, M.D., Hematology Oncology Clinic, Baton Rouge, LA; Arnold I. Miller, D.O.; Regional Oncol/Hematology Assoc., Kissimmee, FL; David B. Myers, M.D., B.I.O.P., Billings, MT; Edward T. O'Brien, M.D., The Regional Cancer Center, Erie, PA; Martin M. Oken, M.D., Virginia Piper Cancer Institute, Minneapolis, MN; Kelly B. Pendergrass, M.D., Kansas City Internal Medicine, Kansas City, MO; Peter V. Pickens, M.D., Abington Hematology Oncology Assoc., Inc., Meadowbrook, PA; Heidi Puc, M.D., Hematology/Oncology Associates, Syracuse, NY; Nicholas J. Robert, M.D., Fairfax-Prince William Hematology Oncology, Annandale, VA; Michael Roberts, M.D., Hematology and Oncology Associates, Ltd., Phoenix, AZ; Larry Schlabach, M.D., University Oncology Associates, Chattanooga, TN; Kala Seetharamen, M.D., Saint Vincent Hospital, Worcester, MA; Frank Senecal, M.D., HemOnc NW PC, Tacoma, WA; Harvey B. Sher, M.D., Jacksonville Oncology Group, Jacksonville, FL; Peter T. Silberstein, M.D., Mercy Cancer Center, North Iowa Mercy Health Center, Mason City, IA; Paula Silverman, M.D., University Hospitals of Cleveland, Cleveland, OH; Mary A. Simmonds, M.D., Central PA Hematology & Med Oncol. Assoc., Lemoyne, PA; Jack J. Sternberg, M.D., Little Rock, AR; Samuel G. Taylor, M.D., Creticos Cancer Center, Chicago, IL; Myo Thant, M.D., PA, Franklin Square Hospital, Baltimore, MD; M. Roy Thomas, M.D., Mid Dakota Clinic, Bismarck, ND; Stuart Tipping, M.D., Marshfield Clinic, 3A Oncology, Marshfield, WI; Nagendra Tirumali, M.D., Hematology/Oncology, Kaiser Permanente, Portland, OR; Katherine Tkaczuk, M.D., University of Maryland Cancer Center, Baltimore, MD; Bill L. Tranum, M.D., Arkansas Oncology Clinic, Little Rock, AR; Debasish Tripathy, M.D., UCSF Cancer Center, Breast Care Center, San Francisco, CA; Charles R. Tweedy, M.D., Amos Cancer Center, Columbus, GA; Michael Ward, M.D., Medical Arts Clinic, Lubbock, TX; Charles F. White, M.D., Lahey Clinic Medical Center, Department of Medical Oncology, Burlington, MA; Janet Wolter, M.D., Rush-Presbyterian–St. Luke's Medical Center, Chicago, IL; Timothy J. Woodlock, M.D., St. Mary's Hospital, Rochester, NY; Richard H. Woods, M.D., Bend Memorial Clinic, Bend, OR; Sharon J. Yee, M.D., Arcadia, CA; Robyn Young, M.D., Scott & White Clinic, Temple, TX.

Address for reprints: Jean-Marc A. Nabholtz, M.D., University of California at Los Angeles, Peter Ueberroth Building 3360B, 10945 Leconte Avenue, Los Angeles, CA 90095-7077; Fax: (310) 267-2092; E-mail: jean-Marc.Nabholtz@bcirg.com

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tive progression and death, irrespective of treatment received.

The study blinding was broken centrally for the purposes of this analysis (which was conducted on all data up to March 10, 1999), but the blinding on individual patients at the treatment centers remained intact.

### Patient Population

All patients were required to be postmenopausal and to have a diagnosis of locally advanced or metastatic breast carcinoma and had to be suitable for endocrine therapy as first-line treatment for advanced disease. Postmenopausal women were defined as one of the following: those aged 50 years or older who had not menstruated during the preceding 12 months or who had castrate follicle-stimulating hormone (FSH) levels ($>$ 40 IU/L), those younger than 50 years of age who had castrate FSH levels ($>$ 40 IU/L), or those who had undergone a bilateral oophorectomy. Prior adjuvant chemotherapy or hormonal therapy for early breast carcinoma was permissible, provided that at least 12 months had passed since the last administration of tamoxifen.

Patients with tumors known to be ER and PgR$-$ were excluded. Other exclusion criteria were previous systemic therapy for advanced breast carcinoma, extensive visceral disease, any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results, or an estimated survival of less than 3 months from the start of trial therapy based on clinical judgement. At the beginning of the study, patients receiving bisphosphonates were excluded; because of increasing numbers of women with advanced breast carcinoma being treated with bisphosphonates, the protocol was subsequently amended (at which stage 810 patients had been enrolled; 540 into TARGET and 270 into the North American trial), and these patients could then be included. In these patients, bone metastases were not considered for evaluation.

All patients gave their written informed consent, and appropriate ethics committee approval was obtained at each site before initiation of the study.

### Treatment Program

In each trial, patients were randomized to receive a daily dose of two tablets (one active and one placebo tablet). Patients were allocated to treatment on a 1:1 basis using a predetermined randomization scheme held centrally. The treatment regimen was the combination of either anastrozole 1 mg once daily and tamoxifen placebo or tamoxifen 20 mg once daily and anastrozole placebo. Patients were instructed to take the two tablets together at approximately the same time each day.

Trial treatment continued until objective disease progression was observed, at which time it was stopped. Further treatment was left to the discretion of the investigator, and follow-up continued until death.

Patients were withdrawn from active treatment because of breast carcinoma progression, a serious adverse event, noncompliance with protocol procedures, unwillingness or inability to continue the trial, or after withdrawal at the investigator's discretion. The randomization code for individual patients could only be broken once the decision had been taken to withdraw them from trial treatment. All patients who were withdrawn for reasons other than objective disease progression were monitored until progression was observed. After objective disease progression, patients were contacted every 6 months until death, to obtain survival information.

Baseline screening assessments were completed within the 4 weeks before randomization. These assessments included demographic information, complete history, and clinical examination to document the sites of disease. Laboratory studies included chest X-ray, liver scan by ultrasound, computed tomography scan, or magnetic resonance imaging, bone scan, and bone survey or X-rays of suspicious areas positive on the bone scan. History of symptoms related to disease also was documented. Blood samples were collected for hematology and blood chemistry. On Day 1 (the date of randomization), eligible patients underwent a complete physical examination. Each patient's disease then was assessed clinically every 4 weeks for the first 12 weeks (North American trial) or 24 weeks (TARGET trial) of treatment and then every 12 weeks (both trials) until objective evidence of disease progression was obtained. When possible, all assessments were repeated at the end of trial therapy.

### Efficacy Assessments

The primary efficacy measures were TTP and OR rate. The secondary efficacy measures were TTF, duration of response, duration of clinical benefit, and survival.

Measurable disease was defined as the presence of bidimensionally or unidimensionally measurable lesions as determined by physical examination, ultrasound, or radiographic scan. Osteolytic bone lesions were considered measurable. Single metastatic lesions smaller than 0.5 cm, malignant pleural effusions or ascites, positive bone scans, and purely osteoblastic or intratrabecular bone lesions were not classified as measurable disease. Lesions not classified as measurable constituted evaluable (nonmeasurable) disease.

All randomized patients were assessed based on International Union Against Cancer (UICC) criteria for tumor response 4 weeks after the initial administration of trial medication, and at all subsequent visits, up to and including the visit at which disease progression was observed. Objective responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) for both measurable and nonmeasurable disease.[6] The best response of a patient was the highest classification that was observed on two consecutive assessments at least 4 weeks apart.

The assessment criteria used were more strict than the UICC criteria in that patients having only nonmeasurable disease could not qualify for a PR, and a best response of SD only was assigned when responses of SD or better were observed for at least 24 weeks. If such responses had been observed for less than 24 weeks because a patient did not have measurements for 24 weeks at the time of data cutoff, then a best response of SD for less than 24 weeks was recorded. This criterion was based on data showing that a response of SD for at least 24 weeks is equivalent to CR and PR in terms of overall survival.[7–9] Responders were those patients with a best OR of CR or PR. Patients with clinical benefit were defined as those responding (CR + PR) plus those with SD for at least 24 weeks.[7–9]

Time to progression, TTF, duration of response, and duration of clinical benefit were calculated from the date of randomization. Time to progression represented the time to objective disease progression or death, whichever occurred first. Time to treatment failure was the time to the earliest occurrence of progression, death, or withdrawal from randomized trial treatment. Duration of response, which was recorded for those with either a CR or a PR, was the time from randomization to the time of the first observation of objective progression or death. Duration of clinical benefit in patients who achieved CR, PR, or SD for 24 weeks or more also was defined as the time from randomization to the time of the first observation of objective progression or death. Any patient who had not progressed at the time of data cutoff was censored at their last disease assessment for the above endpoints.

### Tolerability Assessments

Adverse events were recorded on a treatment-received basis. An adverse event was defined as any detrimental change in a patient's condition after randomization and during any follow-up period, unless considered by the investigator to be related to disease progression. Adverse events that might be expected to occur on the basis of the pharmacology of anastrozole and tamoxifen also were specifically identified ("predefined" events). The predefined events were depression, tumor flare, thromboembolic events, gastrointestinal disturbance, hot flushes, vaginal dryness, lethargy, vaginal bleeding, and weight gain.

In addition to monitoring for adverse events, routine laboratory tests were performed at baseline, at selected times during therapy, and at withdrawal or study end. The results of clinical laboratory tests were reviewed for clinically relevant changes. Physical examinations were performed, and body weight, blood pressure, and pulse rate were recorded at baseline, at selected times during therapy, and at study end or withdrawal.

### Statistical Analysis

The two trials were designed to compare anastrozole with tamoxifen, using TTP and OR rate as the two primary efficacy endpoints, and were designed to show equivalence in each of these endpoints. Both trials were similarly designed to allow for a combined analysis to be performed.

The statistical analyses were performed on an intention-to-treat (ITT) basis, including all patients who entered the trial according to their randomized treatment. In each trial, a population of 660 patients (330 in each treatment group) was estimated to be sufficient to show treatment equivalence with 80% power, based on a one-sided 5% significance level.

For TTP, the comparison between anastrozole and tamoxifen was expressed in terms of the hazard ratio (tamoxifen:anastrozole), which estimates the chance of progression on tamoxifen in a given time period in relation to the chance of progression on anastrozole in the same time period. A hazard ratio of greater than 1 indicates an advantage for anastrozole.

The estimated hazard ratio for TTP from this combined analysis provides the best estimate of the true value of the hazard ratio in the overall population of patients. The lower one-sided 95% confidence limit indicates the range of true values for the hazard ratio, which may be considered to be consistent with the results from these studies. The prespecified criterion for equivalence would be met if the lower one-sided 95% confidence limit was equal to or greater than 0.80.

For response rate (CR + PR), the comparison between treatments was expressed in terms of the difference in response rates (anastrozole minus tamoxifen). A difference greater than zero would indicate a higher response rate for anastrozole, whereas a difference less than zero would indicate a higher response rate for tamoxifen.

The estimated difference in response rates from

these studies provides the best estimate of the true differences in response rates in the overall population of patients. The lower one-sided 95% confidence limit indicates the range of true differences, which may be considered to be consistent with the results from these studies. The prespecified criterion for equivalence would be met if the lower one-sided 95% confidence limit was equal to or greater than −10%.

The Cox regression model was used to assess treatment equivalence for TTP and TTF. The OR rate was compared between the treatment groups using logistic regression. All efficacy analyses were performed on an ITT basis and were adjusted for important prognostic factors: age (≤ 65 years, > 65 years), previous endocrine therapy (yes or no), extent of disease at randomization (soft tissue and/or lung disease only vs. all other disease combinations), and hormonal receptor status at diagnosis (ER and/or PgR+ vs. all other combinations). In addition to the prospectively identified statistical analyses, a retrospective analysis assessed whether anastrozole showed any superiority over tamoxifen for clinical benefit (CR, PR, or SD ≥ 24 weeks).

Duration of response was measured only for responding patients from the date of randomization to the date of first observed progression or death from any cause. Duration of response and duration of clinical benefit were summarized by randomized trial treatment using the Kaplan–Meier method.

In addition, the relative efficacy of anastrozole and tamoxifen has been assessed in the following subgroups: receptor status (ER+ and/or PgR+ vs. all others), prior hormonal treatment history (no vs. yes), presence or absence of visceral (all sites), liver, or bone disease, and age (≤ 65 years vs. > 65 years).

## RESULTS

### Patient Characteristics

One thousand twenty-one patients from 97 centers in North America and 83 centers in Europe, Australia, New Zealand, South America, and South Africa were entered onto the study and randomized to 1 of the 2 treatment groups (511 anastrozole 1 mg, 510 tamoxifen 20 mg).

In total, 668 patients (340 anastrozole 1 mg; 328 tamoxifen 20 mg) were recruited in the TARGET trial between February 26, 1996 and July 1, 1998. Between August 21, 1995 and July 1, 1998, 353 patients (171 anastrozole 1 mg; 182 tamoxifen 20 mg) were recruited into the North American trial. This lower number of patients in the North American trial reflects that recruitment was stopped when the TARGET trial achieved its full prespecified recruitment, which was before unblinding of either trial. The groups formed by randomization were well balanced with respect to demographic and pretreatment characteristics (Table 1). However, there was a major difference between the two individual trials with respect to the proportion of patients with confirmed receptor positive tumors. These data are summarized in Table 2.

At the time of data cutoff for this analysis (March 10, 1999), all patients had completed 8 months follow-up within the trial. The median duration of follow-up

**TABLE 1**
**Demographic and Pretreatment Characteristics**

| | Anastrozole 1 mg (*n* = 511) | | Tamoxifen 20 mg (*n* = 510) | |
|---|---|---|---|---|
| **Characteristic** | ***n*** | **%** | ***n*** | **%** |
| Age (yrs) | | | | |
| Median | 67 | | 67 | |
| Range | 30–91 | | 40–92 | |
| Weight[a] (kg) | | | | |
| Median | 68 | | 67 | |
| Range | 40–121 | | 36–140 | |
| Breast carcinoma disease status (at first diagnosis) | | | | |
| Advanced | 215 | 42.1 | 229 | 44.9 |
| Early | 294 | 57.5 | 280 | 54.9 |
| Unknown | 2.0 | 0.4 | 1.0 | 0.2 |
| Prior adjuvant treatment | | | | |
| Hormonal only | 52 | 10.2 | 40 | 7.8 |
| Cytotoxic only | 96 | 18.8 | 99 | 19.4 |
| Both | 25 | 4.9 | 28 | 5.5 |
| None | 336 | 65.8 | 342 | 67.1 |
| Unknown | 2 | 0.4 | 1 | 0.2 |
| Sites of metastatic disease[b] | | | | |
| Soft tissue | 316 | 61.8 | 316 | 62.0 |
| Skin | 235 | 46.0 | 233 | 45.7 |
| Lymph | 208 | 40.7 | 212 | 41.6 |
| Bone | 268 | 52.4 | 256 | 50.2 |
| Visceral | 186 | 36.4 | 211 | 41.4 |
| Lung | 150 | 29.4 | 168 | 32.9 |
| Liver | 45 | 8.8 | 61 | 12.0 |
| Abdomen | 17 | 3.3 | 13 | 2.5 |
| Other | 1 | 0.2 | 3 | 0.6 |
| No evaluable disease | 4 | 0.8 | 2 | 0.4 |
| Extent of metastatic disease | | | | |
| Soft tissue only | 146 | 28.6 | 139 | 27.3 |
| Bone only | 101 | 19.8 | 86 | 16.9 |
| Bone and soft tissue only | 74 | 14.5 | 72 | 14.1 |
| Visceral disease with no liver involvement | 141 | 27.6 | 150 | 29.4 |
| Visceral disease with liver involvement | 45 | 8.8 | 61 | 12.0 |
| No evaluable disease | 4 | 0.8 | 2 | 0.4 |
| Measurable disease | 418 | 81.8 | 426 | 83.5 |
| No measurable disease | 93 | 18.2 | 84 | 16.5 |

ER: estrogen receptor; PR: progesterone receptor.
[a] Recorded for 168 patients in the anastrozole group and 178 patients in the tamoxifen group.
[b] Patients may be in more than one category.

**TABLE 2**
**Hormone Receptor Status of Tumors of Patients in the Individual Trials and in the Combined Analysis**

| | TARGET trial ($n$ = 668) | | North American trial ($n$ = 353) | | Combined population ($n$ = 1021) | |
|---|---|---|---|---|---|---|
| Receptor status | *n* | % | *n* | % | *n* | % |
| ER+, PgR+ | 165 | 24.7 | 230 | 65.2 | 395 | 38.7 |
| ER+, PgR− | 57 | 8.5 | 63 | 17.8 | 120 | 11.8 |
| ER+, PgR unknown | 66 | 9.9 | 8 | 2.3 | 74 | 7.2 |
| ER−, PgR+ | 9 | 1.3 | 11 | 3.1 | 20 | 2.0 |
| ER−, PgR− | 2 | 0.3 | 1 | 0.3 | 3 | 0.3 |
| ER unknown, PgR+ | 1 | 0.1 | 1 | 0.3 | 2 | 0.2 |
| Unknown | 368 | 55.1 | 39 | 11.0 | 407 | 39.9 |

TARGET: Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability; ER: estrogen receptor; PgR: progesterone receptor.

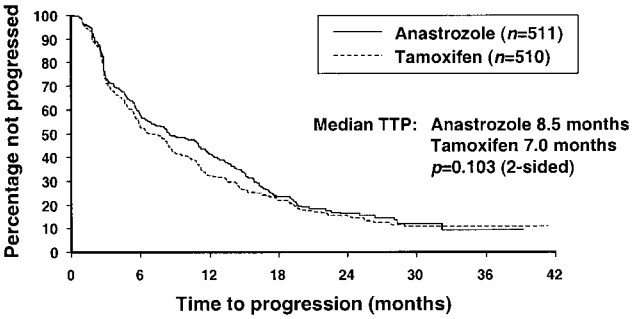


**FIGURE 1.** Kaplan–Meier plot of time to progression in patients receiving anastrozole 1 mg or tamoxifen 20 mg once daily.

was 18.2 months, at which time disease progression had been observed in 363 (71.0%) patients randomized to anastrozole and 385 (75.5%) patients randomized to tamoxifen.

## Efficacy

### *Time to progression*

The median TTP was approximately 8.5 months for the anastrozole group and approximately 7.0 months for the tamoxifen group. Analysis of the TTP data showed that the difference between groups in TTP was not statistically significant ($P$ = 0.103, 2-sided). The estimated progression hazard ratio for tamoxifen versus anastrozole was 1.13 (lower 95% confidence limit, 1.00), showing that anastrozole was at least as effective as tamoxifen. A Kaplan–Meier plot of TTP is presented in Figure 1.

### *Effects of prognostic factors on TTP*

In patients with ER+ and/or PgR+ tumors (59.8% of the total study population), treatment with anastrozole had a significant benefit in TTP compared with treatment with tamoxifen ($P$ = 0.022; Figs. 2 and 3). The median TTP was approximately 10.7 months for the anastrozole group and approximately 6.4 months for the tamoxifen group. When the data were analyzed according to each of the major prognostic factors (tumor receptor status [ER+ and/or PgR+ vs. all others], prior hormonal treatment history [no vs. yes], presence or absence of visceral [all sites], liver [alone], or bone disease, and age), the overall effect of anastrozole relative to tamoxifen was consistent in each of the subgroups (Fig. 2).

### *Tumor response*

In total, 29.0% of patients in the anastrozole group and 27.1% in the tamoxifen group achieved CR or PR (Table 3). The difference in OR rates between the anastrozole and tamoxifen groups was +1.1% (lower 95% confidence limit, −3.5%), showing that anastrozole was as effective as tamoxifen (analysis adjusted for baseline prognostic factors [age, hormonal status, extent, and prior hormonal therapy]).

The clinical benefit rates (CR + PR + SD ≥ 24 weeks) were 57.1% for patients randomized to anastrozole and 52.0% for those randomized to tamoxifen ($P$ = 0.1129, retrospective analysis). The median duration of clinical benefit from the time of randomization was 15.9 months (range, 2.1–39.2 months) and 14.6 months (range, 2.5–41.4 months) for patients randomized to either anastrozole or tamoxifen, respectively. The median duration of response was similar for both groups: 16.4 months (range, 2.1–39.2 months) for anastrozole and 17.2 months (range, 2.7–36.9 months) for tamoxifen.

### *Time to treatment failure*

Treatment failure occurred in 402 patients (78.7%) randomized to anastrozole and 418 patients (82.0%) randomized to tamoxifen. Disease progression was the main reason for treatment failure in both treatment groups (61.8% anastrozole and 64.5% tamoxifen). The estimated treatment failure hazard ratio for tamoxifen versus anastrozole was 1.13 (lower 95% confidence limit, 1.01), again showing that anastrozole was at least equivalent to tamoxifen in these trials.

## Survival

Overall, 265 deaths (26.0% of patients) were reported up until the data cutoff (March 10, 1999). Evaluation of potential differences in terms of survival was not performed at this time, because the data were considered to be immature.

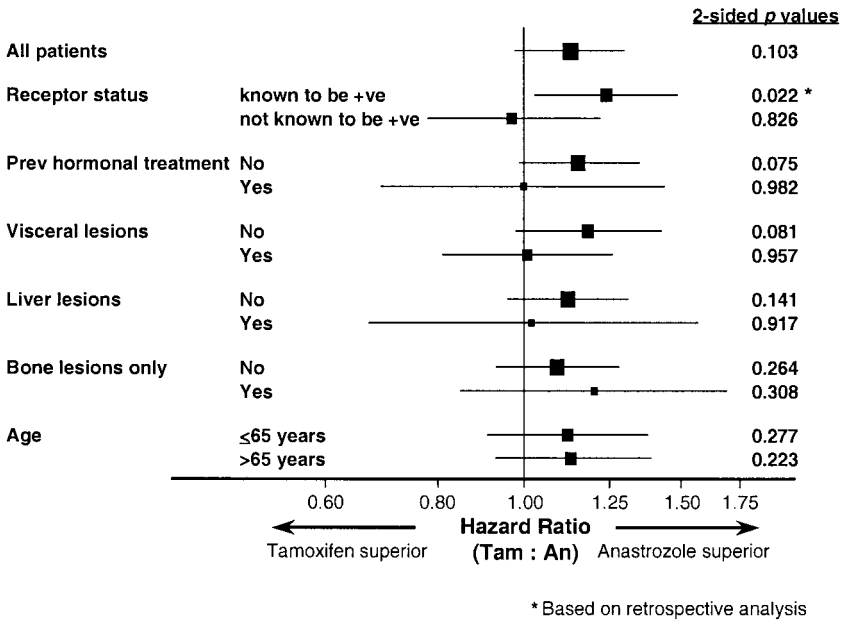


**FIGURE 2.** Subgroup analyses of time to progression by various prognostic factors.

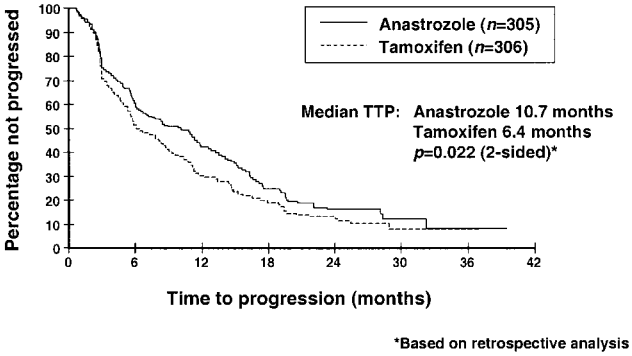


**FIGURE 3.** Kaplan–Meier probability of time to progression in patients receiving anastrozole 1 mg or tamoxifen 20 mg once daily—subgroup of patients with ER+ and/or PgR+ tumors.

**TABLE 3**
**Objective Tumor Response Rates at Median Follow-Up of 18 Mos**

| Response | Anastrozole 1 mg ($n$ = 511) (%) | Tamoxifen 20 mg ($n$ = 510) (%) |
|---|---|---|
| Best objective response (CR + PR) | 29.0 | 27.1 |
| Clinical benefit (CR + PR + SD ≥ 24 wks) | 57.1 | 52.0[a] |
| CR | 4.7 | 4.1 |
| PR | 24.3 | 22.9 |
| SD ≥ 24 wks | 28.2 | 24.9 |
| SD < 24 wks | 3.1 | 2.4 |
| Progression | 39.7 | 45.7 |

CR: complete response; PR: partial response; SD: stable disease.
[a] $P$ = 0.1129 (two-sided, retrospective analysis).

## Tolerability

Anastrozole and tamoxifen were both well tolerated in most patients. All adverse events were collected irrespective of causality. The four most common adverse events reported in both the anastrozole- and tamoxifen-treated groups were hot flushes (reported by 26.5% and 23.1% of patients, respectively), nausea (reported by 18.6% and 20.7% of patients, respectively), asthenia (reported by 16.4% and 15.9% of patients, respectively), and pain (reported by 13.8% and 14.3% of patients, respectively). In total, 51 of 1017 patients (5.0%) experienced an adverse event leading to withdrawal. Of these, 24 of 506 patients (4.7%) were in the anastrozole group and 27 of 511 patients (5.3%) were in the tamoxifen group. However, in only 23 of the 51 patients were the adverse events considered to be drug-related (10 of 506 patients [2.0%] in the anastrozole group and 13 of 511 patients [2.5%] in the tamoxifen group).

Table 4 shows the incidences of predefined adverse events (both irrespective of causality and those considered to be related to treatment). When considering all events, irrespective of causality, gastrointestinal disturbances were the most common adverse events for both treatments, followed by hot flushes. The incidence of gastrointestinal disturbances and hot flushes was similar in both groups (gastrointestinal disturbances and hot flushes: 33.6 and 26.5% in the anastrozole group and 38.4 and 23.1% in the tamoxifen group, respectively). Adverse events related to thromboembolic effects, however, were reported in significantly more patients randomized to tamoxifen (6.5%) compared with those randomized to anastro-

**TABLE 4**
**Incidence of Predefined Adverse Events Reported in Each Treatment Group**

| | Anastrozole 1 mg ($n$ = 506) | | | | Tamoxifen 20 mg ($n$ = 511) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Irrespective of causality | | Treatment-related | | Irrespective of causality | | Treatment-related | | |
| Adverse event category | *n* | % | *n* | % | *n* | % | *n* | % | *P* value[a] |
| Depression | 23 | 4.5 | 2 | 0.4 | 32 | 6.3 | 2 | 0.4 | 0.2676 |
| Tumor flare | 15 | 3.0 | 7 | 1.4 | 18 | 3.5 | 12 | 2.3 | 0.7241 |
| Thromboembolic disease | 18 | 3.6 | 3 | 0.6 | 33 | 6.5 | 7 | 1.4 | 0.0434 |
| Venous thromboembolism | 5 | 1.0 | 2 | 0.4 | 15 | 2.9 | 6 | 1.2 | |
| Coronary & cerebral thrombosis | 13 | 2.6 | 1 | 0.2 | 19 | 3.7 | 2 | 0.4 | |
| Gastrointestinal disturbance | 170 | 33.6 | 55 | 10.9 | 196 | 38.4 | 62 | 12.1 | 0.1173 |
| Nausea | 94 | 18.6 | 42 | 8.3 | 106 | 20.7 | 50 | 9.8 | |
| Vomiting | 38 | 7.5 | 4 | 0.8 | 36 | 7.0 | 8 | 1.6 | |
| Diarrhea | 40 | 7.9 | 8 | 1.6 | 33 | 6.5 | 3 | 0.6 | |
| Hot flushes | 134 | 26.5 | 120 | 23.7 | 118 | 23.1 | 101 | 19.8 | 0.2176 |
| Vaginal dryness | 9 | 1.8 | 7 | 1.4 | 3 | 0.6 | 3 | 0.6 | 0.0890 |
| Lethargy | 6 | 1.2 | 3 | 0.6 | 15 | 2.9 | 6 | 1.2 | 0.0754 |
| Vaginal bleeding[b] | 5 | 1.0 | 2 | 0.4 | 11 | 2.2 | 8 | 1.6 | 0.2066 |
| Weight gain | 11 | 2.2 | 8 | 1.6 | 8 | 1.6 | 6 | 1.2 | 0.4975 |

[a] *P* value for incidence of events irrespective of causality—not adjusted for multiple comparisons.
[b] One and four additional patients in anastrozole and tamoxifen arms, respectively, had metrorrhagia.

zole (3.6% $P = 0.0434$, not adjusted for multiple comparisons [see Table 4]). These numbers include venous thromboembolic, ischemic coronary, and ischemic cerebrovascular events. When considering the severity of adverse events (irrespective of causality), it is noteworthy that the number of patients who received tamoxifen who experienced moderate/severe thromboembolic events was almost twice that of patients who received anastrozole (5.1% vs. 2.6%, respectively). Vaginal bleeding was found to occur more than twice as frequently in patients who received tamoxifen (11 patients; 2.2%) compared with those who received anastrozole (5 patients; 1.0% [Table 4]). The number of bone fractures were similar in both groups with 11 (2.2%) in the anastrozole group compared with 16 (2.9%) fractures in the tamoxifen group.

When considering treatment-related adverse events only, similar results were observed, although for both treatments hot flushes most commonly were reported followed by gastrointestinal disturbances.

There were 17 deaths during the treatment period of this study (10 anastrozole; 7 tamoxifen), which were not considered to be related to breast carcinoma. Deaths while receiving anastrozole were caused by shock (2 of 10), suicide (1 of 10), cardiovascular events (4 of 10), gastrointestinal hemorrhage (1 of 10), dyspnea (1 of 10), and pneumonia (1 of 10). Deaths while receiving tamoxifen were caused by cardiovascular events (4 of 7), pneumonia (1 of 7), hypoglycemia (1 of 7), and angioedema (1 of 7). No deaths were considered by the investigator to be causally related to trial therapy.

## DISCUSSION

The objectives of these two large, randomized, international trials were to compare the efficacy and tolerability of anastrozole and tamoxifen as first-line endocrine therapy for postmenopausal women with advanced breast carcinoma. These trials had similar protocols and were designed for combined analysis. The combined efficacy data from the two studies show that anastrozole is at least as effective as tamoxifen in this patient group.

In terms of TTP, analysis of the combined data showed that anastrozole was equivalent to tamoxifen, and this was in accordance with the results of the larger of the two individual trials, the TARGET trial.[5] However, in the North American trial, anastrozole showed superiority in efficacy compared with tamoxifen in terms of TTP ($P = 0.005$).[4] The major difference between the two individual trials was the proportion of patients whose tumors were confirmed as being ER+ and/or PgR+: these patients represented almost 90% of patients in the North American trial but less than 50% of those in the TARGET trial. A retrospective analysis of subgroups of patients defined by tumor

receptor status (those with ER+ and/or PgR+ tumors compared with those with tumors of unknown receptor status) in the combined study population indicated that anastrozole was significantly more beneficial compared with tamoxifen in terms of extending the TTP in those patients whose tumors were ER+ and/or PgR+ (median TTP was 10.7 and 6.4 months for anastrozole and tamoxifen, respectively, 2-sided $P = 0.022$). This analysis indicates that, for the overall combined results, the benefits of anastrozole compared with tamoxifen may have been diluted by the high proportion (40%) of patients of unknown receptor status in the combined study population.

This finding suggests that receptor status is an important factor when comparing the efficacy of anastrozole with tamoxifen. Reasons for the better antitumor activity observed with anastrozole over tamoxifen in patients whose tumors are hormone-sensitive are currently unclear. The drugs have distinct and different modes of action, and these data suggest that anastrozole, which reduces peripheral and intratumor estrogen to very low levels, may induce a more profound reduction in the proliferative activity of the breast tumor than tamoxifen, an antiestrogen with partial agonist properties.[10] This hypothesis is currently under further investigation in the Arimidex or Tamoxifen, Alone or in Combination (ATAC) trial, which compares the adjuvant use of tamoxifen with anastrozole and the combination of these two endocrine agents in patients with early breast carcinoma.[11]

Anastrozole was at least as effective as tamoxifen in inducing OR. A total of 57.1% of patients in the anastrozole group and 52.0% of patients in the tamoxifen group gained clinical benefit (CR + PR + SD $\geq$ 24 weeks) from treatment ($P = 0.1129$, retrospective analysis). These findings are similar to those of the individual studies, although in the North American trial, a significantly greater number of patients receiving anastrozole achieved clinical benefit from treatment compared with those receiving tamoxifen ($P = 0.0098$). This again may reflect the impact of receptor status on the endpoints assessed.

When looking at the outcome of subgroups defined by prognostic factors other than hormone receptor status (prior hormonal treatment history, presence or absence of visceral, liver or bone disease, and age), although small differences in TTP were sometimes observed, these were not significant.

The results in terms of the efficacy of tamoxifen were similar to previously reported studies of this agent in this patient population,[12] therefore confirming that tamoxifen performed as would be expected. Any differences in favor of anastrozole therefore may be considered to be treatment benefits, especially because this was a randomized study in a large patient population.

In general both treatments were well tolerated. The main difference with anastrozole therapy compared with tamoxifen in terms of adverse events was the lower incidence of thromboembolic events and vaginal bleeding observed in patients randomized to anastrozole. Less than half as many patients reported vaginal bleeding after being randomized to anastrozole, providing indirect evidence of a lack of stimulatory effect of anastrozole on the endometrium.[13] Vaginal bleeding is psychologically distressing for the patient and necessitates further invasive investigation. The impact of these effects on quality of life is currently under further investigation in a substudy of the ATAC trial. A two- to fivefold increase in the risk of developing endometrial carcinoma has been documented in association with long-term tamoxifen use.[14]

An increased incidence of thromboembolic events compared with placebo has been reported with tamoxifen when given for a period of 5 years.[15] Previously published studies investigating the use of tamoxifen compared with other treatment options have reported similar findings.[16] In this combined analysis, a lower incidence of thromboembolic events was observed in patients who received anastrozole compared with those who received tamoxifen (3.6% compared with 6.5%, respectively). The clinical relevance of these differences in thromboembolic and vaginal bleeding events are being evaluated further in the much larger ATAC trial, which has recruited over 9300 postmenopausal women with early breast carcinoma.[12] Reassuringly, the data observed for bone fractures in these trials highlight that potent estrogen suppression to the levels observed with anastrozole did not lead to an excess of bone fractures. This is an important observation because there have been theoretic concerns that potent estrogen suppression may have deleterious effects on bone metabolism. Although the effects on bone may be less important in the metastatic setting, it will be of great importance in the adjuvant setting in which the new aromatase inhibitors, such as anastrozole, are being given for up to 5 years duration. This aspect is being investigated further in the ATAC trial.

Although it is now routine clinical practice to exclude patients whose tumors are known to be ER− from treatment with endocrine therapy, as indicated from the TARGET trial, many patients are assigned to endocrine treatment in the absence of receptor data. This may have been acceptable for tamoxifen in the mid-1990s when it was considered that tamoxifen was effective in both ER+ and ER− tumors.[17] However, data for other endocrine agents in relation to clinical

outcome in ER−/poor tumors are not available. In the North American trial, 90% of patients were known to be hormone receptor positive, and in this population, anastrozole offered significant benefits compared with tamoxifen, and we therefore believe that the results of these studies support the recommendation that all breast carcinoma patients be evaluated for tumor hormone receptor status. As we begin the new millennium, in which cost-effective, high-quality assays for hormone receptor status are widely available, it is surprising to see so many patients assigned to breast carcinoma treatments in the absence of confirmation of receptor status. As far as we are aware, these trials of anastrozole versus tamoxifen are the first to highlight the marked differences in treatment practice that occur throughout the world.

In addition, as a general comment, caution should be exerted for future randomized trials comparing endocrine therapies with respect to selection of patient population. In a recent systematic review[18] analyzing 35 randomized trials comparing tamoxifen with other endocrine agents, only 64% of patients were reported to have known hormonal receptors, of which 78% were ER+. This finding combined with the very low sample sizes of these studies (5160 patients for 35 studies) has definitively limited the capability of these trials to entertain reasonable scientific hypothesis when comparing, in the past, tamoxifen with other endocrine agents. This observation should be put in light with the classic concept of hormonal management of metastatic patients, in which all hormonal manipulations were considered equal in terms of efficacy, whereas toxicity profile was guiding the sequential choice of endocrine therapy. Small sample sizes and diluted scientific hypothesis due to poorly targeted trial populations may have been an important factor in the generation of this concept. The widespread capability of determining the hormonal receptor status and its well accepted predictive value should now allow for the identification of patient populations known to be sensitive to hormone manipulation and thus create the optimal conditions for assessing new endocrine agents, without taking the risk to under or overestimate their impact on breast carcinoma patients.

An important aspect in the treatment of postmenopausal women with advanced breast carcinoma is to optimally use in sequence the various classes of endocrine agents to prolong survival and to achieve maximal palliation. Until now, tamoxifen has been considered the first choice endocrine agent for advanced disease in postmenopausal women, with anastrozole and other new-generation aromatase inhibitors being used in patients progressing on tamoxifen. With the observation of the significant efficacy advantage for anastrozole over tamoxifen, thus indicating that anastrozole should now be considered for first-line use, a common question that arises is whether tamoxifen is effective in patients progressing on anastrozole treatment. This crossover was not addressed in a formal way in the trials described in this article; however, using a questionnaire targeted at all patients crossing from anastrozole to tamoxifen and vice versa, retrospective data were collected from both trials. Preliminary data from 89 patients who received tamoxifen after progression on anastrozole showed 53 patients to have a clinical benefit (CR + PR + SD $\geq$ 24 weeks), suggesting that tamoxifen is an effective second-line therapy for patients who progress on anastrozole.[19]

In conclusion, in the combined analyses of these two large multicenter studies, involving 1021 patients, anastrozole was at least as effective as tamoxifen for the first-line treatment of advanced breast carcinoma in postmenopausal women whose tumors were either receptor positive or of unknown receptor status. In patients whose tumors were ER and/or PgR+, anastrozole therapy provided a significant efficacy benefit over tamoxifen, the current treatment of choice in this patient group. Both treatments were well tolerated, with a low number of withdrawals due to adverse events. However, significantly fewer incidences of thromboembolic events and fewer vaginal bleeding events were reported in patients treated with anastrozole. These data confirm that anastrozole has a favorable efficacy–toxicity ratio and should now be considered as the new standard first-line therapy for postmenopausal women with receptor-positive or receptor-unknown advanced breast carcinoma.

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