THE LANCET

Supplementary appendix

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

Supplement to: Christina Davies, Hongchao Pan, Jon Godwin, et al, for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2012; published online Dec 5. http://dx.doi.org/10.1016/S0140-6736(12)61963-1.

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

C Davies et al, for the ATLAS Collaborative Group
The Lancet (published online on 5 December 2012)

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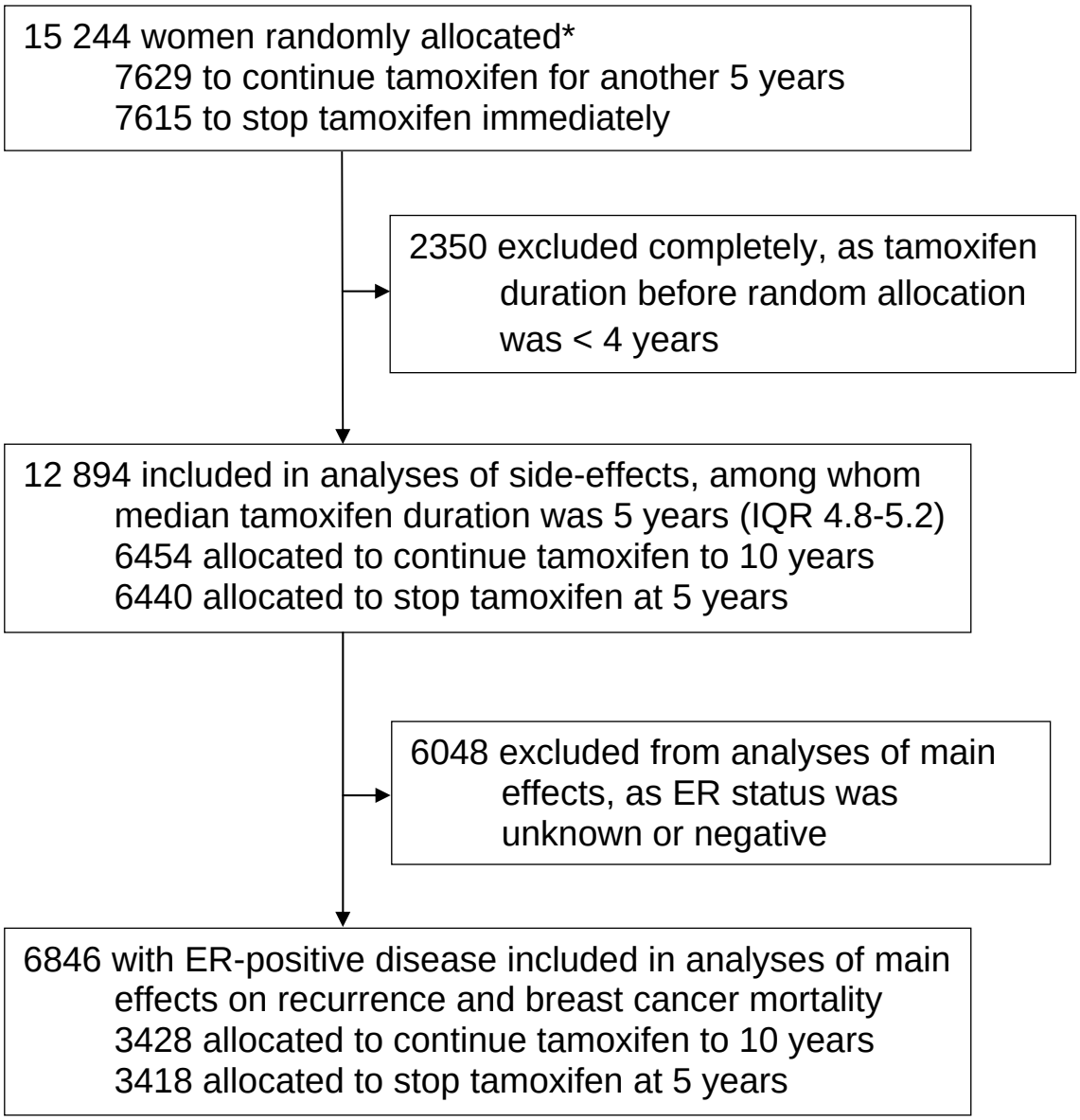
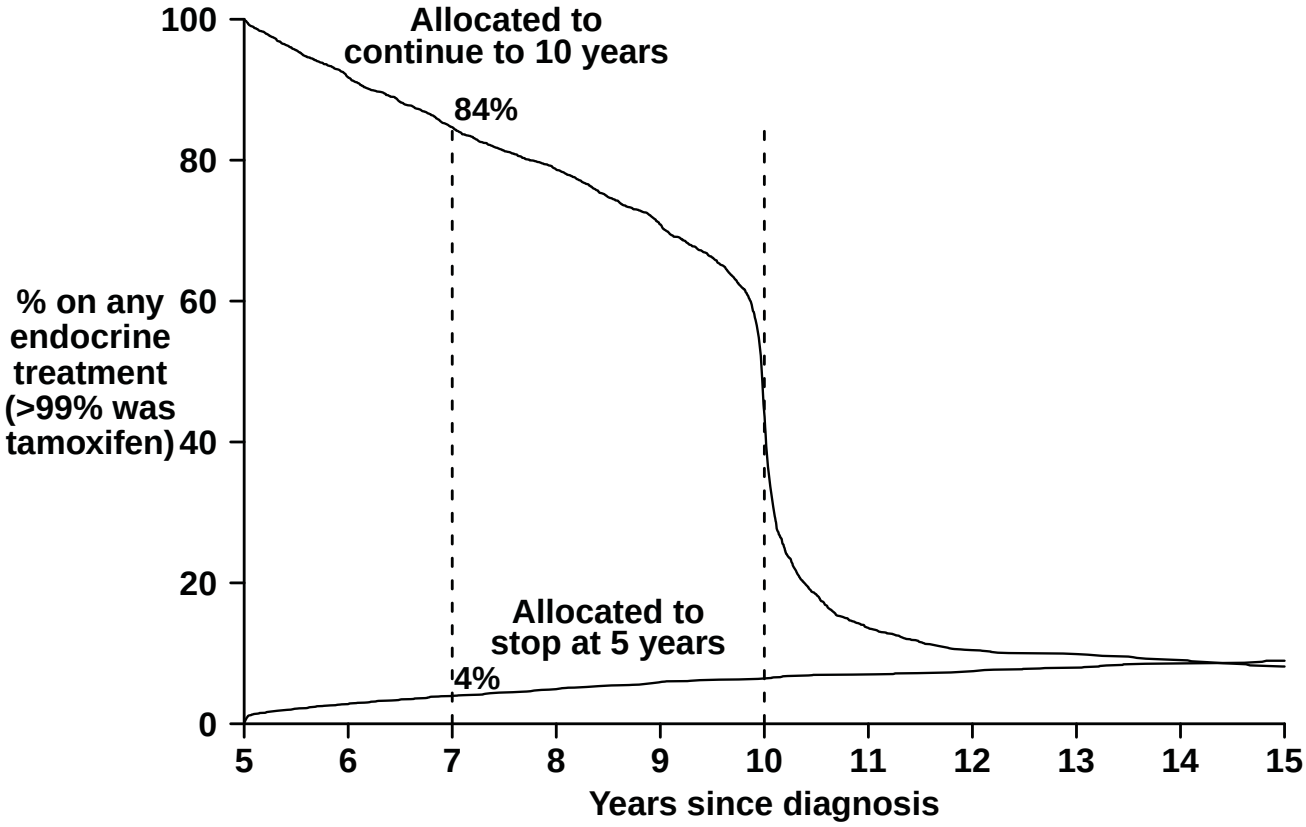
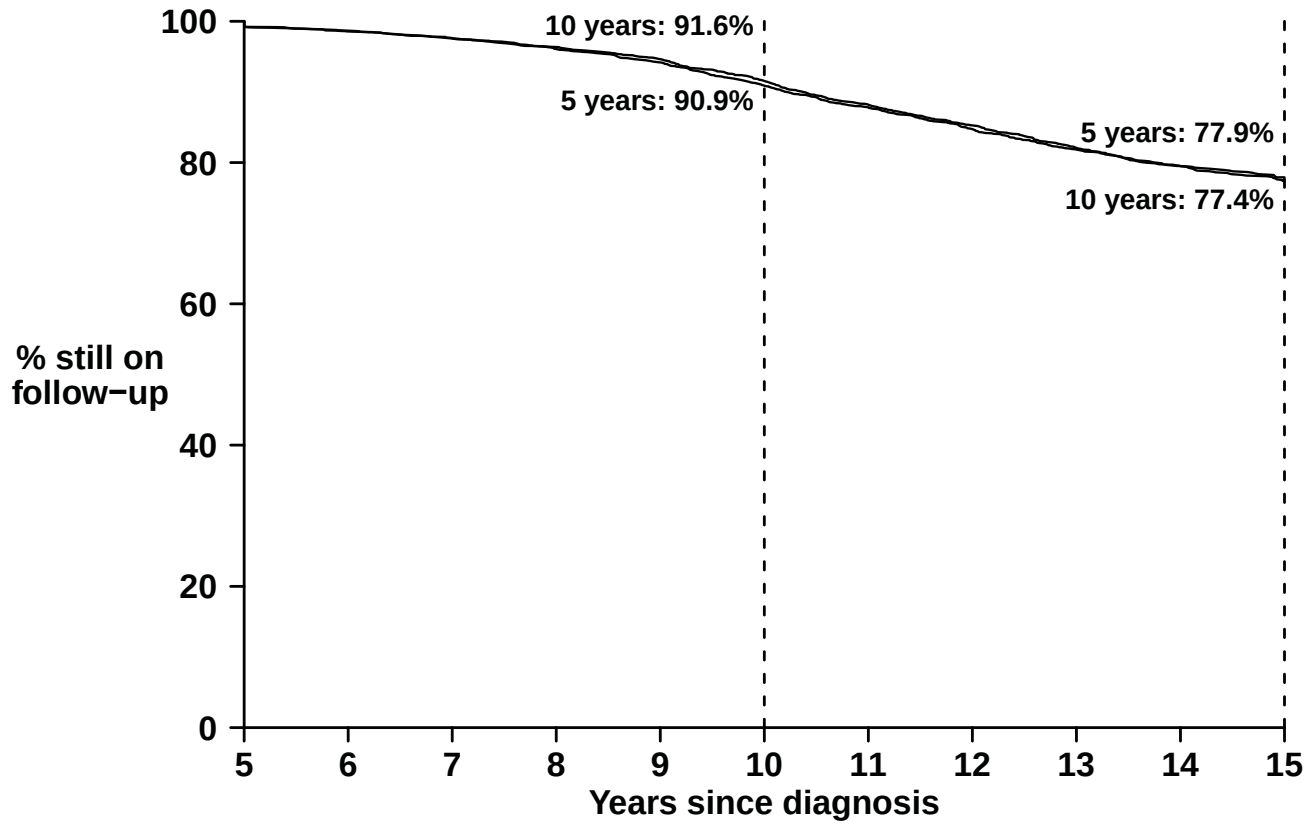


Webfigure 1: Trial profile, showing the different populations analysed to assess the side-effects and the main effects of continuing tamoxifen to 10 years versus stopping tamoxifen at 5 years

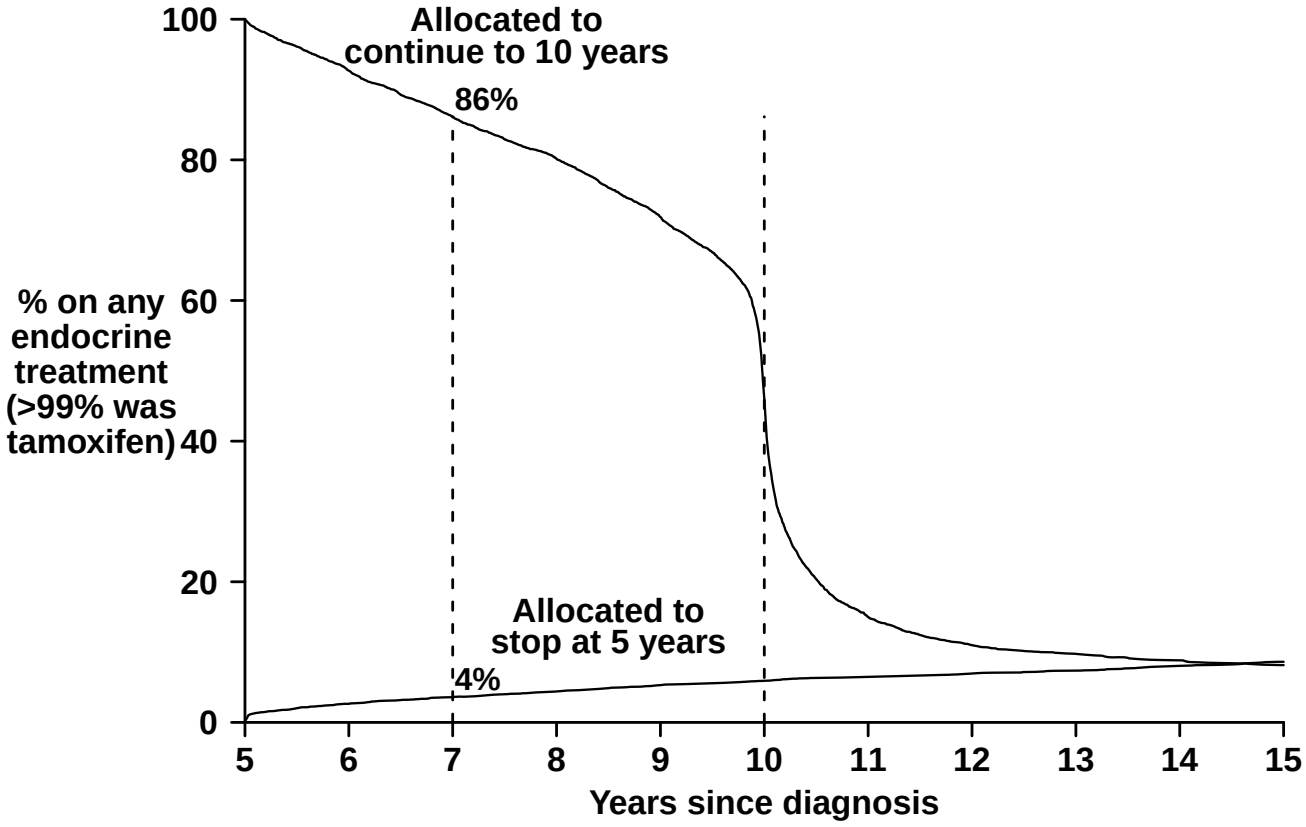
* 39 patients were allocated twice in error, but stayed on their original allocation. Excludes 18 patients entered in error (17 with distant recurrence and 1 without ethics approval).
ER=oestrogen receptor

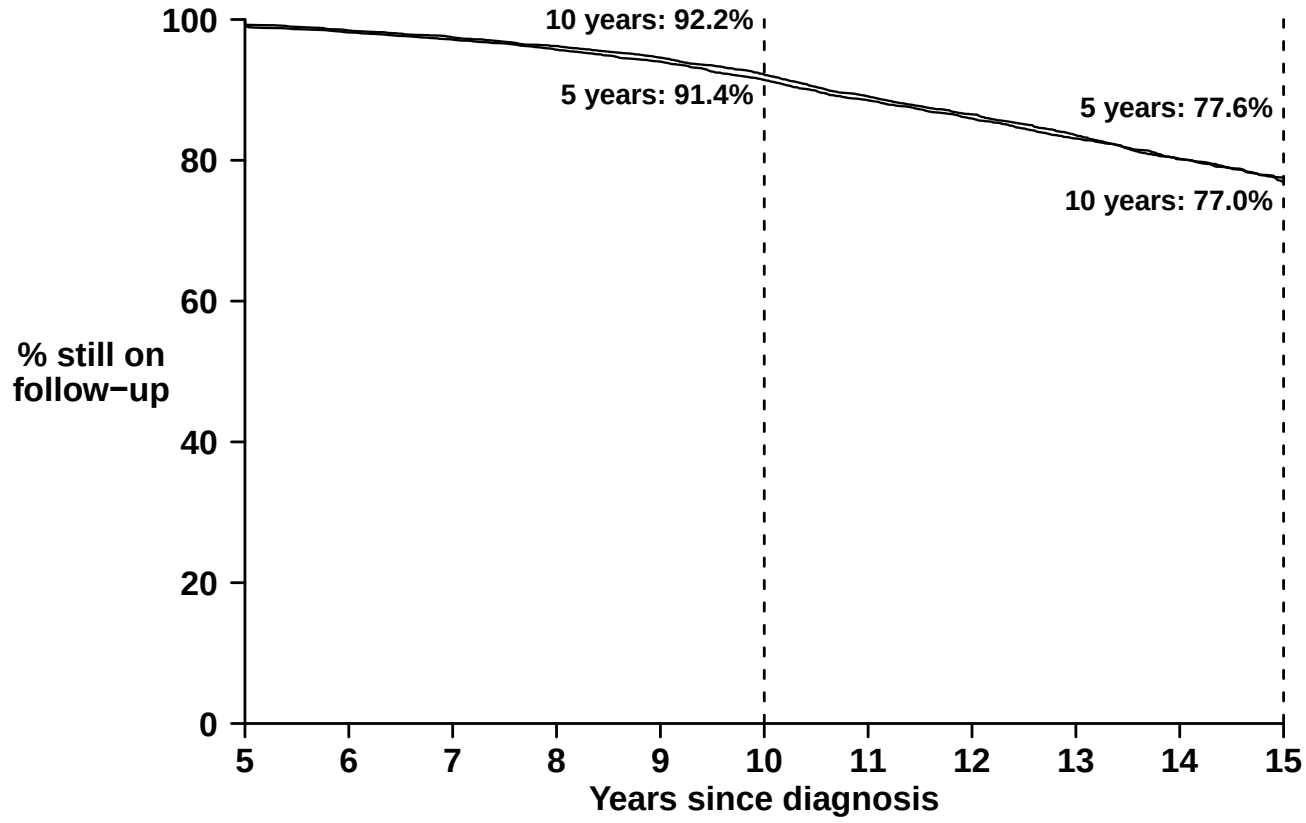




Tamoxifen allocation	Number at risk										
Continue to 10 years	3428	3338	3247	3143	3007	2827	2614	2224	1632	1088	689
Stop at 5 years	3418	3333	3233	3098	2962	2786	2551	2166	1575	1050	682

Webfigure 2: 6846 women with ER-positive disease. Upper: Compliance with random allocation by year since random allocation: % still on any endocrine treatment (>99% was tamoxifen). Lower: Compliance with follow-up by year since random allocation: proportion of those not known to be dead who have not been reported on since 1.1.2010



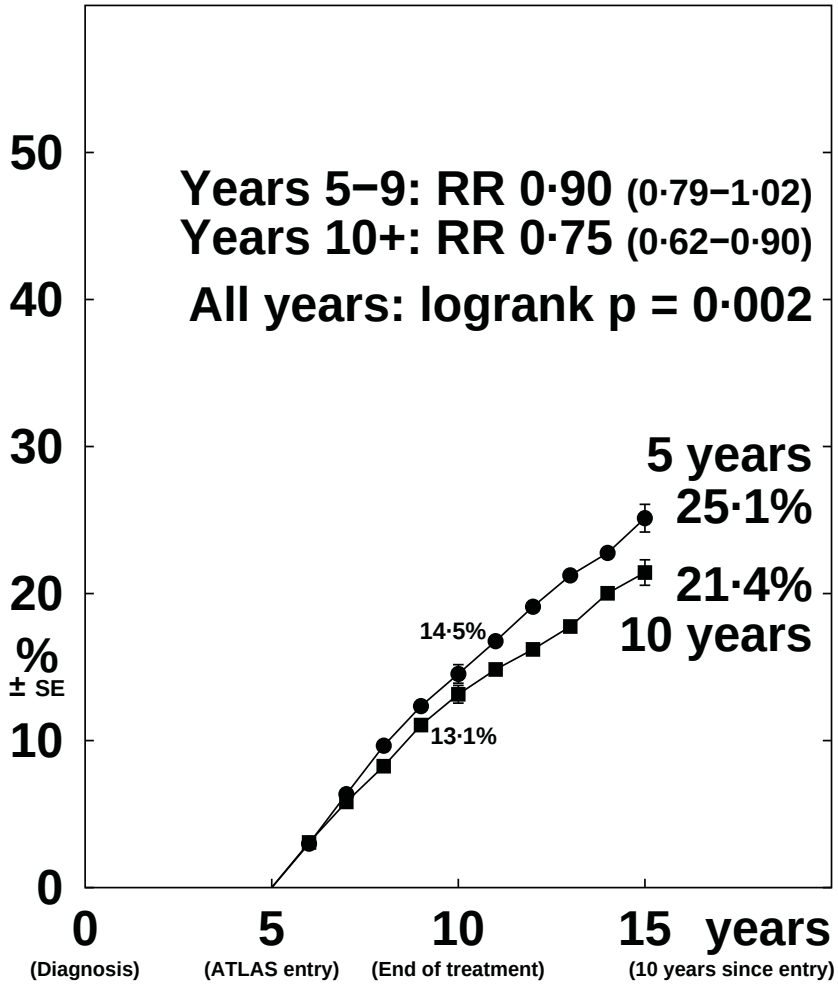


Tamoxifen allocation	Number at risk										
Continue to 10 years	6454	6268	6083	5867	5614	5310	4937	4317	3387	2487	1735
Stop at 5 years	6440	6242	6052	5795	5520	5233	4838	4219	3260	2418	1729

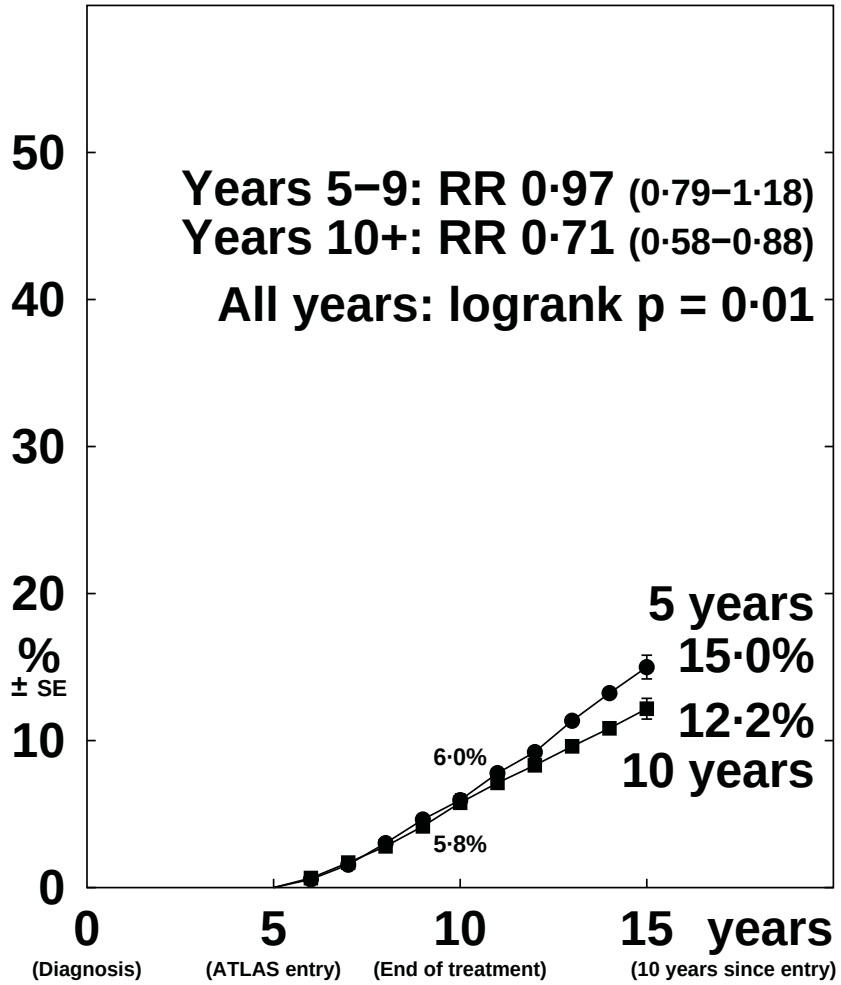
Webfigure 3: 12894 women, all ER status. Upper: Compliance with random allocation by year since random allocation: % still on any endocrine treatment (>99% was tamoxifen). Lower: Compliance with follow-up by year since random allocation: proportion of those not known to be dead who have not been reported on since 1.1.2010

6846 women, definitely ER+ disease at entry (54% node-negative)

RECURRENCE



BREAST CANCER MORTALITY



Recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·83 (428 / 15115)	1·96 (165 / 8439)	2·54 (24 / 945)
Stop at 5 years	3·16 (471 / 14889)	2·66 (214 / 8038)	3·03 (26 / 859)
Rate ratio, from	0·90 SE 0·06	0·74 SE 0·09	0·85 SE 0·26
(O−E) / V	−24·8 / 224·7	−29·1 / 94·7	−2·1 / 12·5

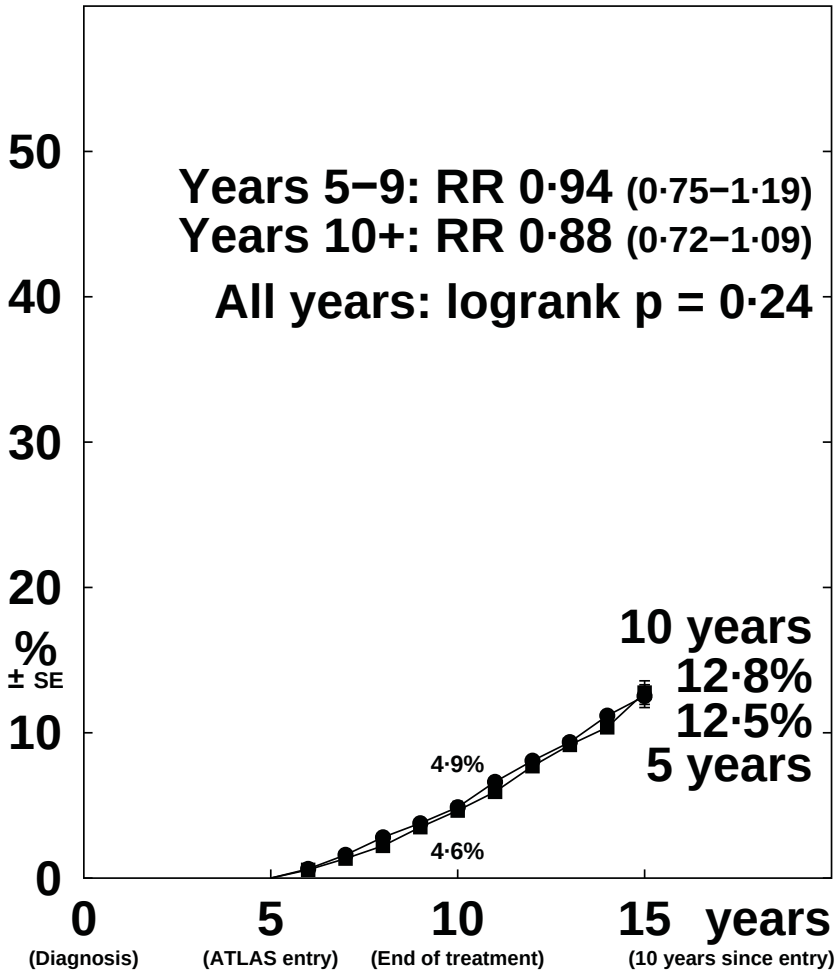
Death rates (% / year: total rate − rate in women without recurrence) & logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	1·17 SE 0·09	1·38 SE 0·12	1·64 SE 0·39
Stop at 5 years	1·21 SE 0·09	2·01 SE 0·15	2·29 SE 0·47
Rate ratio, from	0·97 SE 0·10	0·70 SE 0·10	0·79 SE 0·27
(O−E) / V	−3·2 / 94·0	−27·2 / 77·5	−2·5 / 10·6

Webfigure 4a: Definitely ER-positive disease: recurrence, and breast cancer mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).

6846 women, definitely ER+ disease at entry (54% node-negative)

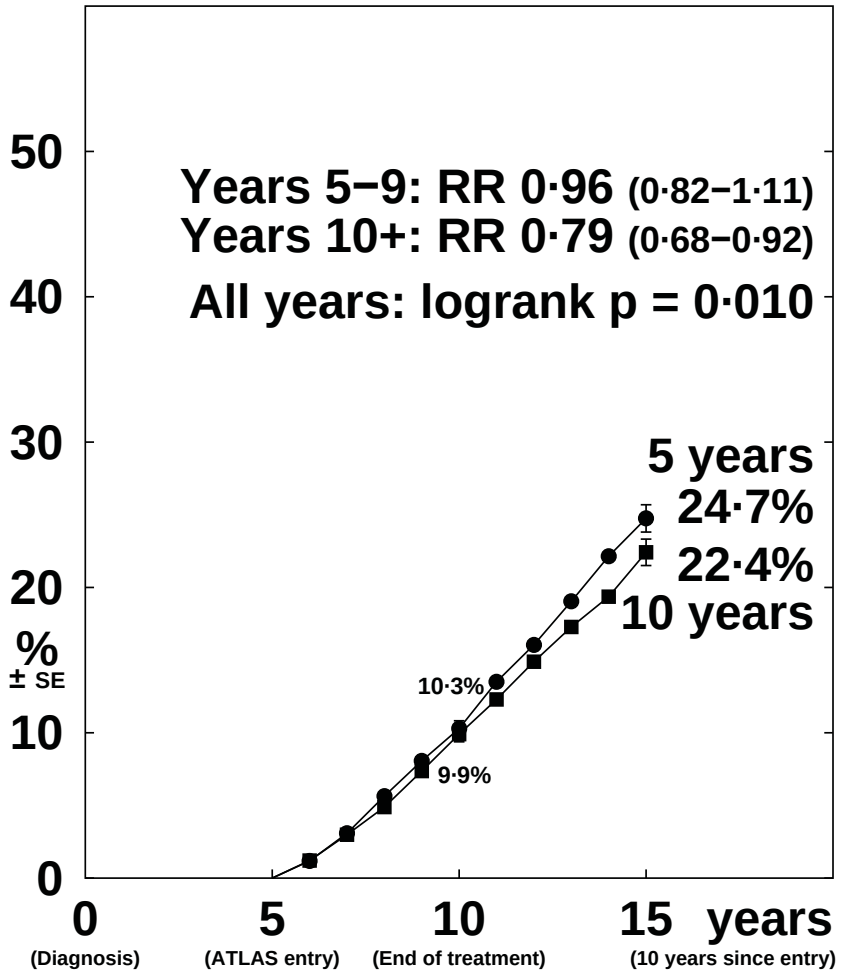
MORTALITY WITHOUT RECURRENCE



Death−without−recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	0·93 (141 / 15115)	1·67 (141 / 8439)	2·75 (26 / 945)
Stop at 5 years	0·99 (147 / 14889)	1·68 (135 / 8038)	5·01 (43 / 859)
Rate ratio, from	0·94 SE 0·11	0·99 SE 0·12	0·55 SE 0·18
(O−E) / V	−4·2 / 72·0	−0·4 / 68·9	−10·2 / 17·2

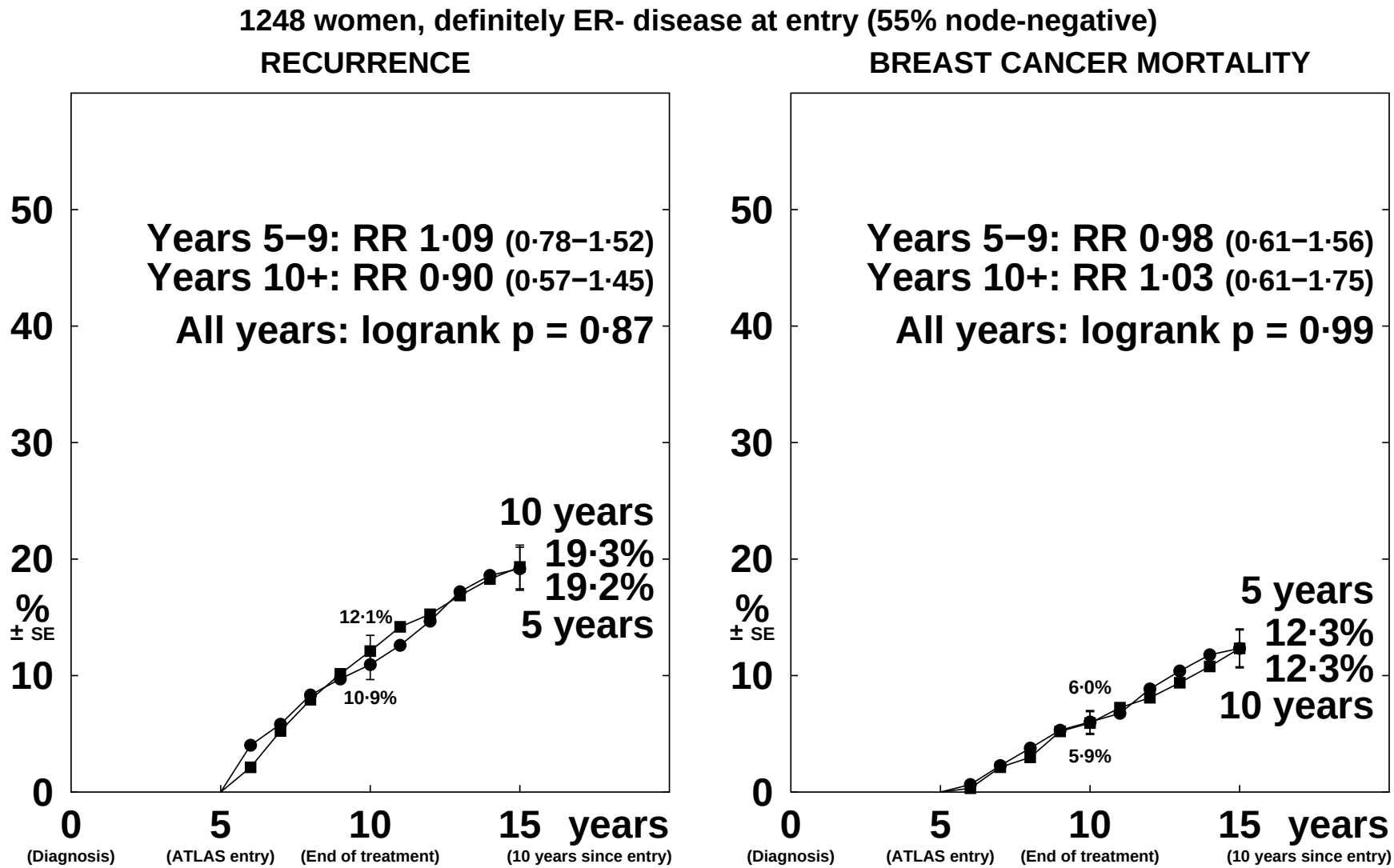
OVERALL MORTALITY



Death rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·06 (326 / 15848)	2·89 (269 / 9297)	4·00 (44 / 1099)
Stop at 5 years	2·15 (338 / 15726)	3·49 (317 / 9075)	6·38 (67 / 1050)
Rate ratio, from	0·96 SE 0·08	0·83 SE 0·08	0·63 SE 0·15
(O−E) / V	−7·5 / 166·0	−27·5 / 146·5	−12·7 / 27·7

Webfigure 4b: Definitely ER-positive disease: mortality without recurrence, and overall mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



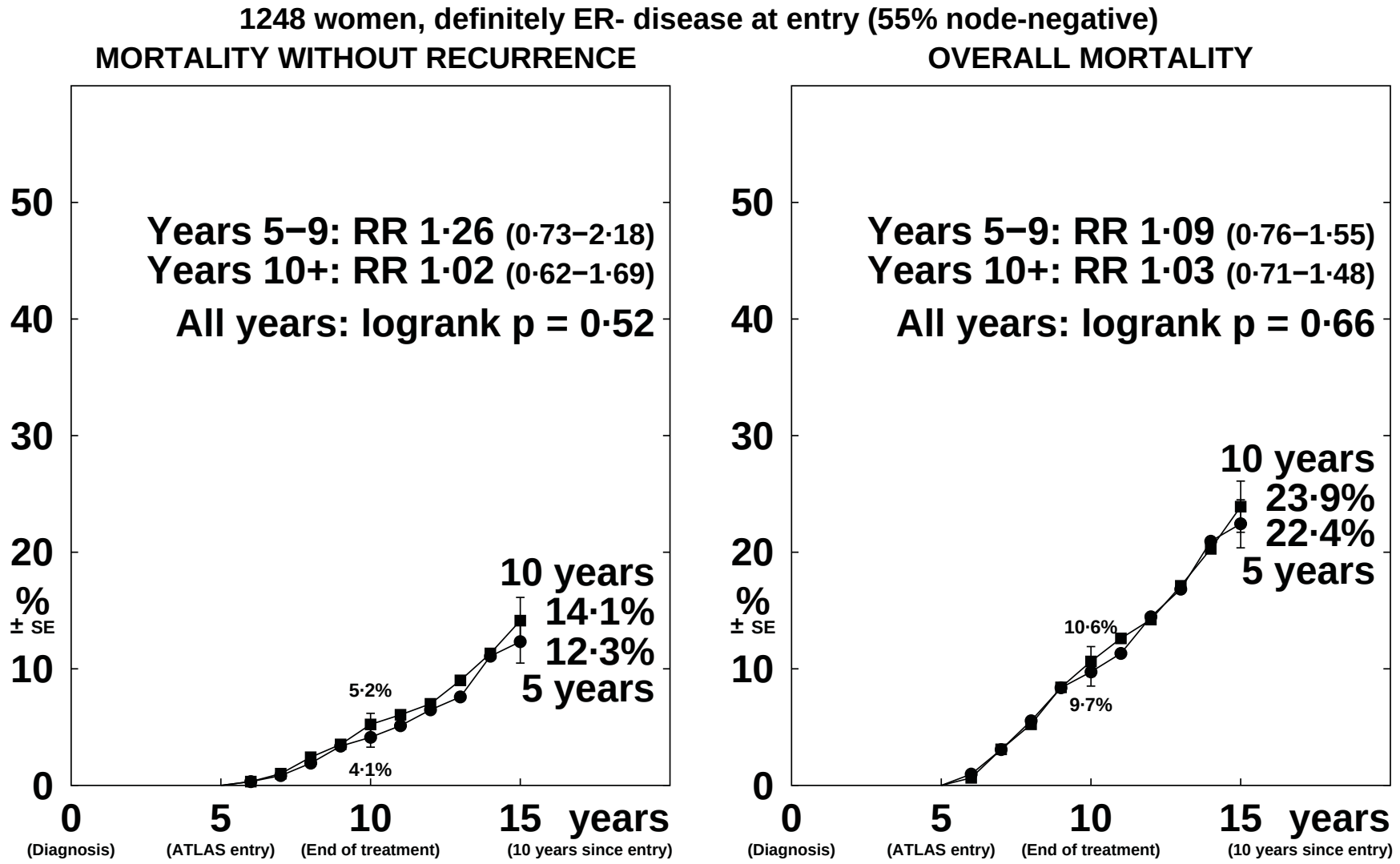
Recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·59 (72 / 2783)	1·79 (28 / 1566)	2·35 (5 / 213)
Stop at 5 years	2·37 (66 / 2786)	2·11 (34 / 1609)	1·60 (3 / 187)
Rate ratio, from	1·09 SE 0·18	0·85 SE 0·23	1·42 SE 0·85
(O−E) / V	3·0 / 34·5	−2·4 / 15·5	0·7 / 2·0

Death rates (% / year: total rate − rate in women without recurrence) & logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	1·21 SE 0·21	1·35 SE 0·28	2·07 SE 0·92
Stop at 5 years	1·24 SE 0·21	1·45 SE 0·29	0·91 SE 0·64
Rate ratio, from	0·98 SE 0·23	0·92 SE 0·28	2·28 SE 1·17
(O−E) / V	−0·4 / 17·8	−1·0 / 12·0	1·4 / 1·8

Webfigure 5a: Definitely ER-negative disease: recurrence, and breast cancer mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



Death−without−recurrence rates (% / year) and logrank analyses

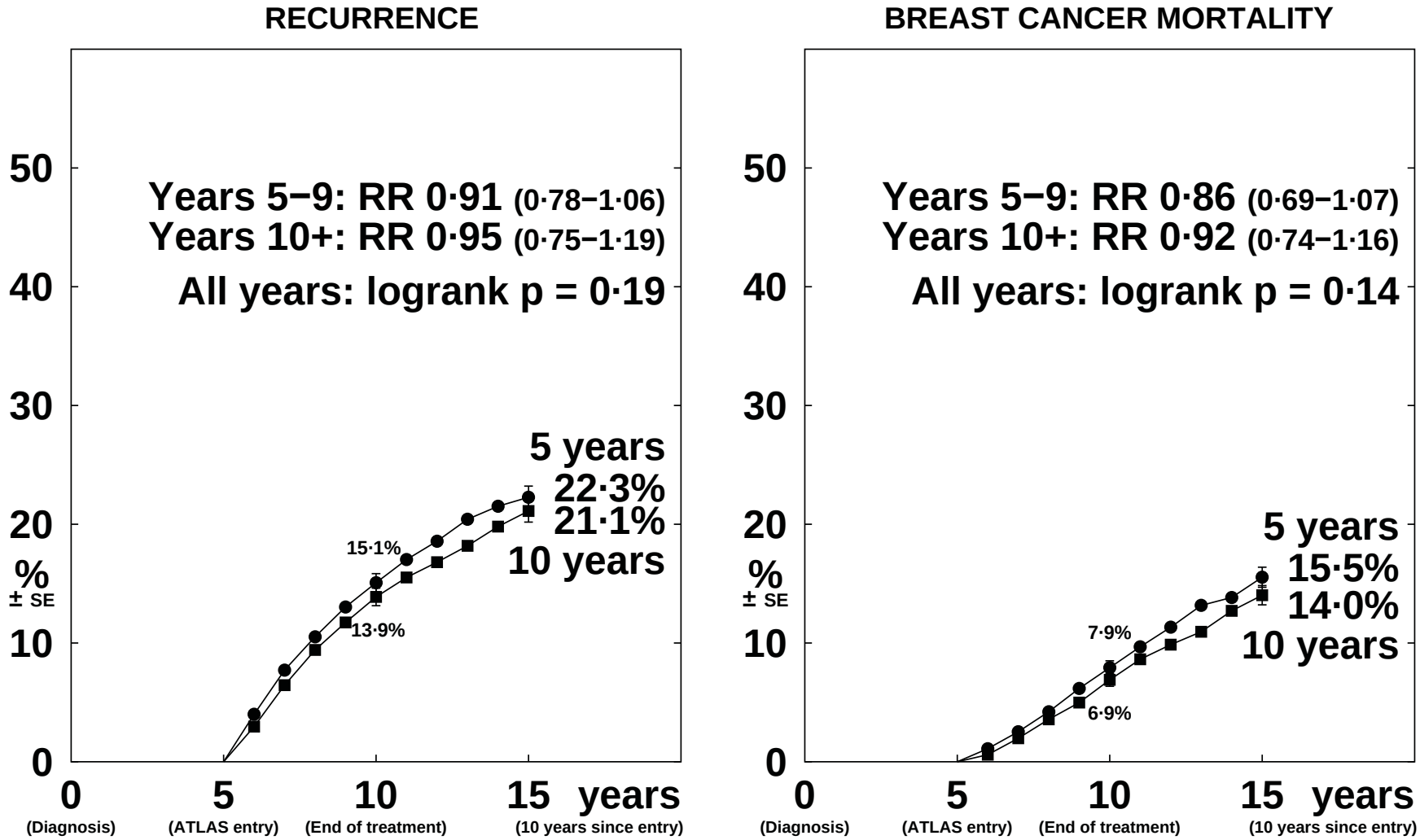
Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	1·04 (29 / 2783)	1·66 (26 / 1566)	2·35 (5 / 213)
Stop at 5 years	0·83 (23 / 2786)	1·62 (26 / 1609)	2·14 (4 / 187)
Rate ratio, from (O−E) / V	1·26 SE 0·31 3·0 / 13·0	1·02 SE 0·28 0·2 / 13·0	1·07 SE 0·69 0·2 / 2·2

Death rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·22 (64 / 2883)	2·87 (49 / 1705)	4·13 (10 / 242)
Stop at 5 years	2·04 (59 / 2897)	2·95 (51 / 1726)	2·73 (6 / 220)
Rate ratio, from (O−E) / V	1·09 SE 0·19 2·6 / 30·8	0·97 SE 0·20 −0·8 / 25·0	1·49 SE 0·62 1·6 / 4·0

Webfigure 5b: Definitely ER-negative disease: mortality without recurrence, and overall mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).

4800 women, ER unknown at entry (49% node-negative)



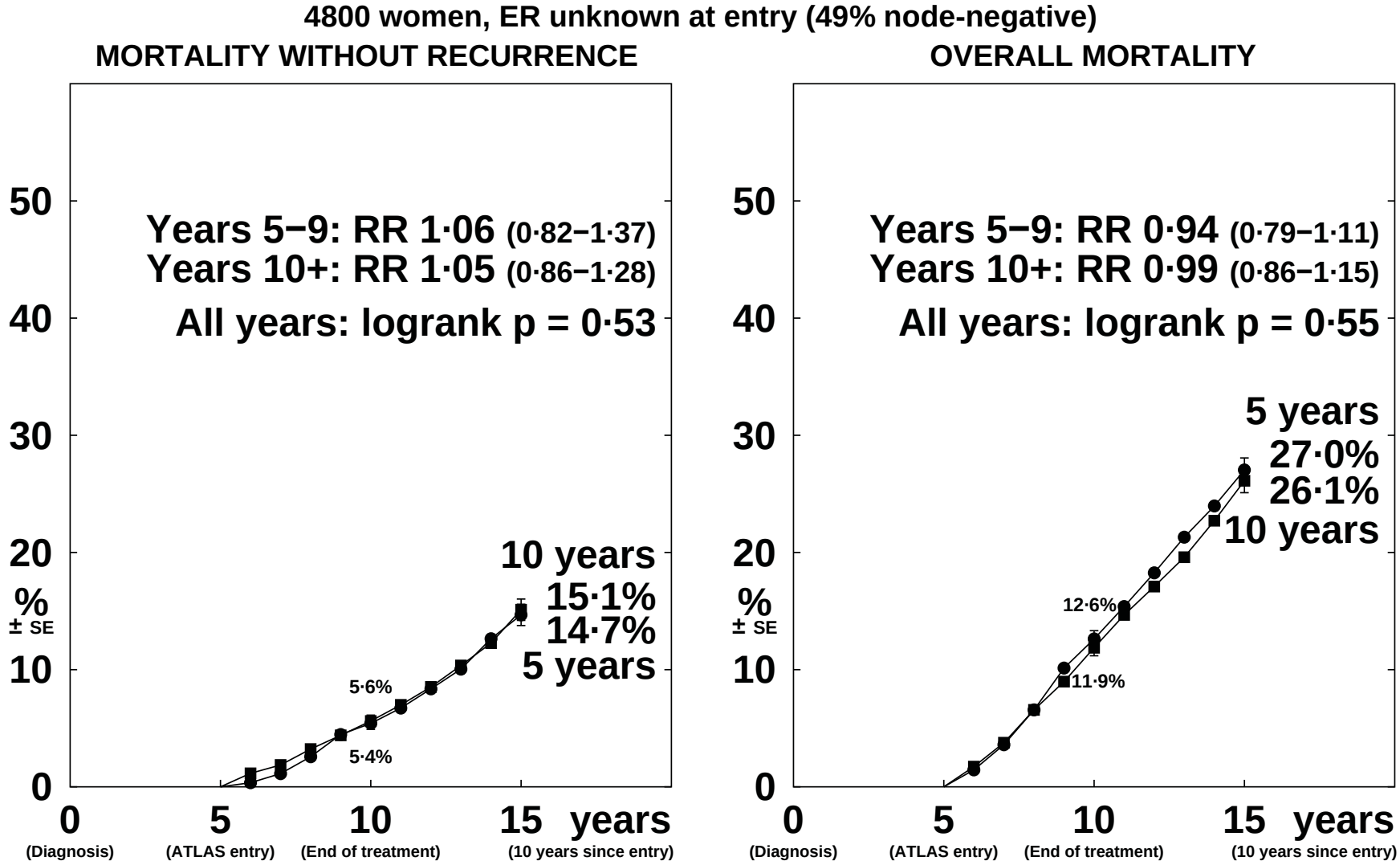
Recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	3·01 (315 / 10462)	1·76 (123 / 7005)	1·70 (26 / 1531)
Stop at 5 years	3·32 (341 / 10257)	1·87 (127 / 6798)	1·68 (26 / 1544)
Rate ratio, from (O−E) / V	0·91 SE 0·07 −16·2 / 164·0	0·94 SE 0·12 −3·9 / 62·5	0·98 SE 0·28 −0·3 / 12·8

Death rates (% / year: total rate − rate in women without recurrence) & logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	1·40 SE 0·11	1·58 SE 0·14	1·59 SE 0·31
Stop at 5 years	1·64 SE 0·12	1·76 SE 0·15	1·51 SE 0·30
Rate ratio, from (O−E) / V	0·86 SE 0·10 −12·5 / 82·7	0·91 SE 0·12 −6·1 / 63·0	1·02 SE 0·28 0·2 / 13·0

Webfigure 6a: ER unknown: recurrence, and breast cancer mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



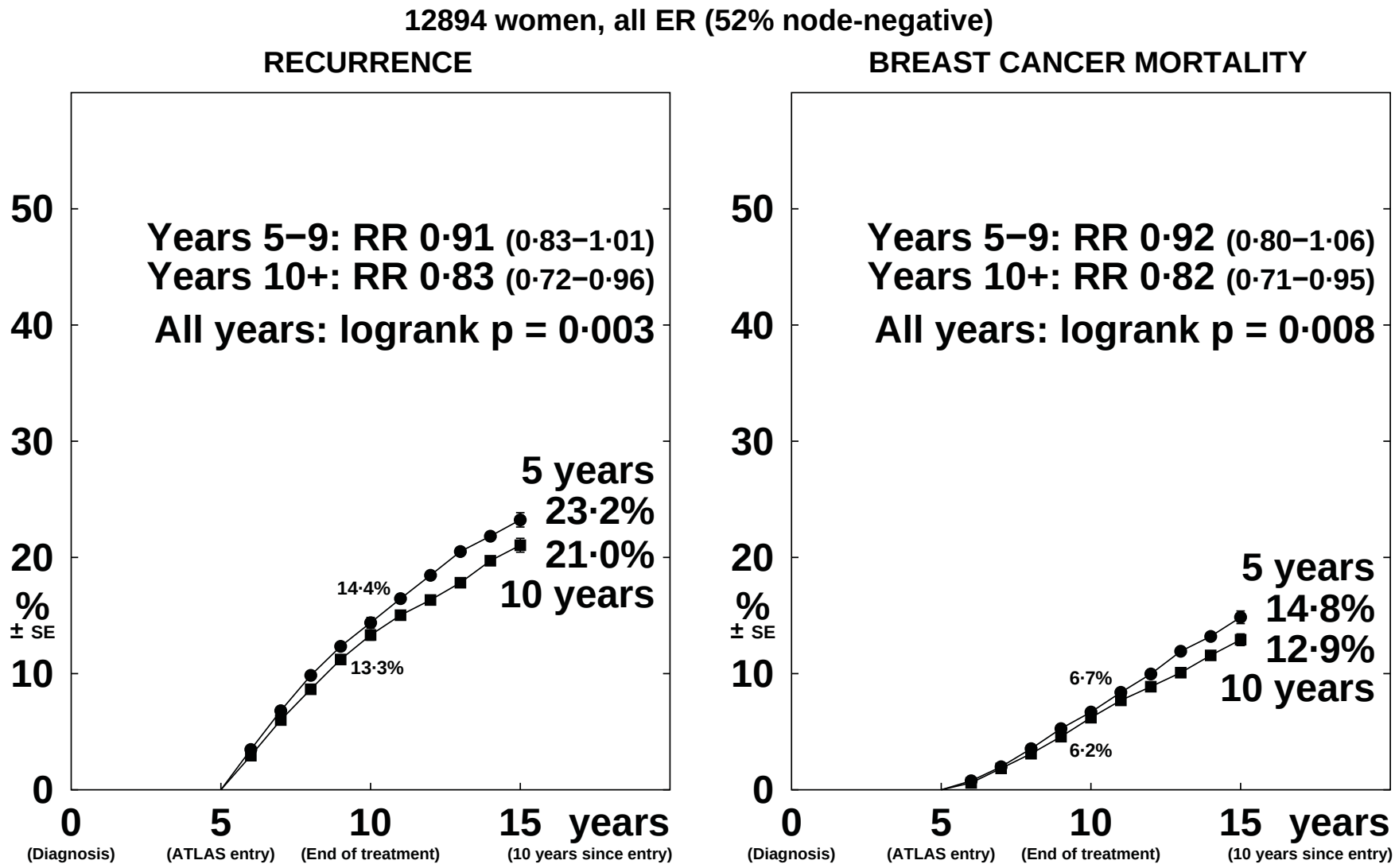
Death−without−recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	1·15 (120 / 10462)	2·00 (140 / 7005)	4·11 (63 / 1531)
Stop at 5 years	1·08 (111 / 10257)	1·97 (134 / 6798)	3·63 (56 / 1544)
Rate ratio, from (O−E) / V	1·06 SE 0·14 3·3 / 57·8	1·01 SE 0·12 0·9 / 68·5	1·13 SE 0·20 3·7 / 29·7

Death rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·50 (274 / 10969)	3·42 (261 / 7635)	5·30 (90 / 1698)
Stop at 5 years	2·66 (288 / 10812)	3·56 (265 / 7447)	4·78 (82 / 1717)
Rate ratio, from (O−E) / V	0·94 SE 0·08 −9·1 / 140·5	0·96 SE 0·09 −5·3 / 131·4	1·10 SE 0·16 3·9 / 42·7

Webfigure 6b: ER unknown: mortality without recurrence, and overall mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



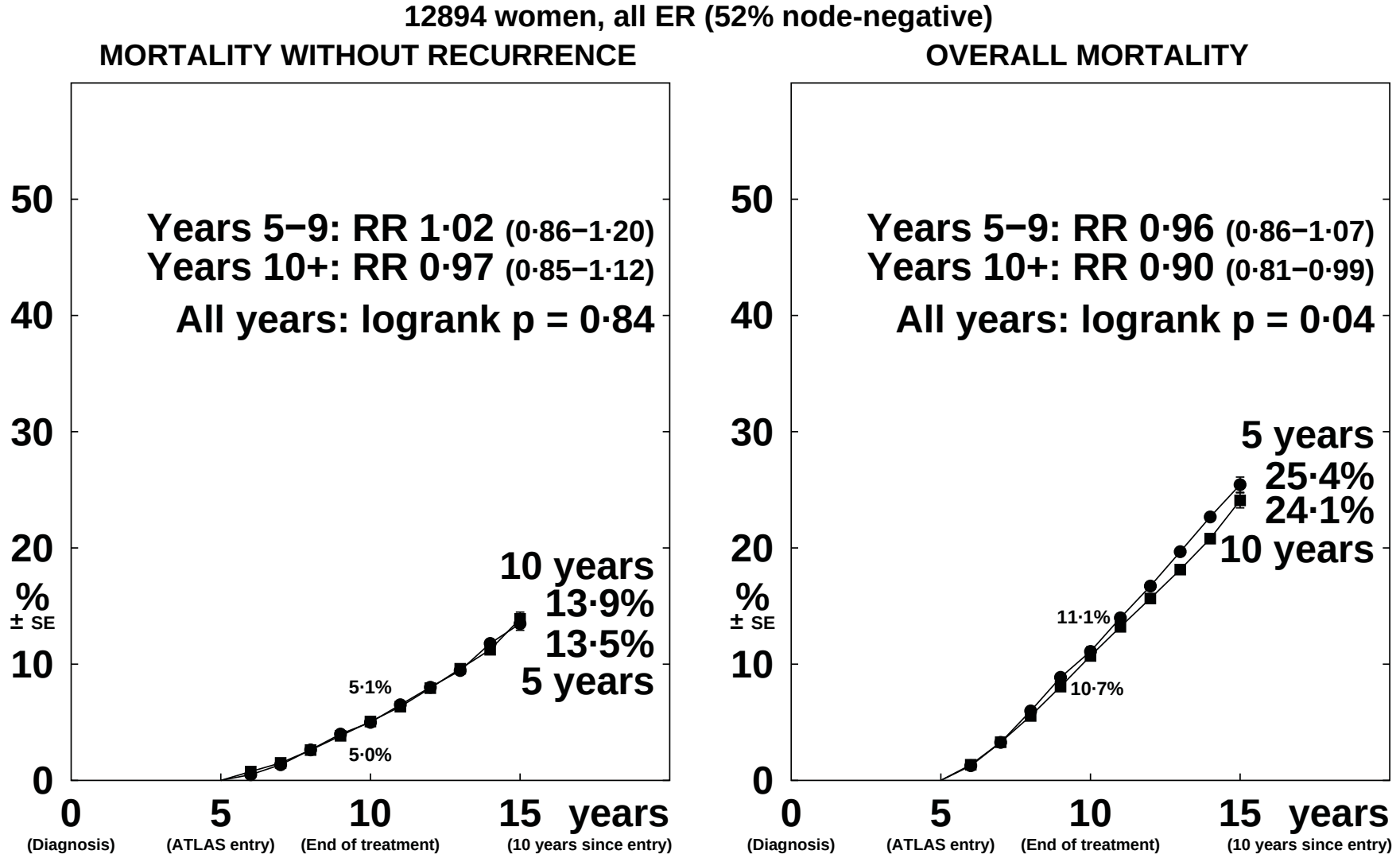
Recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·87 (815 / 28361)	1·86 (316 / 17012)	2·04 (55 / 2691)
Stop at 5 years	3·14 (878 / 27932)	2·28 (375 / 16446)	2·12 (55 / 2591)
Rate ratio, from (O−E) / V	0·91 SE 0·05 −38·0 / 423·2	0·82 SE 0·07 −35·4 / 172·7	0·94 SE 0·19 −1·7 / 27·2

Death rates (% / year: total rate − rate in women without recurrence) & logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	1·26 SE 0·07	1·46 SE 0·09	1·64 SE 0·23
Stop at 5 years	1·37 SE 0·07	1·85 SE 0·10	1·74 SE 0·24
Rate ratio, from (O−E) / V	0·92 SE 0·07 −16·1 / 194·5	0·80 SE 0·07 −34·2 / 152·5	0·97 SE 0·20 −0·8 / 25·3

Webfigure 7a: Any ER: recurrence, and breast cancer mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



Death−without−recurrence rates (% / year) and logrank analyses

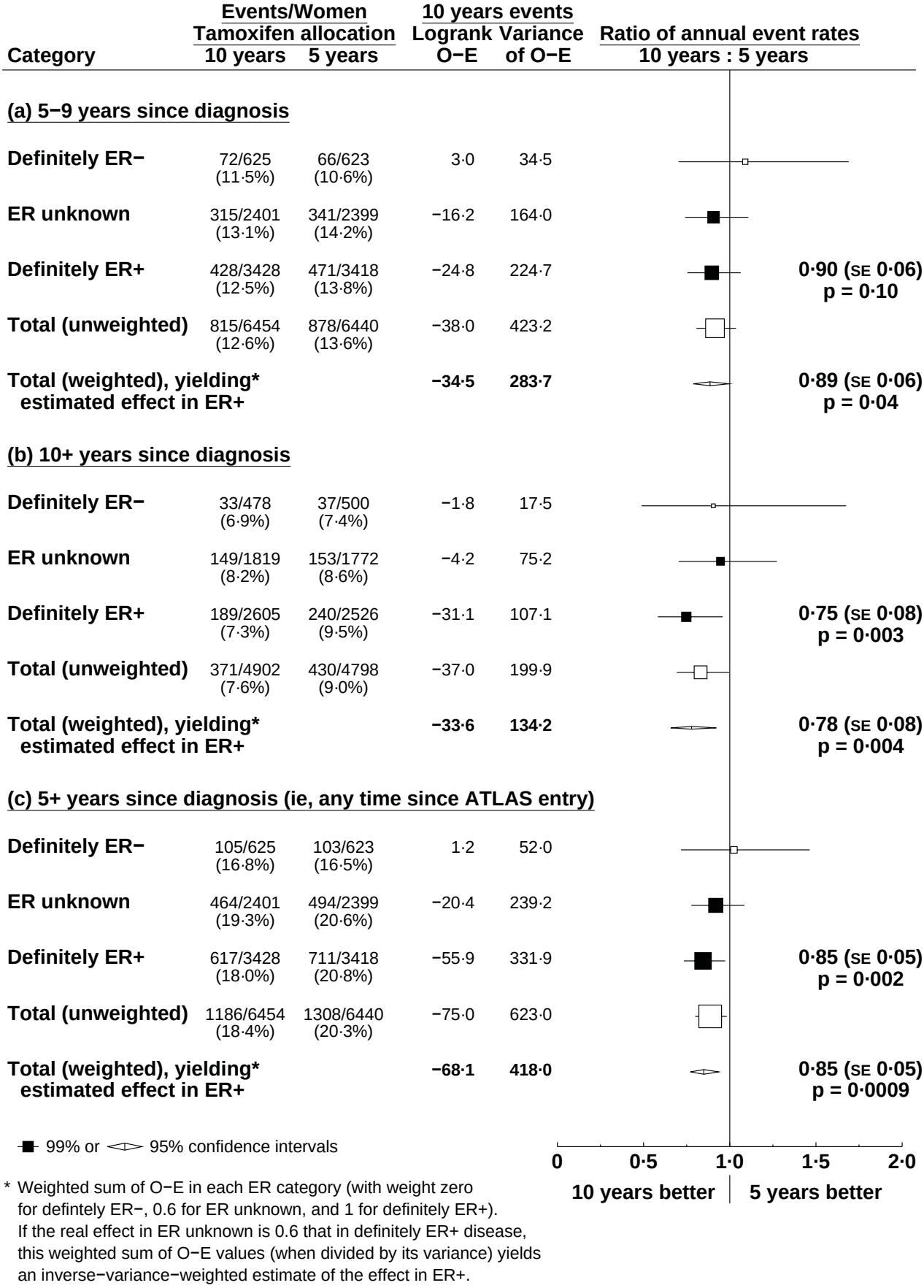
Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	1·02 (290 / 28361)	1·80 (307 / 17012)	3·49 (94 / 2691)
Stop at 5 years	1·01 (281 / 27932)	1·79 (295 / 16446)	3·98 (103 / 2591)
Rate ratio, from (O−E) / V	1·02 SE 0·08 2·2 / 142·8	1·00 SE 0·08 0·7 / 150·4	0·88 SE 0·13 −6·3 / 49·1

Death rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·24 (664 / 29700)	3·11 (579 / 18638)	4·74 (144 / 3040)
Stop at 5 years	2·33 (685 / 29436)	3·47 (633 / 18249)	5·19 (155 / 2988)
Rate ratio, from (O−E) / V	0·96 SE 0·05 −14·0 / 337·2	0·90 SE 0·05 −33·6 / 302·9	0·91 SE 0·11 −7·2 / 74·4

Webfigure 7b: Any ER: mortality without recurrence, and overall mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).

ATLAS: Continue to 10 years vs Stop at 5 years of adjuvant tamoxifen
RECURRENCE

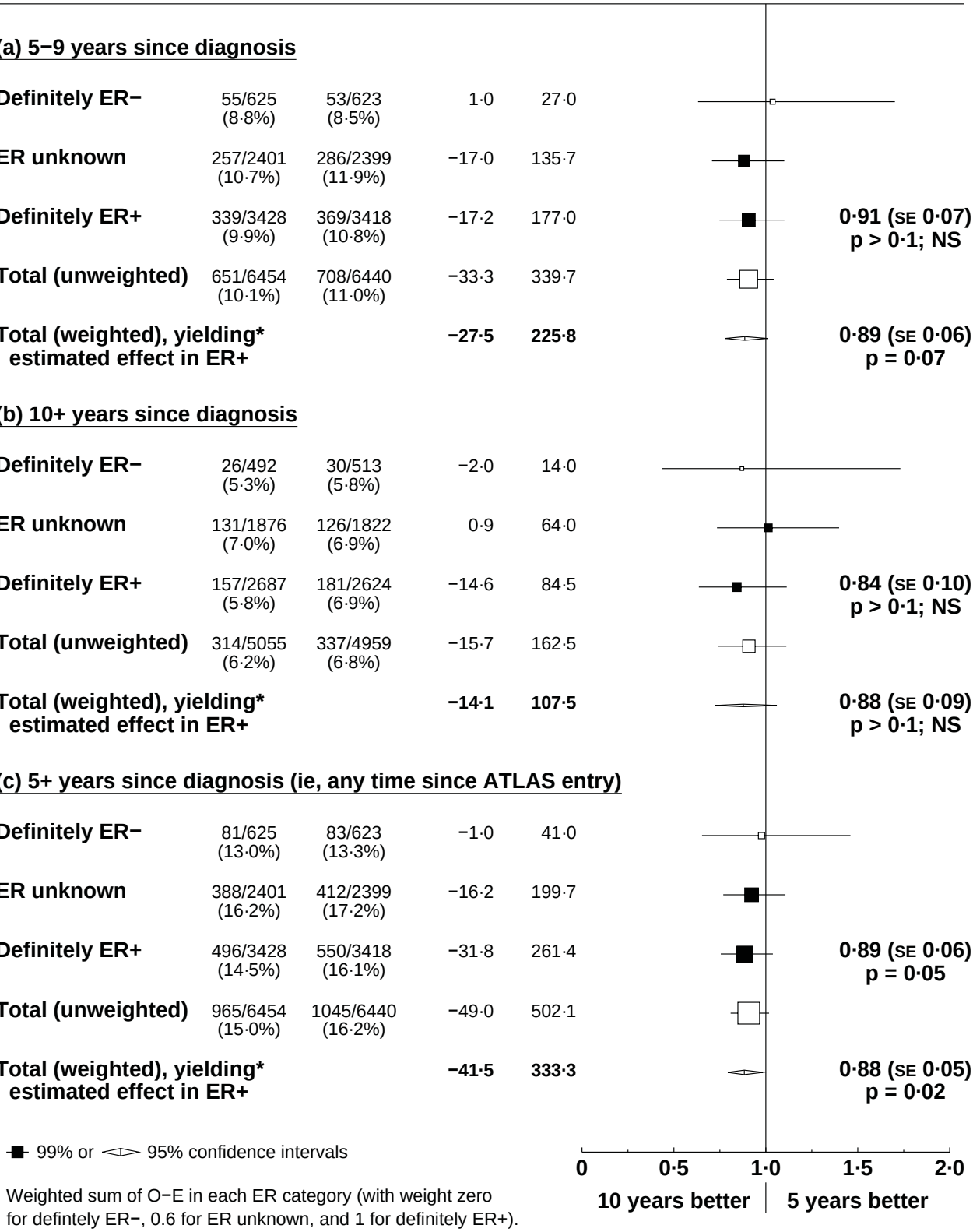


* Weighted sum of O−E in each ER category (with weight zero for defintely ER−, 0.6 for ER unknown, and 1 for definitely ER+). If the real effect in ER unknown is 0.6 that in definitely ER+ disease, this weighted sum of O−E values (when divided by its variance) yields an inverse−variance−weighted estimate of the effect in ER+.

Webfigure 8: Recurrence by years since diagnosis and by ER status at entry If the logrank statistics for ER unknown and definitely ER+ disease are, respectively, (O-E) and (o-e) with variances V and v, the logrank statistic for the weighted total is (O-E)+0.6(o-e) with variance V+0.36v.

ATLAS: Continue to 10 years vs Stop at 5 years of adjuvant tamoxifen
DISTANT RECURRENCE OR DEATH WITH RECURRENCE

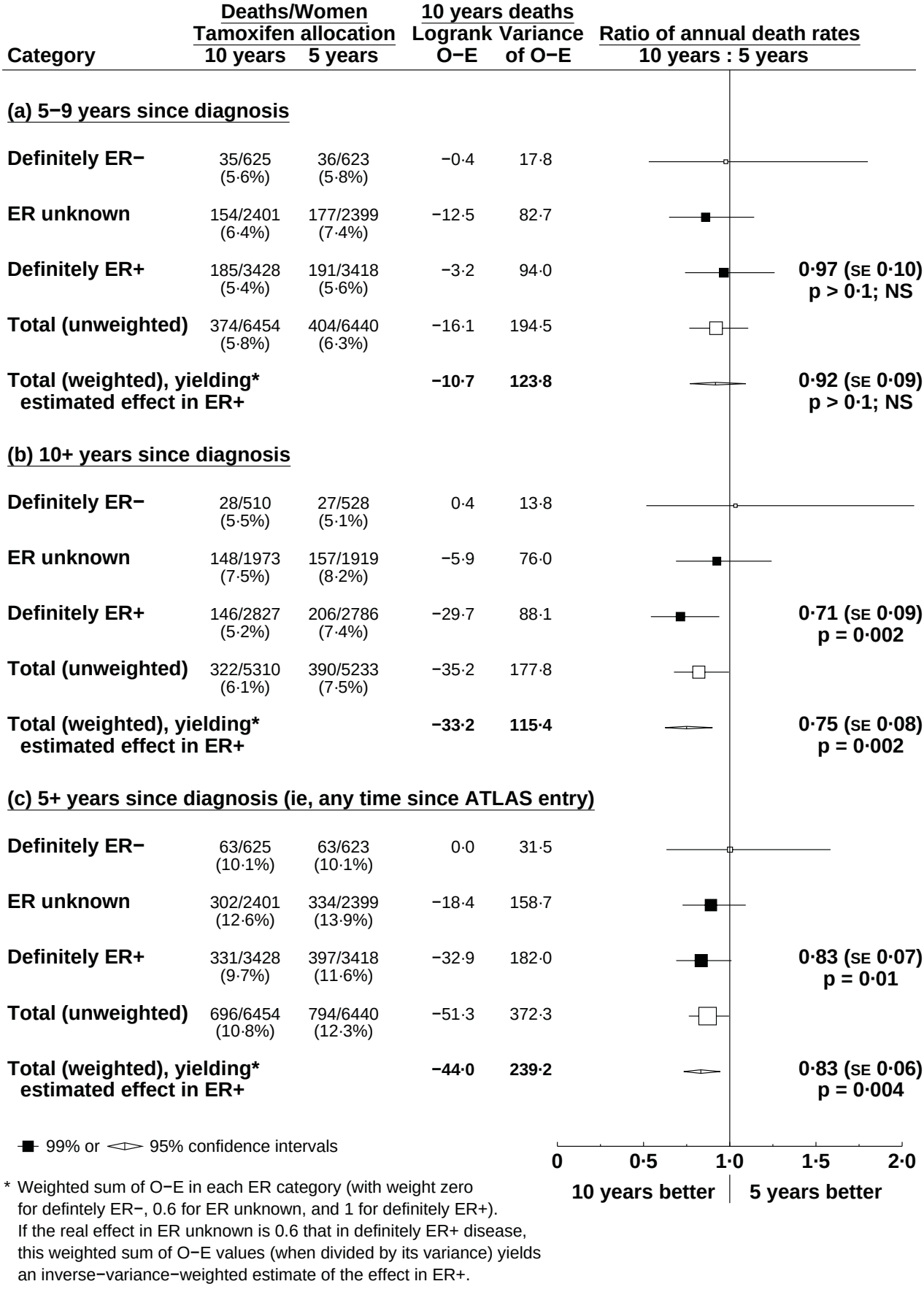
Category	Events/Women Tamoxifen allocation 10 years	5 years	10 years events Logrank O−E	Variance of O−E	Ratio of annual event rates 10 years : 5 years
(a) 5−9 years since diagnosis					
Definitely ER−	55/625 (8·8%)	53/623 (8·5%)	1·0	27·0	
ER unknown	257/2401 (10·7%)	286/2399 (11·9%)	−17·0	135·7	
Definitely ER+	339/3428 (9·9%)	369/3418 (10·8%)	−17·2	177·0	**0·91 (SE 0·07) p > 0·1; NS**
Total (unweighted)	651/6454 (10·1%)	708/6440 (11·0%)	−33·3	339·7	
Total (weighted), yielding* estimated effect in ER+			**−27·5**	**225·8**	**0·89 (SE 0·06) p = 0·07**
(b) 10+ years since diagnosis					
Definitely ER−	26/492 (5·3%)	30/513 (5·8%)	−2·0	14·0	
ER unknown	131/1876 (7·0%)	126/1822 (6·9%)	0·9	64·0	
Definitely ER+	157/2687 (5·8%)	181/2624 (6·9%)	−14·6	84·5	**0·84 (SE 0·10) p > 0·1; NS**
Total (unweighted)	314/5055 (6·2%)	337/4959 (6·8%)	−15·7	162·5	
Total (weighted), yielding* estimated effect in ER+			**−14·1**	**107·5**	**0·88 (SE 0·09) p > 0·1; NS**
(c) 5+ years since diagnosis (ie, any time since ATLAS entry)					
Definitely ER−	81/625 (13·0%)	83/623 (13·3%)	−1·0	41·0	
ER unknown	388/2401 (16·2%)	412/2399 (17·2%)	−16·2	199·7	
Definitely ER+	496/3428 (14·5%)	550/3418 (16·1%)	−31·8	261·4	**0·89 (SE 0·06) p = 0·05**
Total (unweighted)	965/6454 (15·0%)	1045/6440 (16·2%)	−49·0	502·1	
Total (weighted), yielding* estimated effect in ER+			**−41·5**	**333·3**	**0·88 (SE 0·05) p = 0·02**



* Weighted sum of O−E in each ER category (with weight zero for defintely ER−, 0.6 for ER unknown, and 1 for definitely ER+). If the real effect in ER unknown is 0.6 that in definitely ER+ disease, this weighted sum of O−E values (when divided by its variance) yields an inverse−variance−weighted estimate of the effect in ER+.

Webfigure 9: Distant recurrence or death with recurrence by years since diagnosis and by ER status at entry If the logrank statistics for ER unknown and definitely ER+ disease are, respectively, (O-E) and (o-e) with variances V and v, the logrank statistic for the weighted total is (O-E)+0.6(o-e) with variance V+0.36v.

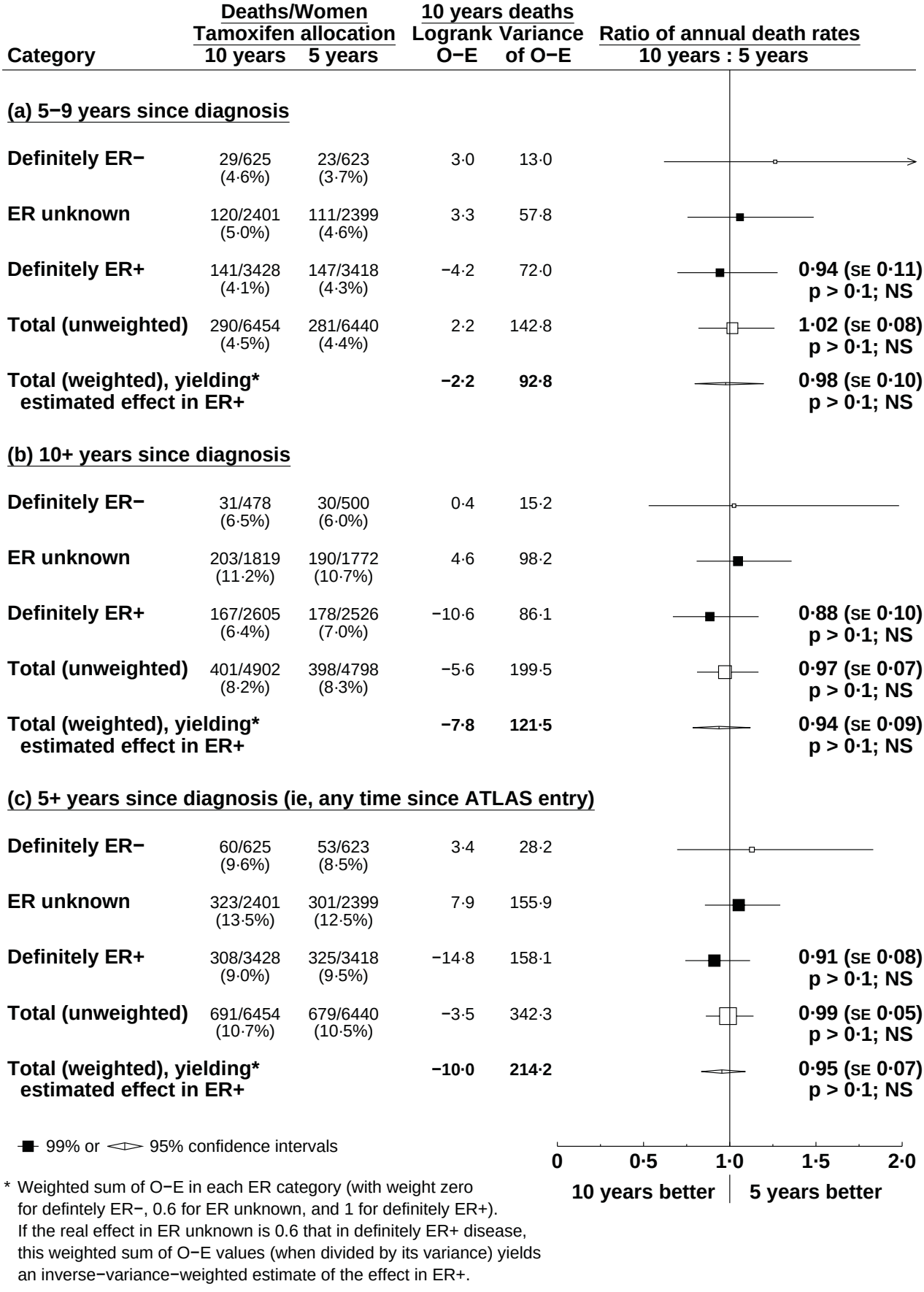
ATLAS: Continue to 10 years vs Stop at 5 years of adjuvant tamoxifen
BREAST CANCER MORTALITY



* Weighted sum of O−E in each ER category (with weight zero for defintely ER−, 0.6 for ER unknown, and 1 for definitely ER+). If the real effect in ER unknown is 0.6 that in definitely ER+ disease, this weighted sum of O−E values (when divided by its variance) yields an inverse−variance−weighted estimate of the effect in ER+.

Webfigure 10: Breast cancer mortality by years since diagnosis and by ER status at entry
If the logrank statistics for ER unknown and definitely ER+ disease are, respectively, (O-E) and (o-e) with variances V and v, the logrank statistic for the weighted total is (O-E)+0.6(o-e) with variance V+0.36v.

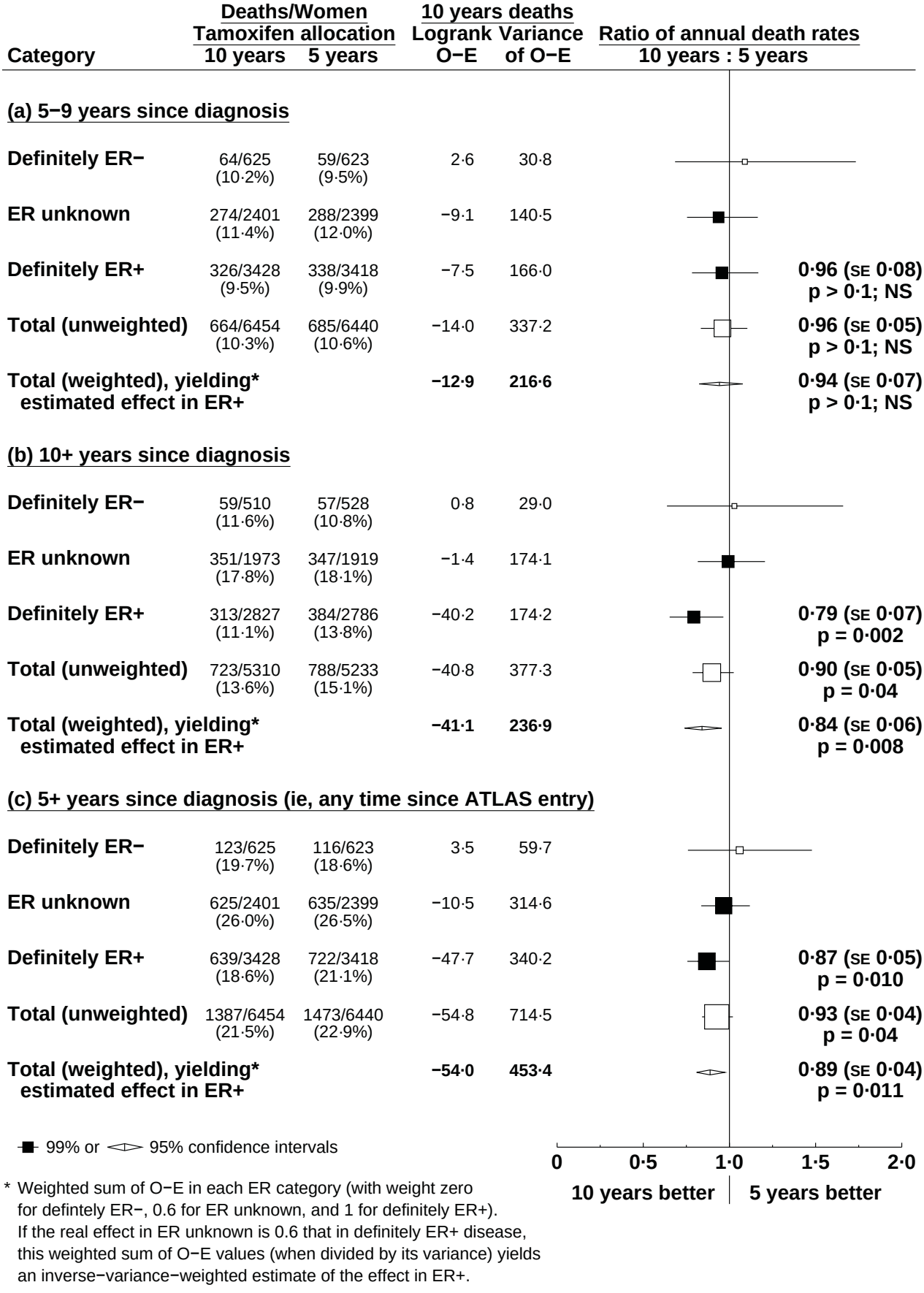
ATLAS: Continue to 10 years vs Stop at 5 years of adjuvant tamoxifen
MORTALITY WITHOUT RECURRENCE



* Weighted sum of O−E in each ER category (with weight zero for defintely ER−, 0.6 for ER unknown, and 1 for definitely ER+). If the real effect in ER unknown is 0.6 that in definitely ER+ disease, this weighted sum of O−E values (when divided by its variance) yields an inverse−variance−weighted estimate of the effect in ER+.

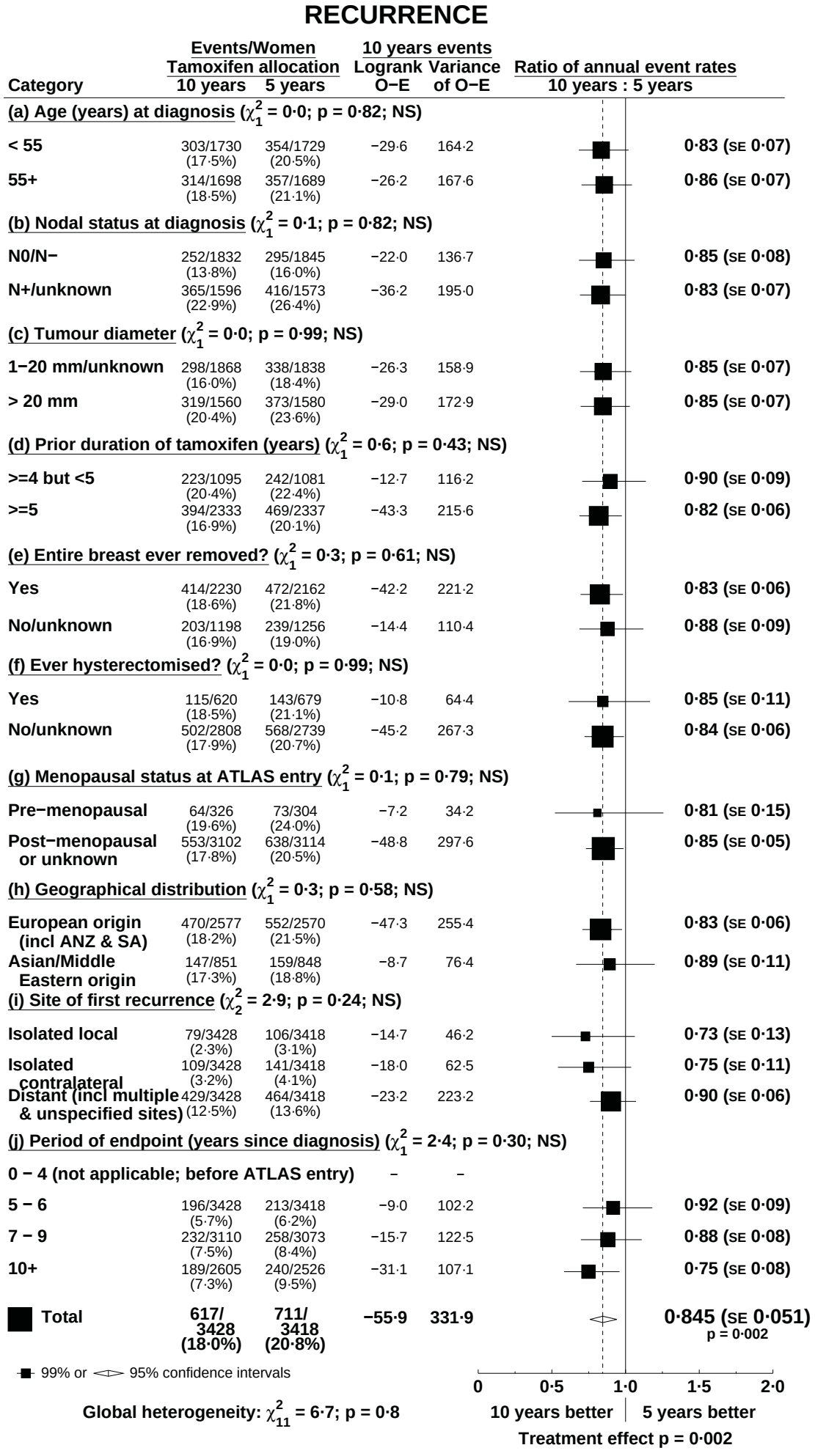
Webfigure 11: Mortality without recurrence by years since diagnosis and by ER status at entry If the logrank statistics for ER unknown and definitely ER+ disease are, respectively, (O-E) and (o-e) with variances V and v, the logrank statistic for the weighted total is (O-E)+0.6(o-e) with variance V+0.36v.

ATLAS: Continue to 10 years vs Stop at 5 years of adjuvant tamoxifen
OVERALL MORTALITY



* Weighted sum of O−E in each ER category (with weight zero for defintely ER−, 0.6 for ER unknown, and 1 for definitely ER+). If the real effect in ER unknown is 0.6 that in definitely ER+ disease, this weighted sum of O−E values (when divided by its variance) yields an inverse−variance−weighted estimate of the effect in ER+.

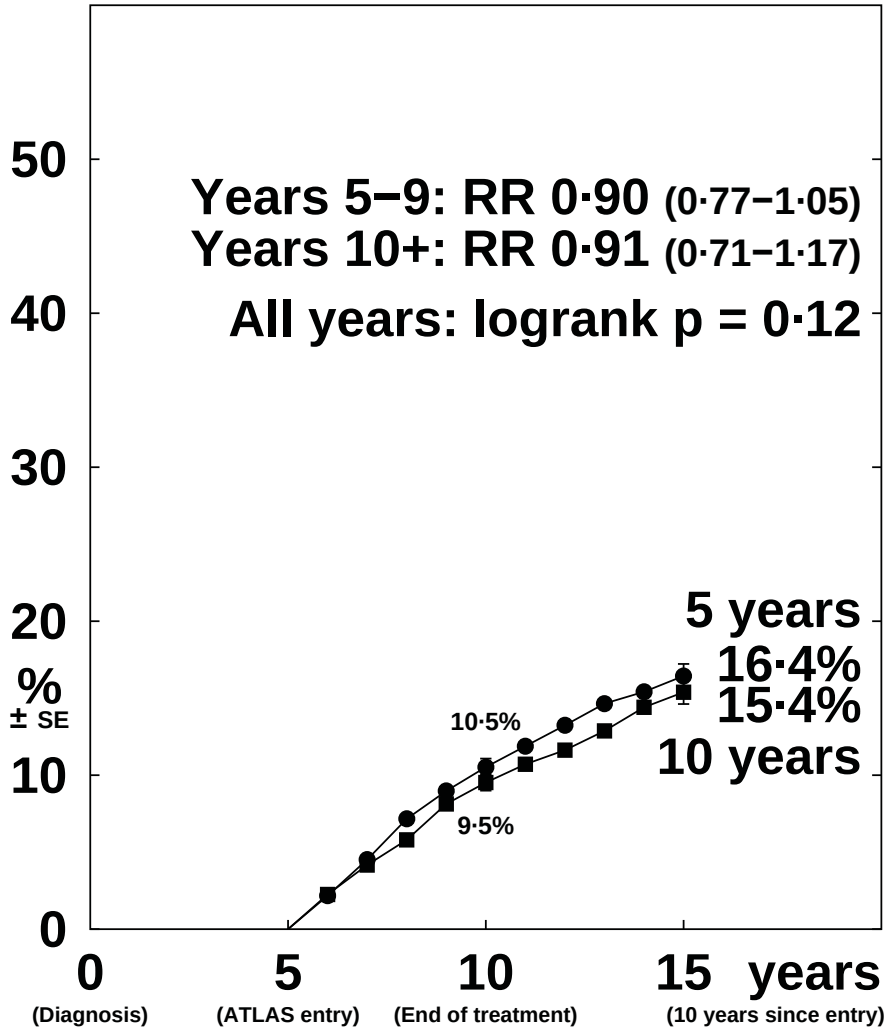
Webfigure 12: Overall mortality by years since diagnosis and by ER status at entry If the logrank statistics for ER unknown and definitely ER+ disease are, respectively, (O-E) and (o-e) with variances V and v, the logrank statistic for the weighted total is (O-E)+0.6(o-e) with variance V+0.36v.



Webfigure 13: Definitely ER+ disease: analyses of time to recurrence by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen), subdivided by patient or tumour characteristics, and location or time of first recurrence

6846 women, definitely ER+ disease at entry (54% node-negative)

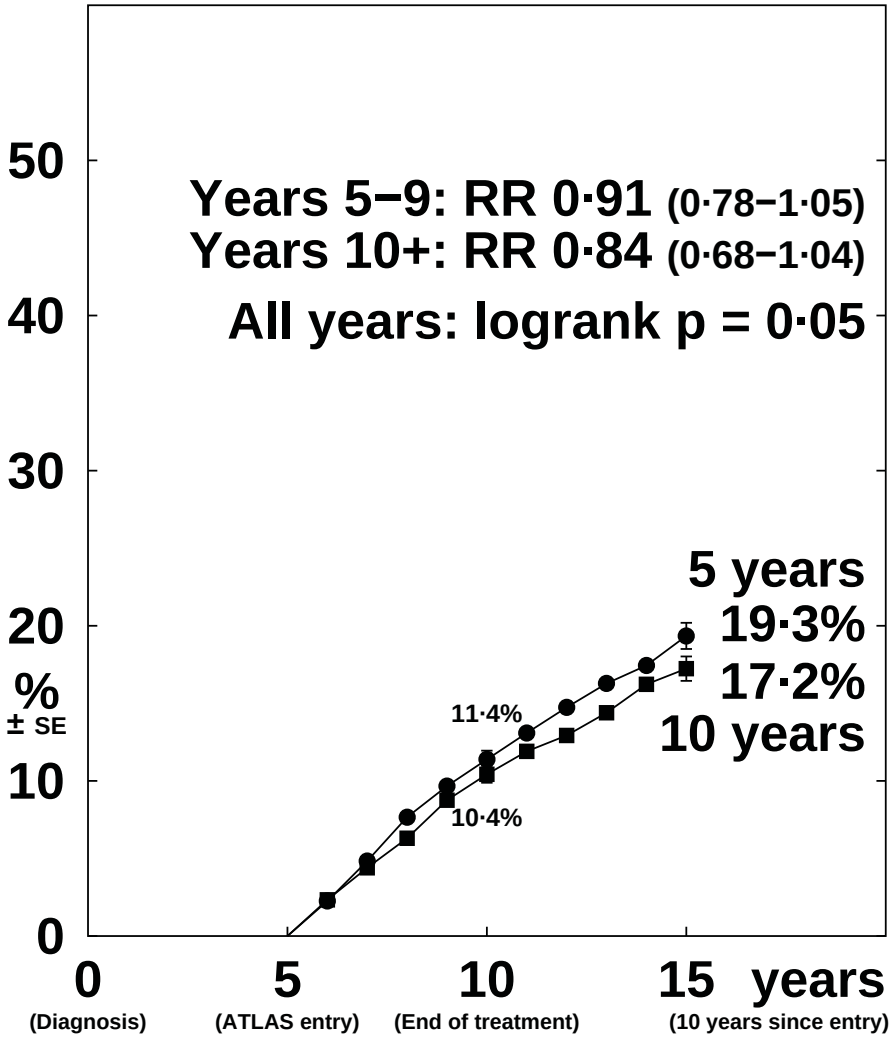
DISTANT RECURRENCE AS FIRST EVENT



Distant recurrence as first event rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·01 (304 / 15115)	1·32 (111 / 8439)	1·48 (14 / 945)
Stop at 5 years	2·24 (334 / 14889)	1·44 (116 / 8039)	1·63 (14 / 860)
Rate ratio, from (O−E) / V	0·90 SE 0·08 −17·3 / 159·5	0·91 SE 0·13 −5·3 / 56·7	0·91 SE 0·36 −0·6 / 7·0

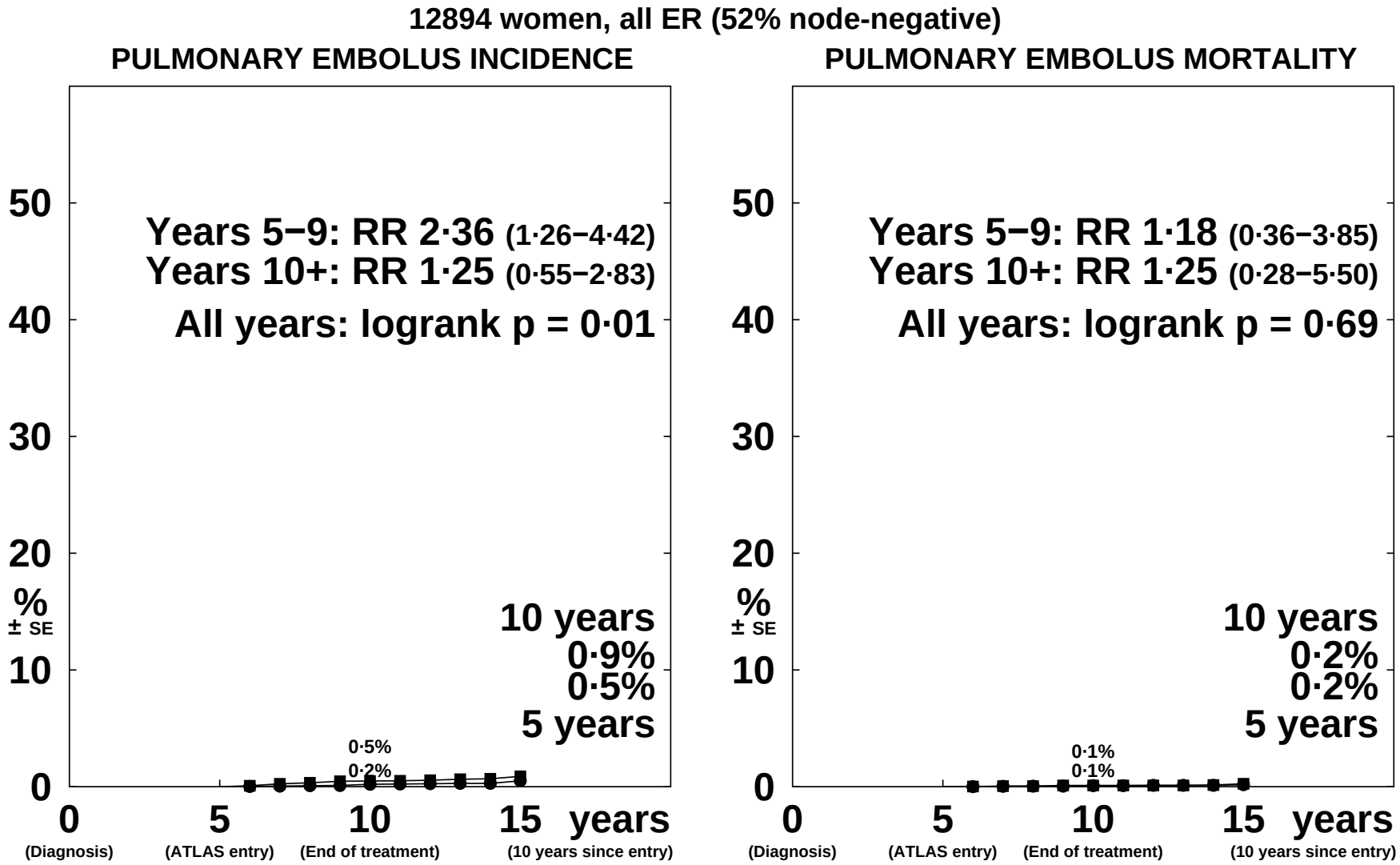
DISTANT RECURRENCE OR DEATH WITH RECURRENCE



Distant recurrence or death with recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	2·21 (339 / 15367)	1·57 (138 / 8786)	1·84 (19 / 1030)
Stop at 5 years	2·43 (369 / 15171)	1·87 (160 / 8537)	2·15 (21 / 977)
Rate ratio, from (O−E) / V	0·91 SE 0·07 −17·2 / 177·0	0·84 SE 0·11 −13·1 / 74·5	0·86 SE 0·29 −1·5 / 10·0

Webfigure 14: Definitely ER+ disease: distant recurrence by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



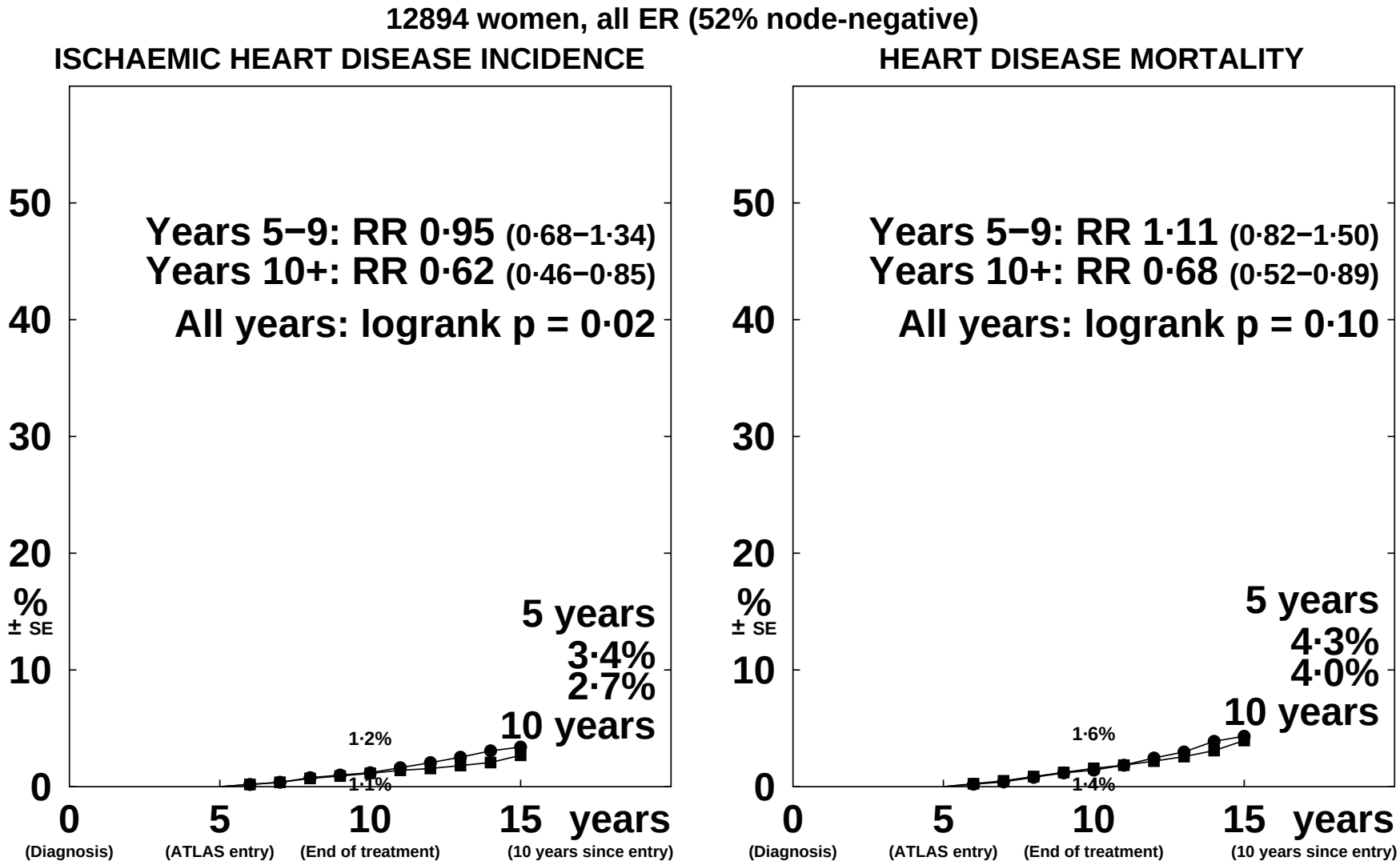
Pulmonary embolus incidence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	0·10 (28 / 28307)	0·06 (11 / 16930)	0·08 (2 / 2666)
Stop at 5 years	0·04 (11 / 27924)	0·04 (7 / 16422)	0·12 (3 / 2585)
Rate ratio, from	2·36 SE 0·51	1·51 SE 0·58	0·64 SE 0·72
(O−E) / V	8·4 / 9·8	1·8 / 4·5	−0·5 / 1·2

Pulmonary embolus death rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	0·02 (6 / 28361)	0·02 (3 / 17012)	0·04 (1 / 2691)
Stop at 5 years	0·02 (5 / 27932)	0·01 (2 / 16446)	0·04 (1 / 2591)
Rate ratio, from	1·18 SE 0·66	1·42 SE 1·07	0·90 SE 1·35
(O−E) / V	0·5 / 2·8	0·4 / 1·2	−0·1 / 0·5

Webfigure 15: Any ER: pulmonary embolus incidence and mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



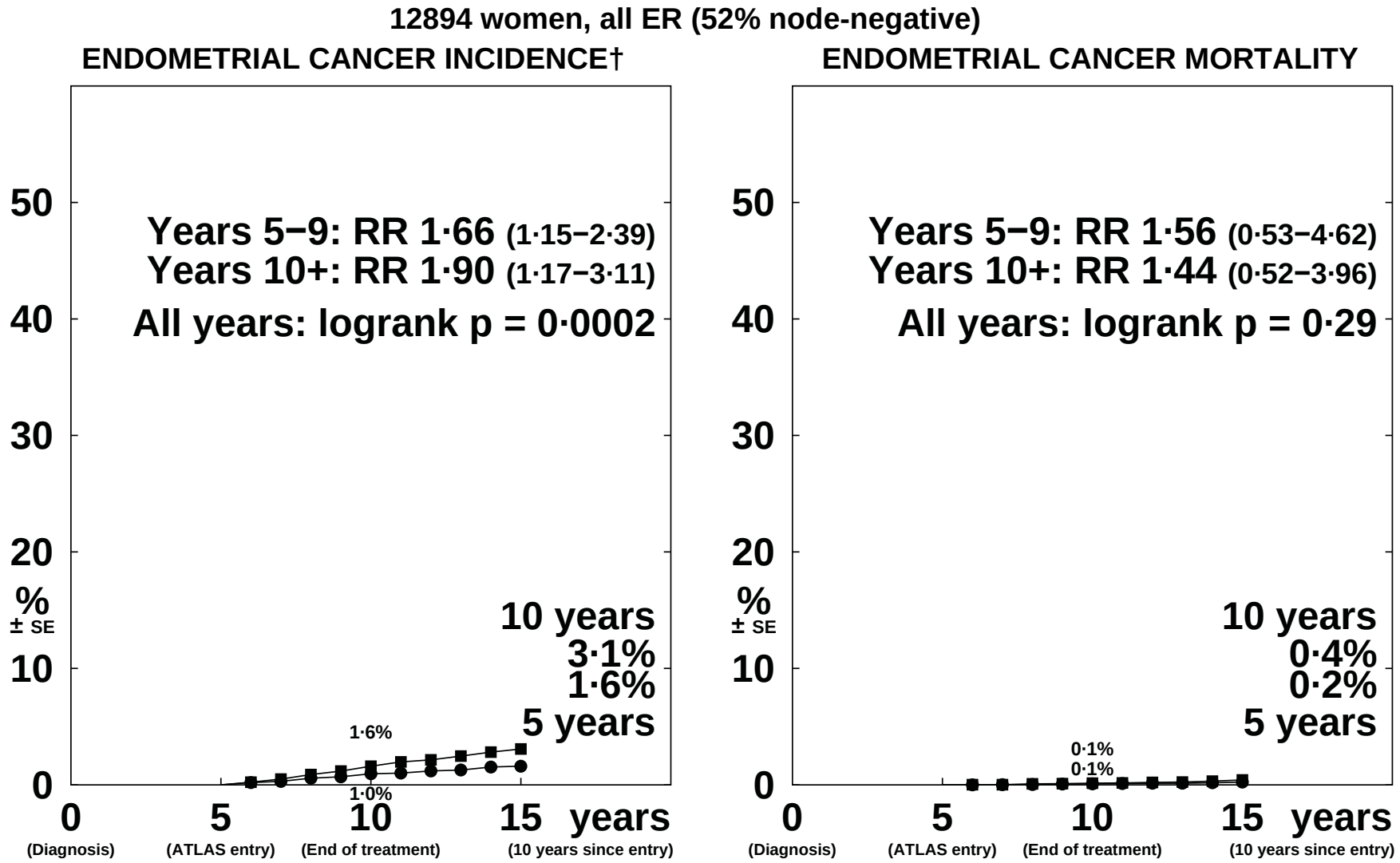
Ischaemic heart disease incidence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	0·23 (65 / 28312)	0·28 (47 / 16948)	0·56 (15 / 2667)
Stop at 5 years	0·24 (67 / 27856)	0·45 (74 / 16280)	0·87 (22 / 2540)
Rate ratio, from	0·95 SE 0·17	0·61 SE 0·14	0·66 SE 0·27
(O−E) / V	−1·5 / 33·0	−14·8 / 30·2	−3·9 / 9·2

Heart disease death rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	0·31 (89 / 28361)	0·43 (73 / 17012)	0·59 (16 / 2691)
Stop at 5 years	0·28 (79 / 27932)	0·58 (96 / 16446)	1·16 (30 / 2591)
Rate ratio, from	1·11 SE 0·16	0·74 SE 0·13	0·53 SE 0·22
(O−E) / V	4·3 / 42·0	−13·0 / 42·2	−7·4 / 11·5

Webfigure 16: Any ER: ischaemic heart disease incidence and heart disease mortality (both include death from all vascular causes except stroke and pulmonary embolus) by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen).



Endometrial cancers as first event rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	0·32 (73 / 23054)	0·30 (40 / 13280)	0·15 (3 / 2040)
Stop at 5 years	0·19 (42 / 22315)	0·13 (16 / 12707)	0·26 (5 / 1903)
Rate ratio, from	1·66 SE 0·24	2·25 SE 0·41	0·59 SE 0·55
(O−E) / V	14·5 / 28·8	11·4 / 14·0	−1·1 / 2·0

Death rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 − 9	Years 10 − 14	Year 15+
Continue to 10 years	0·03 (8 / 28361)	0·05 (8 / 17012)	0·04 (1 / 2691)
Stop at 5 years	0·02 (5 / 27932)	0·02 (4 / 16446)	0·08 (2 / 2591)
Rate ratio, from	1·56 SE 0·70	1·88 SE 0·80	0·50 SE 0·83
(O−E) / V	1·4 / 3·2	1·9 / 3·0	−0·5 / 0·8

Webfigure 17: Any ER: endometrial cancer incidence and mortality by treatment allocation (continue to 10 years versus stop at 5 years of adjuvant tamoxifen). † Analyses of endometrial cancer incidence exclude women with hysterectomy recorded at trial entry.

Webtable 1: Patient characteristics at diagnosis, and at ATLAS trial entry (about 5 years later)

Patient characteristics	All women				Definitely ER+			
	Tamoxifen allocation				Tamoxifen allocation			
	Continue to 10 years (6454)		Stop at 5 years (6440)		Continue to 10 years (3428)		Stop at 5 years (3418)	
	n	%	n	%	n	%	n	%
Status at diagnosis								
Oestrogen receptor (ER) status								
ER+	3428	53.1	3418	53.1				
ER-negative	625	9.7	623	9.7				
ER unknown	2401	37.2	2399	37.3				
Age (years, with median)								
< 45 (40)	1246	19.3	1236	19.2	640	18.7	630	18.4
45-54 (49)	2070	32.1	2076	32.2	1090	31.8	1099	32.2
55-69 (61)	2557	39.6	2567	39.9	1373	40.1	1357	39.7
≥ 70 (73)	581	9.0	561	8.7	325	9.5	332	9.7
Nodal status								
N0/N-	3360	52.1	3354	52.1	1832	53.4	1845	54.0
N1-3	1667	25.8	1621	25.2	938	27.4	893	26.1
N4+	968	15.0	965	15.0	536	15.6	534	15.6
Unknown	459	7.1	500	7.8	122	3.6	146	4.3
Tumour diameter								
1-20 mm	2462	38.1	2463	38.2	1660	48.4	1620	47.4
21-50 mm	2749	42.6	2727	42.3	1309	38.2	1328	38.9
> 50 mm	620	9.6	628	9.8	251	7.3	252	7.4
Unknown	623	9.7	622	9.7	208	6.1	218	6.4
Status at ATLAS trial entry								
Year of entry								
1995-1999	1538	23.8	1541	23.9	521	15.2	527	15.4
2000-2002	2755	42.7	2752	42.7	1415	41.3	1403	41.1
2003-2005	2161	33.5	2147	33.3	1492	43.5	1488	43.5
Prior duration of tamoxifen, years (median 5.0 years, IQR 4.8-5.2)								
4-4.9	2149	33.3	2129	33.1	1095	31.9	1081	31.6
5-5.9	3690	57.2	3702	57.5	2103	61.3	2105	61.6
6+	615	9.5	609	9.5	230	6.7	232	6.8
Local recurrence before entry?								
Yes (successfully managed)	128	2.0	121	1.9	38	1.1	37	1.1
No	6316	97.9	6307	97.9	3382	98.7	3373	98.7
Unknown	10	0.2	12	0.2	8	0.2	8	0.2
Ever any contralateral primary?								
Yes	151	2.3	157	2.4	75	2.2	80	2.3
No	6297	97.6	6276	97.5	3350	97.7	3332	97.5
Unknown	6	0.1	7	0.1	3	0.1	6	0.2
Entire breast ever removed?								
Yes	4634	71.8	4563	70.9	2230	65.1	2162	63.3
No	1819	28.2	1874	29.1	1198	34.9	1255	36.7
Unknown	1	0.0	3	0.0	0	0.0	1	0.0
Hysterectomised?								
Yes	1066	16.5	1160	18.0	620	18.1	679	19.9
No	5359	83.0	5254	81.6	2792	81.4	2728	79.8
Unknown	29	0.4	26	0.4	16	0.5	11	0.3
Menopausal status								
Pre-menopausal	537	8.3	521	8.1	326	9.5	304	8.9
Post-menopausal†	5778	89.5	5784	89.8	3035	88.5	3044	89.1
Perimenopausal or unknown	139	2.2	135	2.1	67	2.0	70	2.0
Geographical distribution								
Europe/ANZ/US/SA‡	2515	39.0	2529	39.3	1595	46.5	1599	46.8
Latin America	1759	27.3	1771	27.5	982	28.6	971	28.4
Asia/Middle East	2180	33.8	2140	33.2	851	24.8	848	24.8

† Artificial or natural menopause

‡ Europe, Australia, New Zealand, United States and South Africa; in each of these (and in Latin America), ATLAS participants were predominantly of European origin

Webtable 2: Effects of allocation (continue tamoxifen to 10 years vs stop at 5 years) on mortality with and without prior recurrence in each category of ER status at entry, and on various outcomes without prior recurrence in all women, of any ER status

	No. of events		Logrank	Variance	Event rate	p, two-
	Continue to 10 yrs	Stop at 5 years	O-E	of O-E	ratio [95% CI]	sided
Mortality analyses, by ER status						
– ER+ (n=3428 vs 3418)						
Any death	639	722	-47.7	340.2	0.87 [0.78-0.97]	0.01
Death with recurrence	331	397	-32.9	182.0	0.83 [0.72-0.96]	0.01
Death without recurrence*	308	325	-14.8	158.1	0.91 [0.78-1.06]	0.24
– ER unknown (n=2401 vs 2399)						
Any death	625	635	-10.5	314.6	0.97 [0.87-1.08]	0.55
Death with recurrence	302	334	-18.4	158.7	0.89 [0.76-1.04]	0.15
Death without recurrence*	323	301	7.9	155.9	1.05 [0.90-1.23]	0.53
– ER– (n=625 vs 623)						
Any death	123	116	3.5	59.7	1.06 [0.82-1.37]	0.66
Death with recurrence	63	63	0.0	31.5	1.00 [0.71-1.42]	0.99
Death without recurrence*	60	53	3.4	28.2	1.13 [0.78-1.63]	0.52
– Any ER status (n=6454 vs 6440)						
Any death	1387	1473	-54.7	714.5	0.93 [0.86-1.00]	0.04
Death with recurrence	696	794	-50.9	372.2	0.87 [0.79-0.97]	0.008
Death without recurrence* (further subdivided below)	691	679	-3.8	342.3	0.99 [0.89-1.10]	0.84
Analyses of events without prior recurrence, any ER status (48 064 vs 46 959 woman-years of recurrence-free follow-up)						
– Death without recurrence						
Vascular death						
Stroke	62	59	0.8	30.2	1.03 [0.72-1.46]	0.89
Pulmonary embolus	10	8	0.8	4.5	1.21 [0.48-3.04]	0.69
Heart disease**	178	205	-16.1	95.7	0.85 [0.69-1.03]	0.10
Neoplastic death						
Endometrial cancer†	17	11	2.8	7.0	1.49 [0.71-3.13]	0.29
Other neoplastic disease	78	75	0.4	38.2	1.01 [0.74-1.39]	0.94
Other death						
Specified cause	171	161	2.3	82.9	1.03 [0.83-1.28]	0.80
Unspecified cause	175	160	5.1	83.7	1.06 [0.86-1.32]	0.58
– Second cancer incidence						
Contralateral breast cancer	419	467	-28.9	221.5	0.88 [0.77-1.00]	0.05
Endometrial cancer†	116	63	24.8	44.8	1.74 [1.30-2.34]	0.0002
Primary liver cancer	3	3	-0.0	1.5	0.99 [0.20-4.90]	0.99
Colorectal cancer	46	52	-3.8	24.5	0.86 [0.58-1.27]	0.44
Unspecified site	254	251	-1.3	126.2	0.99 [0.83-1.18]	0.91
– Non-neoplastic disease, (ever hospitalised/died)						
Stroke	130	119	3.8	62.2	1.06 [0.83-1.36]	0.63
Pulmonary embolus	41	21	9.7	15.5	1.87 [1.13-3.07]	0.01
Ischaemic heart disease	127	63	-20.2	72.5	0.76 [0.60-0.95]	0.02
Gallstones	75	66	3.7	35.2	1.11 [0.80-1.54]	0.54
Cataract	72	63	3.5	33.7	1.11 [0.79-1.56]	0.54
Bone fracture	62	70	-4.9	33.0	0.86 [0.61-1.21]	0.39

NB The logrank analyses of death with recurrence are done by subtraction of the logrank analyses of death without recurrence from those of any death. If O-E is negative, its value is about half the number of events prevented; if V is its variance, event rate ratio is exp ([O-E]/V).

* Delay of recurrence by continuation of tamoxifen increases the woman-years at risk before recurrence by about 3% in ER+ disease; logrank analyses allow for this, but crude comparisons of total numbers of events before recurrence do not. ** Mainly heart disease, but includes all vascular causes except stroke and pulmonary embolus. † Mainly endometrial adenocarcinoma, but includes all other uterine tumours except cervix cancer; analyses of uterine tumour incidence exclude women with hysterectomy recorded at trial entry.

Webtable 3: Event rate ratios (and 95% confidence intervals) in ER+ disease, by time period from diagnosis

(A) Trials of 5 years of tamoxifen (n=10,645; about 80% complied), (B) ATLAS trial of 10 vs 5 years of tamoxifen (n=6846; about 80% complied), (C) Hypothetical trial of 10 years of tamoxifen vs none (with about 80% compliance).

Years from diagnosis	A. Effects in meta-analyses of the trials of 5 years of tamoxifen vs none (n=10,645)	B. Effects in the ATLAS trial of continuing to 10 years vs stopping at 5 (n=6846)	C. Estimated effects in a trial of 10 years of tamoxifen vs none (product of A & B)
Recurrence			
0-4y	**0.53** [0.48-0.57]‡	**1**	**0.53** [0.48- 0.57]‡
5-9y	**0.68** [0.60-0.78]‡	**0.90** [0.79-1.02]	**0.61** [0.51-0.73]‡
10+	**0.94** [0.79-1.12]	**0.75** [0.62-0.90]*	**0.70** [0.54-0.91]*
Breast cancer mortality			
0-4y	**0.71** [0.62-0.80]‡	**1**	**0.71** [0.62-0.80]‡
5-9y	**0.66** [0.58-0.75]‡	**0.97** [0.79-1.18]	**0.64** [0.50-0.82]†
10+	**0.73** [0.62-0.86]†	**0.71** [0.58-0.88]§	**0.52** [0.40-0.68]‡

The two-sided p-values in this table relate to particular time periods; those elsewhere combine all time periods. ‡ p<0.00001, * p<0.01, † p=0.0001, § p=0.0016

Webtable 4: Retrospective assay of ER status in stored pathology specimens from 1509 of the 4800 women with unknown ER status at ATLAS entry

Some time after entry into ATLAS, tumour pathology specimens that had been stored since the time of the original diagnosis (about 5 years before entry) were retrieved and assayed locally for ER status.

Region	Number with ER-unknown at ATLAS entry	ER positivity (in samples tested retrospectively)	Predicted number that would have tested ER positive if all ER-unknown samples had been tested
Europe/ANZ/US/SA	1485	67.3% (434/645)	999/1485 (67.3%)
Latin America	1273	72.8% (286/393)	927/1273 (72.8)
Asia/Middle East	2042	44.6% (210/471)	910/2042 (44.6%)
Total	**4800**	**61.6% (930/1509)***	**2836/4800 (59.1%)****

* Crude, unstratified total

** Appropriately stratified estimate

Reliable assessment of the efficacy and safety of prolonging the use of adjuvant tamoxifen: a large, simple, randomised study.

Adjuvant tamoxifen therapy in early breast cancer: Existing evidence

Trials of adjuvant tamoxifen in women with early breast cancer have demonstrated a highly significant improvement in 10-year survival. However, it is not yet known how long women with early breast cancer should continue to take adjuvant tamoxifen. Most trials of tamoxifen versus no tamoxifen involved only 1, 2 or 5 years of tamoxifen. Within this range, the more prolonged treatments appear more effective at preventing or delaying recurrence and improving 10-year survival. **However, among women who have already had some years of treatment there is no reliable evidence, from direct randomised comparisons of different durations, of an extra therapeutic advantage from more prolonged treatment.** Moreover, while tamoxifen has relatively few short-term or medium-term side-effects (particularly for post-menopausal women), it produces some increase in the incidence of endometrial cancer, and may have some other important long-term side-effects. These risks may increase if the drug is taken for many years. Hence, the balance of benefits and risks of long-term tamoxifen needs to be determined reliably.

If longer tamoxifen improved survival by just a few percent, reliable demonstration of this benefit could save thousands of lives each year

Even if longer-term tamoxifen is somewhat more effective than just a few years of treatment, the net advantage is likely to be only moderate. For example, five additional years of treatment would be unlikely to improve the 10-year survival by more than a few percent, and might not improve it at all. Indeed, if longer treatment produces extra side-effects, and little extra benefit, it might even make the 10-year survival slightly worse. Breast cancer is so common that reliable demonstration of just a small benefit or just a small hazard could save thousands of lives worldwide — and even a null result in a study big enough to be reliable would avoid the unnecessarily prolonged treatment of many hundreds of thousands of women each year.

Need for a large, pragmatic study of longer versus shorter adjuvant tamoxifen therapy

Around the world there are about a million breast cancer patients who are currently taking tamoxifen as an "adjuvant" treatment. These women could become candidates for the **Atlas** study at any time that they and their doctors become **substantially uncertain** whether to carry on taking the drug. Women who have received any type of curative surgery are eligible (irrespective of the original histological type of the disease, nodal status, or whether the tumour was estrogen receptor positive or negative) so long as the woman appears currently to be free from disease **and** is receiving tamoxifen **and** where both the woman and her doctor are uncertain whether to continue. Any other adjuvant treatments (eg chemotherapy, radiotherapy, ovarian ablation) may have been given. This pragmatic approach, by increasing the heterogeneity of the patient population, will enhance the medical value of the trial and make it easier for clinicians to enter their patients into the study. Women will be randomised **EITHER** to stop tamoxifen **OR** to continue tamoxifen for at least 5 extra years. To encourage wide participation, the **Atlas** study involves virtually no extra work for collaborators, so that even the busiest clinicians can take part. The entry procedure is quick and easy, no examinations are required beyond those given as part of routine care, and minimal, annual follow-up information is requested.

If **Atlas** includes many thousands of women then survival differences of just a few percent could be assessed reliably. The success of the study will therefore depend entirely on the extent to which clinicians invite their patients to join it. So, publication of the final results will be in the names of the many collaborators (not the central organisers), and the chief acknowledgement will be to the patients themselves.

The aim of Atlas is to assess reliably the balance of risks and benefits in prolonging the duration of adjuvant tamoxifen by at least 5 extra years.

STEERING AND DATA MONITORING COMMITTEES, CONTACT DETAILS FOR INTERNATIONAL COORDINATING CENTRE & NATIONAL COORDINATING CENTRE

STEERING COMMITTEE

Major organisational and policy decisions

Chair:	C Williams
Principal investigators:	Christina Davies, M Clarke, R Gray, R Peto
National clinical coordinators:	(to be appointed in each country)
International Advisor:	A Goldhirsch

DATA MONITORING COMMITTEE

Interim analyses and response to specific concerns

Chair:	Sir Richard Doll
Members:	D Altman, R Collins, K Dickersin, M Baum, K Pritchard, D Simpson

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Contents

1. Background: a few years, or several years, of tamoxifen?

The first generation of trials of adjuvant tamoxifen in women with early breast cancer compared tamoxifen versus no tamoxifen, and most involved only 1 year, 2 years or 5 years of treatment. These early trials randomised a total of over 30,000 women, half of whom were allocated tamoxifen and half not. A systematic overview of the results[1] has shown a small but highly significant improvement in 10-year survival (overall about 6% absolute difference), with a tendency for the greatest improvement to be seen in the trials that studied the longest tamoxifen durations.

The second generation of adjuvant tamoxifen trials gave all patients tamoxifen, and involved directly randomised comparisons of different durations of tamoxifen with each other. Few of these trials involved more than 5 years of treatment, but again there was a tendency, within this range of durations, for the patients allocated longer treatment to have slightly better 10-year survival.

When really long-term follow-up becomes available from these first two generations of adjuvant tamoxifen trials, it will be possible to compare reasonably reliably the long-term effects of 1, 2 or 5 years of tamoxifen. By about 1990[1-4], however, the longer duration treatment regimens appeared somewhat more promising. Hence, many doctors began to recommend that adjuvant tamoxifen should continue for at least a few years, and, by the mid-1990s, about a million women worldwide were receiving the drug. There remained, however, wide uncertainty as to how long treatment should continue: is a few years generally sufficient, or would it be better to continue for several years (or even indefinitely)?

The first two generations of trials cannot answer this directly, as they do not provide reliable evidence about the additional effects of continuing beyond 5 years of treatment. Nor are there theoretical arguments that can resolve the question satisfactorily. As an anti-oestrogen, tamoxifen has a cytostatic effect, and it might be that maintenance of such an effect for several years would provide better disease control[5]. Conversely, it might be that virtually all of the protective effect against the original breast cancer could be achieved by just a few years of treatment, if this provided enough time without rapid cell growth for any clones that could be controlled by tamoxifen to become nonviable.

Moreover, while in the short term tamoxifen has few serious side-effects (especially among post-menopausal women), in the long term it can occasionally cause serious problems. In particular, the incidence of endometrial cancer is increased by tamoxifen[6-8]. It has also been suggested that the risk of liver tumours may be increased since hepatomas develop in rats (but not mice) who are regularly given large doses of the drug[9,10], although no clear excess of human liver cancer has been reported in the tamoxifen trials. Such tumours might, however, be mistaken for metastases in breast cancer patients[11]. During the first few years of adjuvant treatment the increase in endometrial cancer is outweighed by the decrease in breast cancer recurrence. But, any risks of tamoxifen-induced cancer may increase considerably if the drug is taken for many years, and this could alter the balance of benefits and risks against tamoxifen. There have also been reports from non-randomised studies of tamoxifen-induced retinopathy[12] and depression[13]. Another putative side-effect of tamoxifen is thromboembolism. However, this may be counterbalanced by a reduction in coronary heart disease[14] with prolonged tamoxifen (perhaps due to its cholesterol-lowering effect[15]).

Some of the hypothesised risks of tamoxifen are speculative and some of the established risks are small, but they do indicate the need to evaluate the balance between any benefits and any risks particularly carefully, since long-term use of this drug could be envisaged for hundreds of thousands of women with a past history of breast cancer[16], many of whom may be entirely free of residual disease.

Hence, a third generation of trials is now needed, comparing what appear to be the best of the tamoxifen schedules already widely studied versus substantially longer treatment. By the mid-1990s, however, only about 1000 women have been randomised into trials of 5 years versus longer tamoxifen, whereas tens of thousands may need to be studied if appropriately reliable evidence is to emerge. **The Atlas study aims to contribute substantially to the provision of such evidence.**

2. Atlas Study Design

Large, simple study: minimal data collection and no extra investigations

The Atlas collaboration aims to randomise many thousands of women between stopping tamoxifen after some years of treatment versus continuing for at least 5 extra years. To make large-scale recruitment feasible, the Atlas study procedures are "streamlined" so as to impose almost no extra workload on participating clinicians, beyond that required to treat their patients. Entry can, depending on what is most convenient for particular doctors, be by post, by fax, or by a brief telephone call. The entry procedure ends with the patient's doctor being told (by return of post, return of fax or continuation of the same telephone call) whether the random allocation is to stop tamoxifen now or to continue for at least 5 more years. Thereafter, only the minimum data needed to evaluate the effects of tamoxifen on recurrence and survival are collected. There is just a short annual follow-up form which asks for one line of readily available data on the current status of each randomised patient. This information will be supplemented, wherever possible, by the use of national mortality records to ensure long-term follow-up. Regular newsletters will keep participants informed of the study's progress, and of any problems that are encountered.

Can a large, simple study like this work?

The treatment of acute myocardial infarction provides an example of the successful use of such large, simple randomised trials. The ISIS (International Studies of Infarct Survival) collaborative group of over 1000 hospitals worldwide randomised more than 100,000 heart attack patients into their trials within just a few years by addressing important therapeutic questions, by adopting very simple protocols, by basing eligibility on uncertainty in both the doctor and the patient and by imposing virtually no extra work on participants. Because of the "streamlined" trial designs, doctors who were uncertain which treatments to use found it almost as easy to put their patients into an ISIS study as to choose the treatment arbitrarily outside ISIS. (Even the largest previous trials in myocardial infarction had each recruited fewer than one thousand patients, perhaps because of the considerable extra documentation and investigations that they required.) Because the ISIS trials were so large they produced clear results that had a substantial impact on clinical practice. For example, definite benefits of fibrinolytic treatment and of aspirin were found in the ISIS trials[17-18], and these treatments rapidly became standard throughout the world[19]. As a result of these and other "mega-trials", tens of thousands of unnecessary cardiac deaths are being avoided each year.

Randomise when SUBSTANTIALLY UNCERTAIN whether to stop or continue tamoxifen

There is considerable variability in the length of time that women with operable breast cancer are prescribed adjuvant tamoxifen. Some doctors normally plan to give tamoxifen for just 2 years, some for 5 years and others for life. Individual clinicians have different practices for different patients that depend on the patient's age, risk factors and on how well tamoxifen is tolerated. For example, some doctors use tamoxifen for longer if the original tumour was estrogen-receptor-positive (ER+) than if it was estrogen-receptor-negative (ER-), while other doctors use tamoxifen similarly in both circumstances. Moreover, as new evidence evolves, clinical practice changes. This heterogeneity of clinical opinion means that different doctors would consider different durations to be appropriate for any particular individual. Hence, it is not appropriate to design a rigid protocol for a tamoxifen duration trial — such as 2 years versus 5 years, or 5 years versus life. The Atlas study therefore adopts a pragmatic approach: randomisation will take place when the woman and her own doctor become **substantially uncertain** as to whether to stop or to continue tamoxifen[20]. Women may therefore be randomised after any duration of prior tamoxifen treatment, although the evidence from the previous trials suggests that they **should probably have already received at least two years tamoxifen.**

Who is eligible for randomisation?

Any woman could be eligible if she had breast cancer removed some time ago **(Note A)**, is still now apparently healthy **(Note B)** and is currently taking adjuvant tamoxifen — as long as the woman and her doctor are both **SUBSTANTIALLY UNCERTAIN (Note C)** whether to stop tamoxifen now, or to continue for some years more.

Note A: Initial treatment. The original cancer may have been of any size or histological type (as long as the doctor now responsible for the patient considers it to have been a carcinoma of the breast), and may have been managed initially by any type of surgery and/or radiotherapy and/or systemic therapy (as long as some tamoxifen was eventually included in the initial treatment, and the doctor considers that no clinically detectable deposits of the disease now remain: **there are, however, no mandatory tests for this stipulated by the Atlas protocol**).

Note B: Still apparently healthy. An earlier history of local recurrence would not preclude randomisation into Atlas, again as long as the doctor considers that no clinically detectable deposits remain. No other seriously life-threatening diseases should exist.

Note C: Substantial uncertainty. The patient is eligible if there are not thought to be clear indications or definite contraindications to further tamoxifen — and, therefore, substantial uncertainty exists as to whether to stop or to continue tamoxifen treatment. Definite contraindications to tamoxifen are specified not by the protocol, but by the judgement of the responsible physician and MIGHT include:

- intended or actual pregnancy or breast feeding
- significant endometrial hyperplasia
- retinopathy
- need for anticoagulant therapy (a contra-indication to tamoxifen)
- serious toxicity (e.g. depression) thought to be due to tamoxifen

or Conditions associated with only a small likelihood of worthwhile benefit, e.g.:

- negligibly low risk of breast cancer death
- some major life-threatening disease other than breast cancer (such that management of breast cancer risk is not the main concern)
- low probability of treatment compliance (e.g. psychiatric disorder, extreme old age, likely to move away)

Patient Information and Consent Leaflet

The patient should be told about the trial conversationally by her doctor and should be given time to read the detailed Patient Information and Consent Leaflet **(Appendix 1)**. She may wish to take the leaflet away to consider before deciding whether or not to join. If she decides to join the trial, she should be invited to initial each page of the leaflet and sign a formal statement of informed consent. The main source of information about the study should, however, be the patient's own doctor: the information leaflet is a medico-legal requirement, but it is of paramount importance that the woman understands the key reasons for and implications of the trial, which are as follows:

Entering the study: The woman's own doctor is substantially uncertain whether to stop tamoxifen now or whether to continue it for a few more years. This implies that the real advantages and disadvantages to be expected from either decision are probably quite small. If the woman also feels substantially uncertain whether to stop now or to continue taking tamoxifen for at least a few more years, then she may be willing to join the Atlas study and let the decision be taken just by the play of chance.

Withdrawing from the study: Because it is so difficult to measure small advantages or small disadvantages, the Atlas study is going to invite many thousands of women in hundreds of hospitals worldwide to join in, so it will not matter very much if a few of those who originally agree to join the study later change their minds and withdraw from it. If, after agreeing to

join, a woman later changes her mind, then she is free to do so without needing to give any reason and without adversely affecting other aspects of her medical care. Similarly, the woman's doctor is free to give any other treatment or to change the duration of tamoxifen, if that is considered to be definitely in the patient's best interest.

Heterogeneous patient population required

Women who have received any type of "curative" surgery are eligible — irrespective of whether they had node-positive or node-negative disease, or ER+ or ER- tumours — as long as they seem to be currently free of disease, are currently receiving tamoxifen, and are unsure whether to continue. Any other adjuvant treatments (e.g. chemotherapy, ovarian ablation, radiotherapy), or none, may have been given. Basing eligibility on uncertainty should ensure large scale recruitment of an appropriately heterogeneous group. Heterogeneity of the types of patients randomised increases the medical value of the study, as it may make it possible to determine whether the net effects of tamoxifen are influenced by certain patient characteristics (e.g. high/low-risk, ER+/ER-, pre/post-menopausal) recorded at entry.

Other trials of tamoxifen duration

The Atlas collaboration is designed to supplement the results of other trials of tamoxifen duration, and is not intended to compete with them for patients. However, because of its wide entry criteria, Atlas could run in parallel with other such trials, randomising those patients for whom there is no appropriate other trial of tamoxifen duration for which they are eligible.

Patients already in other trials can be randomised into Atlas

Breast cancer trials that are not of tamoxifen duration may well be compatible with Atlas, as long as some or all of the patients in those trials are being given adjuvant tamoxifen. Hence, collaborative groups that are conducting such trials may wish to consider certain patients for joint entry, first into their existing trial and then, later, into Atlas (or may wish to append an Atlas-like randomisation as part of their own trial, conducting this independently of Atlas: this would be equally valuable).

3. Practical procedures

Listing patients on tamoxifen who may later become suitable for Atlas

You may wish, every year or two, to provide a list of all the women at your clinic who are currently taking adjuvant tamoxifen, and who might eventually become candidates for Atlas. A Future Atlas Patients Form, which may be used to compile such a list is provided in the Atlas Trial materials binder. A reminder can then be automatically sent to you on the date you have indicated that you intend to review the patient's need for further tamoxifen. At this time you can then consider inviting the patient to join Atlas .

Patients who are not yet uncertain

Women become eligible to enter the Atlas study once they and their doctor have become substantially uncertain as to whether to continue tamoxifen. Each time you review a patient who is receiving adjuvant tamoxifen, consider whether you are still reasonably certain that you wish to continue with such treatment. If you and your patient have become substantially uncertain as to whether or not she should continue tamoxifen, then she can be offered the opportunity to take part in the Atlas study. The Patient Information and Consent Leaflet **(Appendix 1)** should be considered by the patient before she decides whether to join the study. Some patients may wish to delay their decision for some days, months or years, and may wish to take away a copy of the information leaflet to help them think things over.

Randomisation by post, fax or telephone

At randomisation, you will be asked to provide patient identifying details and to give details of potentially important patient characteristics and previous treatments. Before randomisation, you should write in answers to ALL the questions on the single-sided Patient Entry Form **(Appendix 2)**. No special tests have to be carried out for a patient to be entered into Atlas and all the necessary information is provided by the Patient Entry Form. A unique patient code number and the randomisation are then obtained by post, fax or telephone:

either: post (using the FREEPOST envelopes [if available]) or fax (+44-1865-726003) the top copy of the Patient Entry Form (completed except for the treatment allocation) to the Atlas Trial Office for the random treatment allocation to be sent back to you **within a few days**

or: telephone +44-1865-240972 (24-hour service) or, where available, the national toll-free number which will be allocated by the Atlas Trial Office, and read out all answers (except ID box) to be given the random treatment allocation **immediately** as to whether tamoxifen should stop now or be continued. The top copy of the Patient Entry Form should then be posted or faxed to the randomisation service with the allocation written in.

The details for obtaining the randomly selected treatment allocation may vary between countries. The telephone and fax numbers and the postal address of the randomisation service given on the Patient Entry Form and on the back of the Protocol will be modified appropriately for each country. Each participating hospital is allocated an Atlas number which is on the Atlas binder and on the back of the pad of Patient Entry Forms. Giving this number at randomisation will speed up the randomisation.

Treatment strategies: continue tamoxifen, or stop now

Women allocated to continue tamoxifen should expect to carry on taking tamoxifen (preferably at a dose of about 20 mg/day, unless you prefer some other dose) for at least 5 more years unless a clear contraindication is thought by their doctor to have arisen. Tamoxifen should be continued at the same dose. In general, it is expected that the tamoxifen should continue to be paid for as before. In some countries this will mean that the patient is responsible for the cost of the drugs, whereas in other countries the cost will be met by the local health service or health insurance (in the same way as other such health costs). It is possible that in some countries, free tamoxifen provided by the pharmaceutical industry will be available and the details of its distribution will be negotiated by the Atlas Trial Office in Oxford and separate National Coordinators. Women allocated to stop tamoxifen should stop tamoxifen as soon as conveniently possible, and should then continue to avoid tamoxifen unless a definite indication is thought by the patient's own doctor to have arisen.

Serious and unexpected adverse events

Tamoxifen is well-tolerated and only infrequently causes side-effects which are severe enough to require discontinuation of therapy. However, there is not enough experience of very long-term use of the drug to have definite evidence of the additional risks and benefits. The expected minor side-effects associated with tamoxifen do not need to be notified to the Atlas Trial Office and, as women in this study will have already received tamoxifen for some time, they will know whether any of these side-effects are relevant to them. Any serious and unexpected adverse events, believed to be attributable to tamoxifen, should be reported by the local coordinator to the Atlas Trial Office. **Serious** adverse events are those which are fatal, life-threatening, disabling and/or incapacitating, require hospitalisation or which is a congenital anomaly, a new cancer or is an overdose. **Unexpected** events are those which do not appear in the current tamoxifen datasheet. If a patient becomes pregnant, tamoxifen therapy **must** be stopped immediately and the Atlas Trial Office informed. In addition, as part of routine practice, clinicians would still be expected to follow their usual procedures for adverse event reporting. Information on serious and unexpected adverse events will be reported to the Data Monitoring Committee.

Minimal data collection and no extra investigations

To produce medically reliable answers about long-term survival, Atlas needs to be very large, recruiting approximately 20, 000 women. But, in addition, Atlas is intended to be "streamlined", involving virtually no extra work for the clinician. To make it practicable for clinicians to participate, the collection of extensive data has been avoided. The current status of all patients will be ascertained through an annual follow-up listing that is sent out by the Atlas Trial Office at the same time each year, which requests only one line of data per patient **(Appendix 3)**. The information routinely recorded in the patient's records should be sufficient for the completion of the Annual Follow-up Form. Long-term mortality follow-up can, in some countries, be supplemented by central government records.

Investigations and management of patients differ at different centres and it is not appropriate to impose from outside rigid patient management procedures or extra investigations that would not be considered "best practice" by the patient's own doctor. Atlas therefore adopts a pragmatic approach with clinical responsibility for all aspects of the management of the patient always entirely remaining with the patient's own doctor. **In general, patients should not need to undergo any tests or examinations especially for the study.**

Details of the general organisation of the study are summarised on the inside of the back cover of the protocol. These may need to be modified for each country and the details will be negotiated by the Atlas Trial Office with the National Coordinators.

4. Analysis

Principal comparisons

The principal analysis will be of all-cause mortality (analysed by the logrank method on all randomised patients). This overall survival analysis will be complemented by subsidiary analyses of deaths from specific causes, such as breast cancer, myocardial infarction, endometrial cancer, etc. The incidence of second primary tumours — in particular, contralateral breast cancer, other female cancers and liver cancer — and of non-fatal myocardial infarctions and other vascular events requiring hospitalization will also be examined. The analyses will be stratified by the duration of tamoxifen given prior to randomisation (0-1yr, 2-3yrs, 4-5yrs,6-7yrs, 8-9 yrs, 10+ yrs), by age (<40, 40-49, 50-59, 60-69, 70-79, 80+), by ER status (ER-, unknown, ER+[i.e. ≥10fmol/mg of cytosol protein]), and by other prognostic factors recorded at randomisation.

Number of patients needed

Tamoxifen is generally well-tolerated, so it would be worth knowing if longer use of tamoxifen produced a difference in 10-year survival that was as small as just 2-3% or so. (By comparison, the difference in 10-year survival between those allocated about 2 years of tamoxifen and those allocated no tamoxifen was about 6%.) In order to detect such a small difference in absolute survival (e.g. 50% vs 52.5%), 20,000 patients would have to be randomised in this and other studies of tamoxifen duration for there to be a 95% chance of detecting a 2-3% difference in survival at $2P < 0.05$, and an 85% chance of doing so at $2P < 0.01$. (This number of randomised women would probably fail to detect a difference of only 1%, but would be virtually certain to detect a difference of 3% or more.) This number is considerably larger than any previous cancer study, but it is not disproportionately large if, during the years after the study ends, long term tamoxifen is prescribed without further controlled evaluation to many hundreds of thousands of women worldwide.

Data monitoring committee: determining when clear answers have emerged

If the survival benefit of longer tamoxifen is substantially greater than 2%, or if substantial side-effects emerge, then this may become apparent well before 20,000 patients are randomised into this and the other such trials.

During the period of intake to the study, interim analyses of mortality (and of any other information on major endpoints that is available) will be supplied, in strict confidence, to an independent data monitoring committee along with any other analyses that the committee may request. Reports of serious and unexpected adverse events attributed to tamoxifen will also be made available. The data monitoring committee will advise the chair of the steering committee if, in their view, the randomised comparisons in Atlas have provided both (a) "proof beyond reasonable doubt"* that for all, or for some, types of patient one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in long-term survival, and (b) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the other main study results. The steering committee can then decide whether to modify intake to the study. Unless this happens, however, the steering committee, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

If the national or international clinical coordinators are unable to resolve any particular concern satisfactorily, collaborators and all others associated with the study may write through the Atlas coordinating office to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant

5. Financial support

Tamoxifen is already out of patent in many countries, and is likely to be out of patent in all countries before the main results emerge from Atlas. Trials of such non-patent treatments are important to patients, but can become large enough to provide reliable information only if doctors will collaborate in them without payment (except for recompense of any minor local costs that may arise). The central organisational costs and meetings costs of the trial are supported by the breast cancer program of the United States Army (log no. B4339128) and the UK Imperial Cancer Research Fund. Zeneca Pharmaceuticals plc have agreed to provide free tamoxifen in the trial, but the design and management of the trial remain entirely independent of the pharmaceutical company involvement. The company has no representative on the Trial Steering Committee to ensure that no suggestions of lack of objectivity of the findings can be justified.

6. Publication

The success of Atlas depends entirely on the commitment and efforts of a large number of collaborating doctors, nurses and patients. A meeting of the collaborators will be held at the end of the study to present and discuss the main results and the main results will then be published in the names of the professional staff who have collaborated in the study (not just the trial organisers), with the chief acknowledgement to the women who have participated.

Appendix 1: PATIENT INFORMATION AND CONSENT LEAFLET

INFORMATION AND CONSENT LEAFLET

Invitation to join an international research study of the efficacy and safety of prolonged tamoxifen treatment for women with a history of breast cancer

- You have been taking tamoxifen for some time, and your doctor is **uncertain** whether you should keep on taking it for a few more years, or whether you should now stop.
- If you too are unsure whether to continue or to stop tamoxifen now, then please consider taking part in a big research study involving thousands of women like you in hundreds of hospitals all around the world.
- If, on the other hand, you would definitely prefer to keep on taking tamoxifen, then ask your doctor to arrange this. Or, if you definitely feel that you have been taking tamoxifen for long enough already and would prefer to stop, then you should do so.

In the study, half stop and half continue tamoxifen

- The women who join the study will, like you, have been breast cancer patients who have been carrying on taking tamoxifen even though their doctors can no longer see any cancer anywhere.
- Half of them will be asked to continue taking tamoxifen for at least another five years (unless, later on, new evidence or some reason emerges why they should stop), and the other half will be asked to stop tamoxifen now and to stay off it (unless, later on, new evidence or some reason emerges why they should restart).
- If you decide to take part in the research study, neither you nor your doctor will know beforehand whether you yourself would be asked to continue or stop tamoxifen: that would be determined at random, just **after you make a decision to take part.**

You may wish to take a copy of this leaflet away to read before deciding whether to take part in the study.

If you eventually decide to take part, please initial and date each page and sign the back of this information leaflet.

Patient initials: _____ **Witness initials:** _____ **Date:** _____

PATIENT INFORMATION AND CONSENT LEAFLET (continued)

What is the study about?

We know from previous studies of many thousands of women with breast cancer that taking tamoxifen each day, for at least the first few years after surgery, reduces the risk of the breast cancer returning. Tamoxifen does this by interfering with the effect of the natural female hormones on the growth of any traces of breast cancer that may have remained. What is not known, though, is exactly how long women should carry on taking tamoxifen. Because of this, there is currently a wide variation in practice, with some doctors prescribing tamoxifen for just one or two years, others for five years, and some for even longer. This is why we are doing this study, called **Atlas**, to help find out reliably which treatment duration is best.

What are the risks of carrying on taking tamoxifen?

Over a million women around the world have already taken tamoxifen for breast cancer and, so far, a few years of tamoxifen treatment has saved many lives and caused few serious side-effects. However, there is not yet enough experience with this drug to be sure about the additional risks and benefits of taking tamoxifen for a lot longer. In particular, we know that there is a small risk that tamoxifen will cause cancer of the lining of the womb (endometrium) — which, if caught early, can be successfully treated by hysterectomy. We also know, though, that a few years of tamoxifen has, so far, prevented many more breast cancers coming back than the few womb cancers it has caused. Eye problems have also been reported with tamoxifen and a rare complication, known as "tamoxifen retinopathy" can cause visual impairment (which usually disappears when treatment is stopped).

It has also been suggested that tamoxifen might have other side-effects: for example, prolonged high doses of tamoxifen produced liver tumours in some types of small laboratory animals (but not in others), although at present there is no good evidence of any increased risk of liver cancer in humans. Tamoxifen might also increase the risk of an internal blood clot (thromboembolism), but this may well be counterbalanced by a reduction in the risk of having a heart attack because of the cholesterol-lowering effect of tamoxifen. Some women taking tamoxifen report depression but, again, it is unclear whether or not this is caused by the tamoxifen. Less serious side-effects, which are usually mild and disappear when treatment has stopped, are reported by some women. These include changes in the pattern of menstrual "periods", hair loss, stomach upsets, itching, fluid retention, skin rashes and, in about 15% of women who are still having their periods (or who only recently stopped doing so), hot flashes. Since you have been taking tamoxifen for some time, you may well know whether any of these side-effects are relevant to you.

Extra years of tamoxifen

We very much hope that taking tamoxifen for longer than a few years will produce enough extra benefit to outweigh any side-effects. But, if the risk of womb cancer — or of any other serious diseases — increases when tamoxifen is taken for longer (or if tamoxifen becomes less effective at preventing the reappearance of breast cancer the longer it is taken) then it may be best not to go on taking it indefinitely. It is, therefore, important to know how long women should carry on taking tamoxifen. To find out the answer, we and many other doctors around the world are inviting women like yourself — for whom it is not clear whether it would be best to stop or to continue tamoxifen — to participate in a study comparing these two options.

Patient initials: _____

PATIENT INFORMATION AND CONSENT LEAFLET (continued)

What would the study involve?

If you are willing to help future women with breast cancer by taking part in Atlas, the only thing that you will be asked to do is **EITHER** to stop taking your tamoxifen tablets now **OR** to carry on taking them for at least another five years. If you are asked to continue taking tamoxifen then the costs of this treatment will have to be paid for in the same way as they have been up to now. If you agree to participate, the decision as to whether you will be asked to stop or to continue with tamoxifen would be made at random, by the central office running the study. This is the only way to find out really reliably which is the best treatment option. If subsequently, after joining the study, you later change your mind, then you are free to do so without needing to give any reason and without adversely affecting other aspects of your care. No extra tests or clinic visits would be needed if you took part in the study. Your doctor will, of course, continue to see you at routine intervals whether or not you take part.

What precautions should women on tamoxifen take?

You have already been taking tamoxifen for some time and so you will be aware of how it makes you feel, and of the precautions you should take and would have to keep taking if you were asked to continue with tamoxifen. In particular, because of the possibility that tamoxifen may affect the unborn child if taken by a pregnant woman, you should not enter the study if you think that you might be, or might become, pregnant. Women who are still fertile should take some reliable contraceptive measure if they are asked to continue tamoxifen and, if they do become pregnant while using tamoxifen, should immediately stop taking the tablets, tell their family doctor and contact the Atlas local coordinator (see below). If you already have a young baby then you should avoid breast-feeding while on tamoxifen. In addition, any unusual vaginal bleeding (which could be a sign of womb cancer but could also be due to a number of other causes), or any unusual problems with eyesight, or other unpleasant or severe side-effects, should also be reported without delay. If you do agree to take part, and you experience any ill effects because of doing so, you will receive all appropriate medical care, but there is no special compensation available to women for participation in this study — although you would, of course, retain your usual legal rights.

Confidentiality of patient details

If you do take part in Atlas, simple information about your progress would be provided each year, in confidence, by your own doctor to the central organisers. In addition, because the study receives funding from the Breast Cancer Program of the United States Army, the records of the research may be inspected by them as part of their legal obligations. The central organisers will have to send them the name, address and dates of participation of all of the women who agree to join the study. This information is to be stored for 75 years in case there are questions about someone's participation in research funded by the US Army, and to ensure that research volunteers can be adequately warned of any important new results that become available. This information, like all of the other information that is collected as part of the Atlas study, will be treated **in strict confidence** by the coordinating centre and all other investigators, in the same way as your other medical records. Neither you nor other patients in the study would be identified when the results are reported.

The protocol has been approved by the independent data monitoring committee, chaired by Professor Sir Richard Doll who can be contacted via the clinical coordinator Dr Christina Davies, Atlas Coordinating Centre, Radcliffe Infirmary, Oxford, England.

Witness initials: _____ **Date:** _____

PATIENT INFORMATION AND CONSENT LEAFLET (continued)

Signed agreement to participate in the Atlas study

Having read this leaflet we hope that you will choose to take part in Atlas. If so, we need to ask you (and a witness) to sign below to confirm that you have agreed to do so, and you should both also initial and date each previous page to show you've read them. If you want further information about the study before deciding whether to join, then please feel free to ask the doctor who gave you the leaflet or the Atlas Local Coordinator (see below). If you want to delay your decision for a time, perhaps to discuss matters further, then please make an appointment to come back later. If you would like to ask anything about your rights while in the study, you can write to the chairman of the study's independent data monitoring committee (see previous page). If you decide not to take part, then you could choose to stop or continue tamoxifen as you wish in consultation with your medical adviser. If you do decide to join the study and then sometime later find there is some aspect of it that you wish to discuss further, then please contact the doctor who gave you this leaflet or the Atlas Local Coordinator (name and telephone number below).

I have been informed about the Atlas study and agree to enter it. I hope to collaborate in this study for several years, but I understand that I am free to withdraw from the study treatment at any time without necessarily giving any reason (and without adversely affecting the medical care I can expect from my own doctors). I agree that simple information about my progress will be provided each year, in confidence, by my doctor to the central organisers and will be used for medical research only.

PATIENT SIGNATURE _____

& name (please PRINT) _____

WITNESS SIGNATURE _____

& name (please PRINT) _____

ATLAS LOCAL COORDINATOR:

STICK LABEL HERE

Appendix 2: ATLAS Study Patient Entry Form

ADJUVANT TAMOXIFEN — LONGER AGAINST SHORTER

PATIENT ENTRY FORM

After the patient has signed her consent, write in answers to ALL questions on this form, then:

Either: telephone the **Randomisation Service** and read out **all** answers (except ID box) for an **immediate** random treatment allocation (then post top copy to the Atlas Trial Office with allocation written in).

Or: post or fax top copy to **Atlas Trial Office** for random treatment allocation to be sent back to you **within a few days**

Date: | | day | | month | | year

ELIGIBILITY

Has the patient consent form been signed and witnessed?
(Please tick ✓) ☐ YES ☐ NO (**MUST** be **YES** to be eligible)

Is the patient currently on tamoxifen?
(Please tick ✓) ☐ YES ☐ NO (**MUST** be **YES** to be eligible)

Is the patient clinically free of cancer now?
(Please tick ✓) ☐ YES ☐ NO (**MUST** be **YES** to be eligible)

Atlas code no. for hospital (see back of this pad, or front of binder) | | | | |

If not known, give hospital name, city and country:

Name of hospital doctor responsible for patient (PRINT):

Patient's family name (PRINT):

Patient's given name(s) (PRINT):

Patient's hospital no. (if available):

Patient's date of birth: | | day | | month | | year

ID BOX — DETAILS TO BE WRITTEN IN, BUT NOT GIVEN OVER THE TELEPHONE

National ID/Social Security No. (if available)

Patient's address: (PRINT)

telephone:

ALTERNATIVE CONTACT

N.B. This person will be contacted only if contact with patient is lost.
(Choose someone at DIFFERENT address, e.g. family doctor/friend/relative) specify which:

Name: (PRINT)

Address: (PRINT)

telephone:

HISTORY OF CANCER

Date of diagnosis of original breast cancer: | | month | | year

Approximate diameter of primary tumour: | | cm ☐ Unknown

Any **ESTROGEN RECEPTORS** on primary? ☐ Negative ☐ Positive ☐ Unknown Exact value if known: | | fmol/mg

	NO	YES	Unknown	(Please tick ✓)
Loco-regional nodes ever involved?	☐	☐	☐	Exact count if known	/	(+/total)
Ever any loco-regional recurrence?	☐	☐	☐	If **YES**, Date:	month	year
Entire breast EVER removed?	☐	☐	☐	If **YES**, Date:	month	year
Ever any **CONTRALATERAL** primary, at diagnosis or later?	☐	☐	☐	If **YES**, Date:	month	year
Ever any other **PRIMARY** cancer, at ANY age?	☐	☐	☐	If **YES**, Date:	month	year

If **YES**, specify primary site(s):

PRESENT CIRCUMSTANCES

	NO	YES	Unknown	(Please tick ✓)
Post-menopausal?	☐	☐	☐	(or perimenopausal)
Ever hysterectomy?	☐	☐	☐	
Ever bilateral ovarian ablation?	☐	☐	☐	

Current TOTAL daily tamoxifen dose: | | mg/day **(CANNOT be zero)**

Duration in months of tamoxifen to date: | | | months

CHECK ALL ANSWERS (ONE per LINE) ARE COMPLETED, AS ANY MISSING WILL PREVENT OR DELAY RANDOMISATION

RANDOMISATION ALLOCATION (stop / continue): LEAVE BLANK UNTIL ALLOCATED BY ATLAS

☐ **STOP tamoxifen now, or** ☐ **CONTINUE for at least 5 more years**

Patient identification number allocated at randomisation: | | | | | | | |

Send **TOP** (Blue) copy to Atlas Trial Office

& keep the **BOTTOM** (White) copy for your clinical records

ATLAS/SE/1/296

ATLAS FOLLOW-UP: OCTOBER 1996

Name of collaborating doctor responsible for patients: _____
Name of local coordinator: _____
Participating hospital: _____

Listed below are patients who have been entered into ATLAS at your hospital and who, as far as we know, are still alive.
Please 1) check that the details given below are correct and 2) fill in ALL available additional information **since last follow-up and/or since entering ATLAS.**

Name of patient Date of birth [*Hospital number*] Date of original diagnosis Date entered into ATLAS ID number (STOP/CONTINUE)	Date last seen:	On tamoxifen when last seen?	Date of first loco-regional recurrence:	Date of first distant recurrence:	Other primary cancer: Date of diagnosis and Site[2]	If patient has died: Date of death and Underlying cause of death[3]	Any events involving hospital admission (e.g. myocardial infarct, hysterectomy etc): Date of admission[4] and Diagnosis	Other comments (e.g. name of hospital doctor currently responsible for patient, if different from above)
	/ m year	☐ Yes ☐ No[1] Date stopped[1] / m year	/ m year	/ m year	/ m year ☐ contralateral breast ☐ endometrial cancer ☐ other (specify below):	/ m year ☐ breast cancer ☐ endometrial cancer ☐ myocardial infarction ☐ other (specify below):	/ m year Diagnosis:	
	/ m year	☐ Yes ☐ No[1] Date stopped[1]: / m year	/ m year	/ m year	/ m year ☐ contralateral breast ☐ endometrial cancer ☐ other (specify below):	/ m year ☐ breast cancer ☐ endometrial cancer ☐ myocardial infarction ☐ other (specify below):	/ m year Diagnosis:	
	/ m year	☐ Yes ☐ No[1] Date stopped[1] / m year	/ m year	/ m year	/ m year ☐ contralateral breast ☐ endometrial cancer ☐ other (specify below):	/ m year ☐ breast cancer ☐ endometrial cancer ☐ myocardial infarction ☐ other (specify below):	/ m year Diagnosis:	

1 If patient was allocated to STOP tamoxifen in ATLAS, date stopped should = date entered into ATLAS. If patient was allocated to CONTINUE tamoxifen in ATLAS, state date when stopped tamoxifen.
2 Other primary cancer includes primary contralateral breast. If more than one primary site, please specify EACH site and date of diagnosis (use "other comments" section).
3 If died, state whether UNCONTROLLED cancer was present (if known).
4 If more than one hospital admission, use "other comments" section.

PLEASE RETURN THIS FORM PROMPTLY IN THE ENCLOSED FREEPOST ENVELOPE (if available) TO:
Atlas Trial Office (see protocol cover for address)

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14. Rutqvist LE, Mattsson A. Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. J Natl Cancer Inst 1993; 85: 1398-1406.
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18. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. A randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992; 339: 753-770.
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ORGANISATION OF THE ATLAS TRIAL

Atlas is designed to provide reliable evidence on the optimal duration of tamoxifen treatment. To be reliable, the study needs to be very large. This is achieved by adopting a very simple design, with streamlined entry and follow-up procedures to enable the trial to be easily integrated into routine clinical practice, so that most doctors can participate.

The overall administration and coordination of the trial is the responsibility of the **Atlas Trial Office** in Oxford, UK. For each country, there is a **National Coordinator** and/or **Regional Coordinator(s)**. Each participating centre will also have a **Local Coordinator**.

HOW TO ENTER A CENTRE INTO ATLAS

1 Each centre should first designate one person as the Local Coordinator who will be responsible for coordinating clinical, pharmaceutical and administrative aspects of the trial at that centre.

2 The Local Coordinator must submit the full study protocol to the local ethics committee/institutional review board for approval. **No patient can be entered into Atlas until ethics approval has been obtained.** An information sheet to assist with ethics committee submission is available either from the National Coordinator or from the Atlas Trial Office.

3 Confirmation of approval by the ethics committee **must** be forwarded to the Atlas Trial Office in Oxford.

4 The Atlas Trial Office will then send the trial materials to the Local Coordinator. Any doctor at the centre can then enter eligible patients into the study.

HOW TO ENTER A PATIENT INTO ATLAS

1 Women will usually be identified at a routine follow-up clinic. When eligible patients have been identified, have read the Patient Information Leaflet and have given their written consent, the Patient Entry Form should be completed fully.

2 The responsible clinician may then obtain the random treatment allocation **EITHER** by telephoning the 24-hour randomisation service in Oxford (+44-1865-240972), or where available the national toll-free number for immediate randomisation, **OR** by sending the Patient Entry Form by fax (+44-1865-726003) or by FREEPOST (if available) for randomisation within a few days.

3 **If telephone randomisation is used:** the random treatment allocation and the patient identification number assigned by the randomisation service should be written on the Patient Entry Form. The top copy of the Patient Entry Form must then be sent by FREEPOST (if available) to the Atlas Trial Office.

4 **If fax or postal randomisation is used:** the random treatment allocation and the patient identification number will be assigned by the randomisation service and then returned to the clinician randomising that patient.

5 "ATLAS Patient" stickers are provided to identify the notes of patients who have been randomised on Atlas.

6 Some patients may definitely wish to continue on tamoxifen at the present time, but may become eligible for Atlas at some time in the future. To help identify these patients, "?ATLAS" stickers, which can be attached to the patients' notes are provided. In addition, a Future Atlas Patients Form can be used to list these patients, and to indicate when they might become eligible for the study. If it would be helpful, the Future Atlas Patients Form may be sent to the Atlas Trial Office, which will send a reminder notice to the responsible clinician at the appropriate time.

FOLLOW-UP OF PATIENTS IN ATLAS

The Atlas Trial Office is responsible, in collaboration with National Coordinators, for the collection of follow-up data. At the same time each year, the Atlas Trial Office will send out simple single sided Annual Follow-up Forms requesting simple information from each clinician on each patient entered into Atlas. This form should be completed and returned as soon as possible to the Atlas Trial Office using the FREEPOST envelope (if available).

HOW TO REPORT ADVERSE EVENTS

Clinicians or the Local Coordinator should telephone the 24-hour randomisation service (+44-1865-240972) if any patient who is receiving tamoxifen in Atlas becomes pregnant, or experiences serious and unexpected adverse events which are considered to be attributable to tamoxifen.

Serious events are those which are fatal, life-threatening, disabling and/or incapacitating, require hospitalisation, or are a congenital anomaly, a new cancer or an overdose. **Unexpected** events are those which do not appear in the current tamoxifen datasheet. In addition, as part of routine practice, clinicians would still be expected to follow their usual procedures for reporting adverse events.

HOW TO GET ADVICE

For **urgent** medical enquiries, call the 24-hour randomisation service (+44-1865-240972), or the National/Regional Coordinator.

For general and administrative enquiries, call the Atlas Trial Office (+44-1865-794569)

HOW TO GET STUDY SUPPLIES

For trial supplies (study protocols, Patient Entry Forms, Patient Information and Consent Leaflets etc.), call the Atlas Trial Office (+44-1865-794569) or the National/Regional Coordinator.

RESPONSIBILITIES OF LOCAL COORDINATORS

1 **Applying for local ethical approval for Atlas.** Any modifications, particularly to the Patient Information and Consent Leaflet, however minor, will need to be sent to the Atlas Trial Office for formal review and, as this will involve delay, any changes are discouraged.

2 **Maximising collaboration in their centre, by ensuring that local medical and nursing staff involved in the long-term care of breast cancer patients are informed about Atlas.** This may be through discussions and meetings. Atlas wall-charts can be displayed, and regular newsletters will be produced and distributed by the Atlas Trial Office.

3 **Maximising randomisation of eligible women into Atlas.**

4 **Answering patients' enquiries about the study.**

5 **Ensuring that the Atlas Trial Office is notified** if any patient who is receiving tamoxifen in Atlas becomes pregnant, or if any patient experiences serious and unexpected adverse events which are considered to be attributable to tamoxifen.

6 **Provision of tamoxifen.** In women allocated to the continuation of tamoxifen arm, tamoxifen should continue to be prescribed as before. In general, it is expected that tamoxifen should continue to be paid for as before. In some countries, this will mean that the patient is responsible for the cost of the drugs, whereas in other countries, the cost will be met by the local health service or health insurance (in the same way as other such health costs). In some countries, free tamoxifen provided by the manufacturers will be available. Details of its distribution will be negotiated by the Atlas Trial Office with the National/Regional Coordinators, who will in turn discuss needs with the Local Coordinators.

RESPONSIBILITIES OF NATIONAL/ REGIONAL COORDINATORS

1 **The National and/or Regional Coordinators are in regular and direct contact with the Atlas Trial Office,** and will be the main source of advice to participating clinicians in those countries about Atlas.

2 **Maximising collaboration in their region, and arranging occasional meetings of collaborators** so that any problems or questions can be dealt with.

3 **Distributing trial materials and newsletters, informing local collaborators about the progress of Atlas and dealing with most of the problems and questions that might arise.** This includes advising the Local Coordinators on the appropriate action to take if any patient on tamoxifen in Atlas might be pregnant or if any patient experiences serious and unexpected adverse events.

4 **Where necessary, coordinating free tamoxifen to participating centres.**

5 **Representing collaborators' views at meetings of the Atlas steering committee of which the National Coordinators would be members.**

GENERAL ORGANISATION OF THE ATLAS TRIAL*

Atlas Trial Office

- **Overall coordination and administration**
- **Production and supply of trial materials and newsletters**
- **Randomisation service**
- **Data analysis**

National and/or Regional Coordinators

- **Promoting collaboration in the region**
- **Advice to participating clinicians**
- **Liaising with the Atlas Trial Office**
- **Distributing trial materials**
- **Coordinating distribution of free tamoxifen (where necessary)**

Local Coordinators at centres

- **Promoting collaboration in the centre**
- **Obtaining local ethical approval for the study**
- **Notifying the Atlas Trial Office of serious and unexpected adverse events**
- **Answering patients' questions about the study**

Clinicians

- **Entering patients in the study**
- **Providing annual follow-up data**

*Details of the practical arrangements for implementing the trial may vary in different countries

ATLAS: An International Tamoxifen Duration Study

ADJUVANT TAMOXIFEN — LONGER AGAINST SHORTER

Breast cancer patients now on tamoxifen: STOP or CONTINUE TAMOXIFEN a few extra years?

ELIGIBILITY

- Breast cancer some time ago **(Note A)**
- Clinically free of cancer now **(Note B)**
- Currently on tamoxifen but woman and doctor both UNCERTAIN whether to STOP tamoxifen now or CONTINUE a few extra years **(Note C)**

INVITATION

- Discuss ATLAS using INFORMATION LEAFLET and invite CONSENT **(Note D)**

ENTRY

- NO extra tests
- Complete all of short ENTRY FORM PRIOR to randomisation
- TELEPHONE for IMMEDIATE randomisation to:

EITHER

STOP CURRENT TAMOXIFEN IMMEDIATELY (restarting ONLY if a definite indication is thought to have emerged)

OR

PLAN TO CONTINUE TAMOXIFEN (Note E) FOR AT LEAST 5 EXTRA YEARS (stopping ONLY if a definite contra-indication is thought to have emerged)

- **or** POST/FAX form for randomisation in a few days

FOLLOW-UP

- NO extra tests
- CONTINUE allocated treatment strategy
- Annual FOLLOW UP: only 1 line of information per woman

Note A: Original cancer may have been of any size /type and original treatment may have been of any type. Tamoxifen **must** have eventually been included and women should **probably** have received at least 2 years of tamoxifen.

Note B: Still eligible if previous local recurrence but **must** be clinically free of breast cancer now.

Note C: Patient is eligible if there are not thought to be clear indications for or definite contraindications to further tamoxifen. Contraindications **might** be:

- significant endometrial hyperplasia
- retinopathy
- intended/actual pregnancy/lactation
- need for anticoagulant therapy
- serious toxicity **OR** little chance of worthwhile benefit
- other major life-threatening disease
- negligible risk of breast cancer death
- low probability of compliance

Note D: The patient should initial and date each page of information leaflet and sign the formal consent section.

Note E: Tamoxifen should be prescribed as before

24-hour randomisation: +44-1865-240972

- also for URGENT medical queries or for reporting SERIOUS and UNEXPECTED adverse events

For randomisation in a few days, fax: +44-1865-404849
or post to Atlas Trial Office in FREEPOST envelope

Atlas Trial Office, CTSU, Radcliffe Infirmary, Oxford OX2 6HE, UK.
Tel: +44-1865-404844 Fax: +44-1865-404845 E-mail: atlas@ctsu.ox.ac.uk
For Administrative Enquiries and Trial Supplies, contact the Atlas Trial Office

ATLAS/W/2/798