Published Ahead of Print on January 2, 2007 as 10.1200/JCO.2006.08.8617
The latest version is at http://www.jco.org/cgi/doi/10.1200/JCO.2006.08.8617
VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Five Years of Letrozole Compared With Tamoxifen As Initial Adjuvant Therapy for Postmenopausal Women With Endocrine-Responsive Early Breast Cancer: Update of Study BIG 1-98

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Submitted September 12, 2006; accepted November 20, 2006; published online ahead of print at www.jco.org on January 2, 2007.

Supported by the Swedish Cancer Society, The Cancer Council Australia, Australian New Zealand Breast Cancer Trials Group, Frontier Science and Technology Research Foundation, Swiss Group for Clinical Cancer Research, National Cancer Institute Grant No. CA-75362, and the Foundation for Clinical Cancer Research of Eastern Switzerland (OSKK).

Presented in part at the 31st Congress of the European Society for Medical Oncology Conference, September 29-October 3, 2006, Istanbul, Turkey.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2505-1/$20.00

DOI: 10.1200/JCO.2006.08.8617

ABSTRACT

Purpose
Previous analyses of the Breast International Group (BIG) 1-98 four-arm study compared initial therapy with letrozole or tamoxifen including patients randomly assigned to sequential treatment whose information was censored at the time of therapy change. Because this presentation may unduly reflect early events, the present analysis is limited to patients randomly assigned to the continuous therapy arms and includes protocol-defined updated results.

Patients and Methods
Four thousand nine hundred twenty-two of the 8,028 postmenopausal women with receptor-positive early breast cancer randomly assigned (double-blind) to the BIG 1-98 trial were assigned to 5 years of continuous adjuvant therapy with either letrozole or tamoxifen; the remainder of women were assigned to receive the agents in sequence. Disease-free survival (DFS) was the primary end point.

Results
At a median follow-up time of 51 months, we observed 352 DFS events among 2,463 women receiving letrozole and 418 events among 2,459 women receiving tamoxifen. This reflected an 18% reduction in the risk of an event (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; $P = .007$). No predefined subsets showed differential benefit. Adverse events were similar to previous reports. Patients on tamoxifen experienced more thromboembolic events, endometrial pathology, hot flashes, night sweats, and vaginal bleeding. Patients on letrozole experienced more bone fractures, arthralgia, low-grade hypercholesterolemia, and cardiovascular events other than ischemia and cardiac failure.

Conclusion
The present updated analysis, which was limited to patients on monotherapy arms in BIG 1-98, yields results similar to those from the previous primary analysis but more directly comparable with results from other trials of continuous therapy using a single endocrine agent.

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INTRODUCTION

Several large studies attest to the value of third-generation aromatase inhibitors in the adjuvant systemic therapy of postmenopausal women with endocrine-responsive early breast cancer,[1-6] and such therapy has been recommended as part of the standard care in this patient group.[7-9] The Breast International Group (BIG) 1-98 study is a four-arm trial comparing 5 years of monotherapy with tamoxifen or with letrozole with sequences of 2 years of one of these agents followed by 3 years of the other. Previously reported results, called the primary core analysis, compared initial tamoxifen and letrozole and included all available data from patients randomly assigned to the monotherapy arms and data from the sequential therapy arms censored at the time of the therapy switch.[3] Such an analysis of all four arms is valid but difficult to compare with other studies because it gives considerable weight to early events. Because prospective meta-analyses of aromatase inhibitor trials are planned (J. Cuzick, J. Bliss, R.D. Gelber, personal communication, September 2006),

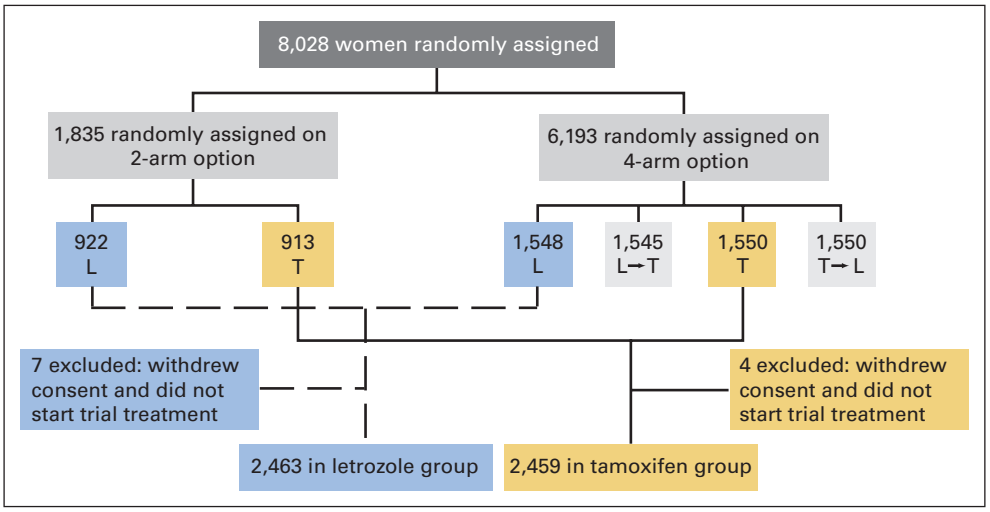

Fig 1. Consort diagram of Breast International Group 1-98 trial. The shaded boxes, denoting the sequential therapy groups, are not included in this analysis. L, letrozole; T, tamoxifen.

we present here an analysis of data derived only from patients randomly assigned to continuous tamoxifen or letrozole on the monotherapy arms of study BIG 1-98. The analysis is based on a protocol-specified update.

PATIENTS AND METHODS

The design and conduct of the study have been described elsewhere.[3] Briefly, BIG 1-98 is a randomized, phase III, double-blind trial comparing the following four options: monotherapy with letrozole or with tamoxifen for 5 years, or sequential administration of tamoxifen for 2 years followed by letrozole for 3 years, or sequential administration of letrozole for 2 years followed by tamoxifen for 3 years. The trial was conducted in postmenopausal women with estrogen receptor– and/or progesterone receptor–positive operable invasive breast cancer. From March 1998 to March 2000, patients were randomly assigned to one of the following two arms: monotherapy with letrozole (2.5 mg daily) or tamoxifen (20 mg daily). From April 1999 to May 2003, patients were randomly assigned to all four arms (Fig 1). Hormone receptor status was based on local assessment.

Table 1. Efficacy End Points

Variable	Letrozole (n = 2,463) No. of Patients	%	Tamoxifen (n = 2,459) No. of Patients	%
Disease-free survival events; primary efficacy end point	352	14.3	418	17.0
Local	19	0.8	38	1.6
Contralateral breast	14	0.6	26	1.1
Regional	13	0.5	11	0.5
Distant	182	7.4	212	8.6
Soft tissue	11	0.5	18	0.7
Bone	83	3.4	88	3.6
Viscera	88	3.6	106	4.3
Second, nonbreast malignancy	63	2.6	82	3.3
Death without prior cancer event	60	2.4	48	2.0
Deaths; overall survival events	194	7.9	211	8.6
Systemic failures; systemic disease-free survival events	331	13.4	374	15.2

The scheduled update of the BIG 1-98 trial was defined in the protocol and reviewed by the BIG 1-98 Data and Safety Monitoring Committee. This analysis is restricted to patients who were randomly assigned to the

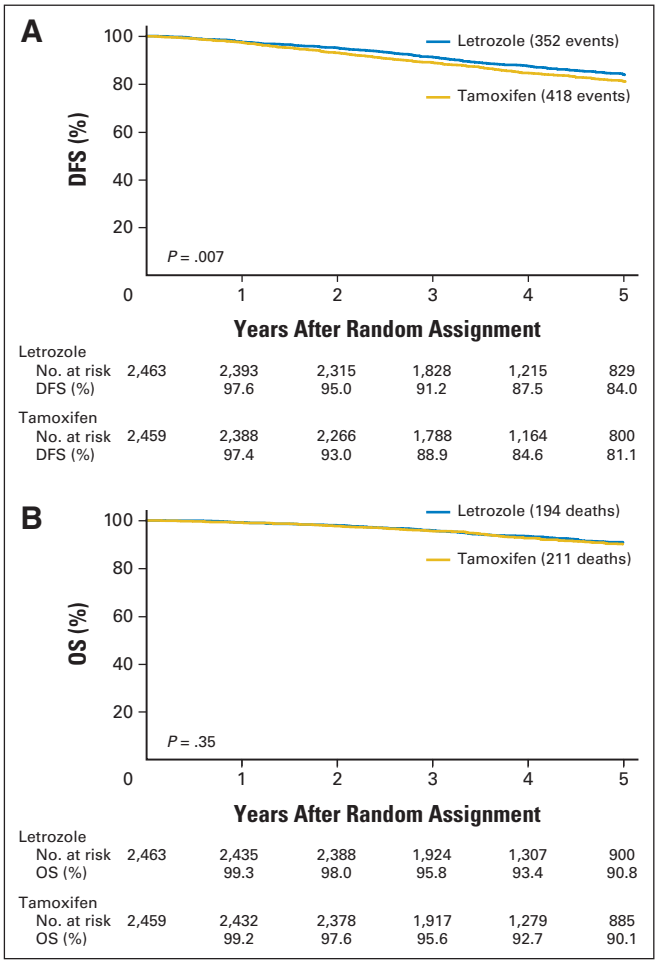

Fig 2. Kaplan-Meier estimates of (A) disease-free survival (DFS) and (B) overall survival (OS) comparing letrozole with tamoxifen. The median follow-up time is 51 months, and 1,785 patients have been observed for at least 5 years.

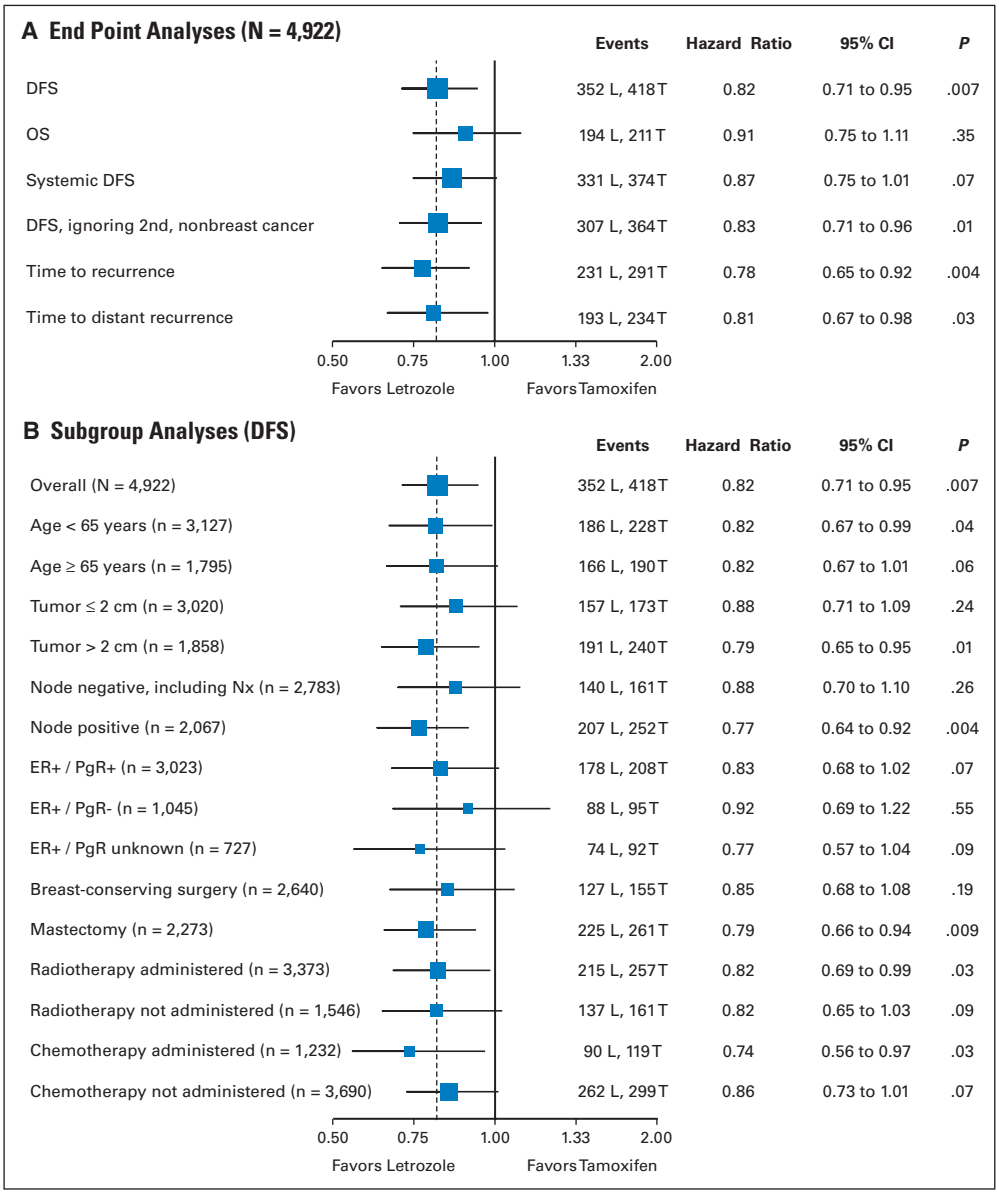

Fig 3. Cox model results of (A) primary, secondary, and exploratory end points and (B) subgroups with primary end point (disease-free survival [DFS]). The size of boxes is inversely proportional to the SE of the hazard ratio. The dashed vertical line is placed at 0.82, which is the hazard ratio estimate for the overall analysis of the primary study end point. L, letrozole; T, tamoxifen; ER, estrogen receptor; PgR, progesterone receptor; Nx, regional lymph nodes.

monotherapy arms. The primary end point was disease-free survival (DFS), which was defined as the time from random assignment to the earliest time of invasive recurrence in local, regional, or distant sites; a new invasive breast cancer in the contralateral breast; any second (nonbreast) malignancy; or death from any cause. Protocol-specified secondary end points included overall survival, which was defined as the time from random assignment to death from any cause, and systemic DFS, which was defined as the time from random assignment to systemic recurrence (ignoring local and contralateral breast events, second (nonbreast) malignancy, or death). The following three exploratory end points were analyzed to facilitate comparison with other published studies: DFS as defined earlier but ignoring second (nonbreast) malignancies; time to recurrence ignoring second (nonbreast) malignancies and censoring deaths without recurrence; and time to distant recurrence additionally ignoring local, regional, and contralateral breast recurrence. Death without prior cancer event is a type of DFS event defined as any death that occurs without evidence of breast cancer recurrence or second primary cancer at any time during or after completion of trial treatment. An adverse event by definition occurs or begins during trial treatment or within 28 days of trial treatment completion, regardless of prior recurrence.

Statistical Analysis

Log-rank tests stratified by two-arm or four-arm random assignment option and chemotherapy use (based on randomized chemotherapy stratum) were used to compare the two groups,[10] and Kaplan-Meier estimates were calculated.[11] Cox proportional hazards regression (adjusting for random assignment option and chemotherapy use) was used to adjust for various prognostic factors.[12] Cumulative incidence calculations were performed to control for competing risks.[13] Fisher's exact tests were used to compare the percentage of patients with adverse events.[14]

Role of Coordinating Group, Trial Steering Committee, and Funding Source

The International Breast Cancer Study Group was responsible for study design and coordination, data collection and management, medical review, data analysis, and reporting (including the decision to publish). The ethics committees and required health authorities of each participating institution approved the study protocol, and all patients gave written informed consent. The independent International Breast Cancer Study Group Data and Safety

Monitoring Committee reviewed safety semiannually throughout the course of the trial in addition to the two predefined interim and final efficacy analyses at 261, 433, and 779 DFS events, respectively.

Novartis, the manufacturer of letrozole, provided drug distribution and financial support and imposed no restrictions on the investigators with respect to trial data. The article was prepared by the authors, who had full access to the data and who made final decisions on content, and the steering committee (including a minority membership of Novartis employees) reviewed the article and offered changes.

RESULTS

Between March 1998 and May 2003, 8,028 women were randomly assigned to receive 5 years of adjuvant endocrine therapy with letrozole, tamoxifen, or a sequence of these agents. Of these women, 4,933 patients were allocated to continuous therapy with either letrozole or tamoxifen (Fig 1). Eleven patients (seven assigned to letrozole and four assigned to tamoxifen) withdrew consent, declined all therapy, and submitted no follow-up data after random assignment. The results of the remaining 4,922 patients are reported here.

Patient characteristics were well-balanced and similar to those reported for the primary core analysis.[3] Details are available in Appendix Table A1 (online only). Median follow-up time of the monotherapy arms for this updated analysis was 51 months, which is substantially longer than that of the primary core analysis because of the exclusion of patients on the sequential arms censored at therapy switch.

Approximately half of the patients were still receiving study therapy, whereas more than 1,200 had completed 5 years of treatment. More patients in the letrozole group discontinued trial treatment early as a result of an adverse event (12.3% of patients on letrozole and 11.1% of patients on tamoxifen), whereas more patients in the tamoxifen group discontinued treatment early as a result of disease progression (7.9% of patients on letrozole and 11.5% of patients on tamoxifen; Appendix Table A2, online only).

Efficacy

Details of events by therapy arm are listed in Table 1. The protocol-defined primary end point was DFS. Altogether, 352 DFS events were recorded among the 2,463 patients assigned to letrozole, and 418 DFS events were recorded among the 2,459 patients assigned to tamoxifen (Fig 2). The hazard ratio for DFS was 0.82 (95% CI, 0.71 to 0.95; $P = .007$), and the 5-year DFS survival estimates were 84.0% and 81.1% for letrozole and tamoxifen, respectively (Fig 2). Hazard ratios for the secondary end points defined earlier were similar to that of the primary end point of DFS (Fig 3A), although the hazard ratios for overall survival and systemic DFS were not statistically significant.

We explored various protocol-defined subgroups to identify whether there was any apparent difference in the relative efficacy of letrozole on DFS compared with the overall benefit observed. No subgroups showed significantly different relative efficacy; in particular, no significant heterogeneity was observed by nodal involvement status or progesterone receptor status (Fig 3B).

Cumulative incidence analyses of breast cancer recurrence, second nonbreast cancer, and death without cancer event are shown in Figure 4. Types of second primary cancers included endometrial (letrozole, n = 4; tamoxifen, n = 16), colon (letrozole, n = 10; tamoxifen, n = 13), lung (letrozole, n = 5; tamoxifen, n = 8), ovarian (letrozole, n = 2; tamoxifen, n = 6), renal (letrozole, n = 3; tamoxifen, n = 8), and other (letrozole, n = 39; tamoxifen, n = 31). Causes of death without prior cancer event included cerebrovascular accident (letrozole, n = 8; tamoxifen, n = 3), thromboembolic event (letrozole, n = 3; tamoxifen, n = 3), cardiac (letrozole, n = 12; tamoxifen, n = 7), sudden death of unknown cause (letrozole, n = 7; tamoxifen, n = 11), and other causes (letrozole, n = 30; tamoxifen, n = 24).

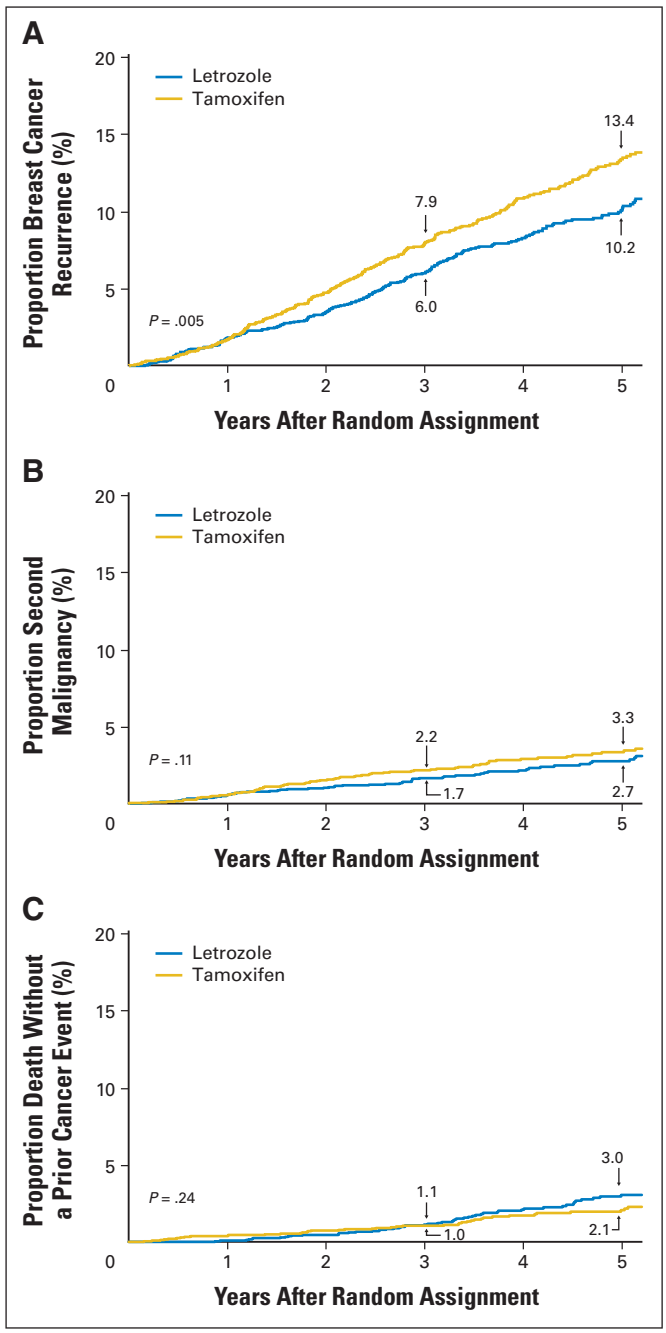

Fig 4. Cumulative incidence of (A) breast relapse, (B) second (nonbreast) malignancy, and (C) death without prior cancer event comparing letrozole with tamoxifen.

Safety

Prespecified adverse events, including cholesterol values (90.8% nonfasting), were collected every 6 months while on study.[3] The analysis population for safety included 4,895 patients, excluding 27

patients who did not receive any trial treatment. More patients receiving letrozole, compared with patients receiving tamoxifen, reported at least one adverse event of any grade (2,292 patients *v* 2,165 patients, respectively) and at least one life-threatening or fatal adverse event (113 of 2,448 patients [4.6%] *v* 92 of 2,447 patients [3.8%], respectively). Table 2 lists the worst grade of adverse events by type. Safety profiles of letrozole and tamoxifen in this updated analysis of monotherapy are generally consistent with the previously reported results of BIG 1-98. Similar to the primary core results,[3] patients on tamoxifen experienced significantly more thromboembolic events, endometrial pathology, hot flashes, night sweats, and vaginal bleeding. Patients on letrozole experienced significantly more bone fractures, arthralgia, low-grade cholesterol elevation, and cardiovascular events other than ischemic heart disease and cardiac failure. The relatively higher recording of low-grade cholesterol elevation on letrozole may be largely an artifact reflecting a cholesterol-lowering effect of tamoxifen. Although the overall incidence of cardiac adverse events did not differ significantly between the two treatments, a trend for higher grade cardiac events on letrozole compared with tamoxifen was seen (Table 2).

Note that grade 5 adverse events in Table 2 include deaths that occurred within 4 weeks of receiving trial treatment, whereas deaths without prior cancer event (which are summarized in Results, under Efficacy, and Table 1) can occur at any time. The difference in number of deaths without recurrence (60 of 2,463 of patients on letrozole, 2.4%; 48 of 2,459 patients on tamoxifen, 2.0%) was not statistically significant ($P = .25$).

DISCUSSION

All reported trials show that modern aromatase inhibitors reduce the risk of relapse of early breast cancer among postmenopausal women with endocrine-responsive early breast cancer, whether in direct comparison to the standard agent tamoxifen or as extended therapy after completion of tamoxifen. Uncertainty persists about the optimal time to introduce aromatase inhibitor therapy (whether initially as in the present analysis of BIG 1-98 and in the Arimidex, Tamoxifen, Alone or in Combination [ATAC] trial[1]; after approximately 2 years of tamoxifen[2,4,5]; or after completion of 5 years of tamoxifen[6]). Models seeking to compare these approaches have been proposed,[15] but direct randomized comparisons are as yet lacking. One such comparison will become available when data from the sequential therapy arms of BIG 1-98 mature.

Meanwhile, a meta-analysis of aromatase inhibitor trials has been proposed. To present data more directly comparable with other studies, we conducted this updated analysis of BIG 1-98 limited to the patients assigned to 5 years of continuous therapy with either letrozole or tamoxifen. The initial report of BIG 1-98 included patients randomly assigned to the two sequential arms, censoring follow-up at the time of therapy switch. Although this allowed optimal examination of the early efficacy results, as the trial matures, the inclusion of these extra patients progressively biases the overall results by stressing events in the first 2 years of therapy. The present analysis avoids

Table 2. Worst Grade of Adverse Events

Adverse Event	Letrozole (n = 2,448) Grade 1 (No.)	Grade 2 (No.)	Grade 3 (No.)	Grade 4 (No.)	Grade 5 (No.)	Any Grade No.	Any Grade %	Tamoxifen (n = 2,447) Grade 1 (No.)	Grade 2 (No.)	Grade 3 (No.)	Grade 4 (No.)	Grade 5 (No.)	Any Grade No.	Any Grade %	*P*
CVA/TIA	—*	—*	12	18	4	34	1.4	—*	—*	11	21	3	35	1.4	.90
Thromboembolic event	2*	23	14	7	4	50	2.0	3*	42	32	14	3	94	3.8	< .001
Cardiac event	34	26	39	24	11	134	5.5	63	24	21	9	5	122	5.0	.48†
Ischemic heart disease	3	9	18	19	5	54	2.2	10	10	12	7	2	41	1.7	.21
Cardiac failure	2	8	6	2	6	24	1.0	3	6	1	2	2	14	0.6	.14
Other cardiovascular event‡	11	4	2	2	0	19	0.8	4	0	1	0	1	6	0.2	.014
Hypercholesterolemia	985	243	10	0	—*	1,238	50.6	537	58	4	2	—*	601	24.6	< .001
Vaginal bleeding	78	13	1	0	0	92	3.8	152	46	5	0	0	203	8.3	< .001
Nausea	173	63	6	—*	—*	242	9.9	184	39	8	—*	—*	231	9.4	.63
Vomiting	44	27	3	0	—*	74	3.0	60	11	5	0	—*	76	3.1	.87
Hot flashes	404	399	—*	—*	—*	803	32.8	423	491	—*	—*	—*	914	37.4	< .001
Night sweating	187	161	—*	—*	—*	348	14.2	197	219	—*	—*	—*	416	17.0	.007
Bone fractures	—*	141	70	—*	—*	211	8.6	—*	105	36	—*	—*	141	5.8	< .001
Arthralgia	272	172	43	2	0	489	20.0	203	104	24	0	0	331	13.5	< .001
Myalgia	112	47	14	1	0	174	7.1	104	33	13	0	0	150	6.1	.19

NOTE. Adverse events were recorded during or within 28 days after stopping trial treatment. The adverse events reported in the table were recorded using specific check boxes on the case report forms, except for arthralgia and myalgia, which were recorded in an "other" category and, thus, may be underestimated. Grades were determined based on the National Cancer Institute Common Toxicity Criteria (version 2.0) if available; otherwise, grades were determined using criteria defined by a senior International Breast Cancer Study Group oncologist in the protocol. Fisher's exact *P* values are reported for the comparison of any grade and are not adjusted for multiple comparisons.

Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack.

*Grade not defined per the National Cancer Institute Common Toxicity Criteria (version 2.0).

†Fisher's exact $P < .001$ for incidence of grade 3 to 5 cardiac event.

‡Other cardiovascular events included cardiovascular disorder not otherwise specified, aneurysm, aortic aneurysm rupture, aortic dilation, aortic stenosis, arteriosclerosis, atherosclerosis (obliterans), femoral arterial stenosis, hypertensive angiopathy, iliac artery stenosis, and intermittent claudication.

this potential problem and yet provides an adequately powered comparison with more prolonged follow-up of the two continuous therapy arms. Nevertheless, more prolonged follow-up of this and other adjuvant trials of aromatase inhibitors is indicated; at the time of this analysis, more than 1,000 patients remain on therapy on each arm. It will also be important to see whether the early benefits of aromatase inhibitors are maintained with prolonged follow-up. Tamoxifen benefits are known to persist for years after the completion of therapy.[16]

The conclusions of the present analysis are essentially confirmatory of the primary core analysis,[3] but the present data should provide a more easily understood and unbiased basis for comparison with other studies. The most relevant comparison is with the hormone receptor–positive cohort in the first update of the ATAC trial, which compared 5 years of tamoxifen with anastrozole. At a median follow-up time of 47 months, ATAC investigators reported 635 DFS events and a hazard ratio of 0.82 (95% CI, 0.65 to 0.93) favoring anastrozole. Definitions of end points varied slightly between ATAC and BIG 1-98, with ATAC ignoring second (nonbreast) primaries in its definition of DFS and BIG 1-98 ignoring ductal carcinoma in situ in its definition of DFS. In the present analysis of BIG 1-98 at a median follow-up time of 51 months, after ignoring second (nonbreast) primary events, 671 DFS events were reported, with a hazard ratio of 0.83 (95% CI, 0.71 to 0.96) favoring letrozole. The hazard ratio for the exploratory end point of time to recurrence was identical between the present analysis of BIG 1-98 (Fig 3A) and the aforementioned ATAC analysis, and neither study shows a significant difference in overall survival. This analysis adds to the body of data supporting a role for the inclusion of an aromatase inhibitor in the adjuvant therapy of postmenopausal women with receptor-positive early breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A **Leadership:** N/A **Consultant:** Henning Mouridsen, Novartis; Louis Mauriac, Novartis; John F. Forbes, Novartis; Robert Paridaens, Novartis; István Láng, Novartis; Lucia Del Mastro, Novartis; Ian Smith, Novartis; Andrew Wardley, Novartis; Aron Goldhirsch, Novartis **Stock:** Beat Thürlimann, Novartis **Honoraria:** Henning Mouridsen, Novartis; Louis Mauriac, Novartis; John F. Forbes, Novartis; Robert Paridaens, Novartis; István Láng, Novartis; Lucia Del Mastro, Novartis; Ian Smith, Novartis; Jacquie Chirgwin, Novartis; Andrew Wardley, Novartis; Aron Goldhirsch, Novartis **Research Funds:** Aparna Keshaviah, Novartis; Louis Mauriac, Novartis; Robert Paridaens, Novartis; Monica Castiglione-Gertsch, Novartis; Richard D. Gelber, Novartis; Jacquie Chirgwin, Novartis; Tadeusz Pienkowski, Novartis; Karen N. Price, Novartis; Aron Goldhirsch, Novartis **Testimony:** N/A **Other:** N/A

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Acknowledgment

We thank the patients, physicians, nurses, and data managers who participated in this clinical trial; Novartis; and the International Breast Cancer Study Group.

Appendix

BIG 1-98 Collaborative Group Participants

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Table A1. Breast International Group 1-98 Trial: Baseline Patient and Disease Characteristics

Characteristic	Letrozole (n = 2,463)		Tamoxifen (n = 2,459)		Overall (N = 4,922)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Menopausal category						
Postmenopausal before chemotherapy, if received	2,384	96.8	2,367	96.3	4,751	96.5
Postmenopausal only after chemotherapy	51	2.1	54	2.2	105	2.1
Premenopausal, ineligible	4	0.2	9	0.4	13	0.3
Uncertain postmenopausal status	24	1.0	29	1.2	53	1.1
Age at random assignment, years						
Median	61		61		61	
Range	38-88		39-90		38-90	
Tumor size, cm						
≤ 2	1,523	61.8	1,497	60.9	3,020	61.4
> 2	920	37.4	938	38.2	1,858	37.8
Unknown/missing	20	0.8	24	1.0	44	0.9
Nodal status						
Negative, including Nx	1,376	55.9	1,407	57.2	2,783	56.5
Positive	1,050	42.6	1,017	41.4	2,067	42.0
Unknown/missing	37	1.5	35	1.4	72	1.5
ER and PgR status						
ER positive and PgR positive	1,526	62.0	1,497	60.9	3,023	61.4
ER positive and PgR negative	520	21.1	525	21.4	1,045	21.2
ER positive and PgR unknown/missing	361	14.7	366	14.9	727	14.8
ER negative and PgR positive	45	1.8	60	2.4	105	2.1
ER unknown/missing and PgR positive	3	0.1	4	0.2	7	0.1
Other	8	0.3	7	0.3	15	0.3
Local therapy						
Breast-conserving surgery and radiotherapy	1,219	49.5	1,240	50.4	2,459	50.0
Breast-conserving surgery and no radiotherapy	81	3.3	98	4.0	179	3.6
Mastectomy and radiotherapy	471	19.1	437	17.8	908	18.5
Mastectomy and no radiotherapy	687	27.9	677	27.5	1,364	27.7
Other	5	0.2	7	0.3	12	0.2
Adjuvant or neoadjuvant chemotherapy or both received						
Yes	612	24.9	620	25.2	1,232	25.0
No	1,851	75.2	1,839	74.8	3,690	75.0

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; Nx, regional lymph nodes.

Table A2. Breast International Group 1-98 Trial: Trial Treatment Status

Status	Letrozole (n = 2,463)		Tamoxifen (n = 2,459)	
	No. of Patients	%	No. of Patients	%
Completed 5 years of treatment	766	31.1	752	30.6
Still receiving treatment	1,061	43.1	1,007	41.0
Did not start trial treatment	15	0.6	12	0.5
Did not complete 5 years of treatment	621	25.2	688	28.0
Adverse event	302	12.3	273	11.1
Disease progression	195	7.9	284	11.5
Patient withdrew consent	50	2.0	55	2.2
Lost to follow-up	16	0.6	11	0.4
Death	36	1.5	31	1.3
Other reason	22	0.9	34	1.4