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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: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol* 2017; published online Dec 11. http://dx.doi.org/10.1016/S1470-2045(17)30777-5.

Contents list of appendix to: Neo-adjuvant versus adjuvant chemotherapy in early breast cancer: patient-level meta-analysis of long-term outcomes among 4756 women in 10 randomised trials

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Webtable 1: Trial eligibility criteria, recruitment period, radiotherapy and surgery details

Trial, entry years	Eligibility	Radiotherapy (RT) sites: breast, chest wall, axilla, SCF, IMC	Type of surgery (RM, MRM, M, Lx=BCS, AD)
BCCA Vancouver (83-90)	Stages I and II, high risk only	Publication of pilot study indicates N+ women with inner or central quadrant tumours received RT, but no details of areas irradiated	Neoadjuvant – 66% had MRM, 31% Lx, 3% unknown Adjuvant – 67% had MRM, 30% Lx, 3% unknown
IB Bordeaux (85-90)	Tumour T2-3, N0-1, M0	Neoadjuvant – B+nodes, IMC & SCF (CR), B (PR), and no RT if SD/PD (had M) Adjuvant – no RT	Neoadjuvant – 37% MRM (SD/PD) , 30% Lx (PR), 33% None (CR) Adjuvant – 100% MRM
Institut Curie S6 (86-90)	Tumour 3-7cm, N0-1, M0	Neoadjuvant – RT (pre-surgery) to B + boost if responded to RT Adjuvant – RT (pre-surgery) to B + boost if responded to RT All women 54 Gy to axilla + 10-15 Gy boost if N1 (if no surgery), 45 Gy to SCF/IMC	Neoadjuvant – 18% MRM±RT, 31% Lx+RT, 51% none Adjuvant – 23% MRM±RT, 32% Lx+RT, 46% none Surgery determined by tumour mass at time of surgery.
NSABP B-18 (88-93)	T1-3, N0-1	Neoadjuvant – RT to B after Lx, none after RM Adjuvant – RT to B after Lx, none after RM	Neoadjuvant – 22% RM, 68% Lx+AD Adjuvant – 40% RM, 60% Lx+AD Lx likely if T ≤ 5cm and N0
St George's London (90-93)	Age 30-69, M0	T<5cm RT to B+boost and RT to axilla & SCF if N+. RT to IMC if medial tumour. T>5cm, no surgery RT to B+optional boost to tumour site; RT to axilla & SCF if N+.	Neoadjuvant – 15% M, 66% Lx+AD1, 19% none Adjuvant – 12% M, 84% Lx+AD1 , 4% none M if T>5cm and no response to RT, Lx+RT if T<5cm, no surgery if T>5cm and response to RT
RMH London (90-95)	Age <70, operable	Neoadjuvant – RT to B +boost and RT to axilla & SCF if N+ after Lx, none after M Adjuvant – RT to B + boost and RT to axilla & SCF if N+ after Lx, none after M	Neoadjuvant – 11% M, 88% Lx, 1% none Adjuvant – 22% M, 77% Lx, 1% none Both arms: surgery appropriate to the size and position of tumour and palpable axillary lymph nodes excised by lower axillary sampling.
NCI Bethesda (90-98)	T2N0-1 , T1N1	Neoadjuvant – RT to B+boost and RT to SCF in N+ after Lx, none after MRM Adjuvant – RT to B+boost and RT to SCF if N+ after Lx, none after MRM	Neoadjuvant – 58% MRM, 42% Lx+AD Adjuvant – 59% MRM, 41% Lx+AD
Austrian BCSG VII (91-99)	T1-3, N0-1, M0	Neoadjuvant – RT (targets unspecified) after Lx, RT discretionary after MRM Adjuvant – RT (targets unspecified) after Lx, RT discretionary after MRM	Neoadjuvant – 34% MRM, 66% Lx+AD Adjuvant – 40% MRM, 60% Lx+AD
EORTC 10902 (91-99)	T1c/2/3/4b, N0-1	Neoadjuvant – RT to B after Lx, RT to CW+IMC if T>5cm, +SCF if N+ after MRM Adjuvant – RT to B after Lx, RT to CW+IMC if T>5cm, +SCF if N+ after MRM RT in all cases if surgery not considered radical	Neoadjuvant – 58% MRM, 34% Lx+AD, 8% none Adjuvant – 75% MRM, 23% Lx+AD , 2% none Surgery determined by tumour mass at time of surgery.
ECTO Italy (96-02)	Operable breast cancer size >2cm	Neoadjuvant – RT to B+boost, RT after M if T4 disease Adjuvant – RT to B+boost, RT after M if T4 disease. Institutional variation accepted	Neoadjuvant – 33% MRM, 65% Lx+AD3, 2% none Adjuvant – 66% MRM, 34% Lx+AD3, 0% none Surgery determined by tumour mass at time of surgery.

ADn=axillary dissection (if given, n=level), B=breast CW=chest wall, CR=complete response, IMC=internal mammary chain, Lx=lumpectomy, M=mastectomy (details unspecified), MRM=modified radical mastectomy, PR=partial response, RM=radical mastectomy, RT=radiotherapy, SCF=supraclavicular fossa, SD/PD=stable/progressive disease.

Webtable 2: Trial systemic treatments and sequencing with surgery, by allocated treatment (N=Neo-adjuvant, A = Adjuvant only)

Trial	Arm	Treatment details
BCCA Vancouver	N	(Cyclophosphamide [600 mg/m^2 iv] + Methotrexate [40 mg/m^2 iv] + 5-Fluorouracil [600 mg/m^2 iv]) × 1 pre-op + (Cyclophosphamide [600 mg/m^2 iv] + Methotrexate [40 mg/m^2 iv] + 5-Fluorouracil [600 mg/m^2 iv]) q3wk × 8 postop
	A	(Cyclophosphamide [600 mg/m^2 iv] + Methotrexate [40 mg/m^2 iv] + 5-Fluorouracil [600 mg/m^2 iv]) q3wk × 9 postop
IB Bordeaux	N	(Epirubicin [50 mg/m^2] + Vincristine [1 mg/m^2] + Methotrexate [20 mg/m^2]) q3wk × 3 pre-op + (Mitomycin-C [10 mg/m^2] + Triethylenephosphoramide [20 mg/m2] + Vindesine [4 mg/m^2]) q3wk × 3 pre-op, then Radiotherapy (in absence of residual tumour) or Radiotherapy + (Tumorectomy for < 2cm residual tumour or Patey Mastectomy for > 2cm residual tumour)
	A	(Epirubicin [50 mg/m^2] + Vincristine [1 mg/m^2] + Methotrexate [20 mg/m^2]) q3wk × 3 (if N+ or ER-poor or PR-poor) post-op + (Mitomycin-C [10 mg/m^2] + Triethylenephosphoramide [20 mg/m^2] + Vindesine [4 mg/m^2]) q3wk × 3 for) postop
Institut Curie S6	N	(Cyclophosphamide [500 mg/m^2] + Doxorubicin [25 mg/m^2] + 5-Fluorouracil [500 mg/m^2]+ P) q4wk × 4 pre-op
	A	(Cyclophosphamide [500 mg/m^2] + Doxorubicin [25 mg/m^2] + 5-Fluorouracil [500 mg/m^2]+ P) q4wk × 4 postop
NSABP B-18	N	(Doxorubicin [60mg/m^2] + Cyclophosphamide [600mg/m^2]) q21d × 4 pre-op
	A	(Doxorubicin [60mg/m^2] + Cyclophosphamide [600mg/m^2]) q21d × 4 postop
NSABP B-18	N	(Doxorubicin [60mg/m^2] + Cyclophosphamide [600mg/m^2]) q21d × 4 pre-op + Tamoxifen [20mg/d] to year 5
	A	(Doxorubicin [60mg/m^2] + Cyclophosphamide [600mg/m^2]) q21d × 4 postop + Tamoxifen [20mg/d] to year 5
St George's London	N	(Mitoxantrone [7mg/m^2] + Methotrexate [30 mg/m^2]) q3wk × 4 + Mitomycin-C [7mg/m^2] q6wk × 2 + Folinic Acid [15mg × 4 in 24h, 24h after chemo] pre-op + (Mitoxantrone [7mg/m^2] + Methotrexate [30 mg/m^2]) q3wk × 4 + Mitomycin-C [7mg/m^2] q6wk × 2 + Folinic Acid [15mg × 4 in 24h, 24h after chemo] postop if the patient responded to pre-op MMM otherwise (5-Fluorouracil [600mg/m^2] + Epirubicin [50mg/m^2] + Cyclophosphamide [600mg/m^2]) q3wk × 8 postop
	A	(Mitoxantrone [7mg/m^2] + Methotrexate [30 mg/m^2]) q3wk × 8 + Mitomycin-C [7mg/m^2] q6wk × 4 + Folinic Acid [15mg × 4 in 24h, 24h after chemo] postop
RMH London	N	(Mitoxantrone [7mg/m^2] + Methotrexate [35 mg/m^2]) q3wk × 4 + Mitomycin-C [7mg/m^2] q6wk × 2 + Tamoxifen [20 mg/d] pre-op + (Mitoxantrone [7mg/m^2] + Methotrexate [35 mg/m^2]) q3wk × 4 + Mitomycin-C [7mg/m^2] q6wk × 2 postop + Tamoxifen [20 mg/d] to year 5
	A	(Mitoxantrone [7mg/m^2] + Methotrexate [35 mg/m^2]) q3wk × 8 + Mitomycin-C [7mg/m^2] q6wk × 4 postop + Tamoxifen [20 mg/d] to year 5
NCI Bethesda	N	(5-Fluorouracil [400 mg/m^2 iv] d1,2,3 + Folinic Acid [500 mg/m^2 iv d1,2,3 1 hour before 5-FU] + Doxorubicin [15 mg/m^2 iv] d1,2,3 + Cyclophosphamide [600 mg/m2 iv] d1 + Mesna [200mg/m^2 iv] + {GM-CSF [10 µg/kg sc daily d4-16] or G-CSF [5 µg/kg sc daily d4-18]}) q3wk × 5 pre-op
	A	(5-Fluorouracil [400 mg/m^2 iv] d1,2,3 + Folinic Acid [500 mg/m^2 iv d1,2,3 1 hour before 5-FU] + Doxorubicin [15 mg/m^2 iv] d1,2,3 + Cyclophosphamide [600 mg/m^2 iv] d1 + Mesna [200mg/m^2 iv] + {GM-CSF [10 µg/kg sc daily d4-16] or G-CSF [5 µg/kg sc daily d4-18]}) q3wk × 5 postop

Continued

Webtable 2 cont'd: Trial systemic treatments and sequencing with surgery, by allocated treatment (N=neo-adjuvant, A = Adjuvant only)

Trial	Arm	Treatment details
Austrian BCSG VII	N	(Cyclophosphamide [600mg/m² d1,8] + Methotrexate [40mg/m² d1,8] + 5-Fluorouracil [600mg/m² d1,8]) × 3 pre-op + (Cyclophosphamide [600mg/m² d1,8] + Methotrexate [40mg/m² d1,8] + 5-Fluorouracil [600mg/m² d1,8]) × 3 postop
	A	(Cyclophosphamide [600mg/m² d1,8] + Methotrexate [40mg/m² d1,8] + 5-Fluorouracil [600mg/m² d1,8]) × 6 postop
Austrian BCSG VII	N	(Cyclophosphamide [600mg/m² d1,8] + Methotrexate [40mg/m² d1,8] + 5-Fluorouracil [600mg/m² d1,8]) × 3 pre-op+ (Epirubicin [70mg/m² d1] + Cyclophosphamide [600mg/m² d1]) × 3 postop
	A	(Cyclophosphamide [600mg/m² d1,8] + Methotrexate [40mg/m² d1,8] + 5-Fluorouracil [600mg/m² d1,8]) × 3 postop + (Epirubicin [70mg/m² d1] + Cyclophosphamide [600mg/m² d1]) × 3 postop
EORTC 10902	N	5-Fluorouracil [600 mg/m^2 iv] + Epirubicin [60 mg/m^2 iv] + Cyclophosphamide [600 mg/m^2 iv]) q3wk × 4 pre-op
	A	5-Fluorouracil [600 mg/m^2 iv] + Epirubicin [60 mg/m^2 iv] + Cyclophosphamide [600 mg/m^2 iv]) q3wk × 4 postop
ECTO Italy	N	(Epirubicin [60mg/m² iv] then Paclitaxel [200mg/m² iv over 3h]) q3wk × 4 then (Cyclophosphamide [600mg/m² iv d1,8] + Methotrexate [40mg/m² iv d1,8] + 5-Fluorouracil [600mg/m² iv d1,8]) q4wk × 4 pre-op then Tam [20mg/d] to year 5
	A	(Epirubicin [60mg/m² iv] then Paclitaxel [200mg/m² iv over 3h]) q3wk × 4 then (Cyclophosphamide [600mg/m² iv d1,8] + Methotrexate [40mg/m² iv d1,8] + 5-Fluorouracil [600mg/m² iv d1,8]) q4wk × 4 postop then Tam [20mg/d] to year 5

Webtable 3: Definitions of tumour response and tumour response assessment within trial

Trial	Tumour response definition and method of assessment
BCCA Vancouver	Not measured, as only 1 cycle of preoperative chemotherapy was given
IB Bordeaux	cCR = complete disappearance of all evidence of tumour, PR = residual tumour size ≤2cm, SD/PD = residual tumour >2cm Method: clinical examination and mammography. Pathological response not assessed.
Institut Curie S6	cCR = complete disappearance of all evidence of tumour, PR (major) = ≥50% reduction in initial tumour size, PR (minor) = 25-50% reduction, SD/PD undefined Method: Clinical examination and mammography (size = greater of the two largest dimensions)
NSABP B-18	cCR = complete disappearance of all evidence of tumour, PR = ≥50% reduction in initial tumour size, SD = not CR/PR/PD , PD = ≥50% increase in tumour size if cCR then, pCR=no histologic evidence of invasive tumour cells (non-invasive cells allowed), pINV=histologic evidence of invasive cells Method: Clinical size quantified by the product of the two greatest tumour dimensions. Patients with complete clinical response, by physical examination, had their surgical specimens evaluated for pathologic tumour status.
St George's London	Employ UICC criteria (use callipers and mammogram). cCR = disappearance of all known disease, cPR = ≥50% reduction in initial tumour size, NC = <50% reduction or <25% increase in size of lesion , PD = some lesions regress whilst others progress or new lesions appear. Method: Tumour size measured with callipers by bi-dimensional measurements, multiplied to give area. Preliminary mammogram and a second 12 weeks before definitive surgery and radiotherapy.
RMH London	cCR = no palpable abnormality, cPR = ≥50% reduction in initial tumour size, NC = <50% reduction, PD = ≥25% increase in size MRD = residual nodularity, classed within the PR category Method: Palpation and tri-dimensional measurements of tumour size and blood flow using colour Doppler signals using an Acuson XP10 scanner. Mammography and ultrasound before surgery.
NCI Bethesda	Criteria from "The Breast Cancer Task Force Treatment Committee NCI. Publication 78-1192. DHEW, 1978. cCR = complete disappearance of all evidence of tumour, cPR = ≥50% reduction in initial tumour size , PD = ≥25% increase or new lesion, SD = not CR/PR/PD Method: Palpation and mammography.
Austrian BCSG VII	pCR = complete disappearance of invasive cancer in final histological specimen of the primary tumour PR = ≥50% reduction in initial tumour size, SD = <50% reduction, PD = any increase in tumour size Method: Evaluated clinically, radiologically and histologically.
EORTC 10902	pCR = no signs of malignant cells at primary site or in lymph nodes, cCR = complete disappearance via palpation as well as mammography, PR = ≥50% reduction in initial tumour size, PD = ≥25% increase in tumour size, or cN0 but developed palpable nodes Method: Palpation and mammography. Product of the two greatest perpendicular diameters used to compare change in tumour size.
ECTO Italy	pCR = no residual invasive cancer in breast, irrespective of nodal status, cCR = no clinical evidence of disease (mammogram or ultrasound) or no new lesions, cPR = ≥50% reduction in initial tumour size, cPR minor = ≥25% but <50% reduction, PD = ≥50% increase in tumour size or new lesion Method: Physical examination. Mammography or ultrasound after chemotherapy completion. Surgical specimens evaluated for pathologic response.

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, NC = no change, PD = progressive disease, c = clinical, p = pathological

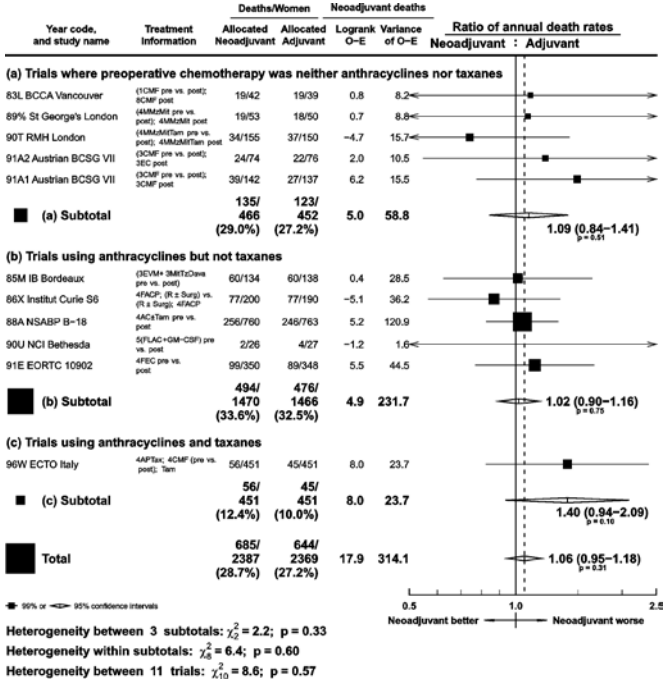
Webtable 4: Participant characteristics, by trial

Characteristic	Category	BCCA Vancouver	IB Bordeaux	Institut Curie S6	NSABP B-18	St George's London	RMH London	NCI Bethesda	Austrian BCSG VII	EORTC 10902	ECTO Italy	Total
Age at entry (years)	<45	66	60	176	505	19	48	25	121	242	252	1514
	45-54	15	81	191	489	40	100	14	162	249	338	1679
	55+	0	131	23	529	44	157	14	146	207	312	1563
Clinical nodal status	Negative	47	0	161	1115	0	247	0	262	333	498	2663
	Positive	19	0	226	408	0	58	0	150	355	381	1597
	Unknown	15	272	3	0	103	0	53	17	10	23	496
Tumour size	1-19 mm	22	5	10	415	33	79	0	103	96	26	789
	20-49 mm	31	243	276	908	52	210	0	272	404	739	3135
	50+ mm	3	24	103	200	18	13	0	39	150	122	672
	Other/unknown	25	0	1	0	0	3	53	15	48	15	160
Biopsy grade	Well	0	39	0	0	0	0	0	0	0	88	127
	Moderate	6	145	0	0	0	0	0	0	0	482	633
	Poor	18	72	0	0	0	0	0	0	0	304	394
	Unknown	57	16	390	1523	103	305	53	429	698	28	3602
Biopsy ER status	ER-poor	34	161	152	0	103	0	0	364	122	340	1276
	ER-positive	40	111	192	0	0	0	0	42	313	548	1246
	Unknown	7	0	46	1523	0	305	53	23	263	14	2234
Biopsy PR status	PR-poor	7	161	156	0	0	0	0	332	0	383	1039
	PR-positive	14	110	187	0	0	0	0	66	0	501	878
	Unknown	60	1	47	1523	103	305	53	31	698	18	2839
Treatment allocation and clinical response	Neoadjuvant - Complete	0	30	0	240	17	27	0	25	23	184	546
	- Partial	0	32	0	304	14	93	0	104	148	108	803
	- Stable/progressive	0	64	0	140	21	23	0	49	144	157	598
	- Unknown	42	8	200	76	1	12	26	38	35	2	440
	Adjuvant only	39	138	190	763	50	150	27	213	348	451	2369
Planned local therapy	Radiotherapy only	0	0	390	0	0	0	0	0	0	0	390
	Lumpectomy	22	0	0	996	85	79	0	103	152	26	1463
	Mastectomy	3	272	0	527	18	13	0	39	536	122	1530
	Unknown	56	0	0	0	0	213	53	287	10	754	1373
Total	**All women**	**81**	**272**	**390**	**1523**	**103**	**305**	**53**	**429**	**698**	**902**	**4756**

ER = Oestrogen receptor, PR = Progesterone receptor

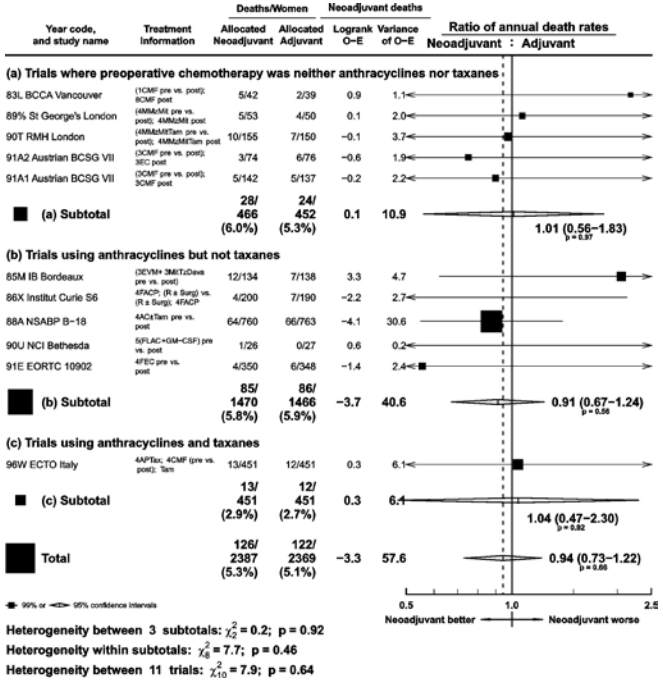
Webfigure 1: Rate ratios for effect of neo-adjuvant versus adjuvant chemotherapy on mortality by trial

Breast cancer mortality



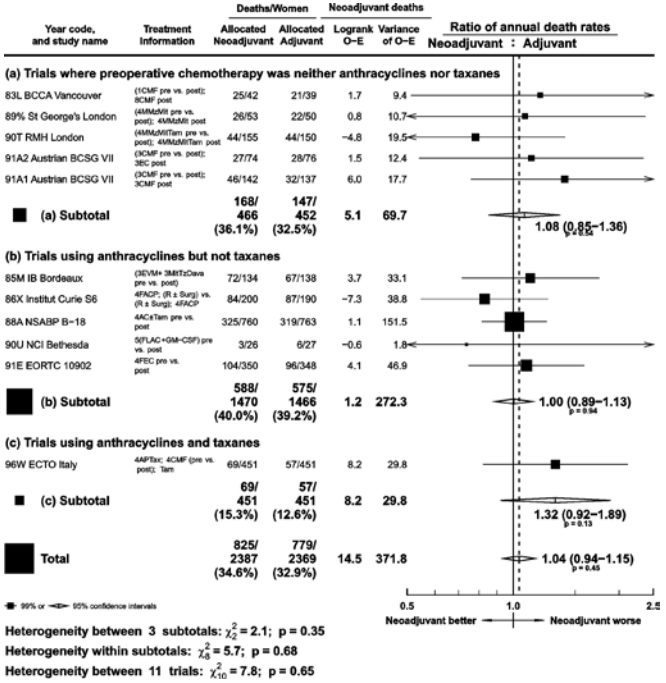
Heterogeneity between 3 subtotals: $\chi^2_2 = 2.2$; p = 0.33
Heterogeneity within subtotals: $\chi^2_8 = 6.4$; p = 0.60
Heterogeneity between 11 trials: $\chi^2_{10} = 8.6$; p = 0.57

Mortality without recurrence



Heterogeneity between 3 subtotals: $\chi^2_2 = 0.2$; p = 0.92
Heterogeneity within subtotals: $\chi^2_8 = 7.7$; p = 0.46
Heterogeneity between 11 trials: $\chi^2_{10} = 7.9$; p = 0.64

Any death



Heterogeneity between 3 subtotals: $\chi^2_2 = 2.1$; p = 0.35
Heterogeneity within subtotals: $\chi^2_8 = 5.7$; p = 0.68
Heterogeneity between 11 trials: $\chi^2_{10} = 7.8$; p = 0.65

Webtable 5: Breast tumour clinical response in women randomised to neo-adjuvant chemotherapy

Breast tumour clinical response*	Number of women	Percentage	
		All women (n=2387)	Women only with known response (n=1947)
Complete (CR)	546	23	28
Partial (PR)	803	34	41
Stable/progressive disease (SD/PD)	598	25	31
Unknown	440	18	-
Total	**2387**	**100**	**100**

*CR = no clinical evidence of disease, PR = ≥50% reduction in initial tumour size, SD/PD = <50% reduction, or increase in size.

Information on individual responses was not available from the Institut Curie S6 and NCI Bethesda trials, but publications from those two trials have reported the numbers of women with CR/PR/SD or PD/Unk to be 46/80/27/47 and 11/2/4/9 respectively.

BCCA Vancouver gave only one cycle of neo-adjuvant chemotherapy, and did not record the clinical response to it.

Webtable 6: Planned surgery versus surgery actually undertaken, by trial and allocated treatment

Trial	Surgery undertaken	Planned surgery									
		Neo-adjuvant					Adjuvant				
		RT only	Lx	Mx	Unk	Total	RT only	Lx	Mx	Unk	Total
BCCA Vancouver	No surgery				1	**1**		1			**1**
	Lumpectomy		6		7	**13**		3		9	**12**
	Mastectomy		7		21	**28**		5	3	18	**26**
IB Bordeaux	No surgery			30		**30**					
	Lumpectomy			32		**32**					
	Mastectomy			64		**64**			138		**138**
	Unknown			8		**8**					
Institut Curie S6	Lumpectomy*	167				**167**	144				**144**
	Mastectomy	33				**33**	46				**46**
NSABP B-18	No surgery		6	2		**8**		1	4		**5**
	Lumpectomy		440	70		**510**		419	35		**454**
	Mastectomy		50	192		**242**		80	223		**303**
	Unknown								1		**1**
St George's London	No surgery		7	3		**10**		1	1		**2**
	Lumpectomy		31	4		**35**		41	1		**42**
	Mastectomy		5	3		**8**			6		**6**
RMH London	Lumpectomy		34	5	98	**137**		40	4	72	**116**
	Mastectomy		2	1	13	**16**		3	3	26	**32**
	Unknown				2	**2**				2	**2**
NCI Bethesda	Unknown				26	**26**				27	**27**
Austrian BCSG VII	Lumpectomy		36	4	93	**133**		39	2	78	**119**
	Mastectomy		10	14	41	**65**		14	15	54	**83**
	Unknown		2	3	13	**18**		2	1	8	**11**
EORTC 10902	No surgery			20	3	**23**		1	9	6	**16**
	Lumpectomy		63	57	1	**121**		64	13		**77**
	Mastectomy		15	191		**206**		9	246		**255**
ECTO Italy	Lumpectomy		11	25	248	**284**		13	4	130	**147**
	Mastectomy		1	37	116	**154**		1	50	243	**294**
	Unknown			3	10	**13**			3	7	**10**
All trials	No Surgery		13	55	4	**72**		4	14	6	**24**
	Lumpectomy	167	621	197	447	**1432**	144	619	59	289	**1111**
	Mastectomy	33	90	502	191	**816**	46	112	684	341	**1183**
	Unknown		2	14	51	**67**		2	5	44	**51**
	Total	**200**	**726**	**768**	**693**	**2387**	**190**	**737**	**762**	**680**	**2369**

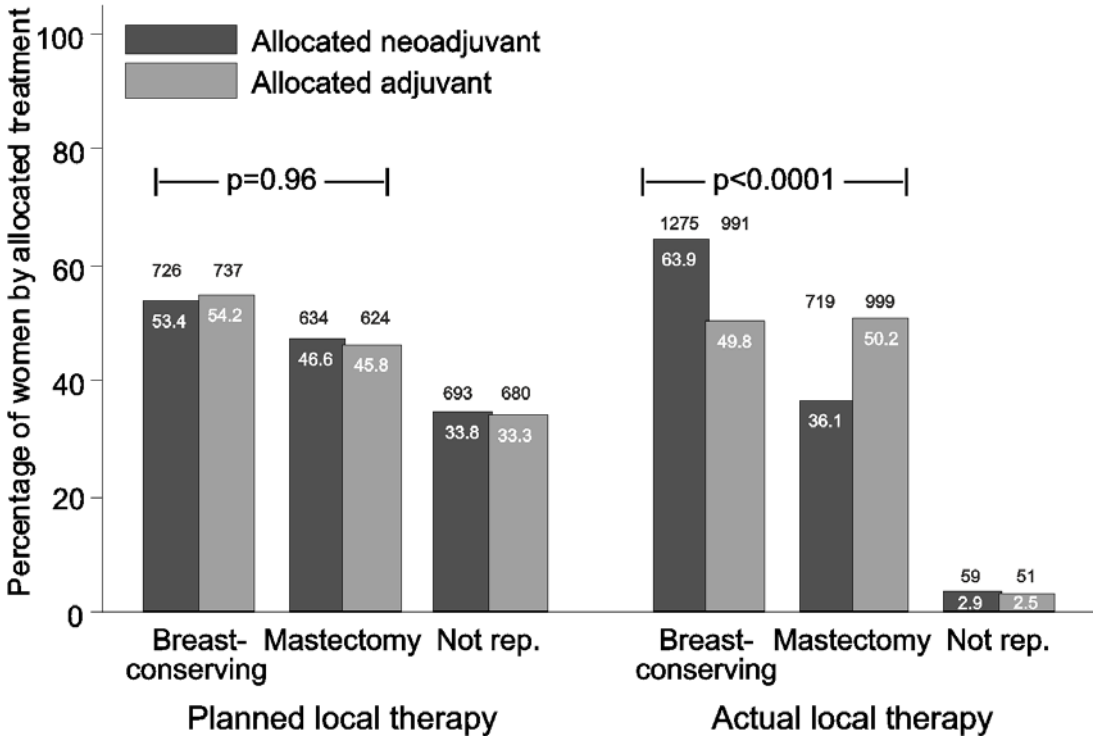
Lx = Lumpectomy, Mx = Mastectomy, RT = Radiotherapy

In the adjuvant arms, 80% with clinical tumour size <2 cm had lumpectomy and 80% with tumour size ≥5 cm had mastectomy. Hence, if the planned surgery was unknown, it was taken as lumpectomy if size was <2 cm and mastectomy if size was ≥5 cm. This convention was used to re-categorise 408 women. (Clinical nodal status was not a good predictor of planned surgery.)

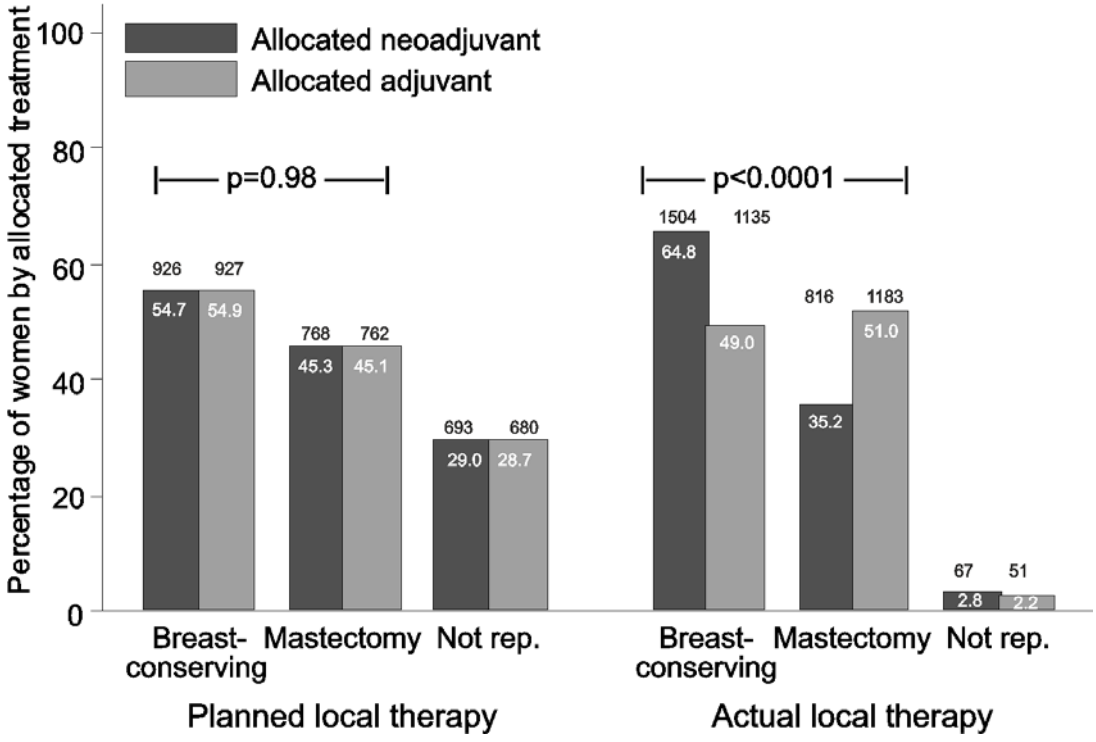
*In the Institut Curie S6 trial, lumpectomy includes "No surgery", and information on each individual was not available. Publications from this trial have reported RT only 102 neo-adjuvant vs 87 adjuvant and BCS+RT 62 neo-adjuvant vs 60 adjuvant.

Webfigure 2: Planned surgery versus surgery actually undertaken, by allocated treatment group

A) Excluding trials IB Bordeaux and Institut Curie S6



B) Including all trials



Percentages for breast-conserving and mastectomy exclude unknowns. Percentages for unknowns show the fraction of the total number of patients, in the respective allocated treatment groups, with missing local therapy information.

Webtable 7: Local recurrence in women randomised to neo-adjuvant chemotherapy by their sequence of planned and actual local therapy.

For women randomised to neo-adjuvant chemotherapy, the table shows the *crude* 10-year cumulative risk of local recurrence according to their combination of planned surgery (ie decision before any chemotherapy) and the surgery they actually received (after chemotherapy). It also shows the hazard ratios for local recurrence for these women by surgery sequence, unadjusted and adjusted for clinical tumour size and stratified by trial.

Planned/ Actual Surgery e	Unadjusted local recurrence risk % at year 10 (95% CI)	Unadjusted hazard ratio (HR)*		Adjusted hazard ratio (HR)*	
		HR	95% CI	HR	95% CI
Mx/BCT (n=252)	23.4 (17.8, 30.2)	1.00	(0.76, 1.32)	1.00	(0.73, 1.36)
Mx/Mx (n=502)	19.8 (15.7, 24.8)	0.88	(0.70, 1.11)	0.97	(0.75, 1.25)
BCT/BCT (n=801)	21.2 (18.2, 24.6)	0.96	(0.83, 1.12)	0.84	(0.65, 1.10)
BCT/Mx (n=123)	13.7 (8.2, 22.4)	0.52	(0.31, 0.88)	0.39	(0.22, 0.68)
P for heterogeneity		0.09		0.01	

BCT = breast-conserving therapy (ie radiotherapy alone or lumpectomy with or without radiotherapy), Mx = Mastectomy.

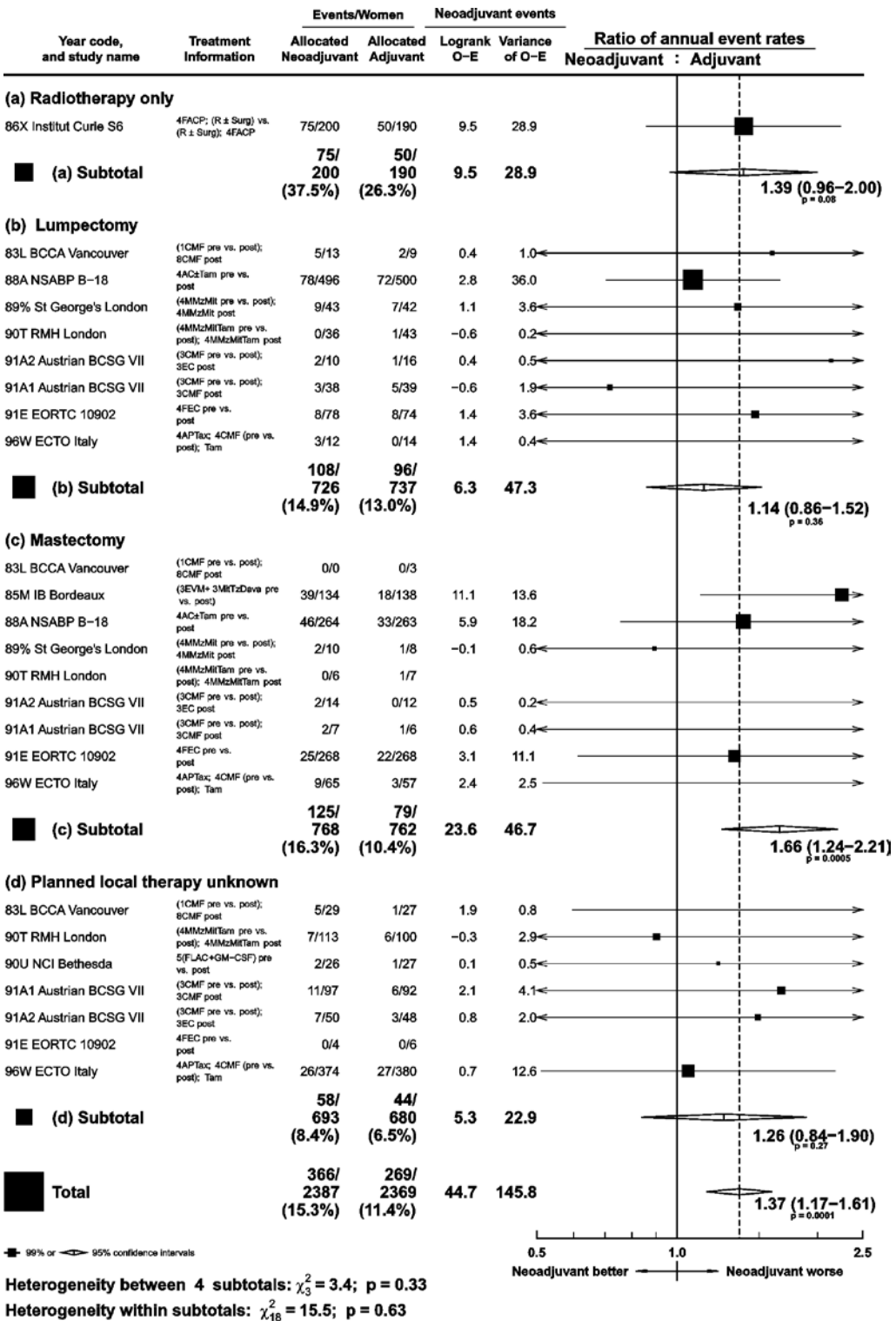
Planned surgery is labelled first and actual surgery last ie, planned/actual. Planned surgery may differ from actual surgery if the response of the breast tumour to neo-adjuvant chemotherapy leads to de-escalation of the planned extent of local therapy.

* HR = hazard ratio for the planned/actual surgery group relative to the Mx/BCT group, derived from a Cox regression either unadjusted, or adjusted for clinical tumour size and stratified by trial. Confidence intervals are group specific (Plummer 2004).

Reference

Plummer M**.** Improved estimates of floating absolute risk. *Stat Med* 2004; **23**(1): 93-104.

Webfigure 3: Rate ratios for effect of neo-adjuvant versus adjuvant chemotherapy on local recurrence by extent of planned local therapy and trial

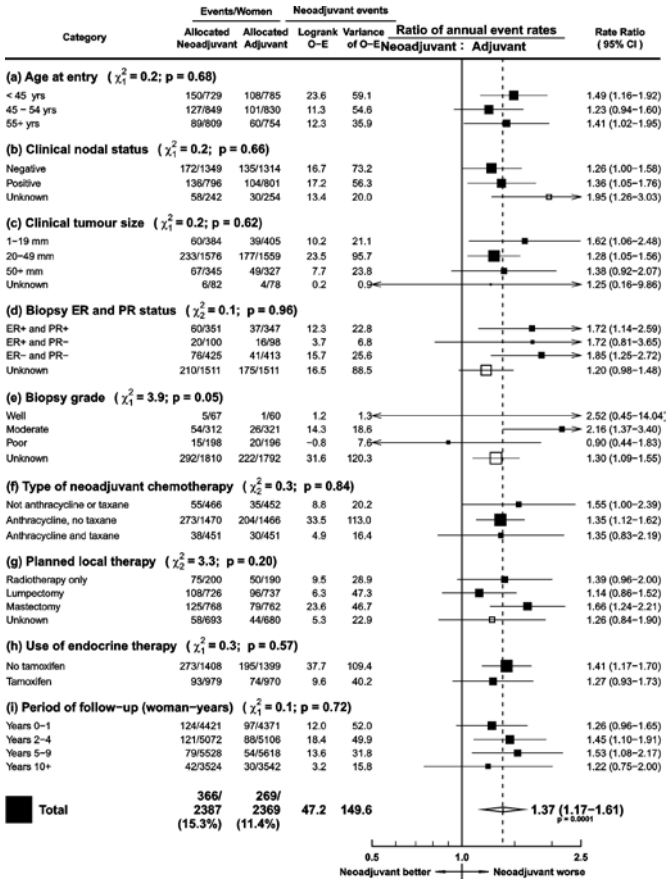


Abbreviations CMF, cyclophosphamide, methotrexate, 5-fluorouracil; MMzMit, methotrexate, mitoxantrone, mitomycin-C; EVM/MitTzDAVA, epirubicin, vincristine, methotrexate/Mitomycin-C, triethylenephosphoramide, vindesine; FAC, fluorouracil, doxorubicin, cyclophosphamide; AC, doxorubicin, cyclophosphamide; Tam, tamoxifen; FLAC, fluorouracil, leucovorin, doxorubicin, cyclophosphamide; GM-CSF, granulocyte-macrophage colony-stimulating factor; FEC, fluorouracil, epirubicin, cyclophosphamide; APTax, doxorubicin, paclitaxel.

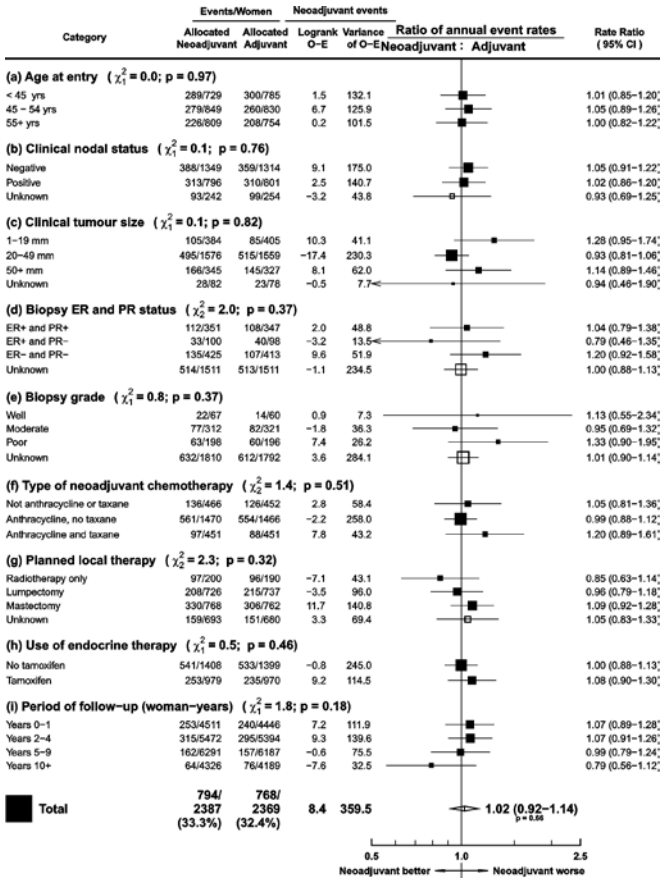
See Webtable 2 for a full description of each chemotherapy regimen.

Webfigure 4: Rate ratios for effect of neo-adjuvant versus adjuvant chemotherapy on recurrence and breast cancer mortality by various factors

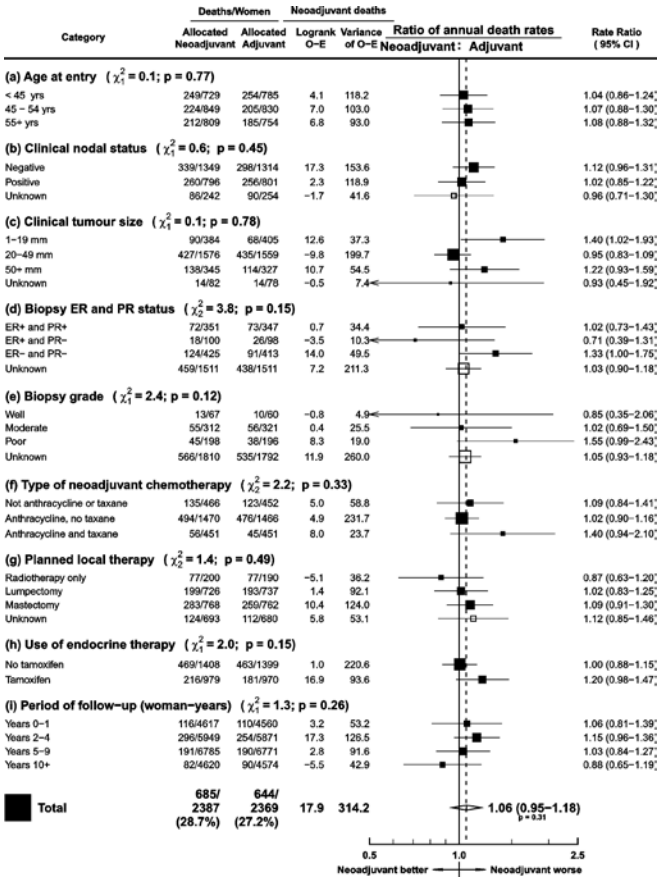
Local recurrence



Distant recurrence*



Breast cancer mortality

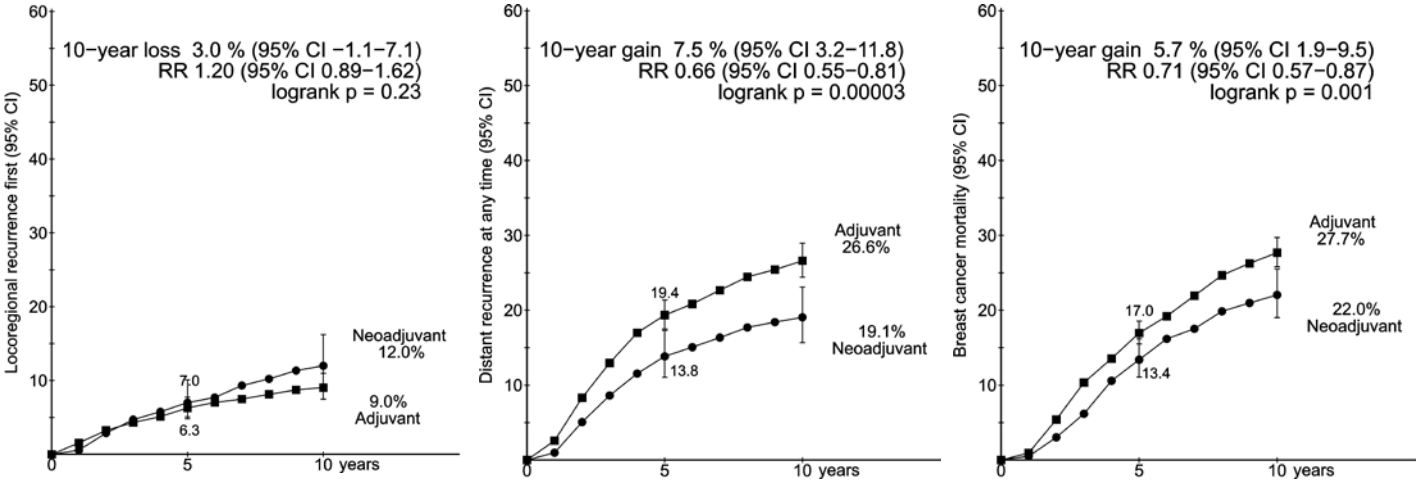


* NSABP B-18, NCI Bethesda, and Austrian BCSG VII recorded only the first event, so distant recurrence means either distant recurrence as first event or death from breast cancer.

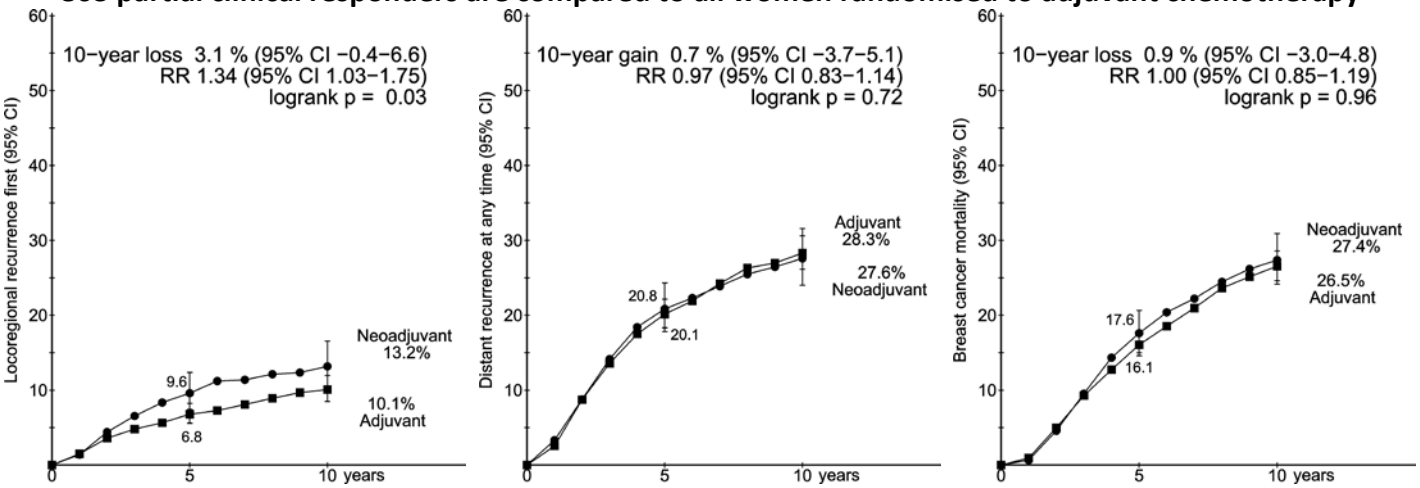
Webfigure 5: Comparison of women who had either a complete, partial or no clinical response to neo-adjuvant chemotherapy to all women randomised to adjuvant chemotherapy for recurrence and mortality (largely reflects patient selection rather than treatment effect)

Local recurrence **Distant recurrence*** **Breast cancer mortality**

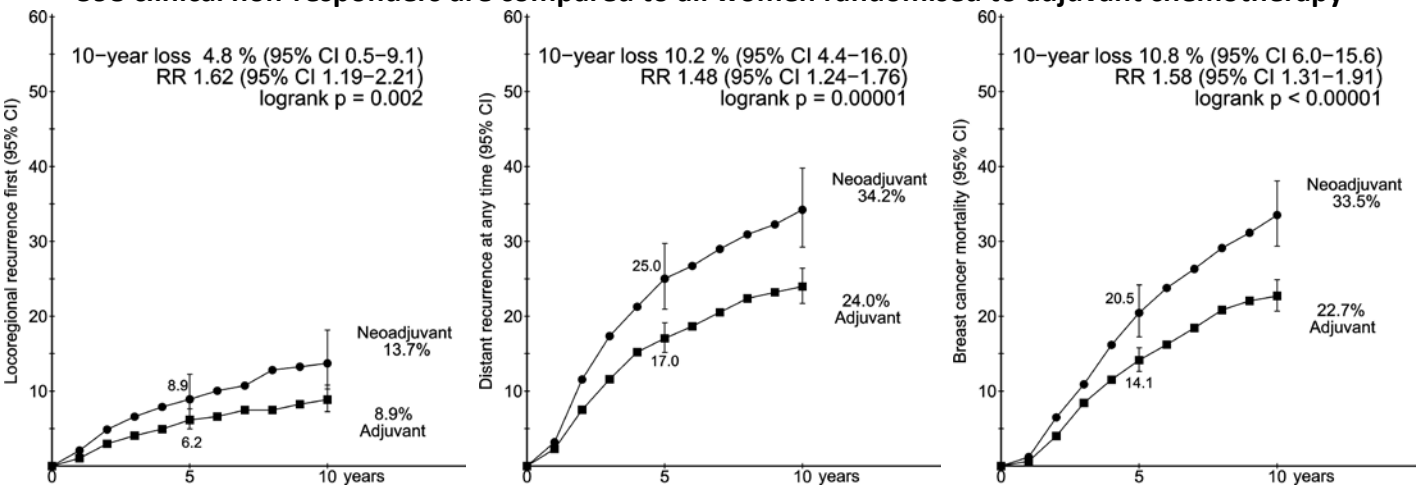
546 complete clinical responders are compared to all women randomised to adjuvant chemotherapy



803 partial clinical responders are compared to all women randomised to adjuvant chemotherapy

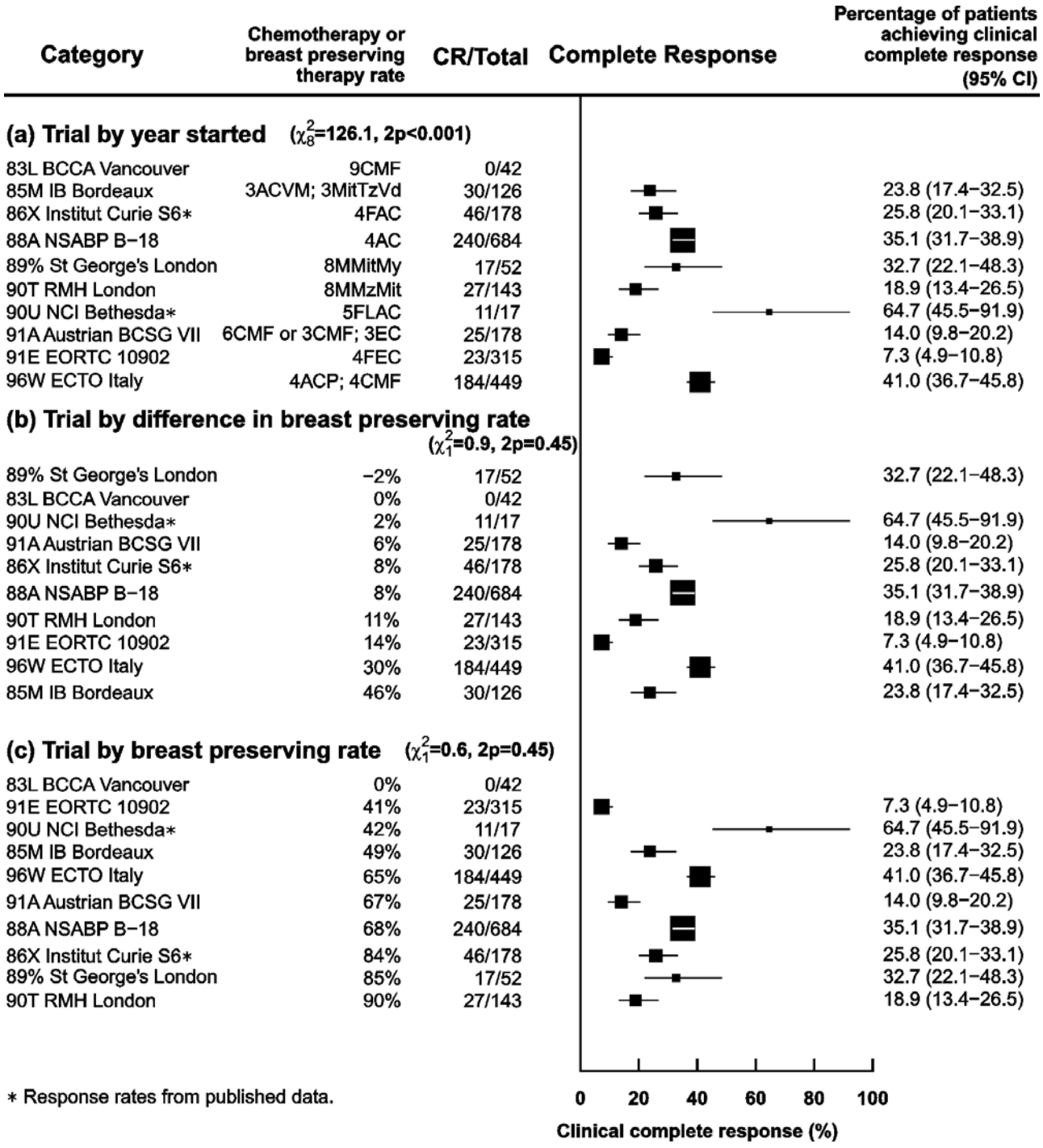


598 clinical non-responders are compared to all women randomised to adjuvant chemotherapy



Analyses stratified by trial, follow-up year, age at entry, pre-randomisation clinical nodal status and tumour size. BCCA Vancouver, Institut Curie S6 and NCI Bethesda trials are excluded because individual breast responses were not available. Complete response: no clinical evidence of disease, partial response: ≥50% reduction in initial tumour size, non-response: <50% reduction or increase. *NSABP B-18 and Austrian BCSG VII recorded only first events, so distant recurrence means as first event, or breast cancer death.

Webfigure 6: Percentage complete clinical response (CR) by trial and breast-conserving therapy rate

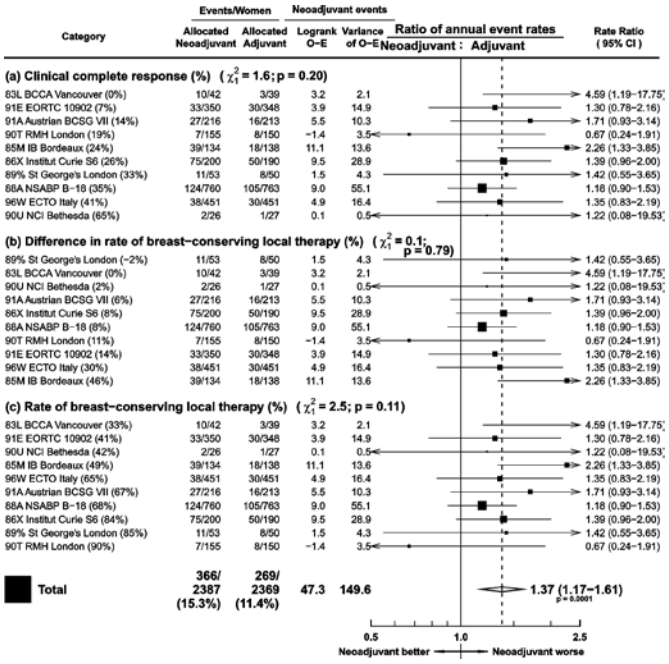


As BCCA Vancouver gave only course of CMF pre-operatively, it is assumed here that CR=0.

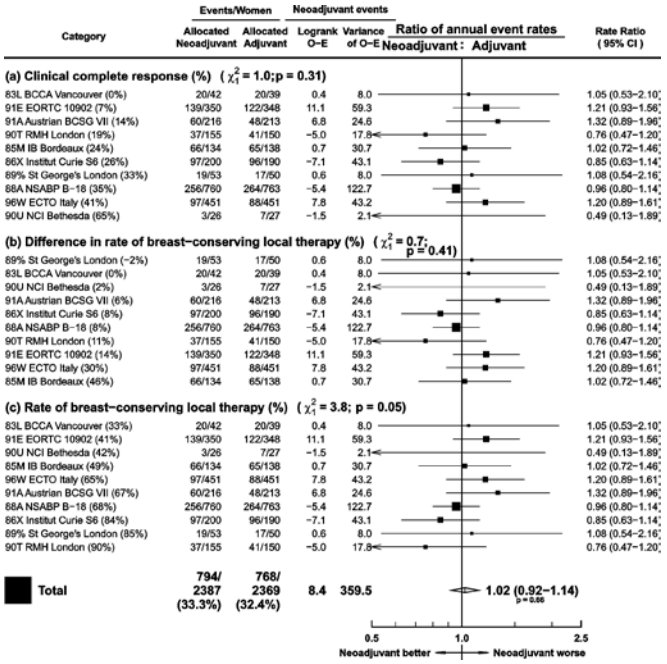
Category (b): Difference is between the breast-conserving rate in the adjuvant-only and the neo-adjuvant arms.

Webfigure 7: Rate ratios for effect of neo-adjuvant versus adjuvant chemotherapy on recurrence and breast cancer mortality by trial and by percentage of women with breast tumour complete clinical response and breast-conserving rate

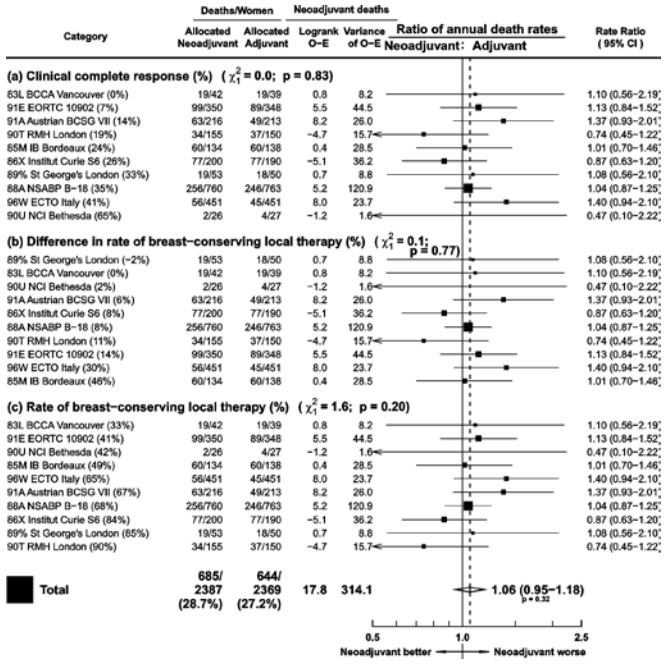
Local recurrence



Distant recurrence*



Breast cancer mortality



As BCCA Vancouver gave only course of CMF pre-operatively, it is assumed here that CR=0.

Tumour response and breast-conserving rates not available as individual data for all trials and therefore are taken from trial publications (Institut Curie S6 and NCI Bethesda).

*NSABP B-18 and Austrian BCSG VII recorded only first events, so distant recurrence means either distant recurrence as first event, or breast cancer death.

Webtable 8: Eligible randomised trials identified but not available for analysis; total ~500 patients

Trial	**Institut Curie S5 - France (1983-1986)**
Description	196 patients entered; trial terminated early, with much incomplete or omitted treatment.
Arms	(Doxorubicin [25mg/m^2 d1,8]+Cyclophosphamide [400mg/m^2 d1,8]+5-Fluorouracil [500mg/m^2 d1,3,5,8]) q4w ×2 pre-op (Doxorubicin [25mg/m^2 d1,8]+Cyclophosphamide [400mg/m^2 d1,8]+5-Fluorouracil [500mg/m^2 d1,3,5,8]) q4w ×4 postop vs (Doxorubicin [25mg/m^2 d1,8]+Cyclophosphamide [400mg/m^2 d1,8]+5-Fluorouracil [500mg/m^2 d1,3,5,8]) q4w ×6 postop
Reference	*Scholl SM, Asselain B, Palangie T et al. Neoadjuvant chemotherapy in operable breast cancer. Eur J Ca 1991; **27:** 1668-71.*
Trial	**All-India Institute of Medical Sciences, New Delhi - India (1997-2001)**
Description	101 patients entered; all received radiotherapy
Arms	(Cyclophosphamide [500mg/m² d1,15]+Epirubicin [50mg/m² d1,15]+5-Fluorouracil [500mg/m² d1,15])q4wk ×3 pre-op (Cyclophosphamide [500mg/m² d1,15]+Epirubicin [50mg/m² d1,15]+5-Fluorouracil [500mg/m² d1,15])q4wk ×3 postop vs (Cyclophosphamide [500mg/m² d1,15]+Epirubicin [50mg/m² d1,15]+5-Fluorouracil [500mg/m² d1,15])q4wk ×6 postop
Reference	*Deo SVS, Bhutani, M, Shukla, NK, Raina V, Rath GK, Purkayasth J. Randomized trial comparing neo-adjuvant versus adjuvant chemotherapy in operable locally advanced breast cancer (T4b N0-2 M0). J Surg Oncol 2003; **84**(4): 192-97.*
Trial	**Shanghai - China (pre-1990)**
Description	57 patients included; all received excisional biopsy followed by either radiotherapy or mastectomy.
Arms	(Cyclophosphamide [600mg/m² d1,8]+Methotrexate [30mg/m² d1,8]+5-Fluorouracil [500mg/m² d1,8]) ×2 pre-op (Cyclophosphamide [600mg/m² d1,8]+Methotrexate [30mg/m² d1,8]+5-Fluorouracil [500mg/m² d1,8]) ×2 postop vs Placebo [d1,8] × 2 pre-op (Cyclophosphamide [600mg/m² d1,8]+Methotrexate [30mg/m² d1,8]+5-Fluorouracil [500mg/m² d1,8]) ×6 postop
Reference	*Shao ZM, Li J, Wu J, et al. Neo-adjuvant chemotherapy for operable breast cancer induces apoptosis. Breast Ca Res Treat 1999; **53**(3): 263-69.*
Trial	**Huguenin Chemotherapy - France (1989)**
Description	<40 patients included; trial abandoned early
Arms	(5-Fluorouracil [500mg/m^2]+Doxorubicin [50mg/m^2]+Cyclophosphamide [500mg/m^2]) ×4 pre-op (5-Fluorouracil [500mg/m^2]+Doxorubicin [50mg/m^2]+Cyclophosphamide [500mg/m^2]) ×2 postop vs (5-Fluorouracil [500mg/m^2]+Doxorubicin [50mg/m^2]+Cyclophosphamide [500mg/m^2]) ×6 postop
Reference	*Tubiana-Hulin M, Kerbrat P. Trial protocol: Chemiothérapie première des cancers du sein opérables. Unpublished, 1989.*
Trial	**Tokyo - Japan (1995-1997)**
Description	50 patients included; all had mastectomy, but some were excluded after randomization.
Arms	(Epirubicin [50mg/m^2]+Cyclophosphamide [200mg/m^2])q3wk ×5 pre-op vs (Epirubicin [50mg/m^2]+Cyclophosphamide [200mg/m^2])q3wk ×5 postop
Reference	*Enomoto K, Ikeda T, Matsui A, et al. Neoadjuvant therapy in stage II with T>=4CM and stage III breast cancer. 6th International Conference on adjuvant therapy for primary breast cancer, St Gallen 1998: Poster P73.*
Trial	**French Adjuvant Study Group - France (GFEA 04) (1990)**
Description	Estimated 50 patients included in a 4-arm study, in which only the last 2 of the 4 arms would have been relevant.
Arms	(Epirubicin+5-Fluorouracil+Cyclophosphamide) ×3 pre-op (Epirubicin+5-Fluorouracil+Cyclophosphamide) ×3 postop (Epirubicin+5-Fluorouracil+Cyclophosphamide) ×3 pre-op; (Epirubicin+5-Fluorouracil+Cyclophosphamide) ×3 postop (Epirubicin+5-Fluorouracil+Cyclophosphamide) ×6 postop
Reference	*No reference available.*

Webtable 9: Sensitivity analyses of using different methods to assess the effect of neo-adjuvant chemotherapy on local and distant recurrence

A. Effect of ignoring competing events (distant recurrence/non-breast death) on local recurrence rate ratio

The local recurrence rate ratio from logrank methods was compared with that from Cox regression (using the same stratification as in the logrank method) and from a competing risks model using Cox regression. The local recurrence rate ratio varied little with the statistical method used.

Statistical method	Local recurrence rate ratio (95% CI)
Logrank	1.37 (1.17-1.61)
Cox regression	1.37 (1.17-1.61)
Competing risks model	1.41 (1.20-1.64)

Reference: Fine JP, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. *JASA* 1999; **94**: 496-509.

B. Distant recurrence and recording of only the first event or of first and subsequent events

Some trials collected only first events, but some recorded first and subsequent events. Analyses of distant recurrence in the two types of trial are compared. Rate ratios and failure rates varied little between them.

Events recorded	Number of women	Rate ratio (95% CI) for distant recurrence	Percentage with distant recurrence (Neoadjuvant vs Adjuvant only)	
			10 years after randomisation	15 years after randomisation
First events and subsequent events	2751	1.04 (0.91-1.19)	36.2% vs 33.9%	40.8% vs 39.5%
Only first events	2005	1.00 (0.85-1.17)	30.8% vs 30.5%	35.3% vs 36.2%
All trials	**4756**	**1.02 (0.92-1.14)**	**33.8% vs 32.4%**	**38.2% vs 38.0%**

Webfigure 8: EBCTCG collaborators, alphabetically by institution or study then alphabetically by name

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