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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Regan MM, Neven P, Giobbie-Hurder A, et al, for the members of the BIG 1-98 Collaborative Group and the International Breast Cancer Study Group (IBCSG). Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8·1 years median follow-up. *Lancet Oncol* 2011; published online Oct 21. DOI:10.1016/S1470-2045(11)70270-4.

Webappendix: Supplementary information for "Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 Randomised clinical trial at 8.1 years median follow-up"

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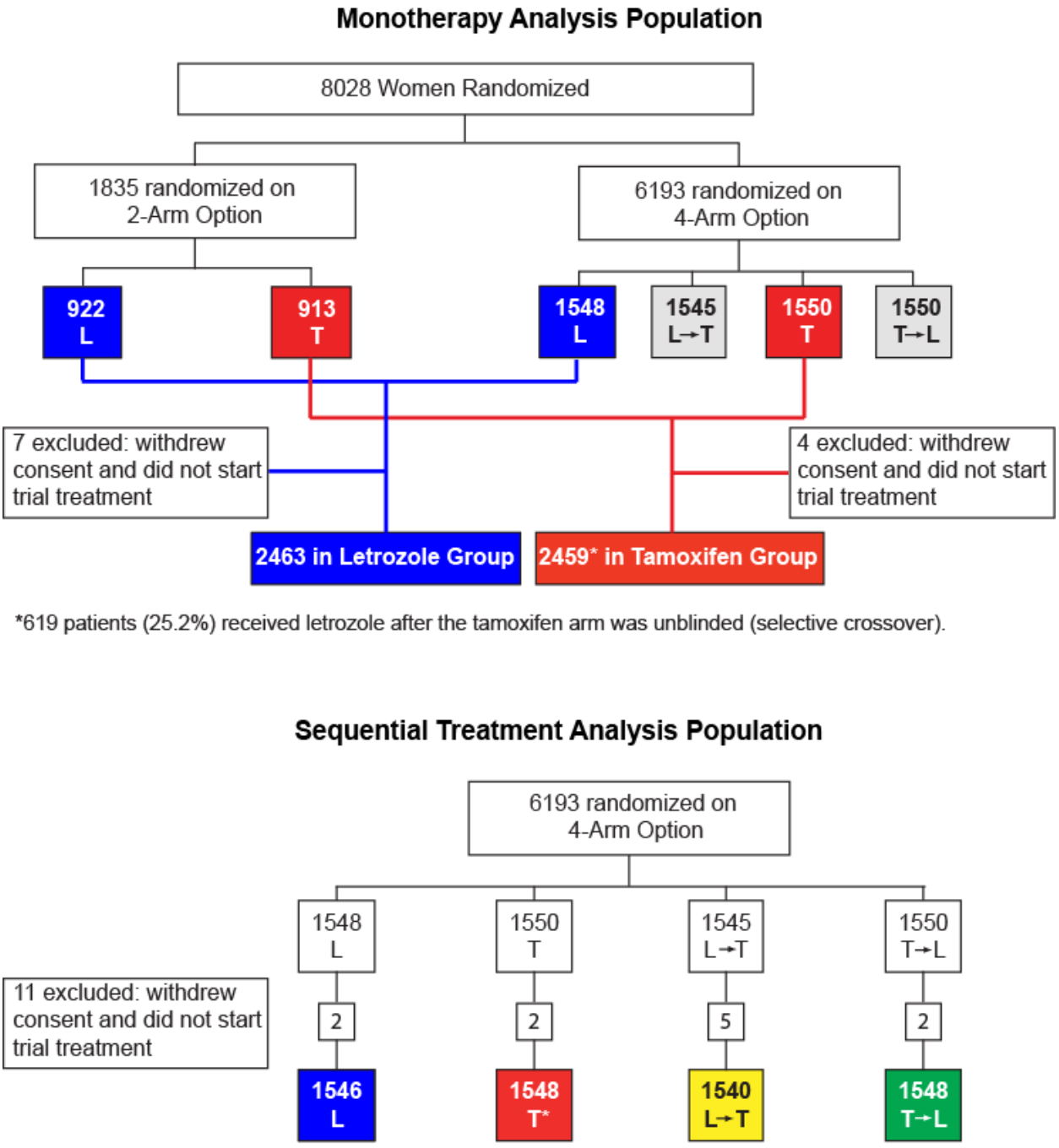
Section 2. Supplementary Tables and Figures

Figure A1. Consort diagram describing BIG 1-98 monotherapy and sequential treatment analysis populations



Sites of first disease-free survival (DFS) event are summarized in Tables A1 and A2 for the monotherapy analysis and sequential treatment analysis, respectively. Table A3 and Figure A2 present Kaplan-Meier estimates for the sequential treatment analysis for disease-free survival, overall survival, distant recurrence-free interval and breast cancer-free interval. Figure A3 shows a Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of 5-year disease-free survival (DFS) according to level of composite measure of prognostic risk (A) among all patients, (B) according to treatment assignment.

Table A1. Monotherapy analysis: Sites of first disease-free survival (DFS) event at 8.7 years median follow-up

	Letrozole		**Tamoxifen***	
	N	**%**	**N**	**%**
N. patients	*2463*		*2459*	
DFS event	646	26.2	727	29.6
Site of first DFS event:				
Local	39	1.6	56	2.3
Contralateral breast	40	1.6	65	2.6
Regional	21	0.9	22	0.9
Distant soft tissue	23	0.9	26	1.1
Bone	119	4.8	126	5.1
Viscera	143	5.8	150	6.1
Second (non-breast) malignancy	133	5.4	149	6.1
Death without prior cancer event	111	4.5	126	5.1
Unknown	17	0.7	7	0.3

*619 patients selectively crossed over and received letrozole after tamoxifen arm was unblinded.

Table A2. Sequential treatment analysis: Sites of first disease-free survival (DFS) event at 8.0 years median follow-up

	Letrozole		**Letrozole→ Tamoxifen**		**Tamoxifen→ Letrozole**		**Tamoxifen***	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
N. Patients	*1546*		*1540*		*1548*		*1548*	
DFS event	329	21.3	348	22.6	353	22.8	371	24.0
Site of first DFS event:								
Local	19	1.2	26	1.7	22	1.4	21	1.4
Contralateral breast	27	1.7	28	1.8	27	1.7	39	2.5
Regional	8	0.5	7	0.5	6	0.4	10	0.6
Distant soft tissue	10	0.6	12	0.8	6	0.4	7	0.5
Bone	58	3.8	61	4.0	77	5.0	58	3.7
Viscera	75	4.9	81	5.3	87	5.6	78	5.0
Second (non-breast) malignancy	85	5.5	81	5.3	89	5.7	89	5.7
Death without prior cancer event	40	2.6	50	3.2	34	2.2	65	4.2
Unknown	7	0.5	2	0.1	5	0.3	4	0.3

*612 patients selectively crossed over and received letrozole after tamoxifen arm was unblinded.

Table A3. Sequential treatment analysis: 5-year and 8-year estimates of the four endpoints calculated by the Kaplan-Meier method.

	Letrozole	Letrozole→ Tamoxifen	Tamoxifen→ Letrozole	Tamoxifen* (IPCW)	Tamoxifen* (ITT)
Number of patients	1546	1540	1548	1548	1548
DFS %					
5-year estimates	87.6	87.4	86.2	83.6	84.5
(SE)	(0.8)	(0.8)	(0.9)	(1.0)	(0.9)
8-year estimates	78.6	77.8	77.3	74.9	76.8
(SE)	(1.1)	(1.1)	(1.1)	(1.4)	(1.1)
OS %					
5-year estimates	93.3	93.6	92.5	92.1	92.6
(SE)	(0.6)	(0.6)	(0.7)	(0.7)	(0.7)
8-year estimates	87.5	87.7	85.9	82.9	86.2
(SE)	(0.9)	(0.9)	(0.9)	(1.3)	(0.9)
DRFI %					
5-year estimates	94.1	93.4	92.3	91.9	92.0
(SE)	(0.6)	(0.6)	(0.7)	(0.7)	(0.7)
8-year estimates	89.9	88.7	88.1	88.2	89.4
(SE)	(0.8)	(0.9)	(0.9)	(1.0)	(0.8)
BCFI %					
5-year estimates	92.5	92.4	90.4	89.3	90.0
(SE)	(0.7)	(0.7)	(0.8)	(0.9)	(0.8)
8-year estimates	86.1	85.3	84.3	84.2	85.9
(SE)	(1.0)	(1.0)	(1.0)	(1.1)	(0.9)

Only patients enrolled in the 4-arm option are included in Table A3. Median follow up was 8.0 years**.**
*612 patients selectively crossed over and received letrozole after tamoxifen arm was unblinded. Both IPCW and ITT estimates are shown for the tamoxifen arm patients enrolled in the 4-arm option of the trial.

Figure A2. Kaplan-Meier Plots for the Sequential Treatment Analysis: (A) disease-free survival (DFS); (B) overall survival (OS); (C) distant recurrence-free interval (DRFI); and (D) breast cancer-free interval (BCFI)

Inverse probability of censoring weighted (IPCW) Kaplan-Meier estimates are shown for the tamoxifen monotherapy arm. Intention-to-treat (ITT) estimates are shown for the letrozole-containing regimens. The median follow-up time is 8.0 years.

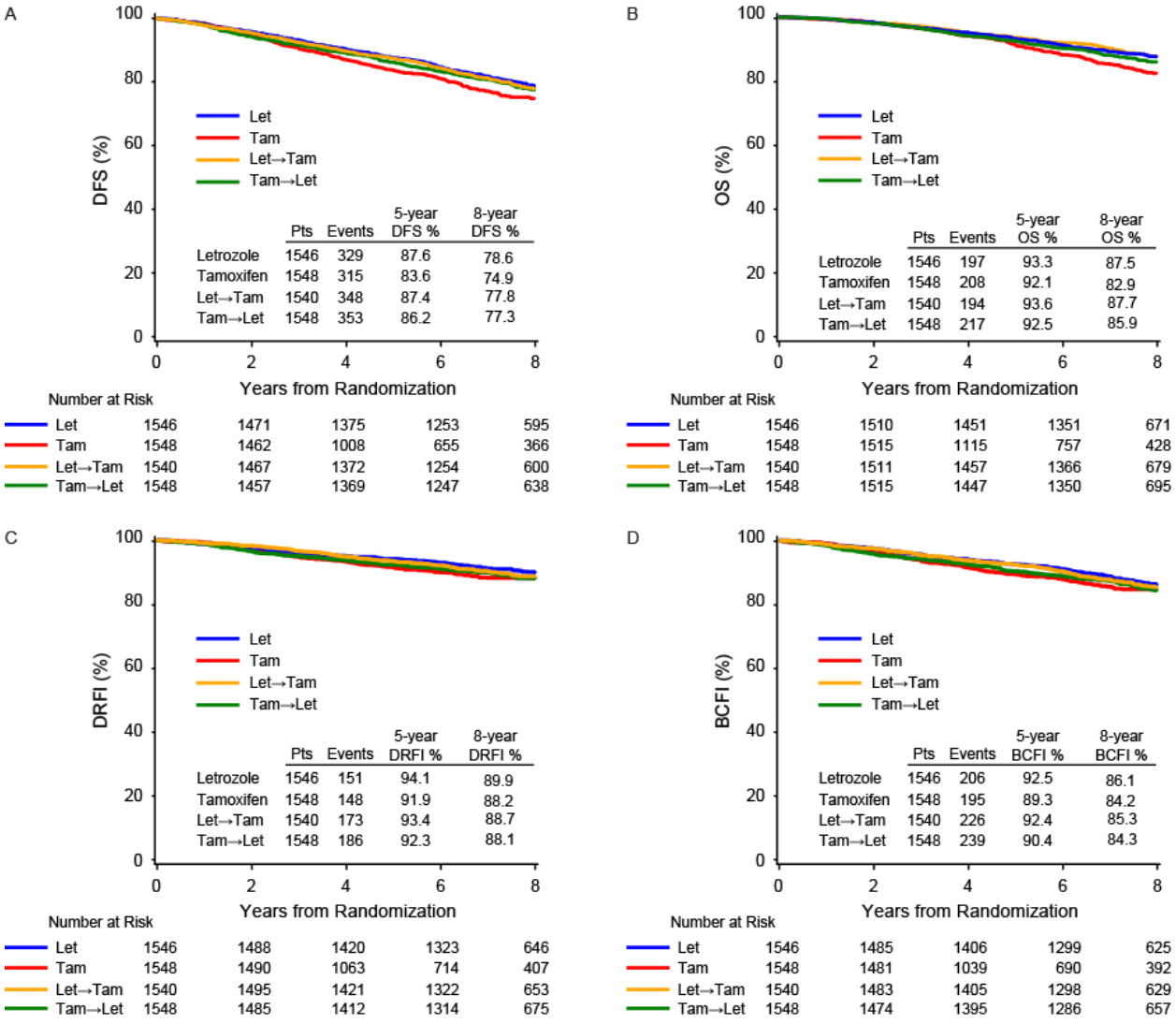
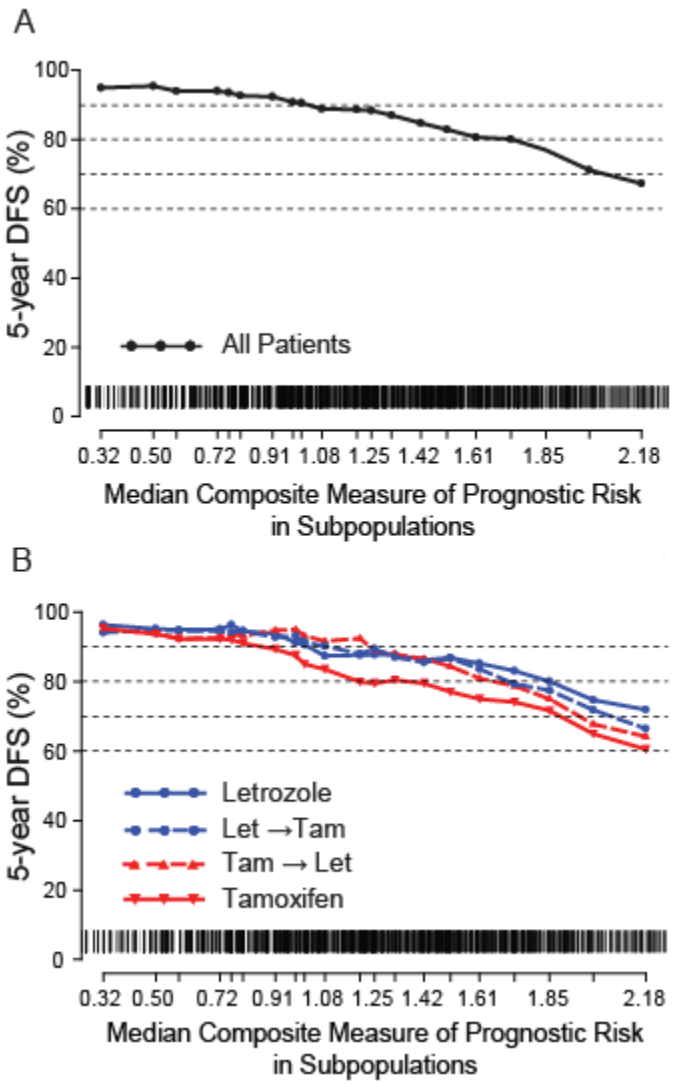


Figure A3. Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of 5-year disease-free survival (DFS) according to level of composite measure of prognostic risk (A) among all patients, (B) according to treatment assignment

The STEPP plots show the 5-year DFS percent (vertical axis) for overlapping subpopulations of patients with increasing levels of the composite measure of prognostic risk (median risk for each subpopulation is shown along the horizontal axis). Rug plots along the x-axis display the distribution of individual values. Reprinted with permission of *Ann Oncol* (Viale et al [1]).



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