

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The BIG 1-98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med* 2009;361:766-76.

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South Africa: Mamma Clinic, Tygerberg Hospital, Cape Town: J. Apffelstaedt; **Southern Cross Hospital, Cape Town:** D. Eedes; **Pretoria Academic Hospital, Pretoria:** C. Slabber; **Pretoria East Hospital, Pretoria:** M. A. Coccia-Portugal; **Eastern Cape Oncology Centre, Port Elizabeth:** K. Maart.

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Switzerland: Universitätsfrauenklinik, Basel: E. Wight, S. Bartens, R. Decio, U. Güth; **Klinik am Park, Zürich:** U. Breitenstein.

Turkey: Ankara University Ibni Sina Hospital, Ankara: F. Icli, D. Dincol; **Hacettepe University Oncology Institute, Ankara:** E. Baltali, Y. Ozisik; **Istanbul University Oncology Institute, Istanbul:** E. Topuz, M. Basaran, A. Aydiner; **Ege University Medical School, Izmir:** E. Ozdedeli; **9 Eylul University Medical School, Izmir:** O. Harmancioglu, A. U. Yilmaz.

United Kingdom: The Royal Marsden Hospital, London, Royal Marsden NHS Trust, Surrey: I. E. Smith; **University of Dundee, Dundee:** A. M. Thompson; **Christie Hospital NHS Trust, South Manchester University Hospital Trust, Manchester:** A. Wardley; **Royal Bournemouth Hospital, Bournemouth:** T. Hickish; **North Middlesex Hospital, London:** F. Neave.

Uruguay: Hospital de Clinicas Dr. Manuel Quintela, Montevideo, Uruguay: G. Sabini.

Section 2. BIG 1-98 Sequential Treatment Analysis from the Time of Switch

(approximately two years from randomization) – Includes Only Patients Enrolled in the Four-Arm Randomization Option

Statistical methods

The protocol-specified landmark analyses (Anderson JR, et al. J Clin Oncol 1983;1:710-9.) from the time of the treatment switch were designed to address the following question: for patients who are alive and disease-free approximately two years after randomization, is it better to remain on their initial adjuvant endocrine therapy or switch to the alternative agent? Each of the two pairwise comparisons evaluating the superiority of the switching strategy, one for patients initially assigned to tamoxifen and one for patients initially assigned to letrozole, was tested at the 2.5% level of significance. Each comparison required at least 331 post-switch disease-free survival events to provide 80% power to detect a 29.3% reduction in the risk of an event by switching rather than maintaining the same endocrine therapy beyond two years from randomization. Three interim analyses and one 'final' analysis were conducted and reported to the Data and Safety Monitoring Committee (DSMC). Stopping boundaries using Lan-DeMets spending function based on the O'Brien-Fleming criterion were used by the DSMC to assess whether or not to recommend releasing results and/or modifying the trial. Results are reported with 97.5 percent confidence intervals to account for the multiple (two) pairwise comparisons. The time of treatment switch was defined as the time when the fifth six-monthly supply of oral study medication was dispensed to the patient (approximately two year after randomization). The required number of events was reached at the time of the International Breast Cancer Study Group Data and Safety Monitoring Committee meeting in October, 2008, and the trial results reported here were released to the BIG 1-98 Steering Committee for presentation and publication. These results are based on the database lock dated July 2, 2008.

Results

Of the 6182 patients in the intent-to-treat (ITT) population enrolled in the four-arm randomization option, 354 were not disease free when the fifth visit pack was scheduled to be dispensed, leaving an ITT population of 5828 patients for analyses conducted from the time of the switch (Fig A2-1). The median follow up from the time of the treatment switch was 45 months. The Kaplan-Meier plots for disease-free survival for each of the two pairwise comparisons are shown in Fig. A2-2. The left panel shows that patients assigned to treatment commencing with two years of letrozole have similar outcomes whether they were assigned to switch to tamoxifen or continue on letrozole. The 97.5 percent confidence interval for the hazard ratio comparing the switch to tamoxifen with continuing on letrozole ranges from 0.72 to 1.17. The upper limit of this confidence interval suggests that it is unlikely that a switch to tamoxifen following two years of letrozole therapy will increase the relative risk of a subsequent disease-free survival event by more than 17%. These results apply for a median follow up of 45 months from the time of the switch.

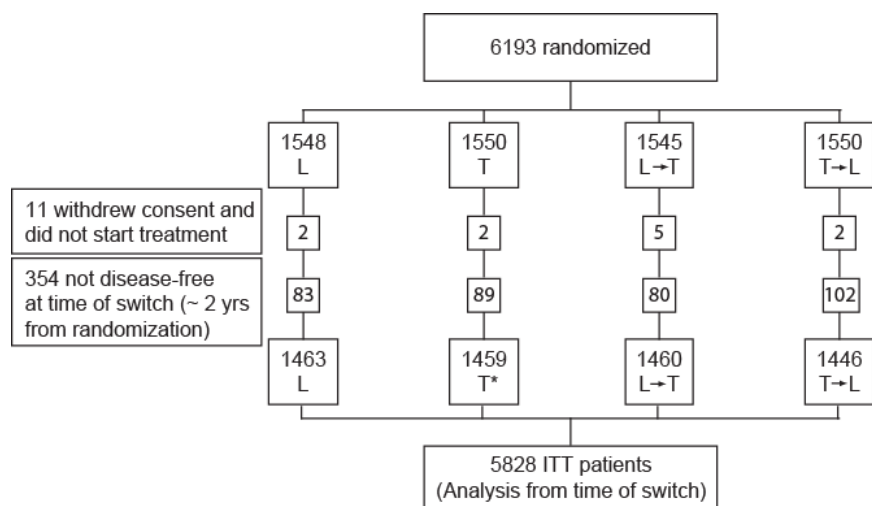


Figure A2-1. **CONSORT diagram for the population of the sequential treatment analysis from the time of the switch (approximately 2 years from randomization). Only includes patients enrolled in the four-arm randomization option. (*includes 612 patients who crossed over to letrozole)**

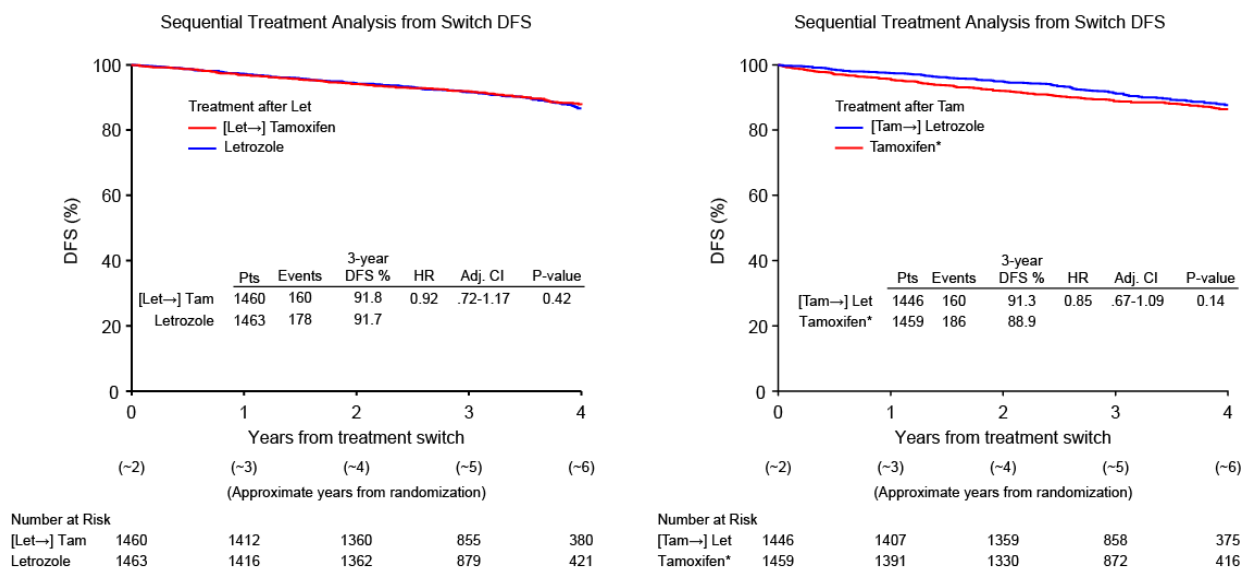


Figure A2-2. **Kaplan-Meier plots of disease-free survival for the two pairwise comparisons from the time of treatment switch. (*includes 612 patients who crossed over to letrozole)**

The right panel in Fig. A2-2 shows the Kaplan-Meier plots of disease-free survival for patients whose assigned treatment commenced with tamoxifen for two years and switched to letrozole compared with those assigned to continue on tamoxifen. All of the patients in this analysis were disease-free at approximately two years from study entry. This comparison evaluating the role of switching to an aromatase inhibitor after 2 to 3 years of tamoxifen therapy has been studied in several other trials and summarized in a meta-analysis. A significant reduction in the risk of a disease-free survival event has been reported in these other trials.

The observed 15 percent relative reduction in the risk of a disease-free survival event (hazard ratio, 0.85) associated with the switch to letrozole shown in the ITT analysis from the time of treatment switch presented in Fig. A2-2 does not reach statistical significance (P=0.14). Initial results showing the superiority of letrozole compared with tamoxifen were presented on January 26, 2005. Amendment 5 (April 2005) provided for the unblinding of all patients who were randomized to receive continuous tamoxifen for 5 years. Patients who were within 4.5 years of randomization could elect to either complete five years of treatment with tamoxifen or change to “adjuvant” letrozole for the remainder of their five-year adjuvant therapy. Patients who had been treated with 4.5 to 5 years of tamoxifen could choose to receive “extended adjuvant” letrozole for up to five additional years. Of the 1459 patients in the ITT population of patients for analyses conducted from the time of the switch who were assigned to tamoxifen monotherapy, 612 (41.9%) selectively crossed over to letrozole. In order to be included in the selective crossover cohort, the crossover to letrozole had to have occurred after January 26, 2005 and prior to a DFS event. The ITT analysis is compromised by this selective crossover. We use the term ‘selective crossover’ to distinguish the crossover to letrozole of patients who were randomly assigned to tamoxifen monotherapy from the ‘planned switch’ of patients who were randomly assigned to receive tamoxifen followed by letrozole.

Fig. A2-3 illustrates the timing of the selective crossover using cumulative incidence competing risk analysis, with a disease-free survival event (recurrence or death) counted as a competing risk.

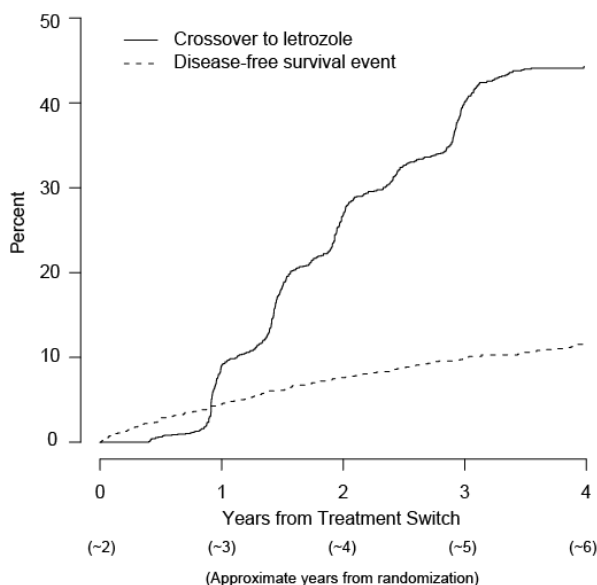


Figure A2-3. BIG Trial 1-98 Cumulative Incidence of Selective Crossover to Letrozole Among Patients Assigned to Tamoxifen Monotherapy in the Population of Patients Available for Analyses Conducted from the Time of Planned Therapy Switch.

The total number of patient-months of follow-up from the time that the fifth six-monthly study drug pack was dispensed for patients in the tamoxifen monotherapy arm was 60,393, with 12,355 patient-months of this time accrued after selective crossover to either adjuvant or extended letrozole. This represents 20.4% of the follow-up time for patients in the ITT population for analyses conducted from the time of the switch who were assigned to continue

tamoxifen for 5 years. For patients who selectively crossed over to letrozole, the median number of months of follow up after starting letrozole was 20.9 [range: 0 to 36.1]. The median duration of letrozole therapy for the 612 patients who selectively crossed over was 18 months.

Given the proven benefit of letrozole to reduce the risk of relapse compared with tamoxifen, the letrozole benefit compared with tamoxifen estimated in the ITT analysis conducted from time of treatment switch is likely to be attenuated by the selective crossover. An exploratory analysis censoring data at the time of selective crossover was, therefore, conducted. As the censored analysis is also likely to be subject to bias of unknown direction and magnitude, more extensive exploration of the effects of the selective crossover will be presented elsewhere.

Censoring data at the time of selective crossover resulted in a reduction of 20 disease-free survival events (from 186 to 166) in the tamoxifen monotherapy arm after the time of planned therapy switch and reduced the median follow up from 45 months to 35 months compared with the ITT analysis from time of planned therapy switch. The estimate of 3-year disease-free survival from the time of treatment switch decreased from 88.9% to 88.0%.

Table A2-1 shows that the hazard ratio of a disease-free survival event in the censored analysis was 0.76 with a 97.5% confidence interval of 0.59 to 0.98. Thus, the observed 24% relative reduction in the risk of a disease-free survival event was statistically significant at the 0.025 level. Further exploration of the potential biases that influence the censored analysis is required.

Table A2-1. ITT and Censored Analyses Assessing the Benefit in Terms of Disease-free Survival of Switching to Letrozole Following Approximately Two Years of Tamoxifen Compared with Remaining on Tamoxifen.

		Pts	DFS events	Median follow-up (months)	3-year DFS %	Hazard Ratio [T→]L:T	97.5% C.I.	Cox model p-value
ITT	[T→] L	1446	160	44.75	91.3	0.85	0.67-1.09	0.14
	Tam	1459	186	45.03	88.9			
Tam Censored at Crossover	[T→] L	1446	160	44.75	91.3	0.76	0.59-0.98	
	Tam	1459	166	35.33	88.0			

Types of first DFS events observed for each treatment group from the time of planned therapy switch are shown in Table A2-2. Fig A2-4 shows the cumulative incidence of breast cancer recurrence according to treatment, both overall and separately for node-negative and node-positive subgroups.

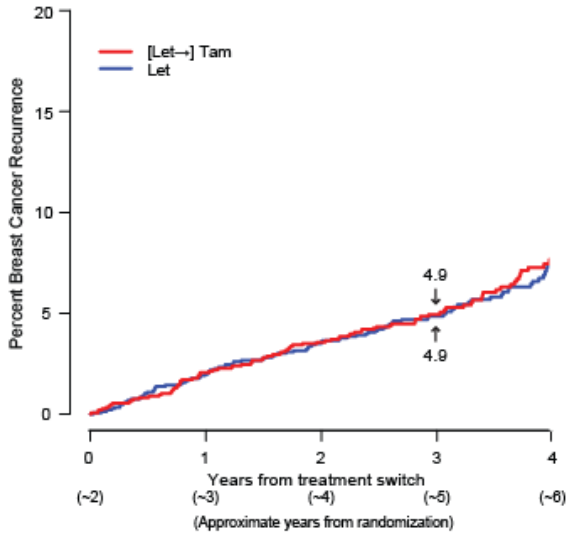
Table A2-2. Types of First Disease-free Survival Events According to the Four Treatment Arms; Events Occurring After the Switch (Approximately 2 Years from Randomization).

	[Letrozole →] Tamoxifen		Letrozole		[Tamoxifen →] Letrozole		Tamoxifen*	
	N	%	N	%	N	%	N	%
First disease-free survival events	160	11.0	178	12.2	160	11.1	186	12.7
Local	12	0.8	11	0.8	10	0.7	10	0.7
Contra breast	11	0.8	15	1.0	11	0.8	18	1.2
Regional	3	0.2	7	0.5	2	0.1	4	0.3
Distant soft tissue	9	0.6	2	0.1	2	0.1	3	0.2
Bone	26	1.8	34	2.3	37	2.6	31	2.1
Viscera	41	2.8	38	2.6	35	2.4	47	3.2
2nd (non-breast) primary	37	2.5	42	2.9	38	2.6	42	2.9
Death w/o recurrence	21	1.4	29	2.0	22	1.5	30	2.1
Unknown**	0	0	0	0	3	0.2	1	< 0.1
Deaths	72	4.9	86	5.9	85	5.9	94	6.4
Total patients	1460		1463		1446		1459	

*includes 612 patients who crossed over to letrozole

**included with breast cancer events for cumulative incidence analysis

Sequential Treatment Analysis from Switch
After ~2 years of Letrozole



Sequential Treatment Analysis from Switch
After ~2 years of Tamoxifen

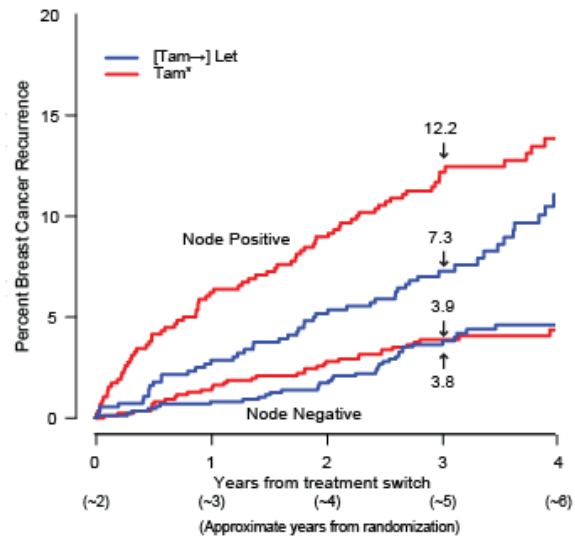
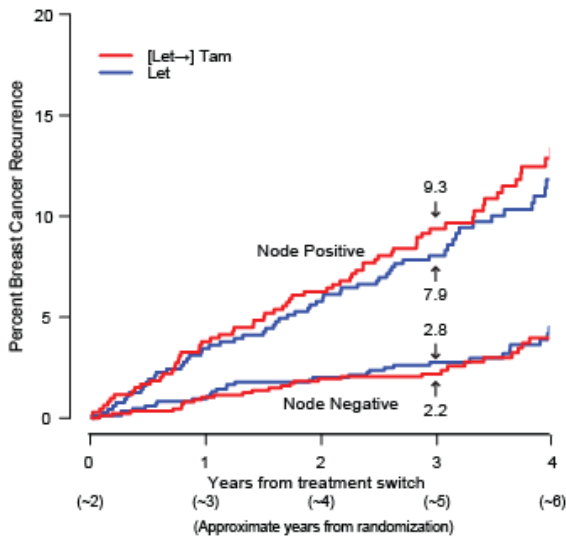
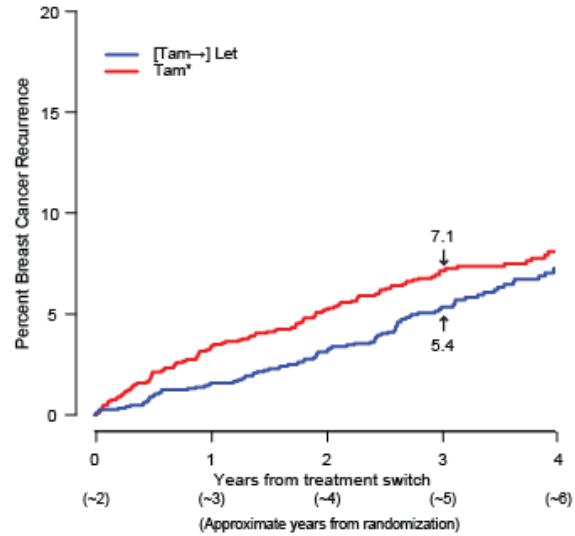


Figure A2-4. **Cumulative Incidence of Breast Cancer Recurrence for all Patients and According to Nodal Status.** (*includes 612 patients who crossed over to letrozole)

Section 3. BIG 1-98 Sequential Treatment Analysis from Randomization Includes Only Patients Enrolled in the Four-Arm Randomization Option

On the basis of emerging data from BIG 1-98 and other trials, the Data and Safety Monitoring Committee recommended that the BIG 1-98 Steering Committee revise the protocol to include five additional pairwise treatment comparisons, with analyses starting from the time of randomization. Amendment 5 (April 2005), which was activated before any evaluation of results for the sequential treatment groups, specifies these comparisons, including the two most clinically relevant that are the main focus of the current report. In addition to the ITT analyses, analyses censoring data for the tamoxifen monotherapy arm at the time of selective crossover to letrozole are presented.

Statistical methods

Five-year disease-free survival percents and hazard ratios for the pairwise comparisons are estimated using Kaplan-Meier method and Cox proportional hazards model, respectively. Results are reported with 99 percent confidence intervals to account for the multiple (five) pairwise comparisons. Tests of statistical significance are not reported for these analyses from the time of randomization. Tests of statistical significance were envisioned for the analyses from the time of treatment switch (see Appendix Section 2), but the pairwise analyses from the time of randomization, recommended by the Data and Safety Monitoring Committee, are intended to provide descriptive information of particular value for patient care decision-making at the time of diagnosis and adjuvant treatment initiation.

Results

Of the 6193 patients enrolled in the four-arm randomization option, 6182 comprise the ITT population for analyses of the sequential treatments from the time of randomization (Fig. A3-1).

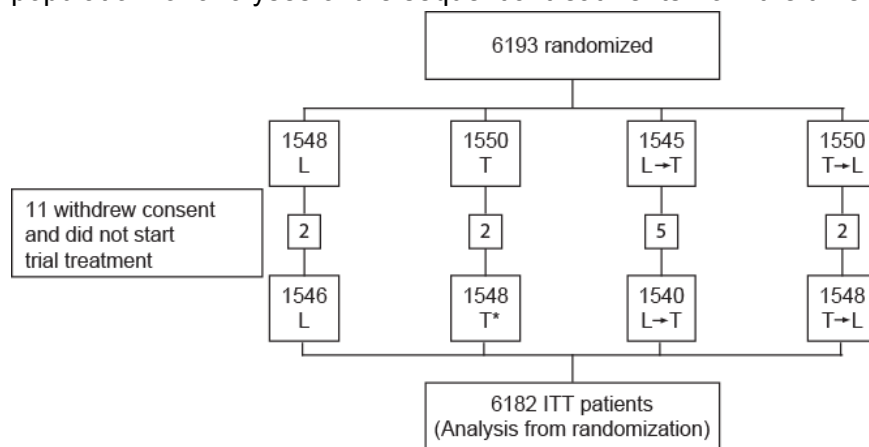
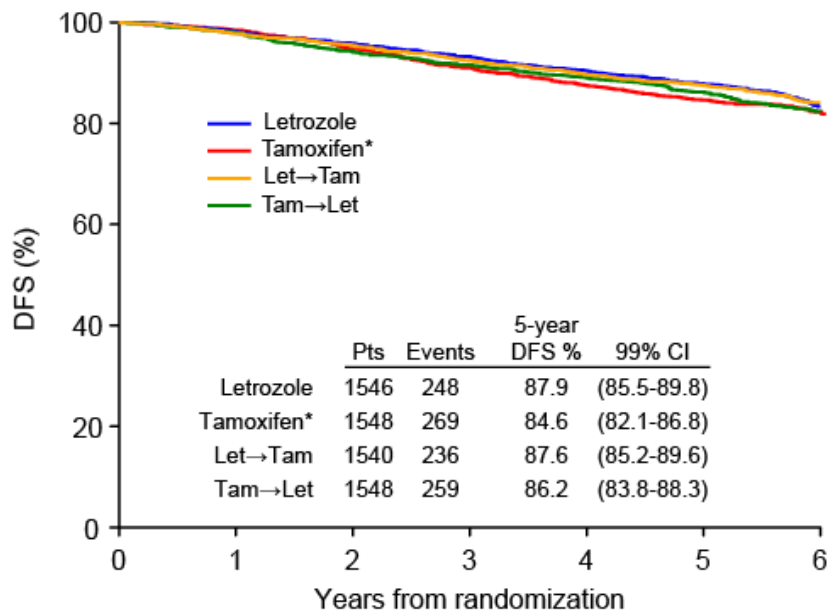


Figure A3-1. **CONSORT Diagram for the Sequential Treatment Analysis from Randomization.** (*includes 612 patients who crossed over to letrozole)

Figure A3-2 shows the Kaplan-Meier plots of disease-free survival for the ITT analysis of the four treatment groups from the time of randomization. Table A3-1 shows the ITT hazard ratio estimates and 99% CI for each of the five protocol-specified pairwise comparisons, and Table A3-2 shows the types of disease-free survival events according to treatment arm.



Number at Risk							
Letrozole	1546	1514	1470	1422	1371	1185	565
Tamoxifen*	1548	1523	1462	1395	1338	1130	549
Let→Tam	1540	1504	1467	1416	1369	1179	546
Tam→Let	1548	1513	1457	1412	1369	1153	561

Figure A3-2. **Kaplan-Meier Plots of Disease-free Survival from the Time of Randomization for the Four Treatment Groups.** (*includes 612 patients who crossed over to letrozole)

Table A3-1. Hazard Ratio Estimates for Each of the Five Protocol-Specified Pairwise Comparisons from the Time of Randomization Based on the ITT Analysis.

Comparison		Nr. of Patients	Nr. of DFS events	5-year DFS %	Hazard Ratio ¹	99% C.I.
1.	Tamoxifen→Letrozole	1548	259	86.2	1.05	0.84-1.32
	Letrozole	1546	248	87.9		
2.	Letrozole→Tamoxifen	1540	236	87.6	0.96	0.76-1.21
	Letrozole	1546	248	87.9		
3.	Letrozole→Tamoxifen	1540	236	87.6	0.91	0.72-1.14
	Tamoxifen→Letrozole	1548	259	86.2		
4.	Letrozole→Tamoxifen	1540	236	87.6	0.87	0.69-1.09
	Tamoxifen ²	1548	269	84.6		
5.	Tamoxifen→Letrozole	1548	259	86.2	0.95	0.76-1.19
	Tamoxifen ²	1548	269	84.6		

¹Hazard ratios < 1.0 favor the treatment listed first

²Includes 612 patients who crossed over to letrozole.

Table A3-2. Types of First Disease-free Survival Events According to the Four Treatment Arms. (*includes 612 patients who crossed over to letrozole)

	Letrozole		Tamoxifen→ Letrozole		Letrozole→ Tamoxifen		Tamoxifen*	
	N	%	N	%	N	%	N	%
First disease-free survival events	248	16.0	259	16.7	236	15.3	269	17.4
Local	12	0.8	14	0.9	17	1.1	15	1.0
Contralateral breast	18	1.2	19	1.2	16	1.0	21	1.4
Regional	7	0.5	3	0.2	6	0.4	7	0.5
Distant soft tissue	3	0.2	6	0.4	10	0.6	4	0.3
Bone	51	3.3	58	3.7	39	2.5	49	3.2
Viscera	58	3.8	66	4.3	56	3.6	67	4.3
2nd (non-breast) malignancy	64	4.1	65	4.2	59	3.8	67	4.3
Death w/o prior cancer event	35	2.3	25	1.6	33	2.1	38	2.5
Unknown site**	0	0	3	0.2	0	0	1	< 0.1
Deaths	137	8.9	154	9.9	123	8.0	148	9.6
Total patients	1546		1548		1540		1548	

*Includes 612 patients who crossed over to letrozole.

**Included with breast cancer events for cumulative incidence analysis

Comparisons 4 and 5 shown in Table A3-1 assess sequential treatment compared with tamoxifen monotherapy (Let→Tam versus Tam, and Tam→Let versus Tam). These two comparisons are influenced by the selective crossover to letrozole of patients randomized to tamoxifen monotherapy (see Appendix Section 2) after the first results from BIG 1-98 in 2005. Of 1548 patients in the 4-arm option tamoxifen monotherapy ITT analysis from the time of randomization, 612 (39.5%) received either adjuvant or extended letrozole as described in Amendment 5. Fig. A3-3 illustrates the timing of the selective crossover using cumulative incidence competing risk analysis with a disease-free survival event (recurrence or death) counted as a competing risk.

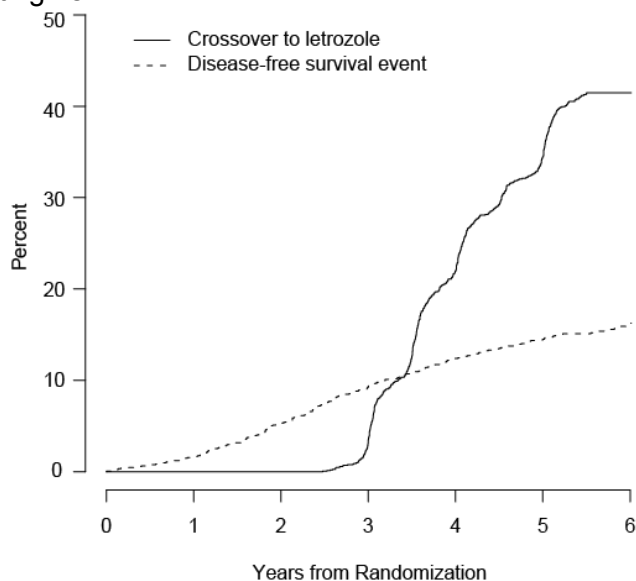


Figure A3-3. BIG Trial 1-98 Cumulative Incidence of Selective Crossover to Letrozole: Tamoxifen Monotherapy Patients from Randomization, Four-Arm Option Only.

In this analysis of patients in the 4-arm option evaluated from randomization, the total number of patient-months of follow-up for patients in the tamoxifen monotherapy arm from the time of randomization was 98,478, with 12,355 patient-months of this time accrued following selective crossover to either adjuvant or extended letrozole. This represents 12.5% of the follow-up time for patients in the ITT analysis of the 4-arm option tamoxifen monotherapy arm. For patients who selectively crossed over to letrozole, the median number of months of follow up after starting letrozole was 20.9 [range: 0 to 36.1]. The median duration of letrozole therapy for patients who selectively crossed over was 18 months.

Exploratory analyses censoring data at the time of selective crossover were conducted for comparisons 4 and 5. Censoring data at the time of selective crossover resulted in a loss of 20 disease-free survival events (from 269 to 249) in the tamoxifen monotherapy arm and reduced the median follow up from 70 months to 61 months compared with the ITT analysis. The Kaplan-Meier estimate of 5-year disease-free survival from randomization decreased from 84.6% to 84.0%.

Table A3-3 shows that the hazard ratios of a disease-free survival event comparing sequential treatments with tamoxifen monotherapy are lower in the censored analyses than in the ITT analyses. This suggests that the ITT estimate of the benefit of the letrozole-containing regimens

compared with tamoxifen monotherapy is attenuated, but further exploration of the potential biases that influence the censored analyses is required.

Table A3-3. ITT and Censored Analyses Assessing the Benefit in Terms of Disease-free Survival from the Time of Randomization for Sequential Treatment Regimens Compared with Tamoxifen Monotherapy.

		Pts	DFS events	Median follow-up (months)	5-year DFS%	Hazard Ratio ¹	99% C.I.:
Letrozole-Tamoxifen versus Tamoxifen (Let→Tam:T)							
Intention-to-Treat	Let→Tam	1540	236	70.6	87.6	0.87	0.69-1.09
	Tam	1548	269	70.4	84.6		
Tam Censored at Crossover	Let→Tam	1540	236	70.6	87.6	0.80	0.63-1.01
	Tam	1548	249	60.5	84.0		
Tamoxifen-Letrozole versus Tamoxifen (Tam→Let:T)							
Intention-to-Treat	Tam→Let	1548	259	70.7	86.2	0.95	0.76-1.19
	Tam	1548	269	70.4	84.6		
Tam Censored at Crossover	Tam→Let	1548	259	70.7	86.2	0.88	0.70-1.11
	Tam	1548	249	60.5	84.0		

¹Hazard ratios < 1.0 favor the treatment listed first

Section 4. BIG 1-98 Adverse Events in the Sequential Treatment Population

Adverse Event	Tamoxifen (N=1540)†	Letrozole (N=1534)	Tamoxifen → Letrozole (N=1540)	Letrozole → Tamoxifen (N=1526)
	Number (%)			
Cerebrovascular accident or transient ischemic attack				
Years 1 and 2				
Grade 3–5	15 (1.0)	9 (0.6)	18 (1.2)	12 (0.8)
Grade 1–5	15 (1.0)	9 (0.6)	18 (1.2)	12 (0.8)
Years 3–5				
Grade 3–5	13 (0.9)	13 (0.9)	13 (0.9)	14 (1.0)
Grade 1–5	13 (0.9)	13 (0.9)	13 (0.9)	14 (1.0)
Overall				
Grade 3–5	27 (1.8)	22 (1.4)	30 (1.9)	26 (1.7)
Grade 1–5	27 (1.8)	22 (1.4)	30 (1.9)	26 (1.7)
Thromboembolic event				
Years 1 and 2				
Grade 3–5	25 (1.6)	9 (0.6)	43 (2.8)	9 (0.6)
Grade 1–5	47 (3.1)	18 (1.2)	60 (3.9)	21 (1.4)
Years 3–5				
Grade 3–5	18 (1.2)	8 (0.6)	10 (0.7)	28 (1.9)
Grade 1–5	33 (2.3)	20 (1.4)	15 (1.0)	43 (3.0)
Overall				
Grade 3–5	41 (2.7)	17 (1.1)	51 (3.3)	36 (2.4)
Grade 1–5	76 (4.9)	37 (2.4)	74 (4.8)	62 (4.1)
Any cardiac event‡				
Years 1 and 2				
Grade 3–5	12 (0.8)	24 (1.6)	17 (1.1)	17 (1.1)
Grade 1–5	44 (2.9)	56 (3.7)	61 (4.0)	52 (3.4)
Years 3–5				
Grade 3–5	21 (1.4)	29 (2.0)	17 (1.2)	16 (1.1)
Grade 1–5	55 (3.8)	53 (3.6)	55 (3.8)	42 (2.9)
Overall				
Grade 3–5	29 (1.9)	51 (3.3)	34 (2.2)	35 (2.3)
Grade 1–5	88 (5.7)	103 (6.7)	108 (7.0)	93 (6.1)

Adverse Event	Tamoxifen (N=1540)†	Letrozole (N=1534)	Tamoxifen → Letrozole (N=1540)	Letrozole → Tamoxifen (N=1526)
Ischemic heart disease				
Years 1 and 2				
Grade 3–5	5 (0.3)	8 (0.5)	8 (0.5)	7 (0.5)
Grade 1–5	15 (1.0)	17 (1.1)	16 (1.0)	15 (1.0)
Years 3–5				
Grade 3–5	10 (0.7)	18 (1.2)	12 (0.8)	5 (0.3)
Grade 1–5	13 (0.9)	23 (1.6)	21 (1.5)	11 (0.8)
Overall				
Grade 3–5	13 (0.8)	26 (1.7)	20 (1.3)	14 (0.9)
Grade 1–5	23 (1.5)	40 (2.6)	36 (2.3)	26 (1.7)
Cardiac failure				
Years 1 and 2				
Grade 3–5	4 (0.3)	7 (0.5)	4 (0.3)	5 (0.3)
Grade 1–5	8 (0.5)	12 (0.8)	6 (0.4)	10 (0.7)
Years 3–5				
Grade 3–5	5 (0.3)	3 (0.2)	1 (<0.1)	3 (0.2)
Grade 1–5	8 (0.6)	4 (0.3)	6 (0.4)	5 (0.3)
Overall				
Grade 3–5	9 (0.6)	10 (0.7)	5 (0.3)	8 (0.5)
Grade 1–5	16 (1.0)	16 (1.0)	12 (0.8)	15 (1.0)
Cardiovascular events (excluding hypertension)				
Years 1 and 2				
Grade 3–5	0	2 (0.1)	0	0
Grade 1–5	5 (0.3)	10 (0.7)	4 (0.3)	10 (0.7)
Years 3–5				
Grade 3–5	0	0	0	2 (0.1)
Grade 1–5	9 (0.6)	11 (0.8)	3 (0.2)	3 (0.2)
Overall				
Grade 3–5	0	2 (0.1)	0	2 (0.1)
Grade 1–5	14 (0.9)	21 (1.4)	7 (0.5)	13 (0.9)
Hypercholesterolemia				
Years 1 and 2				
Grade 3–5	1 (<0.1)	4 (0.3)	2 (0.1)	7 (0.5)

Adverse Event	Tamoxifen (N=1540)†	Letrozole (N=1534)	Tamoxifen → Letrozole (N=1540)	Letrozole → Tamoxifen (N=1526)
Grade 1–5	285 (18.5)	661 (43.1)	245 (15.9)	646 (42.3)
Years 3–5				
Grade 3–5	2 (0.1)	1 (<0.1)	4 (0.3)	2 (0.1)
Grade 1–5	272 (18.7)	311 (21.4)	461 (32.0)	127 (8.8)
Overall				
Grade 3–5	3 (0.2)	5 (0.3)	6 (0.4)	9 (0.6)
Grade 1–5	461 (29.9)	816 (53.2)	637 (41.4)	679 (44.5)
Vaginal bleeding				
Years 1 and 2				
Grade 3–5	1 (0.1)	1 (0.1)	0	2 (0.1)
Grade 1–5	83 (5.4)	56 (3.7)	90 (5.8)	53 (3.5)
Years 3–5				
Grade 3–5	2 (0.1)	0	0	1 (<0.1)
Grade 1–5	77 (5.3)	30 (2.1)	33 (2.3)	49 (3.4)
Overall				
Grade 3–5	3 (0.2)	1 (0.1)	0	3 (0.2)
Grade 1–5	152 (9.9)	78 (5.1)	116 (7.5)	97 (6.4)
Nausea				
Years 1 and 2				
Grade 3–5	5 (0.3)	4 (0.3)	1 (0.1)	0
Grade 1–5	139 (9.0)	153 (10.0)	166 (10.8)	131 (8.6)
Years 3–5				
Grade 3–5 (undefined)	—	—	—	—
Grade 1–5	51 (3.5)	60 (4.1)	49 (3.4)	41 (2.8)
Overall				
Grade 3–5	5 (0.3)	4 (0.3)	1 (0.1)	0
Grade 1–5	176 (11.4)	189 (12.3)	194 (12.6)	160 (10.5)
Vomiting				
Years 1 and 2				
Grade 3–5	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.2)
Grade 1–5	42 (2.7)	43 (2.8)	36 (2.3)	41 (2.7)
Years 3–5				
Grade 3–5	0	0	1 (0.1)	0

Adverse Event	Tamoxifen (N=1540)†	Letrozole (N=1534)	Tamoxifen → Letrozole (N=1540)	Letrozole → Tamoxifen (N=1526)
Grade 1–5	18 (1.2)	17 (1.2)	16 (1.1)	17 (1.2)
Overall				
Grade 3–5	3 (0.2)	3 (0.2)	4 (0.3)	3 (0.2)
Grade 1–5	57 (3.7)	59 (3.8)	49 (3.2)	56 (3.7)
Hot flashes				
Years 1 and 2				
Grade 3–5 (undefined)	—	—	—	—
Grade 1–5	608 (39.5)	521 (34.0)	645 (41.9)	580 (38.0)
Years 3–5				
Grade 3–5 (undefined)	—	—	—	—
Grade 1–5	127 (8.7)	119 (8.2)	116 (8.1)	135 (9.3)
Overall				
Grade 3–5 (undefined)	—	—	—	—
Grade 1–5	660 (42.9)	578 (37.7)	677 (44.0)	637 (41.7)
Night sweats				
Years 1 and 2				
Grade 3–5 (undefined)	—	—	—	—
Grade 1–5	270 (17.5)	217 (14.1)	253 (16.4)	232 (15.2)
Years 3–5				
Grade 3–5 (undefined)	—	—	—	—
Grade 1–5	67 (4.6)	51 (3.5)	54 (3.8)	71 (4.9)
Overall				
Grade 3–5 (undefined)	—	—	—	—
Grade 1–5	298 (19.4)	239 (15.6)	282 (18.3)	272 (17.8)
Fractures				
Years 1 and 2				
Grade 3–5	11 (0.7)	22 (1.4)	11 (0.7)	14 (0.9)
Grade 1–5	50 (3.2)	65 (4.2)	54 (3.5)	55 (3.6)
Years 3–5				
Grade 3–5	22 (1.5)	26 (1.8)	24 (1.7)	16 (1.1)
Grade 1–5	67 (4.6)	90 (6.2)	97 (6.7)	62 (4.3)
Overall				
Grade 3–5	32 (2.1)	49 (3.2)	36 (2.3)	30 (2.0)

Adverse Event	Tamoxifen (N=1540)†	Letrozole (N=1534)	Tamoxifen → Letrozole (N=1540)	Letrozole → Tamoxifen (N=1526)
Grade 1–5	112 (7.3)	150 (9.8)	145 (9.4)	115 (7.5)
Arthralgia or myalgia				
Years 1 and 2				
Grade 3–5	27 (1.8)	45 (2.9)	26 (1.7)	42 (2.8)
Grade 1–5	260 (16.9)	397 (25.9)	273 (17.7)	387 (25.4)
Years 3–5				
Grade 3–5	11 (0.8)	7 (0.5)	20 (1.4)	5 (0.3)
Grade 1–5	266 (18.3)	204 (14.0)	272 (18.9)	163 (11.3)
Overall				
Grade 3–5	38 (2.5)	51 (3.3)	44 (2.9)	46 (3.0)
Grade 1–5	464 (30.1)	533 (34.7)	491 (31.9)	504 (33.0)

* Any significant differences in adverse events among these groups are noted in the text of the main paper. Some women dropped out of the study owing to a recurrence of disease and are not included in the analysis of years 3–5; that analysis is calculated on the basis of 1452 women in the tamoxifen group, 1454 in the letrozole group, 1439 in the tamoxifen followed by letrozole group, and 1447 in the letrozole followed by tamoxifen group.

† The tamoxifen group includes 612 women who crossed over to letrozole.

‡ Cardiac events included ischemic heart disease, arrhythmia, cardiac failure, cardiopathy, valvular disease, changes in the electrocardiogram, sudden cardiac death, and cardiac event not otherwise specified.

Section 5. BIG 1-98 Updated Monotherapy Comparisons

The primary core analysis providing the first assessment of the effect of letrozole compared with tamoxifen was conducted on the basis of data received as of November 12, 2004 (BIG 1-98 Collaborative Group. *N Engl J Med* 2005;353:2747-57.). The protocol specified that updated efficacy analyses were to be prepared and published approximately every two years, at 8, 10 and 12 years after trial initiation. On the basis of the database lock dated February 21, 2006, results for the comparison of letrozole monotherapy versus tamoxifen monotherapy (excluding patients randomly assigned to the sequential groups) were presented to the Data and Safety Monitoring Committee and published with 51 months of median follow up (Coates et al. *J Clin Oncol* 2007;25:486-92.). The current analysis of letrozole monotherapy versus tamoxifen monotherapy is the protocol specified update scheduled for 10 years after trial initiation. It is conducted on the basis of the database lock dated July 2, 2008, and was reviewed by the Data and Safety Monitoring Committee in October 2008. The median follow up for this updated monotherapy analysis is 76 months.

The results of the monotherapy update including selective crossover to letrozole among patients assigned tamoxifen monotherapy are presented in the main paper (Fig. 4). Further aspects of the selective crossover are presented in this Section.

Figure A5-1 shows the consort diagram for the monotherapy analysis population. Patients are included if they were randomly assigned to one of the two monotherapy regimens in either the two-arm or the four-arm randomization option. The ITT analysis includes 2463 patients in the letrozole group and 2459 in the tamoxifen group.

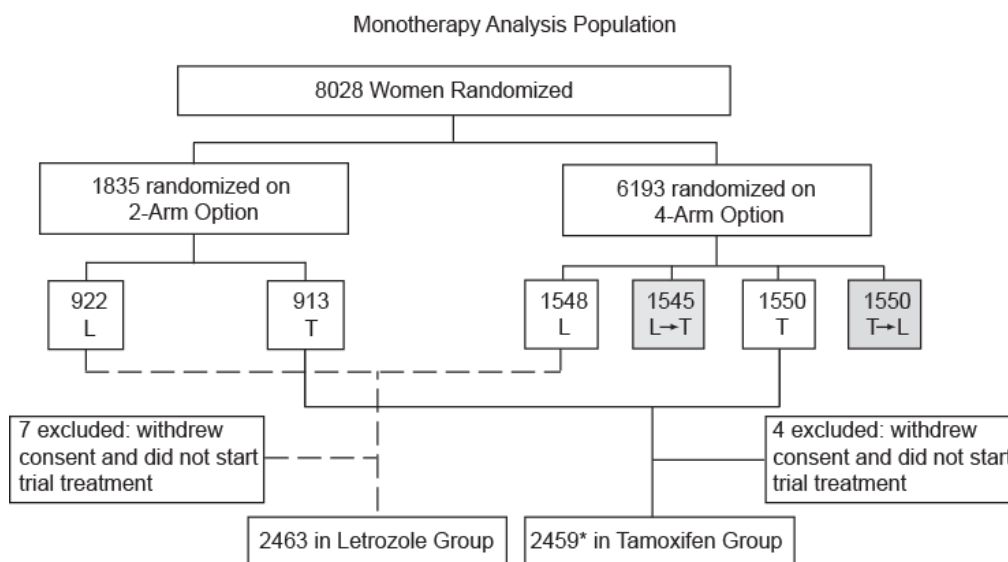


Figure A5-1. **Consort Diagram for Monotherapy Update Analysis Population.** (*includes 619 patients who crossed over to letrozole, 7 from the 2-arm option and 612 from the 4-arm option)

Figure A5-2 shows the Kaplan-Meier plots of disease-free survival for the ITT analysis of the two monotherapy treatment groups from the time of randomization. Table A5-1 shows the types of first disease-free survival events according to treatment arm.

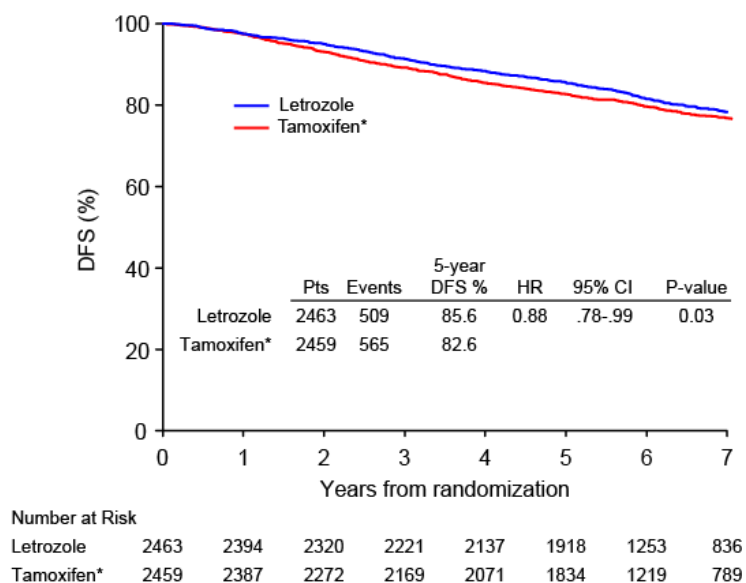


Figure A5-2. Kaplan-Meier Plots of Disease-free Survival (DFS) from the Time of Randomization for the Two Monotherapy Treatment Groups. (*includes 619 patients who crossed over to letrozole)

	Letrozole		Tamoxifen*	
	N	%	N	%
First disease-free survival events	509	20.7	565	23.0
Local	30	1.2	45	1.8
Contralateral breast	30	1.2	37	1.5
Regional	19	0.8	17	0.7
Distant soft tissue	15	0.6	21	0.9
Bone	109	4.4	111	4.5
Viscera	115	4.7	128	5.2
2nd (non-breast) malignancy	101	4.1	115	4.7
Death w/o prior cancer event	87	3.5	87	3.5
Unknown site	3	0.1	4	0.2
Deaths	303	12.3	343	13.9
Total patients	2463		2459	

Table A5-1. **Types of First Disease-free Survival Events According to the Two Treatment Arms.** (*includes 619 patients who crossed over to letrozole)

The updated monotherapy comparison is influenced by the selective crossover to letrozole of patients randomized to tamoxifen monotherapy (see Appendix Section 2).

Of 2459 patients in the updated tamoxifen monotherapy ITT analysis, 619 (25.2%) received either adjuvant or extended letrozole. Fig. A5-3 illustrates the timing of the selective crossover using cumulative incidence competing risk analysis with a disease-free survival event (recurrence or death) counted as a competing risk. Almost all of the patients in the tamoxifen monotherapy arm who selectively crossed over to letrozole did so between 3 and 5 years from randomization.

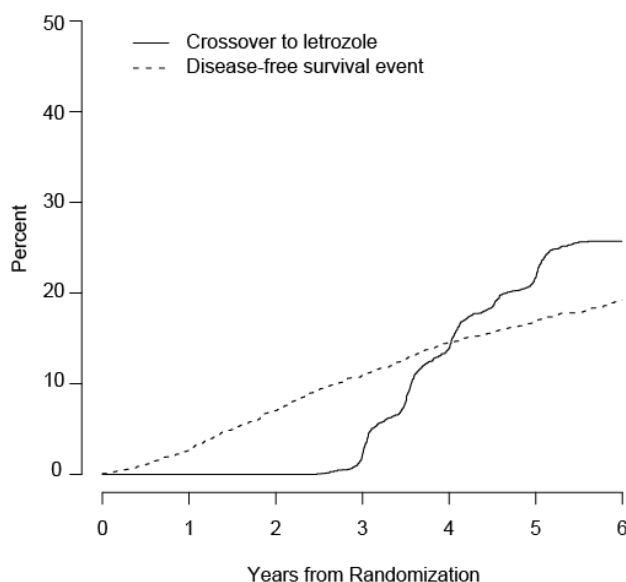


Figure A5-3. BIG Trial 1-98 Cumulative Incidence of Selective Crossover to Letrozole: Tamoxifen Monotherapy Patients from Both the Two-Arm and the Four-Arm Randomization Option.

Data from the EBCTCG overview of randomized trials (main paper reference 13), at a mean of 3.7 women-years of follow up from the time of the switch, show that switching to an AI after 2 to 3 years of tamoxifen statistically significantly reduces the risk of recurrence by 29 percent, the risk of distant recurrence by 23 percent, and the risk of death by 21 percent. This evidence shows that the 25 percent of the patients in the ITT tamoxifen monotherapy arm who selectively crossed over to letrozole actually received a sequential endocrine therapy regimen that is superior to tamoxifen alone. Thus, the estimated outcomes of the tamoxifen arm in the ITT analysis is likely to be better than if all patients randomly assigned to tamoxifen continued to receive the drug for five years. Hence, the estimates of letrozole benefit in the ITT analyses of the monotherapy comparison (main paper Figure 4) are likely to be attenuated by the selective crossover to letrozole of patients randomly assigned to receive tamoxifen.

Exploratory analyses censoring data at the time of the selective crossover were, therefore, conducted for disease-free survival, overall survival, and time to distant recurrence. As the censored analyses are likely to be subject to several biases of unknown direction and magnitude, further exploration of the effects of the selective crossover will be presented

elsewhere. Examples of factors to consider and their possible effect on the estimates of letrozole benefit in the censored analyses include: i) patients who selectively crossed over to letrozole were more likely to have node-positive disease (47% vs. 29%) and tumors larger than 2 cm (35% vs. 26%) than patients who remained on tamoxifen - biases the censored analyses results in favor of tamoxifen; ii) it is possible that women experiencing treatment-emergent side effects on tamoxifen would be more likely to elect crossover, and such patients may be those most likely to benefit from tamoxifen as recently described (Cuzick et al. *Lancet Oncol* 9:1143-1148, 2008.) – biases the censored analyses results in favor of letrozole; iii) patients who crossed over were randomized within the past five years (612 of 619 were enrolled in the four arm option) and thus have shorter overall follow up than those who remained on tamoxifen – direction of bias uncertain; and iv) specifically for the censored overall survival analysis, the fact that patients with recurrent disease are not candidates for crossover - biases the result in favor of letrozole.

Inverse probability of censoring weighted (IPCW) estimation is one method that has been used to adjust ITT analyses for potential bias caused by non-adherence with the randomized treatment assignment (Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics* 2000;56:779-788). Inverse probability weighting is generally used in scenarios where data are missing because of some disease or patient-related reason, so-called “informative” missing data, which may result in a selection bias. In the tamoxifen arm of the BIG 1-98 trial, the informative missing data are induced when we censor patients’ follow-up at the time of selective crossover, as in the “censored” rows of Figure 4 of the main paper. To adjust for selection bias, the IPCW method yields hazard ratio estimates that are valid assuming no unmeasured common causes of non-adherence and outcome, including baseline factors or time-dependent factors. In this trial, several baseline factors, including patient age, prior local therapy, nodal status, ER/PgR status, tumor grade, and tumor size (for DFS only) were associated both with outcome and with selective crossover. Performance status over time was also associated with outcome and selective crossover. The IPCW method weights the follow-up information provided by patients while remaining on tamoxifen so that in the analysis they account not only for themselves but also for patients with similar characteristics (both baseline and time-dependent) whose follow-up was censored at selective crossover to letrozole. IPCW estimates of hazard ratios for DFS and OS are presented below; the weights were calculated based upon baseline characteristics including those listed above and performance status over time (note however that the models for DFS and OS did not adjust for these covariates in order to facilitate direct comparison with the unadjusted hazard ratio estimates from the ITT and censored analyses presented in Figure 4).

Disease-Free Survival (DFS) – Considering Selective Crossover

The total number of patient-months of follow-up for patients in the tamoxifen monotherapy arm was 172,330, with 12,481 patient-months of this time accrued after starting either adjuvant or extended letrozole. This represents 7.2% of the follow-up time for patients in the updated ITT tamoxifen monotherapy arm. For patients who selectively crossed over to letrozole, the median number of months of follow-up after starting letrozole was 20.9 [range: 0 to 36.1]. The median duration of letrozole therapy for the patients who crossed over was 18 months.

The censored analysis resulted in a reduction of 21 DFS events (from 565 to 544) from the ITT analysis, and reduced the amount of follow-up by 1040 patient-years. The estimate of 5-year DFS was 82.6% in the ITT analysis compared with 82.1% in the censored analysis. Fig. 4 (main paper) shows the ITT and censored analyses for disease-free survival. The IPCW estimate of the hazard ratio (HR) for letrozole monotherapy as compared with tamoxifen monotherapy (HR=0.85, 95% CI 0.76 – 0.96) was smaller than the ITT estimate (HR=0.88, 95% CI 0.78 – 0.99) and larger than the estimate obtained from the censored analysis (HR=0.84, 95% CI 0.74 – 0.95).

Overall Survival (OS) – Considering Selective Crossover

The ITT comparison showed a trend toward improved OS with letrozole. While the ITT analysis is likely to be biased in favor of the tamoxifen group as a result of the selective crossover to letrozole, the exploratory censored analysis shown in Fig. 4 of the main paper may overall be biased in favor of letrozole. In addition to the multiple biases that may influence the censored analysis of DFS, a specific bias clearly favoring letrozole contributes to the estimated OS effect in the censored analysis, arising from the group of 182 women in the tamoxifen arm who were alive with recurrent disease at the time they might have crossed over to letrozole. These patients both remain uncensored in the tamoxifen arm and have a higher risk of death compared with patients who, at the time when they were candidates to selectively cross over to letrozole, did not have recurrent disease. Thus a group of patients with an inherently poor prognosis for survival (based on a prior DFS event) are selectively left in the tamoxifen arm in the censored analysis of overall survival (Fig. A5-4). The best estimate of the magnitude of survival benefit from letrozole is, therefore, likely to lie somewhere between the extremes defined by the ITT and censored analyses.

The IPCW estimate of the hazard ratio (HR) for letrozole monotherapy as compared with tamoxifen monotherapy (HR=0.83, 95% CI 0.71 – 0.97) was smaller than the ITT estimate (HR=0.87, 95% CI 0.75 – 1.02) and larger than the estimate obtained from the censored analysis (HR=0.81, 95% CI 0.69 – 0.94).

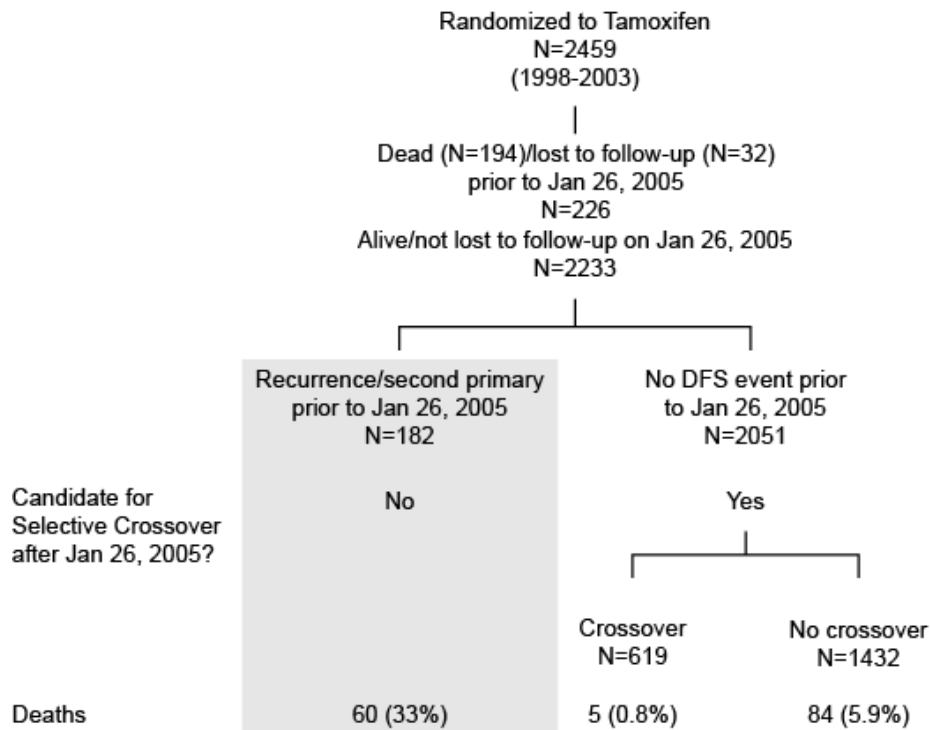


Figure A5-4. **Tamoxifen Monotherapy Arm Selective Crossover to Letrozole: Effect on Censored Analysis of Overall Survival.** January 26, 2005 is the date that the first results of BIG 1-98 were presented. The cohort of 182 patients (shaded area) who were alive with prior disease recurrence as of January 26, 2005, were both not candidates to crossover (i.e., not censored) and had a high risk of subsequent death (33% have died by the time of the current analysis). This cohort in the tamoxifen monotherapy arm particularly biases the censored analysis of overall survival in favor of letrozole. Further exploration is required to assess the influence on the censored analysis of the 2051 patients who were candidates to selectively crossover to letrozole.