Supplementary Appendix

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

Supplement to: Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016;374:209-19. DOI: 10.1056/NEJMoa1604700

(PDF updated June 23, 2016.)

Appendix

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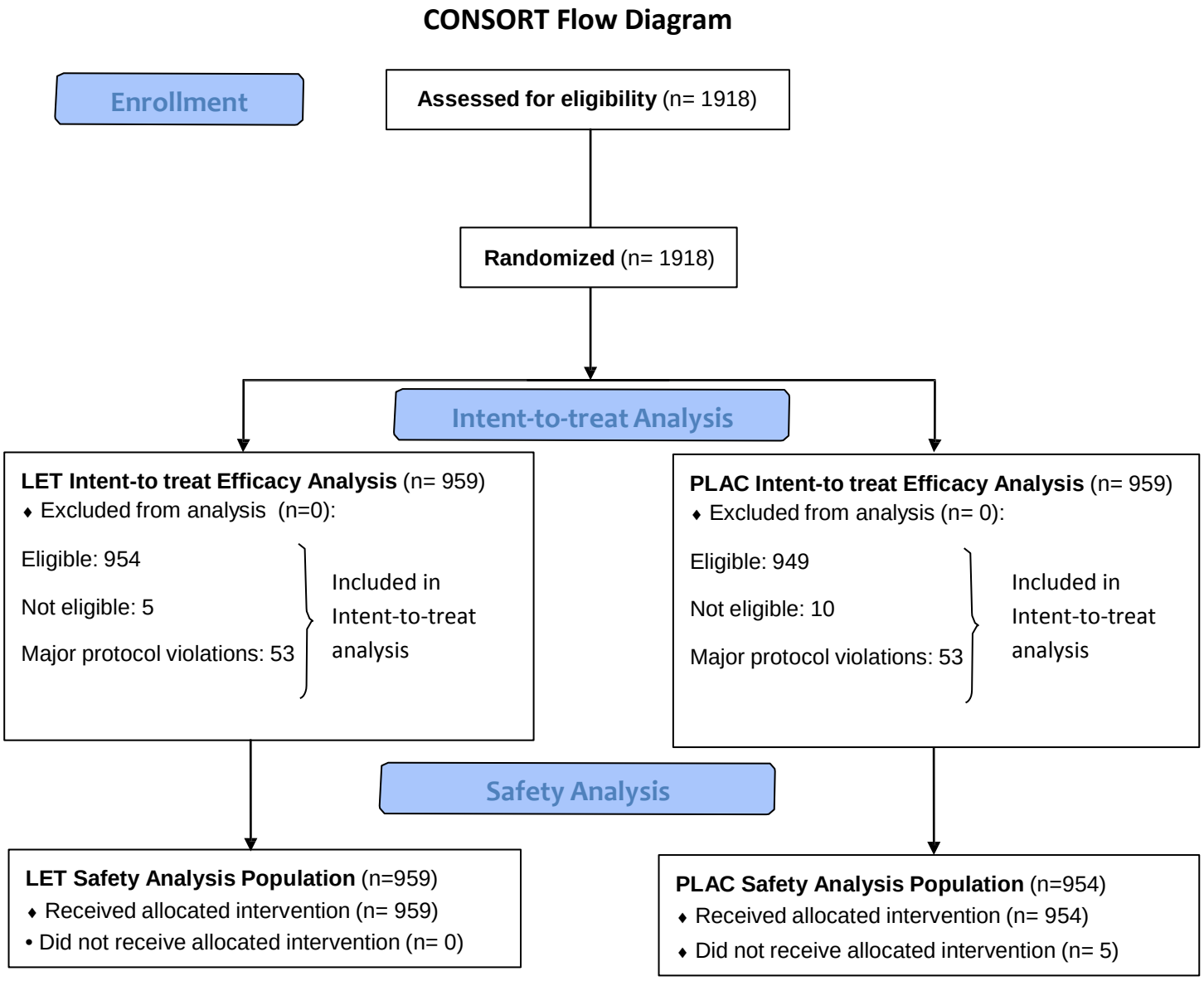
Suppl S1: Methods of Quality of Life Analysis

For the SF36 physical and mental component summary scores, the 8 subscales, and the MENQOL 4 symptom subscales, between-treatment group comparisons of change scores from baseline were conducted using longitudinal linear mixed models, which include all women who had at least one assessment. Treatment group and time (of assessment), and interactions of treatment group with time (group x time) were included as fixed covariates in the initial models. Random intercepts in the model was used to account for the dependence of repeated measures. If interaction term was significant at 0.05 level, comparisons between treatment groups at each assessment time point are conducted using Wilcoxon tests. Otherwise, a reduced model without the interaction term was refitted and overall differences between change scores of treatment groups were assessed based on the coefficient of the treatment term in the reduced model.

Suppl S2: Adjudication of Cause of Death

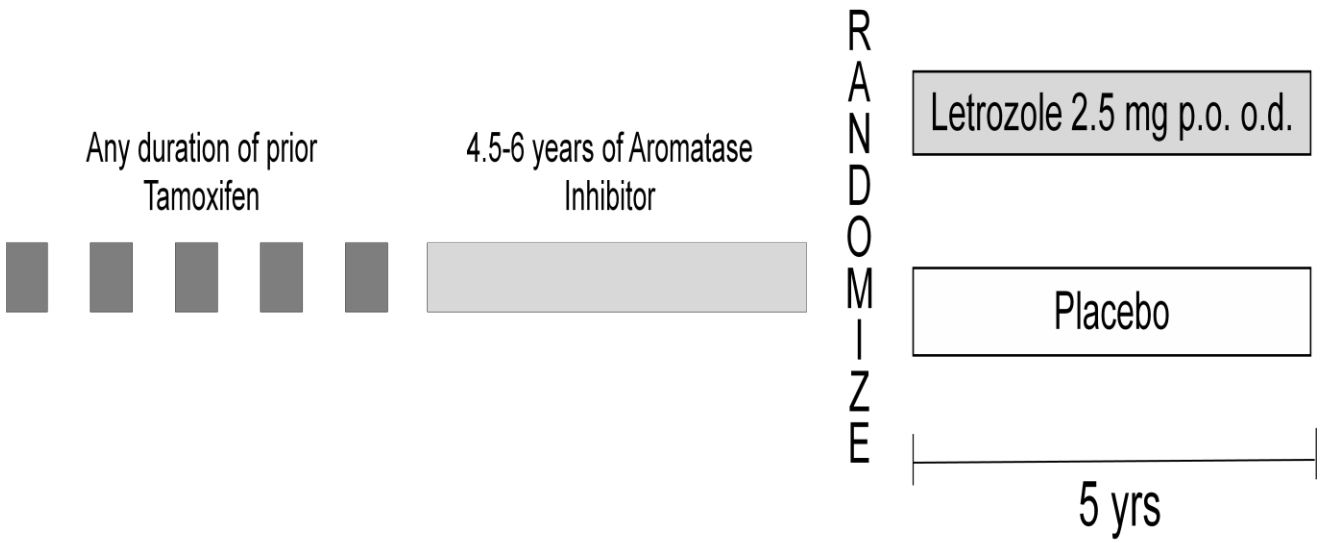
The approved protocol does not make reference to adjudication of deaths. Our standard operating procedure requires all data on cause of death reported by the investigators to be centrally monitored, with selected data, including primary endpoint and death (as well as other serious adverse events etc.), undergoing medical review. If after medical review the physician reviewer requires additional information to confirm investigator assessment of cause of death, a query is issued so that cause of death can be properly categorized. We do not routinely collect supporting documentation related to cause of death (e.g. discharge summary, death certificate, autopsy report) but physician reviewing can request these if necessary for clarification.

Suppl Figure S1: CONSORT Flow Diagram



LET: Letrozole; PLAC: Placebo

Suppl Figure S2: MA.17R Study Schema



Suppl Table S1: Protocol Reportable Serious Adverse Events

	Letrozole							Placebo						
Evaluable Patients	N=959							N=954						
	Grade[§]							Grade[§]						
Adverse Event	1	2	3	4	5	TOTAL (%)	%[$]	1	2	3	4	5	TOTAL (%)	%R[$]
Secondary Malignancy														
Secondary Malignancy					3	3 (0)	(0)					3	3 (0)	(0)
Cardiovascular														
Ventricular arrhythmia					1	1 (0)	(0)				1		1(0)	(0)
Edema		1				1 (0)	(0)							
Cardiac LVF					1	1 (0)	(0)					1	1 (0)	(0)
Ischemia/ infarction					2	2 (0)	(0)					4	4 (0)	(0)
Supraventricular arrythmia			1			1 (0)	(0)							
Cardiac troponin I											1		1 (0)	(0)
Thrombosis/ embolism												1	1 (0)	(0)
Other					1	1 (0)	(0)							
Flu-Like Symptoms														
Fatigue		1				1 (0)	(0)							
Other										1			1 (0)	(0)
Renal														
Creatinine										1			1 (0)	(0)
Renal Failure					3	3 (0)	(0)					2	2 (0)	(0)
Hemorrhage														
CNS hemorrhage/ bleeding												1	1 (0)	(0)
Melena/GI bleeding					1	1 (0)	(0)							
Rectal bleeding					1	1 (0)	(0)							
Hepatic														
Liver dysfunction					1	1 (0)	(0)							
Other					1	1 (0)	(0)							
Infection														
Infection w/o neutropenia					2	2 (0)	(0)			1		2	3 (0)	(0)
Infection-unknown ANC												1	1 (0)	(0)
Neurology														
CNS cerebrovascular ischemia												3	3 (0)	(0)

Neuropathy-motor											1		1 (0)	(0)
Other														
Other					4	4 (0)	(0)					1	1 (0)	(0)
Pulmonary														
Pleural effusion										1			1 (0)	(0)
Hypoxia			1			1 (0)	(0)					1	1 (0)	(0)
Pneumonitis											1		1 (0)	(0)
Dyspnea											1		1 (0)	(0)
Other										1		1	2 (0)	(0)
Worst Overall Grade					15	15 (2)	(0)					19	19 (2)	(0)

[§]Adverse events were graded according to Common Toxicity Criteria Version 2.0

[$]Considered by investigator to be 'possibly', 'probably' or 'definitely' related to protocol treatment.

LVF: left ventricular failure; w/o: without; GI: gastrointestinal

Table S2: Baseline Characteristics

	Number of subjects (%)		
	Letrozole N= 959	Placebo N= 959	Total N= 1918
Race/ethnicity			
White (not of Hispanic origin)	884 (92.2)	878 (91.6)	1762 (91.9)
Hispanic	11 (1.1)	13 (1.4)	24 (1.3)
Black (not of Hispanic origin)	34 (3.5)	26 (2.7)	60 (3.1)
Asian or Pacific Islander	17 (1.8)	23 (2.4)	40 (2.1)
Native North American or Native Alaskan	3 (0.3)	6 (0.6)	9 (0.5)
Other	2 (0.2)	6 (0.6)	8 (0.4)
Unknown (or refusal)	8 (0.8)	7 (0.7)	15 (0.8)
Age (Years)*			
N	959	959	1918
Median [interquartile range]	65.6 [60.3–72.0]	64.8 [59.6–71.1]	65.1 [60.0–71.5]
< 70	642 (66.9)	686 (71.5)	1328 (69.2)
≥70	317 (33.1)	273 (28.5)	590 (30.8)
ECOG Performance Status			
0	852 (88.8)	856 (89.3)	1708 (89.1)
1	100 (10.4)	95 (9.9)	195 (10.2)
2	7 (0.7)	8 (0.8)	15 (0.8)
Times (years) from first initial pathologic diagnosis to the date of randomization			
N	959	959	1918
Median years [interquartile range]	10.6 [7.5-11.5]	10.6 [7.8-11.6]	10.6 [7.6-11.5]
Pathological T stage of disease at first diagnosis			
0	1 (0.1)	0 (0.0)	1 (0.1)
1	552 (57.6)	535 (55.8)	1087 (56.7)
2	312 (32.5)	335 (34.9)	647 (33.7)
3	66 (6.9)	67 (7.0)	133 (6.9)
4	21 (2.2)	12 (1.3)	33 (1.7)
x	7 (0.7)	10 (1.0)	17 (0.9)
Pathological stage N of disease at first diagnosis			
0	446 (46.5)	448 (46.7)	894 (46.6)
1	456 (47.5)	455 (47.4)	911 (47.5)
2	28 (2.9)	30 (3.1)	58 (3.0)
3	8 (0.8)	9 (0.9)	17 (0.9)
x	21 (2.2)	17 (1.8)	38 (2.0)
Estrogen receptor status*			

Positive	904 (94.3)	920 (95.9)	1824 (95.1)
Negative	44 (4.6)	31 (3.2)	75 (3.9)
Unknown	4 (0.4)	7 (0.7)	11 (0.6)
Missing	7 (0.7)	1 (0.1)	8 (0.4)
Progesterone receptor status			
Positive	767 (80.0)	751 (78.3)	1518 (79.1)
Negative	132 (13.8)	147 (15.3)	279 (14.5)
Unknown	40 (4.2)	38 (4.0)	78 (4.1)
Missing	20 (2.1)	23 (2.4)	43 (2.2)
Hormone receptor status (estrogen and/or progesterone)			
Positive	945 (98.5)	950 (99.1)	1895 (98.8)
Negative	3 (0.3)	2 (0.2)	5 (0.3)
Unknown	4 (0.4)	5 (0.5)	9 (0.5)
Missing	7 (0.7)	2 (0.2)	9 (0.5)
Years on tamoxifen			
N	959	959	1918
median [interquartile range]	5.0 [2.0-5.0]	5.0 [2.0-5.0]	5.0 [2.0-5.0]
0 years	199 (20.8)	198 (20.6)	397 (20.7)
< 2 years	40 (4.2)	40 (4.2)	80 (4.2)
2-4.5 years	43 (4.5)	29 (3.0)	72 (3.8)
4.5 to 5 years	315 (32.8)	322 (33.6)	637 (33.2)
5 to 5.5 years	336 (35.0)	342 (35.7)	678 (35.3)
5.5 to 6 years	19 (2.0)	20 (2.1)	39 (2.0)
> 6 years	7 (0.7)	8 (0.8)	15 (0.8)
Duration of previous AI therapy			
N	959	958	1917
Median [interquartile range]	5.0 [5.0-5.1]	5.0 [5.0-5.1]	5.0 [5.0-5.1]
Missing	0 (0.0)	1 (0.1)	1 (0.1)
< 4.5 years	3 (0.3)	2 (0.2)	5 (0.3)
4.5 to 5 years	356 (37.1)	347 (36.2)	703 (36.7)
5 to 5.5 years	557 (58.1)	568 (59.2)	1125 (58.7)
5.5 to 6 years	36 (3.8)	35 (3.6)	71 (3.7)
> 6 years	7 (0.7)	6 (0.6)	13 (0.7)
Type of previous AI therapy			
Letrozole	714 (74.5)	718 (74.9)	1432 (74.7)
Anastrozole	212 (22.1)	210 (21.9)	422 (22.0)
Exemestane	55 (5.7)	54 (5.6)	109 (5.7)
Continuous breaks of longer than 6 months in treatment with AI			

No	955 (99.6)	953 (99.4)	1908 (99.5)
Yes	4 (0.4)	6 (0.6)	10 (0.5)
Interval between last dose of aromatase inhibitor therapy and randomization			
Missing	0 (0.0)	1 (0.1)	1 (0.1)
Negative[§]	11 (1.1)	9 (0.9)	20 (1.0)
< 6 months	863 (90.0)	864 (90.1)	1727 (90.0)
6 months to 2 years	81 (8.4)	81 (8.4)	162 (8.4)
> 2 years	4 (0.4)	4 (0.4)	8 (0.4)
Prior adjuvant chemotherapy			
No	398 (41.5)	402 (41.9)	800 (41.7)
Yes	561 (58.5)	557 (58.1)	1118 (58.3)
Prior surgery			
Lymph Node Dissection	861 (89.8)	872 (90.9)	1733 (90.4)
Lumpectomy	583 (60.8)	575 (60.0)	1158 (60.4)
Mastectomy	459 (47.9)	472 (49.2)	931 (48.5)

* P<0.05 for the comparison between treatment groups.

§Very few patients continued taking their original AI therapy after randomization but most of them stopped after randomization.

AI: aromatase inhibitor

Trial Registration

The MA.17R trial was considered an amendment to the original MA.17 trial (NCT00003140) registered in 1999 and published in 2003 (Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in post-menopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349:1793-802).

Patients began entering the MA.17R study amendment in October 2004. In 2008, the MA.17R study was registered independently and given a separate NCT number (NCT00754845).