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: Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. *Lancet* 2023; **401:** 1277–92.

Webappendix: Supplementary figures and tables for "Anthracycline and taxane containing chemotherapy for early-stage operable breast cancer: meta-analyses of 100,000 women in 86 randomised trials"

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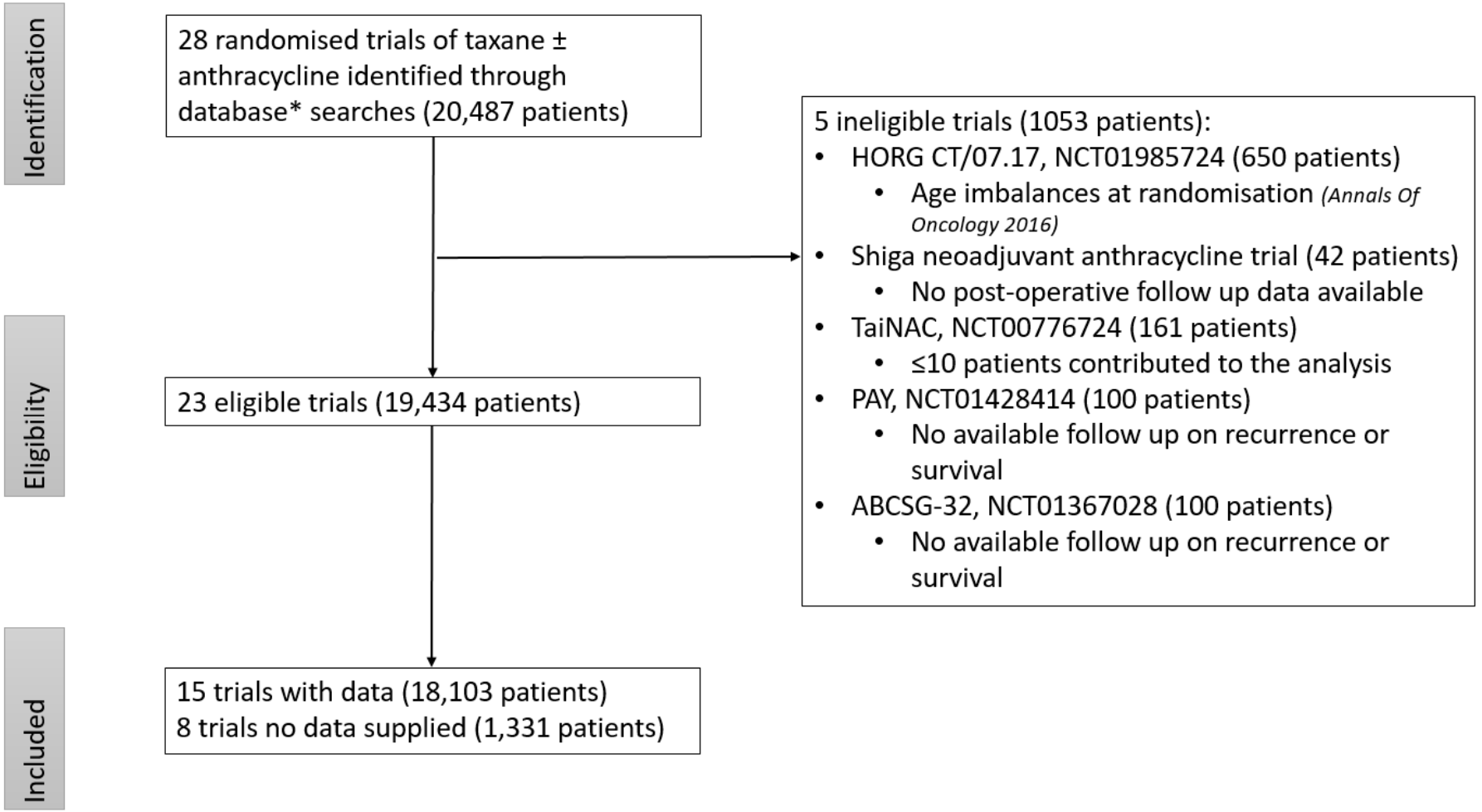
P3: CONSORT of trials included in the meta-analysis of taxane plus anthracycline versus taxane without anthracycline



*Including MEDLINE, Embase, Cochrane Library

P4-5: Table of eligibility and baseline characteristics by trial

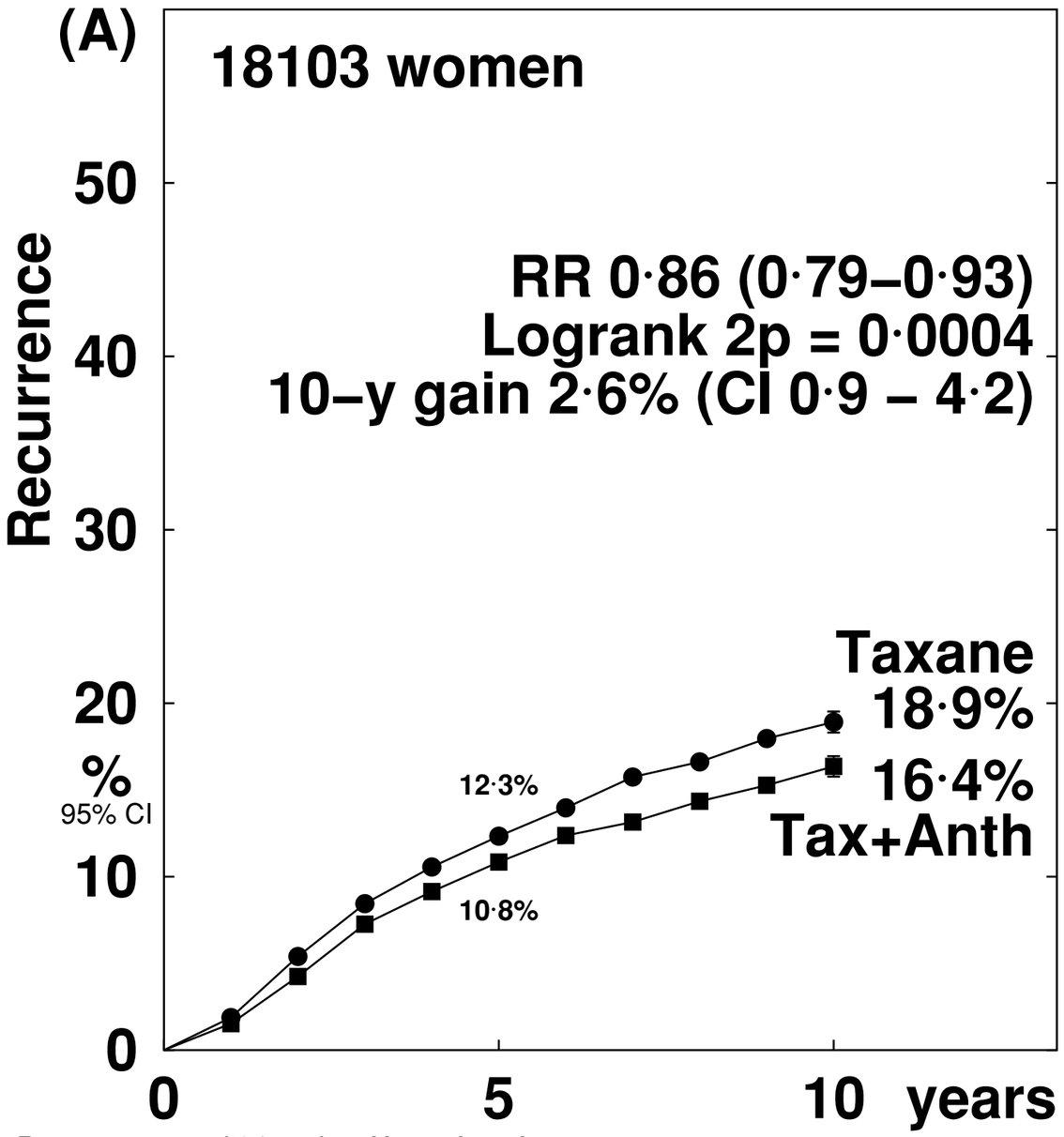
Trial name (years of recruitment)	No. of patients randomised	Key eligibility criteria	Median age in years (range)	Nodal status	Tumour size	Tumour grade	ER status	HER2 status	Median follow up in years
(a) Concurrent docetaxel plus anthracycline versus same dose docetaxel plus cyclophosphamide									
USO 06090/11271 (2007-2009)	1296	18 to 70yrs N+ or high risk N0 ER any HER2-negative	53 (26 - 71)	35% N0 51% N1-3 11% N4-9 3% N10+	38% T1 57% T2 5% T3/T4	12% Well differentiated 38% Moderately 45% Poorly 5% Unknown	30% ER-negative 70% ER-positive	100% HER2-negative	9.4 (7.8 – 10.0)
NSABP B-46-I (2009-2012)	1077	18 to 70yrs N+ or high risk N0 ER any HER2-negative	53 (26 - 70)	38% N0 43% N1-3 14% N4-9 5% N10+	39% T1 54% T2 8% T3/T4	10% Well differentiated 37% Moderately 52% Poorly 1% Unknown	33% ER-negative 67% ER-positive	100% HER2-negative	6.3 (5.1 – 7.1)
Shanghai Jiao Tong (2009-2011)	96	18 to 70yrs TNBC or HER2-positive	48 (25 - 69)	*17% N0 *83% N+	100% Unknown	24% Moderately differentiated 31% Poorly differentiated 45% Unknown	84% ER-negative 16% ER-positive	51% HER2-negative 49% HER2-positive	4.7 (4.1 – 5.3)
(b) Sequential taxane plus anthracycline versus higher cumulative dose docetaxel plus cyclophosphamide									
HORG CT/07.17 *(2007-2013)* *Ineligible due to age imbalances*	*650*	*18 to 75yrs* *N+* *HER2-negative*	*24 (56 - 80)*	*63% N1-3* *28% N4-9* *9% N10+*	*100% Unknown*	*6% Well-differentiated* *53% Moderately* *36% Poorly* *5% Unknown*	*15% ER-negative* *84% ER-positive* *1% ER-unknown*	*100% HER2-negative*	*4.0* *(2.8 – 4.9)*
DBCG 07 READ (2008-2012)	2012	18 to 75yrs N+ or high risk N0 ER any HER2-any TOP2A normal	51 (23 - 74)	45% N0 41% N1-3 10% N4-9 4% N10+	59% T1 39% T2 2% T3/T4	17% Well differentiated 46% Moderately 32% Poorly 6% Unknown	26% ER-negative 74% ER-positive	89% HER2-negative 11% HER2-positive	8.4 (7.5 – 7.4)
Kanagawa Japan (2009-2011)	103	20 to 80yrs HR negative	55 (26 - 78)	*40% N0 *60% N+	*17% T1 *64% T2 *18% T3/T4	*17% Well differentiated *24% Moderately *58% Poorly *1% Unknown	93% ER-negative 7% ER-positive (Allred score 3-6)	72% HER2-negative 28% HER2-positive	3.9 (3.3 – 5.1)
NSABP B-49 (2012-2013)	1870	≥18yrs N+ or high risk N0 Any ER HER2-negative	55 (21 - 82)	45% N0 40% N1-3 11% N4-9 4% N10+	43% T1 51% T2 6% T3/T4	9% Well differentiated 36% Moderately 55% Poorly	31% ER-negative 69% ER-positive	100% HER2-negative	4.4 (4.0 – 4.8)
LMU SUCCESS C (2009-2011)	3643	≥18yrs N+ or high risk N0 ER any HER2-negative	55 (24 - 79)	42% N0 47% N1-3 8% N4-9 3% N10+	44% T1 50% T2 6% T3/T4	6% Well differentiated 51% Moderately 43% Poorly	25% ER-negative 75% ER-positive	100% HER2-negative	5.4 (5.0 – 5.5)
WSG Plan B (2009-2011)	2449	18 to 75yrs N+ or high risk N0 ER any HER2-negative	55 (25 - 77)	59% N0 34% N1-3 5% N4-9 2% N10+	54% T1 43% T2 3% T3/T4	4% Well differentiated 50% Moderately 42% Poorly 4% Unknown	19% ER-negative 73% ER-positive 8% Unknown	99% HER2-negative 1% HER2-positive	5.0 (4.6 – 5.1)

JBCRG-10 (2009-2011)	67	20 to 70yrs T1c-3, N0-1, M0 ER any HER2-positive	54 (34 - 70)	*63% N0 *37% N+	11% T1 76% T2 13% T3/T4	12% Well differentiated 40% Moderately 34% Poorly 14% Unknown	41% ER-negative 59% ER-positive	100% HER2-positive	4.4 (4.2 – 4.9)
JBCRG-09 (2009-2012)	195	20 to 70yrs T1c-3, N0-1, M0 ER-positive HER2-negative	48 (26 - 69)	*49% N0 *51% N+	14% T1 73% T2 13% T3/T4	18% Well differentiated 40% Moderately 14% Poorly 28% Unknown	100% ER-positive	100% HER2-negative	5.9 (5.3 – 6.5)
MASTER Fudan (2010-2017)	1047	18 to 75yrs N+ or high risk N0 ER any HER2-negative	50 (27 - 70)	41% N0 59% N+	44% T1 56% T2	66% Moderately 34% Poorly	8% ER-negative 92% ER-positive	100% HER2-negative	4.7 (3.7 – 6.3)
(c) Taxane plus anthracycline versus taxane ± capecitabine									
N-SAS-BC 02 (2000-2006)	1060	18 to 70yrs N+ ER any HER2-any	53 (24 - 70)	100% N1-3	37% T1 55% T2 7% T3/T4 1% Unknown	100% Unknown	43% ER-negative 57% ER-positive	100% Unknown	7.5 (6.1 – 8.4)
MINDACT (2006-2011)	392	18 to 70yrs N1-3 ER any HER2-any	53 (28 - 70)	99% N1-3 1% N4-9	54% T1 42% T2 4% T3/T4	9% Well differentiated 61% Moderately 30% Poorly	10% ER-negative 90% ER-positive	90% HER2-negative 10% HER2-positive	4.9 (4.3 – 5.5)
TaiNAC *(2009-2014)* *Ineligible as ≤10 randomised*	*10*	*Age 20+* *Size 30mm+* *HER2-negative*	*46 (30 - 63)*	*100% Unknown*	*20% T1* *60% T2* *10% T3* *10% Unknown*	*10% Well-differentiated* *20% Moderately* *20% Poorly* *50% Unknown*	*20% ER-negative* *60% ER-positive* *20% ER-unknown*	*100% HER2-negative*	*2.6* *(0.7 – 3.0)*
ABCSG-32 *(2011-2014)* *Ineligible no follow-up*	*100*	*≥18yrs* *ER any* *HER2-positive*	*52 (23 – 79)*	**63% N0* **37% N+*	**35% T1* **53% T2* **11% T3/4*	**2% Well differentiated* **30% Moderately* **63% Poorly* **5% Unknown*	*47% ER-negative* *53% ER-unknown*	*100% HER2-positive*	*0.5* *(0.4 – 0.5)*
(d) Taxane plus anthracycline versus taxane plus carboplatin (confounded)									
BCIRG 006 (2001-2004)	2149	18 to 70yrs N+ or high risk N0 ER any HER2-positive	49 (22 - 74)	29% N0 38% N1-3 22% N4-9 11% N10+	39% T1 54% T2 6% T3/T4	1% Well differentiated 29% Moderately 65% Poorly 5% Unknown	50% ER-negative 50% ER-positive	100% HER2-positive	10.5 (9.0 – 10.6)
TaiNAC *(2009-2014)* *Ineligible as ≤10 randomised*	*8*	*Age 20+* *Size 30mm+* *HER2-negative*	*52 (38 – 61)*	*100% Unknown*	*25% T1* *75% T2*	*25% Well-differentiated* *38% Moderately* *37% Unknown*	*75% ER-positive* *25% ER-unknown*	*100%- HER2-negative*	*1.6* *(1.0 – 3.4)*
PATTERN Fudan (2011-2016)	647	18 to 70yrs N+ or N0 if T>10mm TNBC	51 (23 - 70)	74% N0 26% N+	54% T1 46% T2/3	27% Moderately 73% Poorly	100% ER-negative	100% HER2-negative	5.0 (4.0 – 6.9)

*Before neo-adjuvant therapy

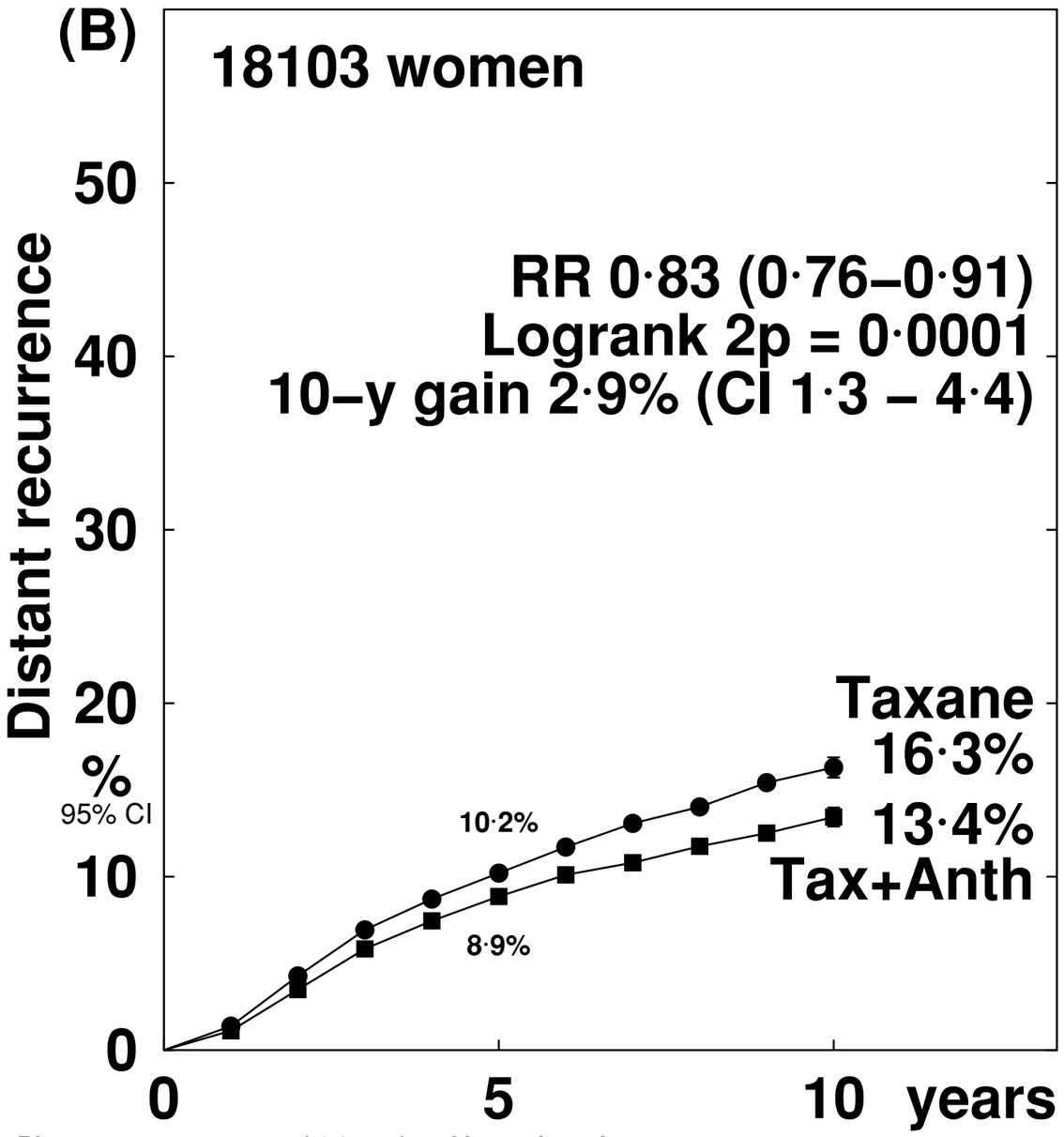
HORG CT/07.17, ABCSG-32 and TaiNAC provided data but these trials were ineligible for this meta-analysis. See CONSORT on page 3.

P6: 10-year (*5-year) cumulative risk of (A) any recurrence, (B) distant recurrence at any time, (C)* isolated local recurrence as first event, (D)* contralateral recurrence as first event in trials of taxane plus anthracycline versus taxane without anthracycline



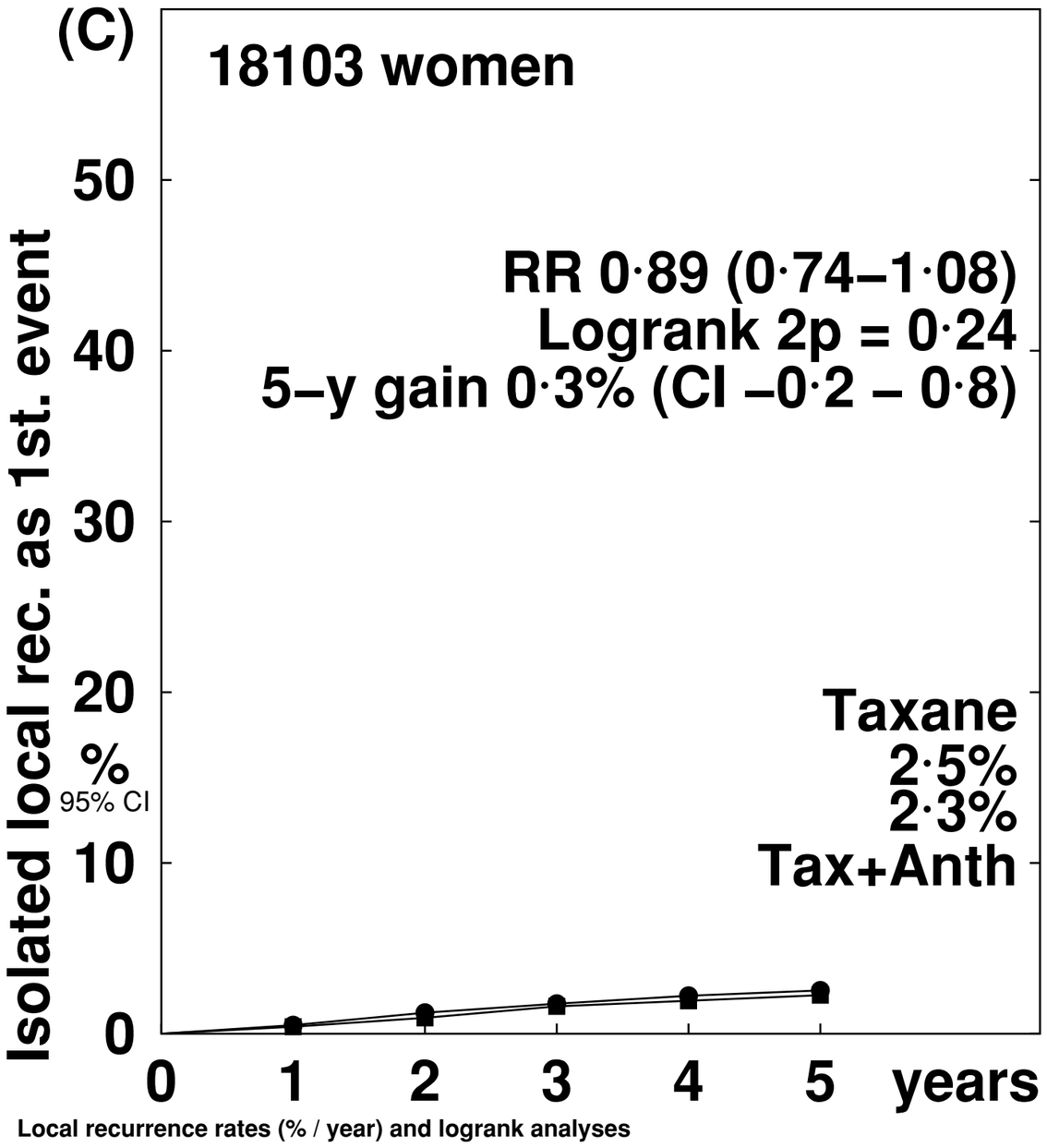
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	2·34 (900 / 38514)	1·37 (158 / 11575)	0·95 (4 / 420)
Taxane	2·63 (1008 / 38389)	1·65 (188 / 11388)	0·76 (3 / 396)
Rate ratio, from	0·87 CI 0·79 – 0·95	0·80 CI 0·64 – 0·99	1·83 CI 0·36 – 9·22
(O–E) / V	–63·8 / 443·9	–19·1 / 83·3	0·9 / 1·5



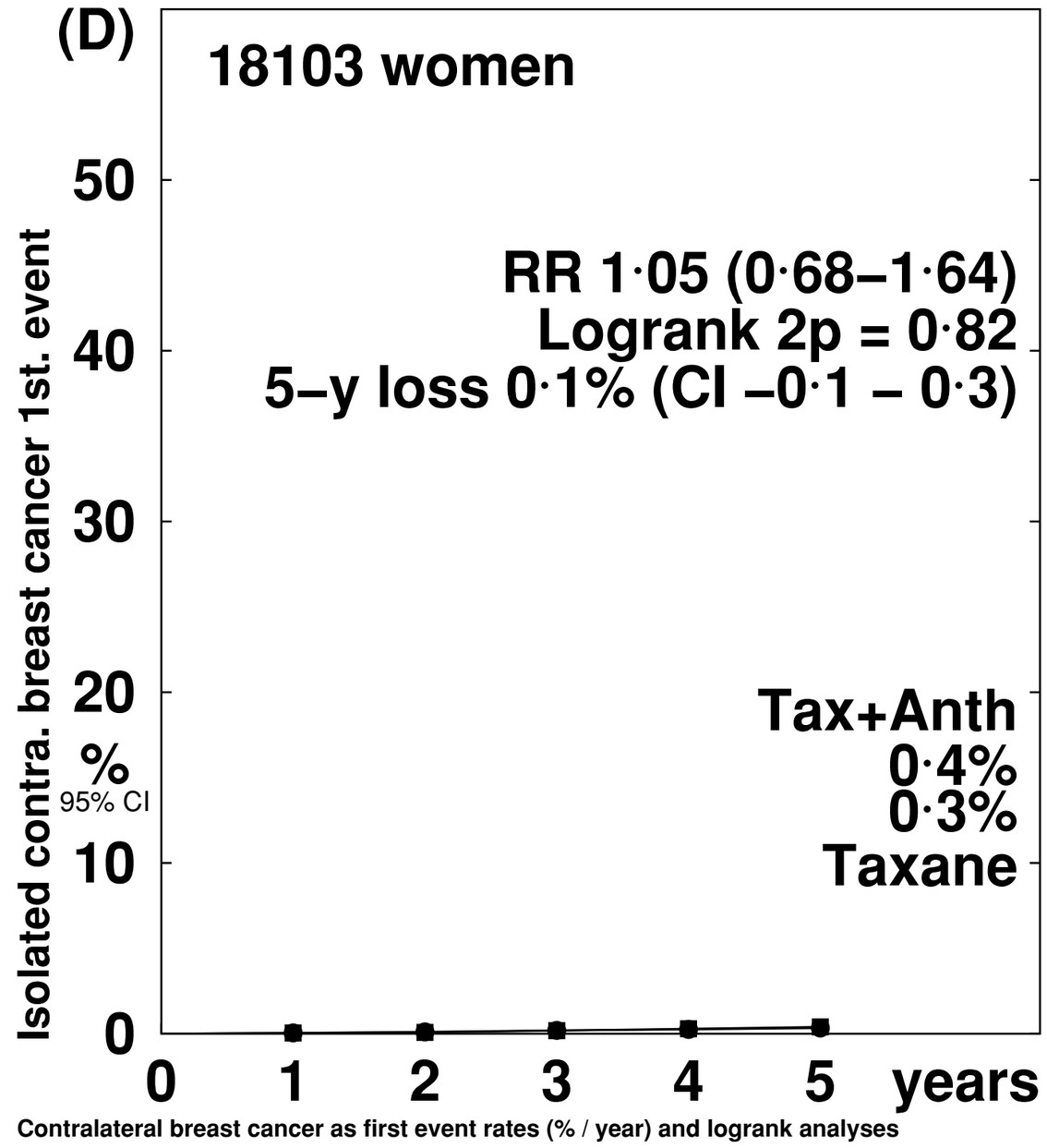
Distant recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Tax+Anth	1·88 (732 / 38875)	1·10 (131 / 11893)	0·23 (1 / 434)
Taxane	2·15 (833 / 38790)	1·46 (171 / 11714)	0·73 (3 / 412)
Rate ratio, from	0·86 CI 0·77 – 0·95	0·73 CI 0·58 – 0·91	0·42 CI 0·06 – 3·02
(O–E) / V	–56·8 / 368·4	–23·2 / 72·9	–0·9 / 1·0



Local recurrence rates (% / year) and logrank analyses

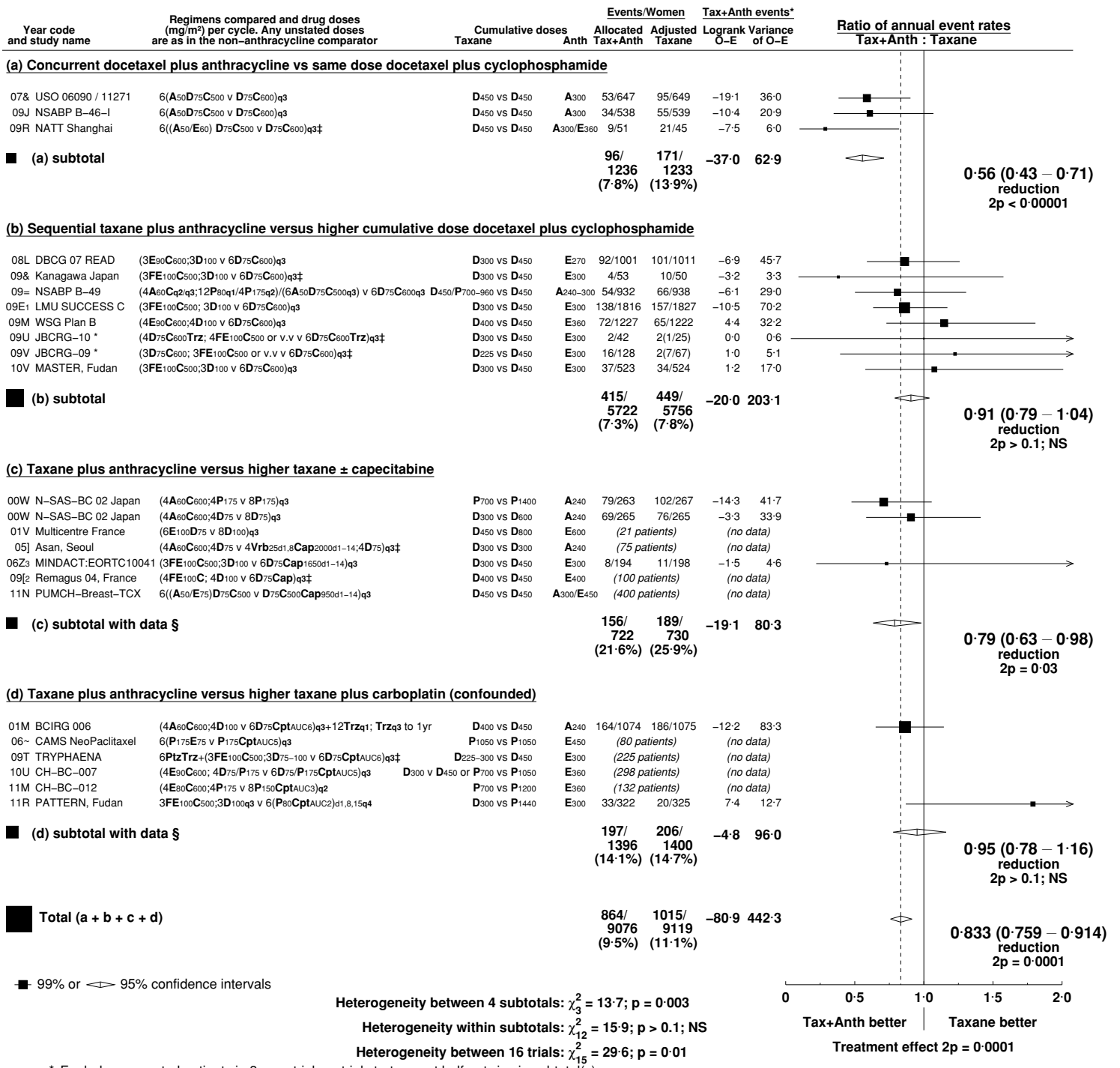
Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	0·47 (81 / 17098)	0·47 (101 / 21416)	0·27 (32 / 11995)
Taxane	0·61 (104 / 17041)	0·44 (94 / 21347)	0·28 (33 / 11784)
Rate ratio, from	0·76 CI 0·56 – 1·02	1·02 CI 0·77 – 1·36	0·95 CI 0·58 – 1·55
(O–E) / V	–12·3 / 44·1	1·0 / 47·0	–0·9 / 15·7



Contralateral breast cancer as first event rates (% / year) and logrank analyses

Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	0·04 (7 / 17098)	0·11 (23 / 21416)	0·10 (12 / 11995)
Taxane	0·05 (9 / 17041)	0·07 (16 / 21347)	0·11 (13 / 11784)
Rate ratio, from	0·71 CI 0·26 – 1·93	1·44 CI 0·76 – 2·72	0·83 CI 0·37 – 1·83
(O–E) / V	–1·3 / 3·9	3·5 / 9·5	–1·2 / 6·1

P7: Distant recurrence at any time in trials of taxane plus anthracycline versus taxane without anthracycline



Heterogeneity between 4 subtotals: $\chi^2_3 = 13{\cdot}7$; p = 0·003

Heterogeneity within subtotals: $\chi^2_{12} = 15{\cdot}9$; p > 0·1; NS

Heterogeneity between 16 trials: $\chi^2_{15} = 29{\cdot}6$; p = 0·01

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of events/patients.

‡ Pre–operative chemotherapy

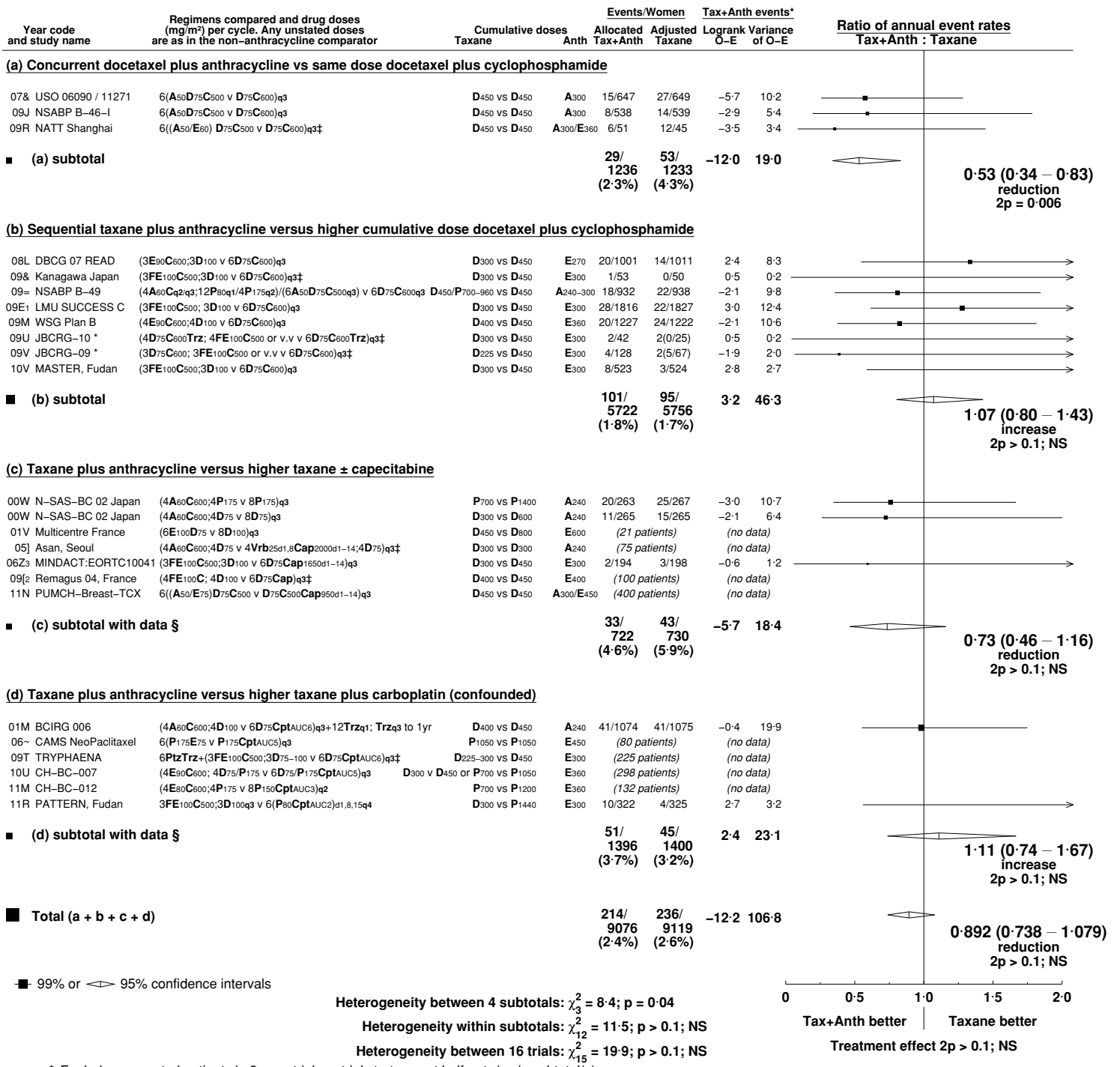
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

P8: Isolated local recurrence as first event in trials of taxane plus anthracycline versus taxane without anthracycline



* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of events/patients.

‡ Pre–operative chemotherapy

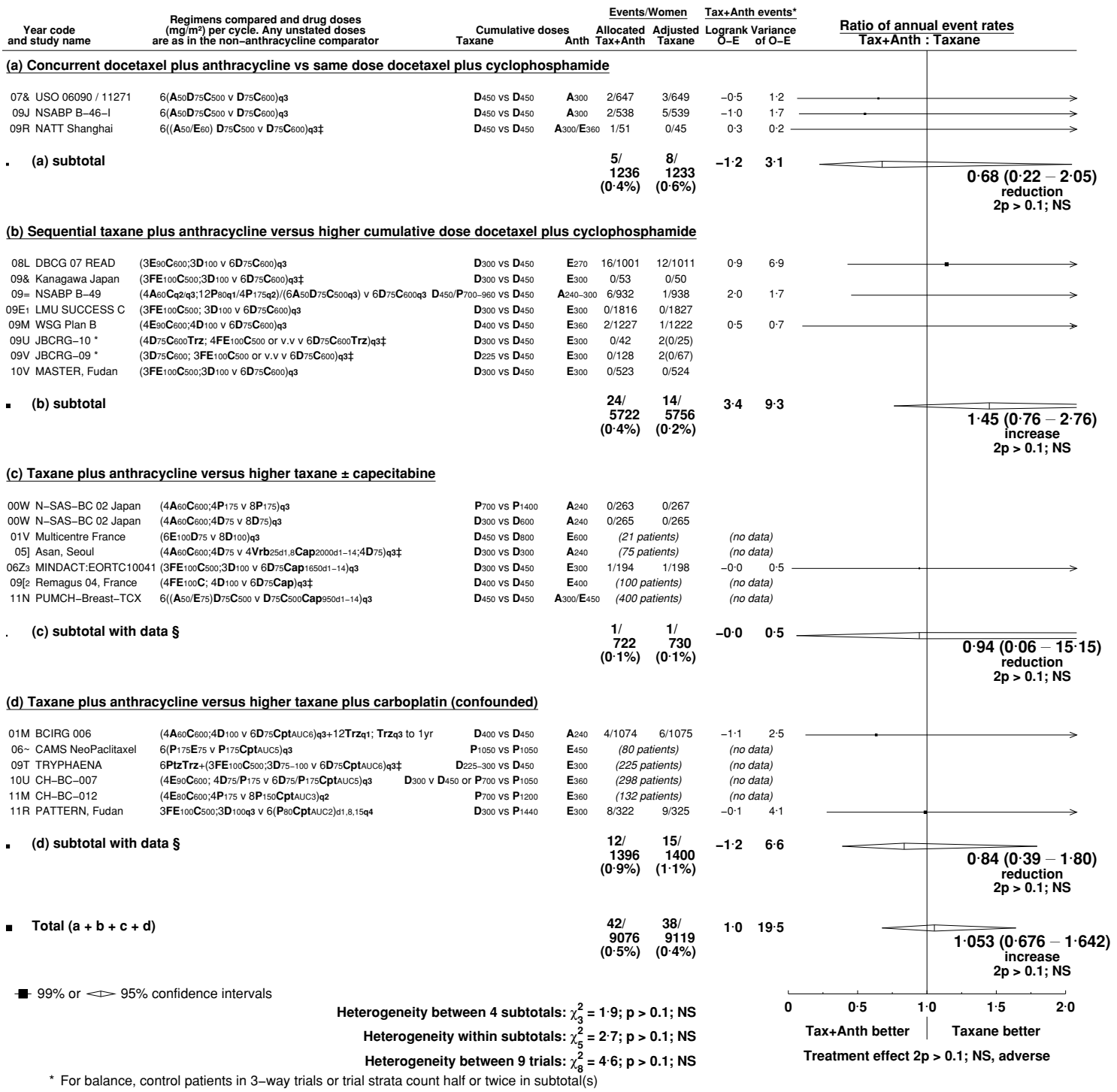
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

P9: Contralateral recurrence as first event in trials of taxane plus anthracycline versus taxane without anthracycline



* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of events/patients.

‡ Pre–operative chemotherapy

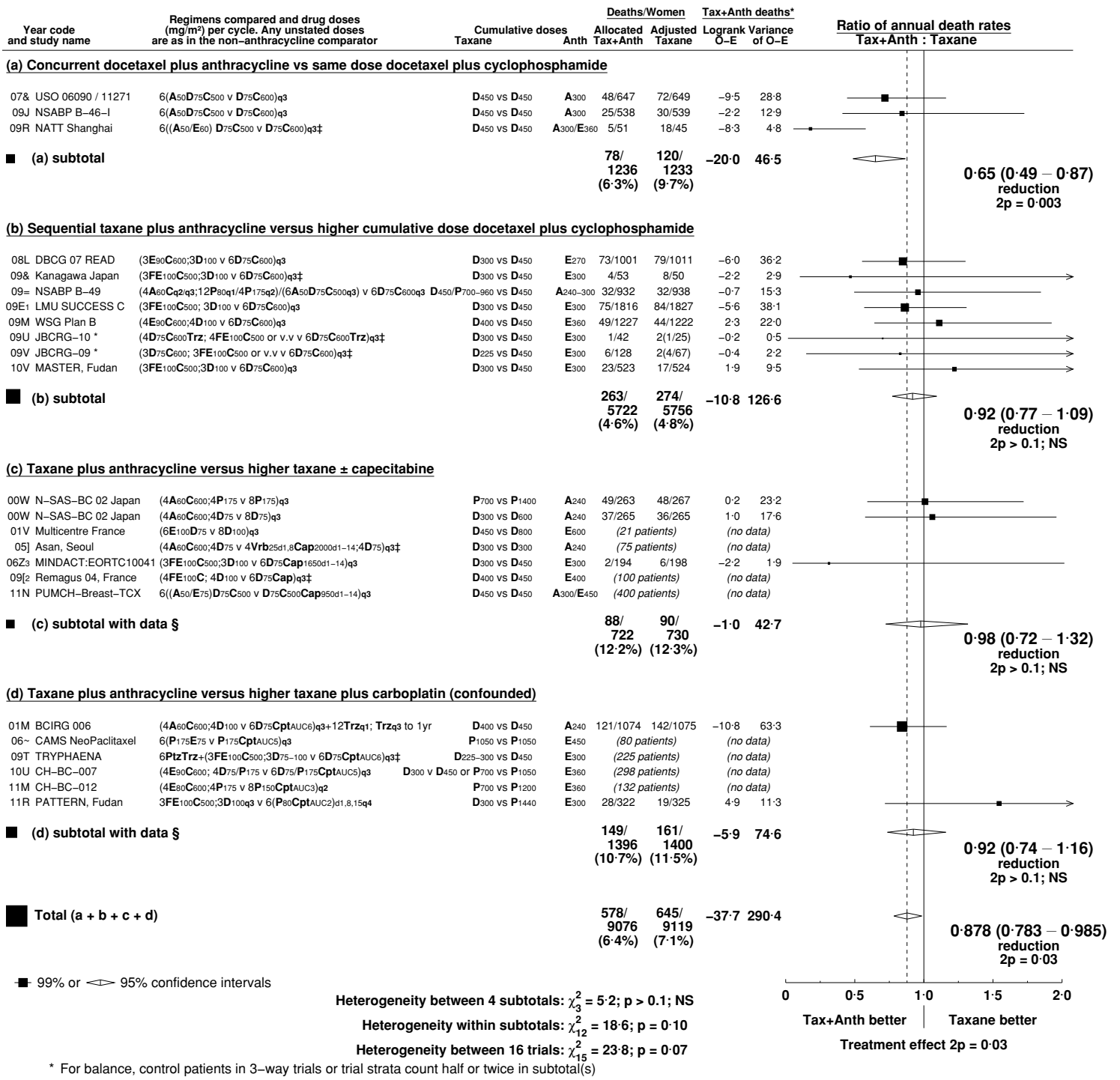
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

P10: Breast cancer mortality in trials of taxane plus anthracycline versus taxane without anthracycline



* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.

‡ Pre–operative chemotherapy

v.v Vice versa

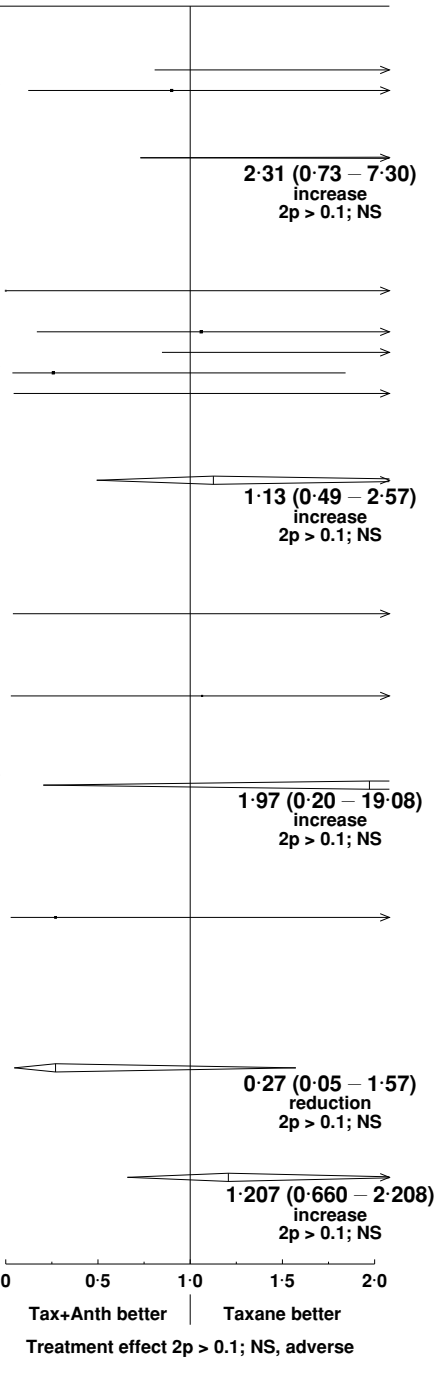
Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

P11: Death without recurrence in year 0 in trials of taxane plus anthracycline versus taxane without anthracycline

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the non–anthracycline comparator	Cumulative doses: Taxane	Cumulative doses: Anth	Deaths/Women: Allocated Tax+Anth	Deaths/Women: Adjusted Taxane	Tax+Anth deaths*: Logrank O–E	Tax+Anth deaths*: Variance of O–E
(a) Concurrent docetaxel plus anthracycline vs same dose docetaxel plus cyclophosphamide							
07& USO 06090 / 11271	6(**A**$_{50}$**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$	5/647	0/649	2·6	1·2
09J NSABP B–46–I	6(**A**$_{50}$**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$	3/538	4/539	−0·2	1·7
09R NATT Shanghai	6((**A**$_{50}$/**E**$_{60}$) **D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$/**E**$_{360}$	0/51	0/45		
(a) subtotal				**8/ 1236 (0·6%)**	**4/ 1233 (0·3%)**	**2·4**	**2·9**
(b) Sequential taxane plus anthracycline versus higher cumulative dose docetaxel plus cyclophosphamide							
08L DBCG 07 READ	(3**E**$_{90}$**C**$_{600}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{270}$	0/1001	1/1011	−0·5	0·2
09& Kanagawa Japan	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	0/53	0/50		
09= NSABP B–49	(4**A**$_{60}$**C**$_{q2/q3}$;12**P**$_{80q1}$/4**P**$_{175q2}$)/(6**A**$_{50}$**D**$_{75}$**C**$_{500q3}$) v 6**D**$_{75}$**C**$_{600q3}$	**D**$_{450}$/**P**$_{700–960}$ vs **D**$_{450}$	**A**$_{240–300}$	4/932	4/938	0·1	2·0
09E$_1$ LMU SUCCESS C	(3**FE**$_{100}$**C**$_{500}$; 3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	6/1816	0/1827	2·9	1·5
09M WSG Plan B	(4**E**$_{90}$**C**$_{600}$;4**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{400}$ vs **D**$_{450}$	**E**$_{360}$	1/1227	6/1222	−2·3	1·7
09U JBCRG–10 *	(4**D**$_{75}$**C**$_{600}$**Trz**; 4**FE**$_{100}$**C**$_{500}$ or v.v v 6**D**$_{75}$**C**$_{600}$**Trz**)**q3**‡	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	2/42	2(0/25)	0·5	0·2
09V JBCRG–09 *	(3**D**$_{75}$**C**$_{600}$; 3**FE**$_{100}$**C**$_{500}$ or v.v v 6**D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{225}$ vs **D**$_{450}$	**E**$_{300}$	0/128	2(0/67)		
10V MASTER, Fudan	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	0/523	0/524		
(b) subtotal				**13/ 5722 (0·2%)**	**11/ 5756 (0·2%)**	**0·7**	**5·6**
(c) Taxane plus anthracycline versus higher taxane ± capecitabine							
00W N–SAS–BC 02 Japan	(4**A**$_{60}$**C**$_{600}$;4**P**$_{175}$ v 8**P**$_{175}$)**q3**	**P**$_{700}$ vs **P**$_{1400}$	**A**$_{240}$	1/263	0/267	0·5	0·2
00W N–SAS–BC 02 Japan	(4**A**$_{60}$**C**$_{600}$;4**D**$_{75}$ v 8**D**$_{75}$)**q3**	**D**$_{300}$ vs **D**$_{600}$	**A**$_{240}$	0/265	0/265		
01V Multicentre France	(6**E**$_{100}$**D**$_{75}$ v 8**D**$_{100}$)**q3**	**D**$_{450}$ vs **D**$_{800}$	**E**$_{600}$	*(21 patients)*		*(no data)*	
05] Asan, Seoul	(4**A**$_{60}$**C**$_{600}$;4**D**$_{75}$ v 4**Vrb**$_{25d1,8}$**Cap**$_{2000d1–14}$;4**D**$_{75}$)**q3**‡	**D**$_{300}$ vs **D**$_{300}$	**A**$_{240}$	*(75 patients)*		*(no data)*	
06Z$_3$ MINDACT:EORTC10041	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**Cap**$_{1650d1–14}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	1/194	1/198	0·0	0·5
09[$_2$ Remagus 04, France	(4**FE**$_{100}$**C**; 4**D**$_{100}$ v 6**D**$_{75}$**Cap**)**q3**‡	**D**$_{400}$ vs **D**$_{450}$	**E**$_{400}$	*(100 patients)*		*(no data)*	
11N PUMCH–Breast–TCX	6((**A**$_{50}$/**E**$_{75}$)**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{500}$**Cap**$_{950d1–14}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$/**E**$_{450}$	*(400 patients)*		*(no data)*	
(c) subtotal with data §				**2/ 722 (0·3%)**	**1/ 730 (0·1%)**	**0·5**	**0·7**
(d) Taxane plus anthracycline versus higher taxane plus carboplatin (confounded)							
01M BCIRG 006	(4**A**$_{60}$**C**$_{600}$;4**D**$_{100}$ v 6**D**$_{75}$**Cpt**$_{AUC6}$)**q3**+12**Trz**$_{q1}$; **Trz**$_{q3}$ to 1yr	**D**$_{400}$ vs **D**$_{450}$	**A**$_{240}$	1/1074	4/1075	−1·6	1·2
06~ CAMS NeoPaclitaxel	6(**P**$_{175}$**E**$_{75}$ v **P**$_{175}$**Cpt**$_{AUC5}$)**q3**	**P**$_{1050}$ vs **P**$_{1050}$	**E**$_{450}$	*(80 patients)*		*(no data)*	
09T TRYPHAENA	6**PtzTrz**+(3**FE**$_{100}$**C**$_{500}$;3**D**$_{75–100}$ v 6**D**$_{75}$**Cpt**$_{AUC6}$)**q3**‡	**D**$_{225–300}$ vs **D**$_{450}$	**E**$_{300}$	*(225 patients)*		*(no data)*	
10U CH–BC–007	(4**E**$_{90}$**C**$_{600}$; 4**D**$_{75}$/**P**$_{175}$ v 6**D**$_{75}$/**P**$_{175}$**Cpt**$_{AUC5}$)**q3**	**D**$_{300}$ v **D**$_{450}$ or **P**$_{700}$ vs **P**$_{1050}$	**E**$_{360}$	*(298 patients)*		*(no data)*	
11M CH–BC–012	(4**E**$_{80}$**C**$_{600}$;4**P**$_{175}$ v 8**P**$_{150}$**Cpt**$_{AUC3}$)**q2**	**P**$_{700}$ vs **P**$_{1200}$	**E**$_{360}$	*(132 patients)*		*(no data)*	
11R PATTERN, Fudan	3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$**q3** v 6(**P**$_{80}$**Cpt**$_{AUC2}$)$_{d1,8,15}$**q4**	**D**$_{300}$ vs **P**$_{1440}$	**E**$_{300}$	0/322	0/325		
(d) subtotal with data §				**1/ 1396 (0·1%)**	**4/ 1400 (0·3%)**	**−1·6**	**1·2**
Total (a + b + c + d)				**24/ 9076 (0·3%)**	**20/ 9119 (0·2%)**	**2·0**	**10·5**



■ 99% or ◁▷ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 4{\cdot}2$; p > 0.1; NS

Heterogeneity within subtotals: $\chi^2_6 = 14{\cdot}7$; p = 0·02

Heterogeneity between 10 trials: $\chi^2_9 = 18{\cdot}9$; p = 0·03

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.

‡ Pre–operative chemotherapy

v.v Vice versa

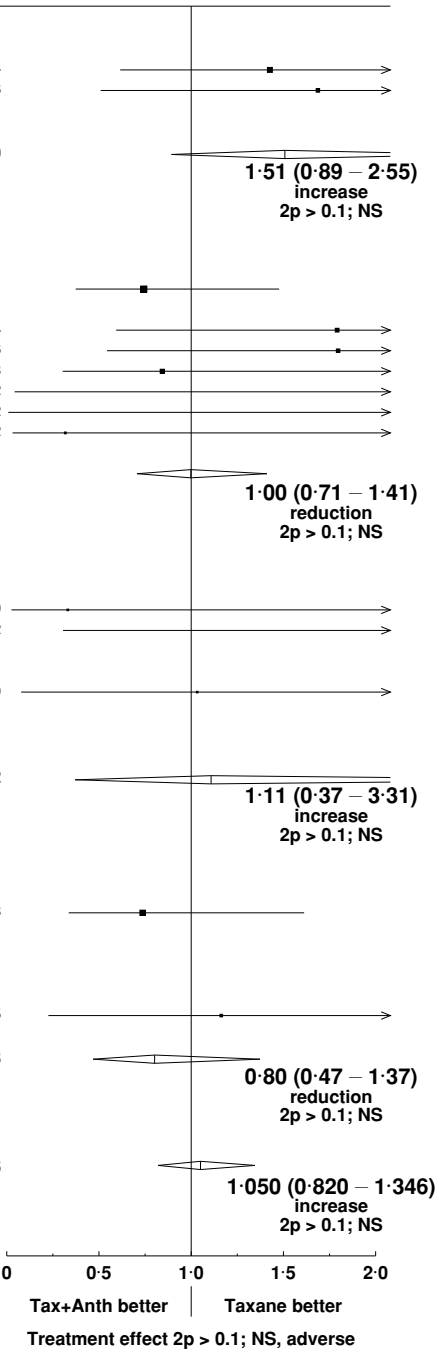
Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

P12: Death without recurrence in trials of taxane plus anthracycline versus taxane without anthracycline

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the non–anthracycline comparator	Cumulative doses: Taxane	Anth	Deaths/Women: Allocated Tax+Anth	Deaths/Women: Adjusted Taxane	Tax+Anth deaths*: Logrank O–E	Tax+Anth deaths*: Variance of O–E
(a) Concurrent docetaxel plus anthracycline vs same dose docetaxel plus cyclophosphamide							
07& USO 06090 / 11271	6(**A**$_{50}$**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$	23/647	17/649	3·3	9·4
09J NSABP B–46–I	6(**A**$_{50}$**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$	12/538	7/539	2·4	4·6
09R NATT Shanghai	6((**A**$_{50}$/**E**$_{60}$) **D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$/**E**$_{360}$	0/51	0/45		
■ **(a) subtotal**				**35/ 1236 (2·8%)**	**24/ 1233 (1·9%)**	**5·7**	**14·0**
(b) Sequential taxane plus anthracycline versus higher cumulative dose docetaxel plus cyclophosphamide							
08L DBCG 07 READ	(3**E**$_{90}$**C**$_{600}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{270}$	26/1001	32/1011	–4·2	14·1
09& Kanagawa Japan	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	0/53	0/50		
09= NSABP B–49	(4**A**$_{60}$**C**$_{q2/q3}$;12**P**$_{80q1}$/4**P**$_{175q2}$)/(6**A**$_{50}$**D**$_{75}$**C**$_{500q3}$) v 6**D**$_{75}$**C**$_{600q3}$	**D**$_{450}$/**P**$_{700–960}$ vs **D**$_{450}$	**A**$_{240–300}$	14/932	8/938	3·2	5·4
09E$_1$ LMU SUCCESS C	(3**FE**$_{100}$**C**$_{500}$; 3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	13/1816	7/1827	2·7	4·6
09M WSG Plan B	(4**E**$_{90}$**C**$_{600}$;4**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{400}$ vs **D**$_{450}$	**E**$_{360}$	12/1227	14/1222	–1·1	6·3
09U JBCRG–10 *	(4**D**$_{75}$**C**$_{600}$**Trz**; 4**FE**$_{100}$**C**$_{500}$ or v.v v 6**D**$_{75}$**C**$_{600}$**Trz**)**q3**‡	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	2/42	2(0/25)	0·5	0·2
09V JBCRG–09 *	(3**D**$_{75}$**C**$_{600}$; 3**FE**$_{100}$**C**$_{500}$ or v.v v 6**D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{225}$ vs **D**$_{450}$	**E**$_{300}$	1/128	2(0/67)	0·2	0·2
10V MASTER, Fudan	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	1/523	4/524	–1·4	1·2
■ **(b) subtotal**				**69/ 5722 (1·2%)**	**65/ 5756 (1·1%)**	**–0·1**	**32·1**
(c) Taxane plus anthracycline versus higher taxane ± capecitabine							
00W N–SAS–BC 02 Japan	(4**A**$_{60}$**C**$_{600}$;4**P**$_{175}$ v 8**P**$_{175}$)**q3**	**P**$_{700}$ vs **P**$_{1400}$	**A**$_{240}$	1/263	3/267	–1·1	1·0
00W N–SAS–BC 02 Japan	(4**A**$_{60}$**C**$_{600}$;4**D**$_{75}$ v 8**D**$_{75}$)**q3**	**D**$_{300}$ vs **D**$_{600}$	**A**$_{240}$	5/265	1/265	1·4	1·2
01V Multicentre France	(6**E**$_{100}$**D**$_{75}$ v 8**D**$_{100}$)**q3**	**D**$_{450}$ vs **D**$_{800}$	**E**$_{600}$	*(21 patients)*		*(no data)*	
05] Asan, Seoul	(4**A**$_{60}$**C**$_{600}$;4**D**$_{75}$ v 4**Vrb**$_{25d1,8}$**Cap**$_{2000d1–14}$;4**D**$_{75}$)**q3**‡	**D**$_{300}$ vs **D**$_{300}$	**A**$_{240}$	*(75 patients)*		*(no data)*	
06Z$_3$ MINDACT:EORTC10041	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**Cap**$_{1650d1–14}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	2/194	2/198	0·0	1·0
09[$_2$ Remagus 04, France	(4**FE**$_{100}$**C**; 4**D**$_{100}$ v 6**D**$_{75}$**Cap**)**q3**‡	**D**$_{400}$ vs **D**$_{450}$	**E**$_{400}$	*(100 patients)*		*(no data)*	
11N PUMCH–Breast–TCX	6((**A**$_{50}$/**E**$_{75}$)**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{500}$**Cap**$_{950d1–14}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$/**E**$_{450}$	*(400 patients)*		*(no data)*	
▪ **(c) subtotal with data §**				**8/ 722 (1·1%)**	**6/ 730 (0·8%)**	**0·3**	**3·2**
(d) Taxane plus anthracycline versus higher taxane plus carboplatin (confounded)							
01M BCIRG 006	(4**A**$_{60}$**C**$_{600}$;4**D**$_{100}$ v 6**D**$_{75}$**Cpt**$_{AUC6}$)**q3**+12**Trz**$_{q1}$; **Trz**$_{q3}$ to 1yr	**D**$_{400}$ vs **D**$_{450}$	**A**$_{240}$	20/1074	25/1075	–3·3	10·8
06~ CAMS NeoPaclitaxel	6(**P**$_{175}$**E**$_{75}$ v **P**$_{175}$**Cpt**$_{AUC5}$)**q3**	**P**$_{1050}$ vs **P**$_{1050}$	**E**$_{450}$	*(80 patients)*		*(no data)*	
09T TRYPHAENA	6**PtzTrz**+(3**FE**$_{100}$**C**$_{500}$;3**D**$_{75–100}$ v 6**D**$_{75}$**Cpt**$_{AUC6}$)**q3**‡	**D**$_{225–300}$ vs **D**$_{450}$	**E**$_{300}$	*(225 patients)*		*(no data)*	
10U CH–BC–007	(4**E**$_{90}$**C**$_{600}$; 4**D**$_{75}$/**P**$_{175}$ v 6**D**$_{75}$/**P**$_{175}$**Cpt**$_{AUC5}$)**q3**	**D**$_{300}$ v **D**$_{450}$ or **P**$_{700}$ vs **P**$_{1050}$	**E**$_{360}$	*(298 patients)*		*(no data)*	
11M CH–BC–012	(4**E**$_{80}$**C**$_{600}$;4**P**$_{175}$ v 8**P**$_{150}$**Cpt**$_{AUC3}$)**q2**	**P**$_{700}$ vs **P**$_{1200}$	**E**$_{360}$	*(132 patients)*		*(no data)*	
11R PATTERN, Fudan	3**FE**$_{100}$**C**$_{500}$;3**D**$_{100q3}$ v 6(**P**$_{80}$**Cpt**$_{AUC2}$)$_{d1,8,15q4}$	**D**$_{300}$ vs **P**$_{1440}$	**E**$_{300}$	5/322	5/325	0·4	2·5
▪ **(d) subtotal with data §**				**25/ 1396 (1·8%)**	**30/ 1400 (2·1%)**	**–2·9**	**13·3**
■ **Total (a + b + c + d)**				**137/ 9076 (1·5%)**	**125/ 9119 (1·4%)**	**3·1**	**62·6**



■ 99% or ◁▷ 95% confidence intervals

Heterogeneity between 4 subtotals: χ^2_3 = 2·9; p > 0.1; NS

Heterogeneity within subtotals: χ^2_{10} = 11·1; p > 0.1; NS

Heterogeneity between 14 trials: χ^2_{13} = 14·0; p > 0.1; NS

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.

‡ Pre–operative chemotherapy

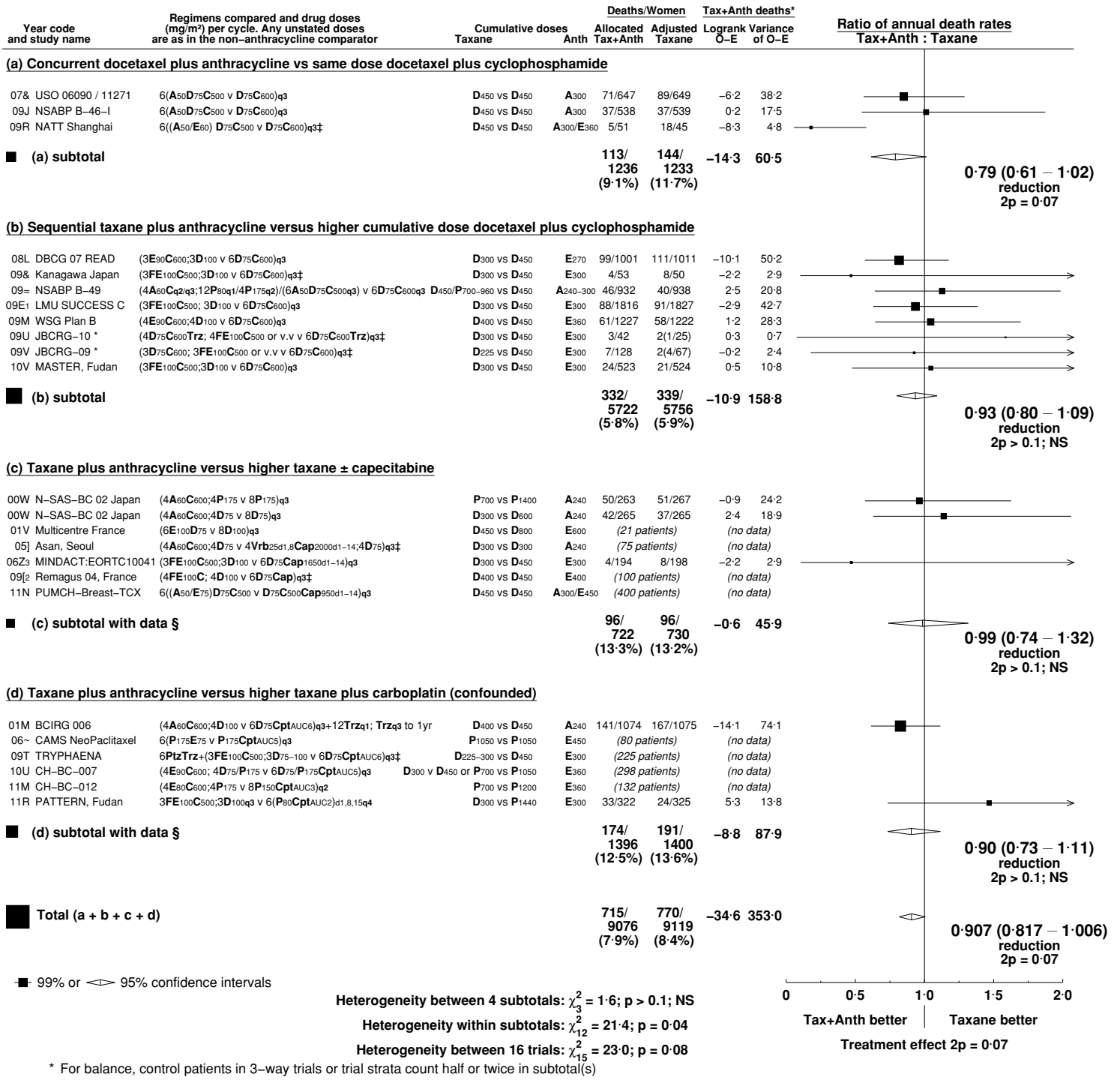
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

P13: All-cause mortality in trials of taxane plus anthracycline versus taxane without anthracycline



Heterogeneity between 4 subtotals: $\chi^2_3 = 1{\cdot}6$; **p > 0·1; NS**

Heterogeneity within subtotals: $\chi^2_{12} = 21{\cdot}4$; **p = 0·04**

Heterogeneity between 16 trials: $\chi^2_{15} = 23{\cdot}0$; **p = 0·08**

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.

‡ Pre–operative chemotherapy

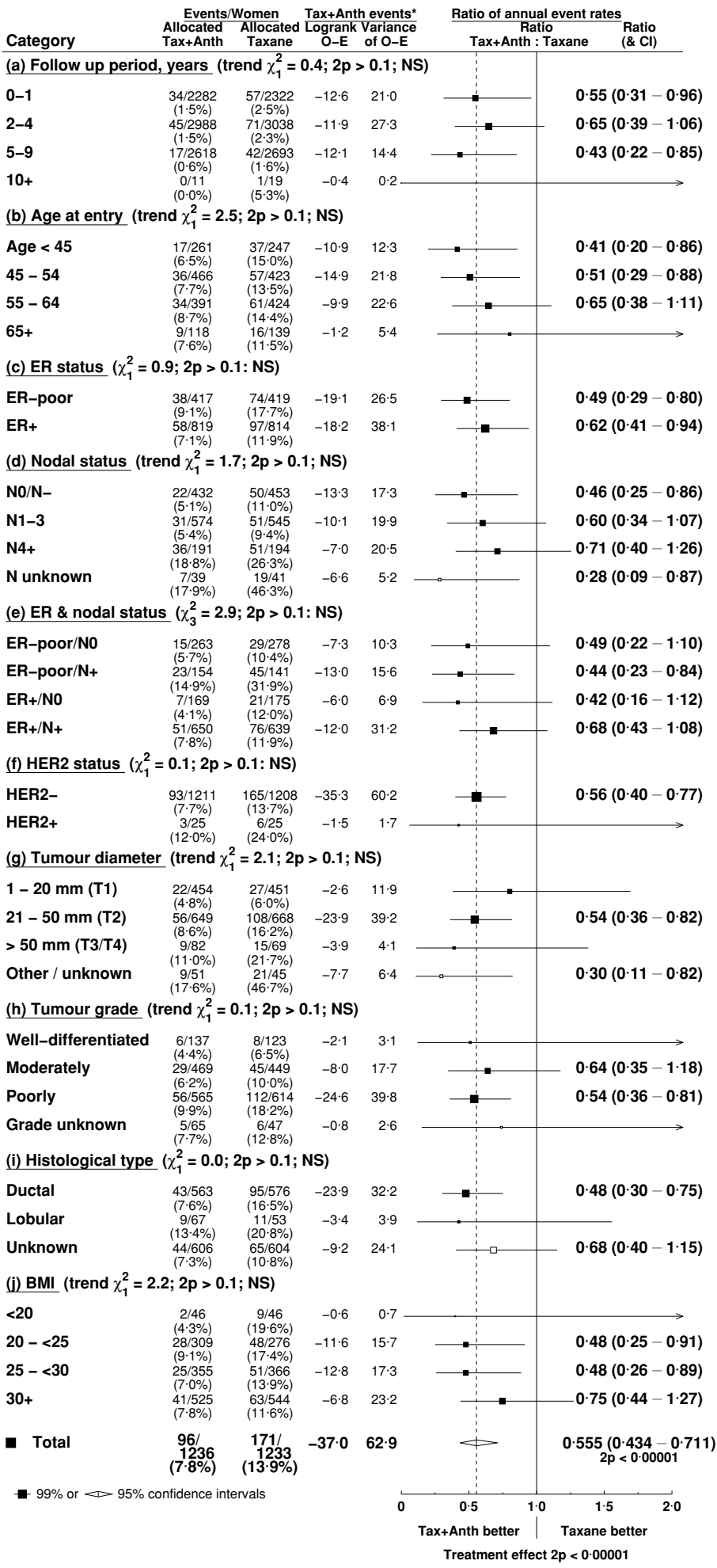
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

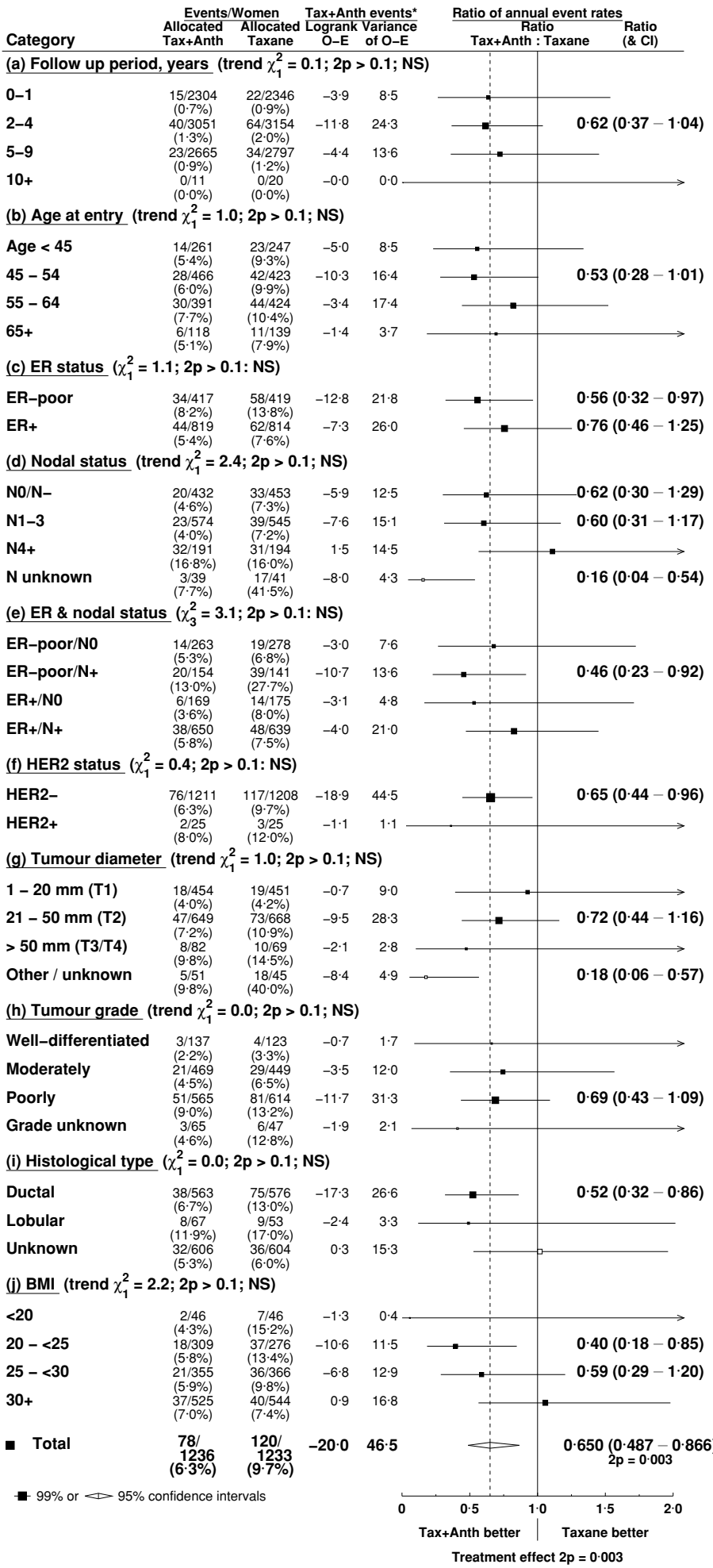
Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

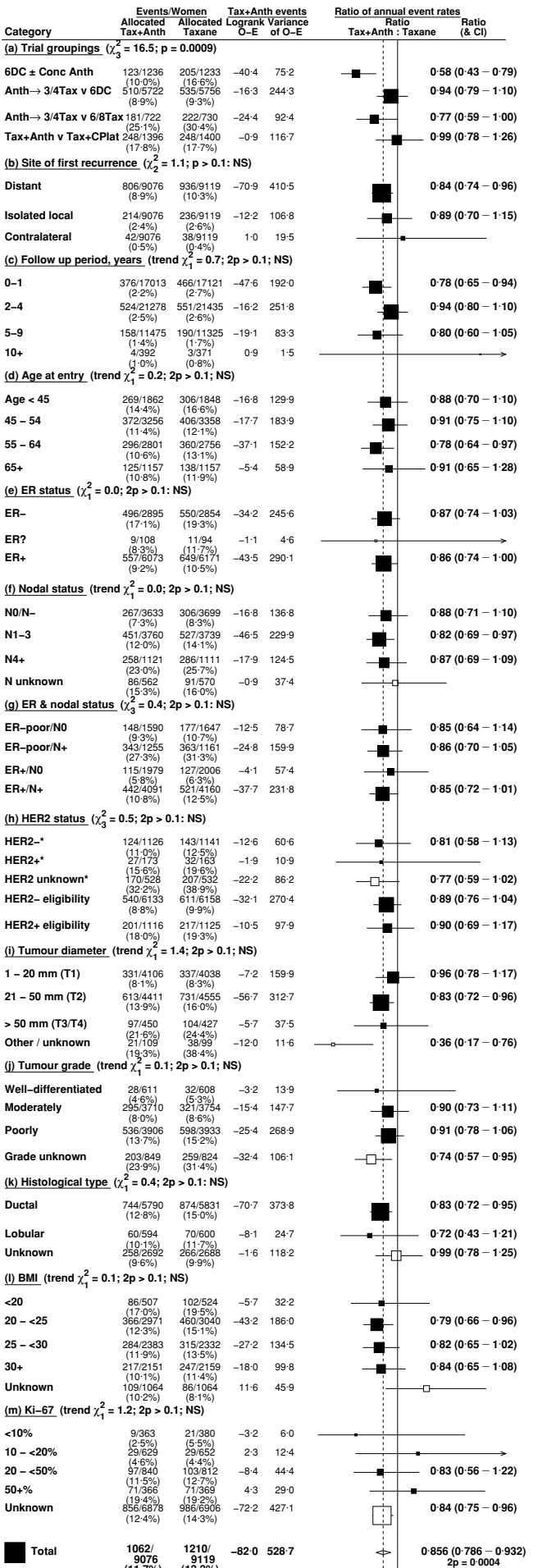
P14: Subgroup analyses of concurrent anthracycline plus docetaxel plus cyclophosphamide versus same dose docetaxel plus cyclophosphamide; distant recurrence at any time



P15: Subgroup analyses of concurrent anthracycline plus docetaxel plus cyclophosphamide versus same dose docetaxel plus cyclophosphamide; breast cancer mortality

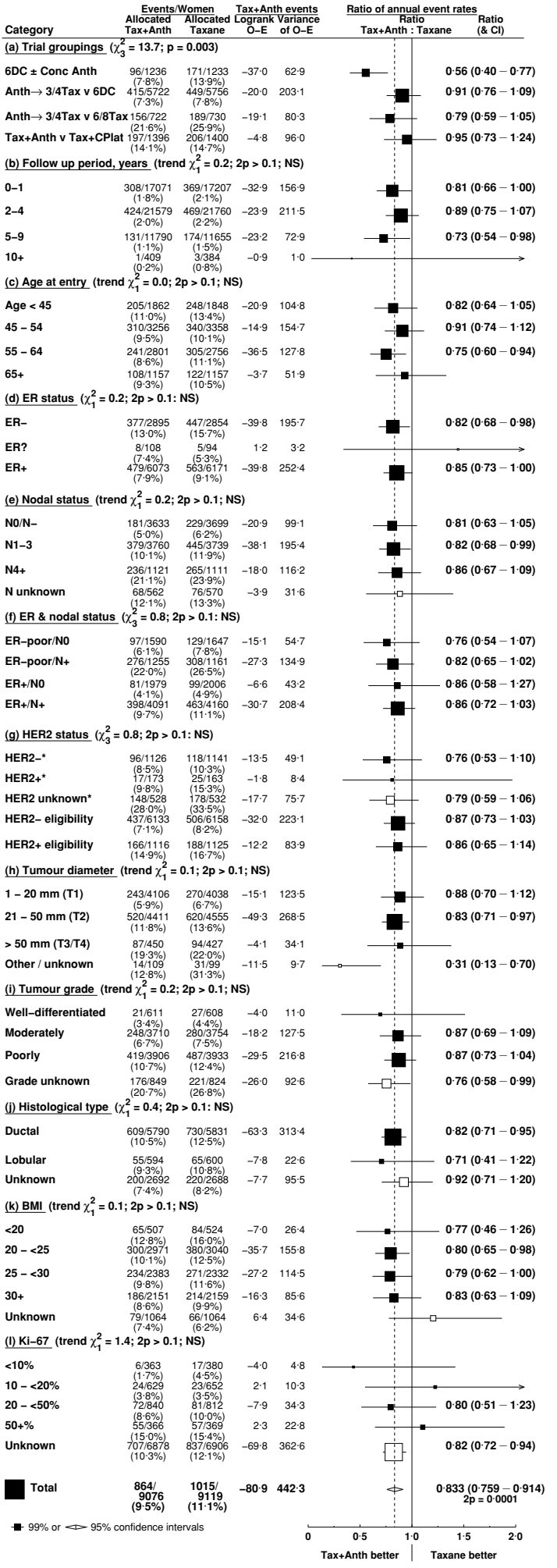


P16: Subgroup analyses of taxane plus anthracycline versus taxane without anthracycline; any recurrence. All trial comparisons (a)-(d).



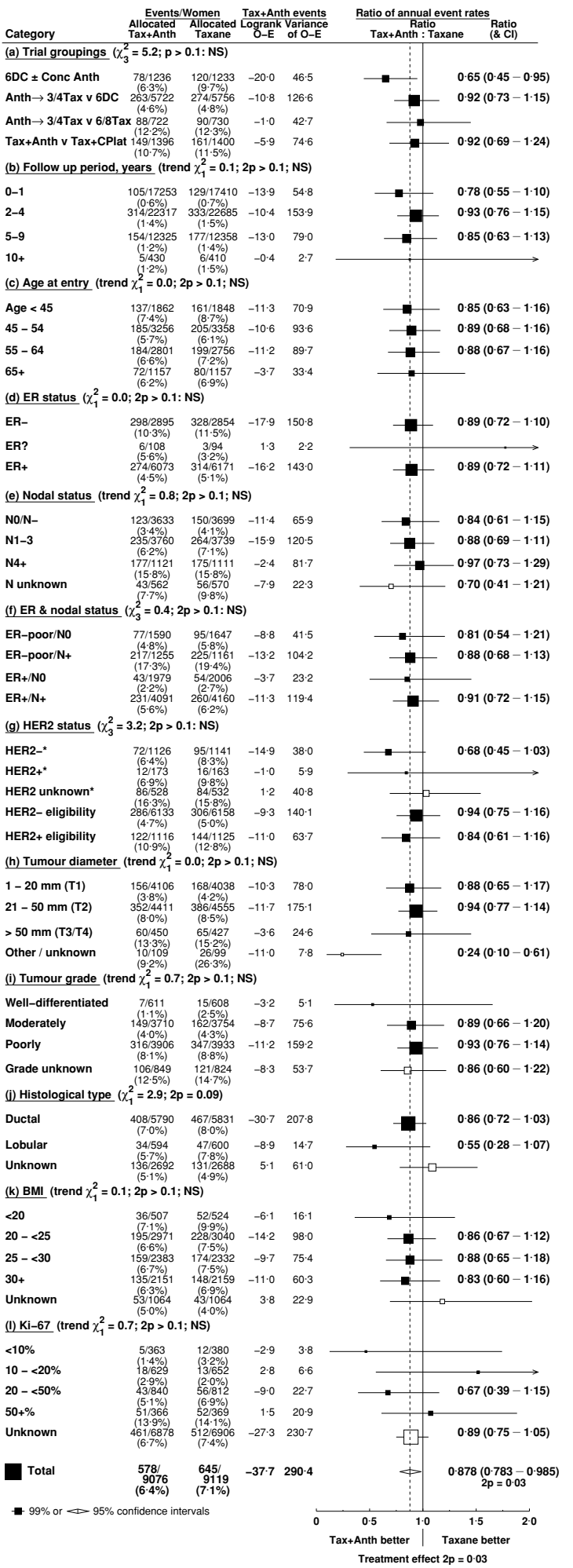
*Trials which randomised both HER2 negative and positive tumours shown separately to those trials which had HER2 negative only or positive only eligibility criteria.

P17: Subgroup analyses of taxane plus anthracycline versus taxane without anthracycline; distant recurrence at any time. All trial comparisons (a)-(d).



*Trials which randomised both HER2 negative and positive tumours shown separately to those trials which had HER2 negative only or positive only eligibility criteria.

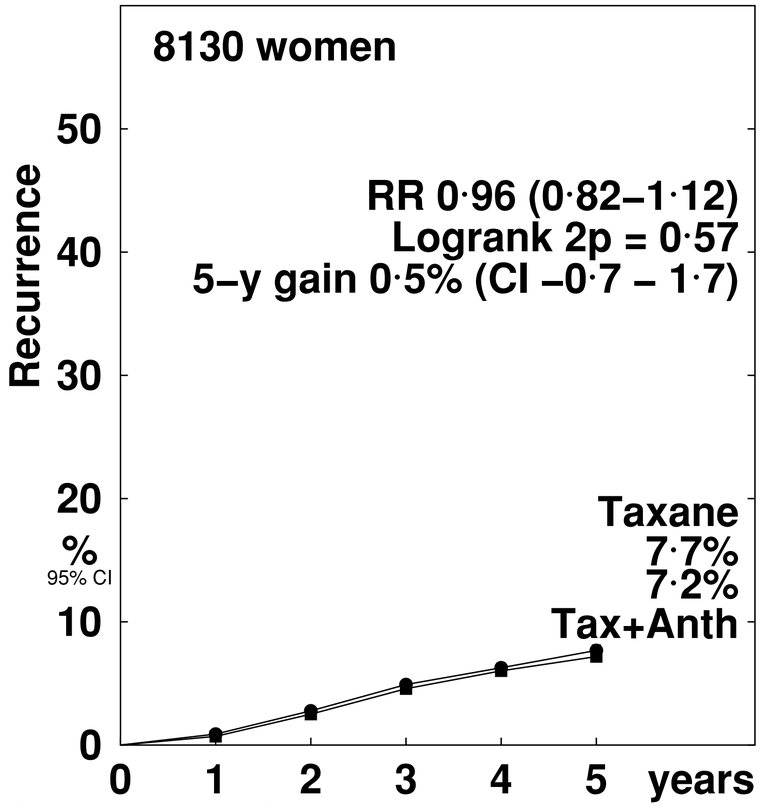
P18: Subgroup analyses of taxane plus anthracycline versus taxane without anthracycline; breast cancer mortality. All trial comparisons (a)-(d).



*Trials which randomised both HER2 negative and positive tumours shown separately to those trials which had HER2 negative only or positive only eligibility criteria.

P 19: 5-year risk of recurrence split by tumour size in trials of taxane plus anthracycline versus taxane without anthracycline. All trial comparisons (a)-(d).

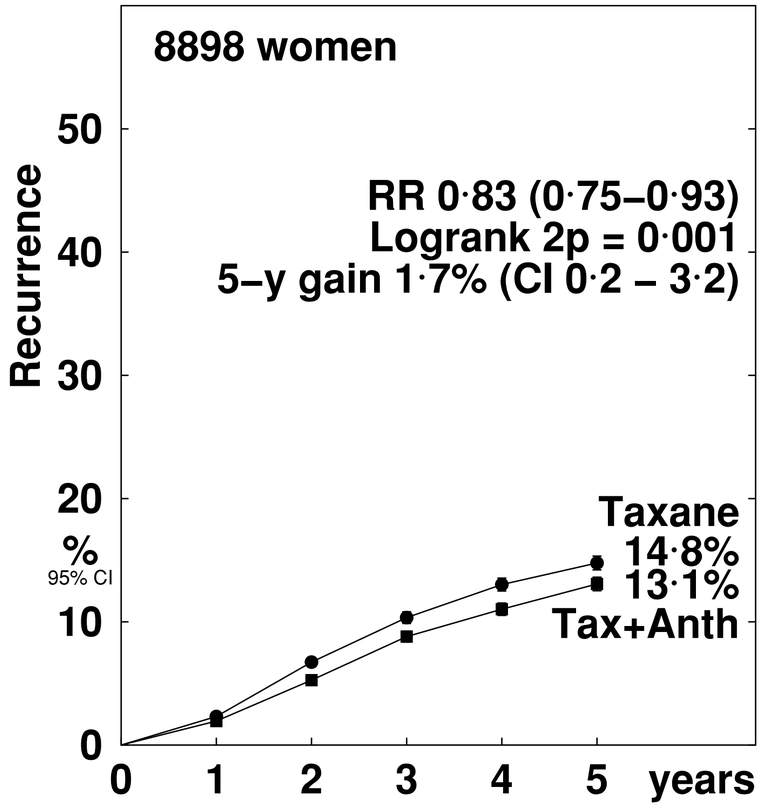
1–20 mm (T1)



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	1·28 (100 / 7802)	1·68 (169 / 10075)	1·10 (62 / 5660)
Taxane	1·38 (106 / 7681)	1·73 (173 / 9989)	1·05 (58 / 5535)
Rate ratio, from	0·90 CI 0·68 – 1·19	0·95 CI 0·77 – 1·19	1·06 CI 0·74 – 1·53
(O–E) / V	–5·2 / 49·0	–3·8 / 81·9	1·8 / 28·9

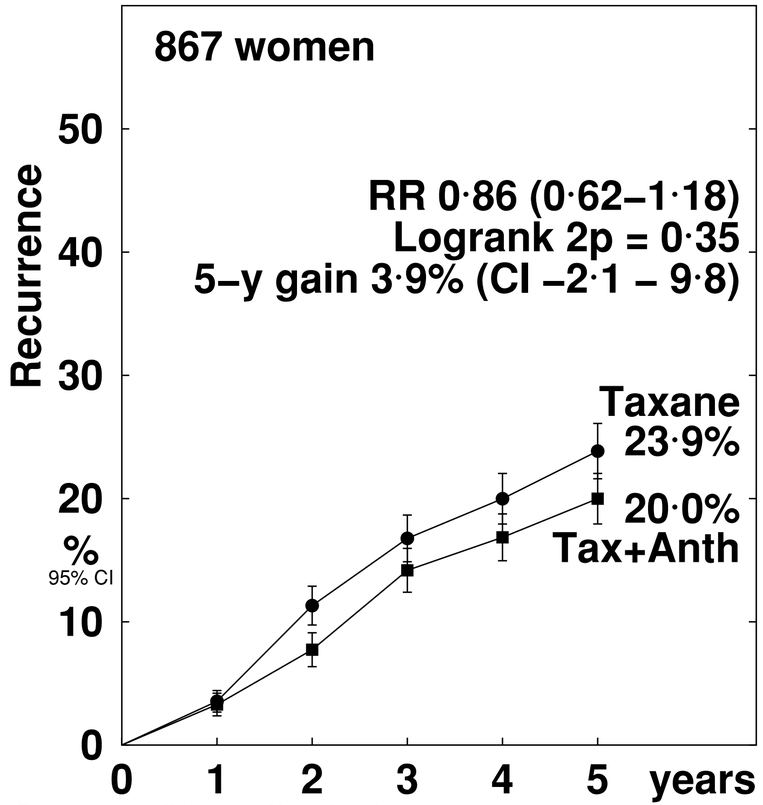
Entry age 21–50 mm (T2)



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	2·73 (226 / 8274)	2·96 (301 / 10155)	1·48 (86 / 5797)
Taxane	3·40 (286 / 8419)	3·03 (313 / 10316)	2·10 (122 / 5806)
Rate ratio, from	0·78 CI 0·65 – 0·93	0·95 CI 0·80 – 1·11	0·68 CI 0·52 – 0·90
(O–E) / V	–29·9 / 117·9	–7·9 / 145·3	–18·8 / 49·5

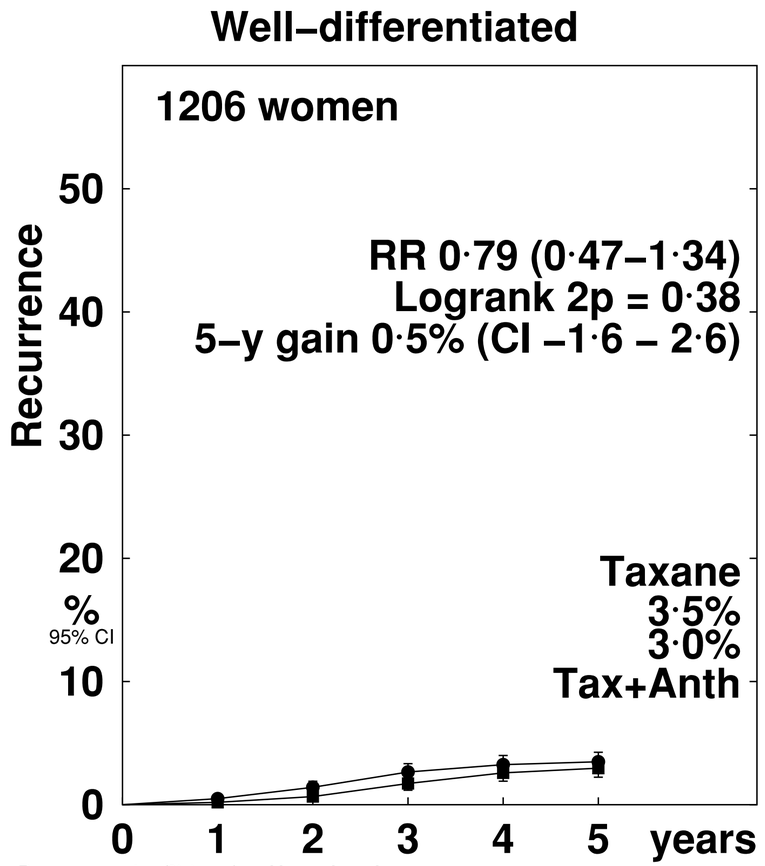
> 50 mm (T3/T4)



Recurrence rates (% / year) and logrank analyses

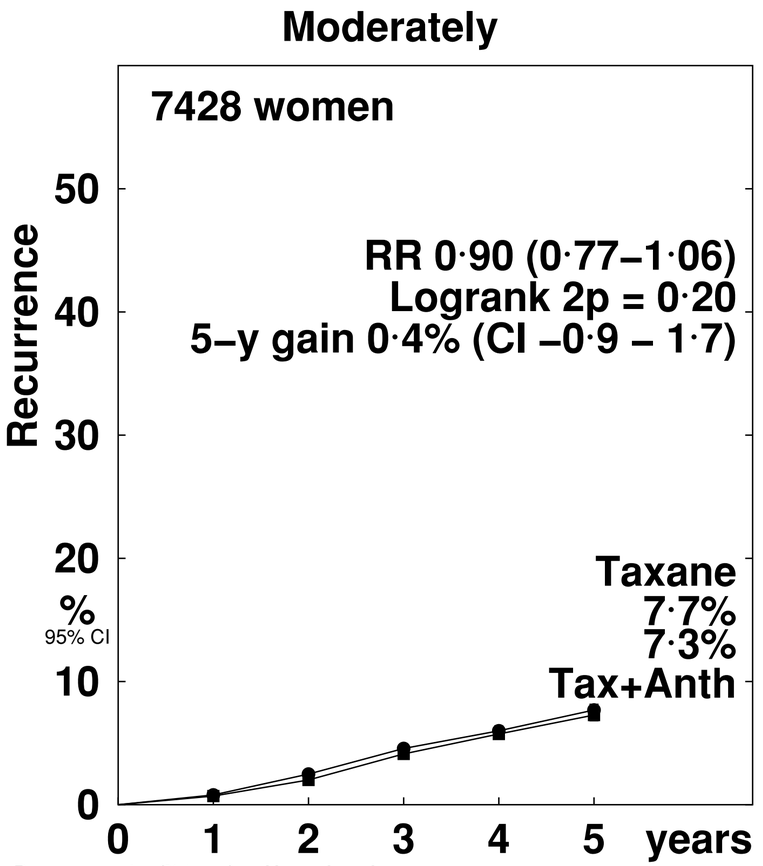
Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	4·34 (36 / 829)	4·74 (47 / 992)	2·68 (14 / 523)
Taxane	5·61 (44 / 784)	5·30 (48 / 906)	2·53 (11 / 434)
Rate ratio, from	0·66 CI 0·39 – 1·09	0·93 CI 0·59 – 1·48	1·47 CI 0·59 – 3·65
(O–E) / V	–6·2 / 14·8	–1·3 / 18·0	1·8 / 4·7

P 20: 5-year risk of recurrence split by tumour grade in trials of taxane plus anthracycline versus taxane without anthracycline. All trial comparisons (a)-(d).



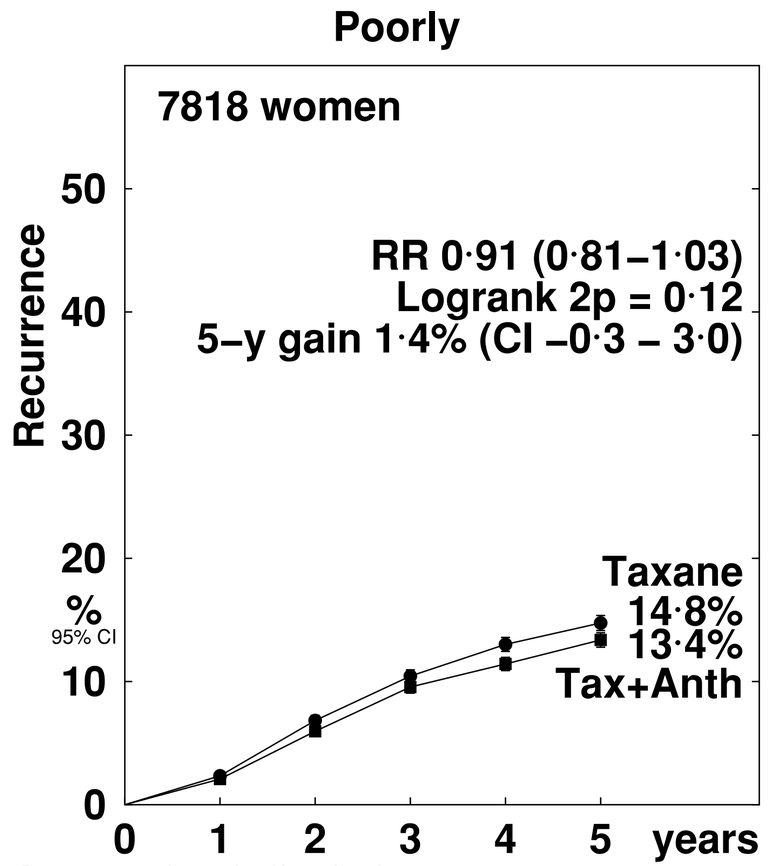
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	0·34 (4 / 1169)	0·82 (13 / 1581)	1·05 (11 / 1044)
Taxane	0·70 (8 / 1141)	0·71 (11 / 1544)	1·24 (13 / 1045)
Rate ratio, from	0·48 CI 0·15 – 1·52	1·10 CI 0·48 – 2·51	0·73 CI 0·31 – 1·71
(O–E) / V	–2·1 / 2·9	0·5 / 5·6	–1·7 / 5·3



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	1·04 (73 / 7053)	1·88 (170 / 9063)	1·16 (52 / 4491)
Taxane	1·23 (87 / 7098)	1·82 (166 / 9134)	1·48 (64 / 4315)
Rate ratio, from	0·81 CI 0·59 – 1·11	1·01 CI 0·82 – 1·26	0·75 CI 0·52 – 1·08
(O–E) / V	–8·3 / 38·4	1·1 / 81·0	–8·3 / 28·3



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 1	Years 2 – 4	Year 5+
Tax+Anth	3·04 (221 / 7277)	2·80 (247 / 8817)	1·35 (68 / 5043)
Taxane	3·51 (257 / 7315)	3·04 (271 / 8926)	1·30 (67 / 5154)
Rate ratio, from	0·87 CI 0·72 – 1·04	0·92 CI 0·77 – 1·10	1·04 CI 0·74 – 1·46
(O–E) / V	–16·1 / 111·9	–10·5 / 124·3	1·1 / 32·8

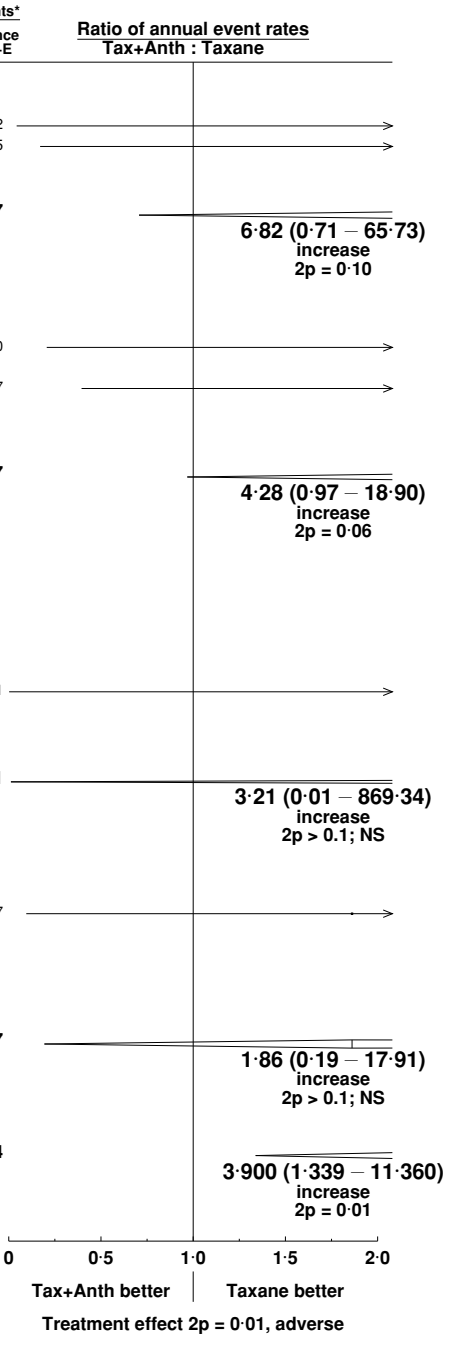
P21: Mortality by cause and incidence of second cancers. All trial comparisons (a)-(d).

	Events		(O-E)	Variance	Rate Ratio	95% CI	p
	Tax+Anth (n=9076)	Taxane (n=9169)					
Death without recurrence	137	125	3.1	62.6	1.05	0.82 - 1.35	0.70
Death with recurrence	578	645	-37.7	290.4	0.88	0.78 – 0.99	0.03
Any death	715	770	-34.6	353.0	0.91	0.82 – 1.01	0.07
Death without recurrence (selected groups of causes)							
Vascular disease:	30	20	4.6	12.1	1.46	0.83 – 2.57	0.19
Stroke	8	6	1.0	3.5	1.33	0.47 – 3.79	0.59
Pulmonary embolus	2	1	0.5	0.7	2.04	0.20 – 21.3	0.55
Heart & other vascular	20	13	3.1	7.9	1.48	0.74 – 2.97	0.27
Other primary cancer:	34	29	0.4	14.7	1.03	0.62 – 1.71	0.92
Acute myeloid leukaemia	4	2	1.0	1.5	1.93	0.39 – 9.57	0.42
Lung	5	7	-0.9	3.0	0.74	0.24 – 2.30	0.60
Other cancer	25	20	0.3	10.3	1.03	0.56 – 1.90	0.93
Other specified cause	30	36	-2.9	15.8	0.83	0.51 – 1.36	0.47
Unknown cause	43	40	1.0	20.1	1.05	0.68 – 1.63	0.82
Death without recurrence							
By entry age (years) %/woman-years							
<55	0.16 (47/29125)	0.12 (36/29615)	6.4	20.5	1.37	0.89 – 2.11	0.16
55 – 69	0.35 (70/19832)	0.39 (75/19358)	-4.3	35.5	0.89	0.64 – 1.23	0.47
≥70	1.39 (20/1439)	0.92 (14/1525)	1.0	6.6	1.16	0.54 – 2.50	0.70
All ages	0.27 (137/50396)	0.25 (125/50498)	3.1	62.6	1.05	0.82 – 1.35	0.70
Death without recurrence during first year							
By entry age (years) %/woman-years							
<55	0.06 (3/4855)	0.04 (2/4928)	0.5	1.2	1.52	0.25 – 9.08	0.65
55 – 69	0.47 (16/3430)	0.44 (15/3407)	1.0	7.6	1.14	0.56 – 2.32	0.72
≥70	1.81 (5/276)	1.04 (3/286)	0.5	1.7	1.34	0.30 – 6.03	0.70
All ages	0.28 (24/8561)	0.23 (20/8621)	2.0	10.5	1.21	0.66 – 2.22	0.54
Second primary cancer incidence							
By entry age (years) %/woman-years							
<55	0.41 (99/24386)	0.35 (88/24867)	6.9	45.9	1.16	0.87 – 1.55	0.31
55 – 69	0.57 (87/15698)	0.57 (88/15439)	-2.8	42.8	0.94	0.69 – 1.26	0.67
≥70	0.82 (7/854)	0.45 (4/901)	0.2	1.9	1.11	0.27 – 4.61	0.89
All ages	0.47 (193/40938)	0.44 (180/41207)	4.3	90.5	1.05	0.85 – 1.29	0.65

Second cancer incidence	Tax+Anth	Taxane
Haematological		
AML	12	2
Lymphoma	4	2
Lung/Thoracic	23	33
Colorectal	15	9
Upper Gastrointestinal		
Gastric	7	4
Oesophagus	1	0
Small intestine	0	2
Pancreas	3	7
Gynaecological		
Uterine/Endometrial	12	8
Ovarian	6	10
Cervical	3	8
Vulva	0	3
Urological		
Renal	4	3
Bladder	2	0
Thyroid	17	14
Epiglottis / Tonsil	2	0
Melanoma	8	11
Brain	1	1
Soft tissue /Bone	3	3
Unspecified	70	60
	193	180

P22: AML incidence in trials of taxane plus anthracycline versus taxane without anthracycline. All trial comparisons (a)-(d)

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the non–anthracycline comparator	Cumulative doses: Taxane	Cumulative doses: Anth	Events/Women: Allocated Tax+Anth	Events/Women: Allocated Taxane	Tax+Anth events*: Logrank O–E	Tax+Anth events*: Variance of O–E
(a) Concurrent docetaxel plus anthracycline vs same dose docetaxel plus cyclophosphamide							
07& USO 06090 / 11271	6(**A**$_{50}$**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$	1/647	0/649	0·5	0·2
09J NSABP B–46–I	6(**A**$_{50}$**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$	2/538	0/539	0·9	0·5
09R NATT Shanghai	6((**A**$_{50}$/**E**$_{60}$) **D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$/**E**$_{360}$	0/51	0/45		
(a) subtotal				**3/ 1236 (0·2%)**	**0/ 1233 (0·0%)**	**1·4**	**0·7**
(b) Sequential taxane plus anthracycline versus higher cumulative dose docetaxel plus cyclophosphamide							
08L DBCG 07 READ	(3**E**$_{90}$**C**$_{600}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{270}$	3/1001	1/1011	1·0	1·0
09& Kanagawa Japan	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**‡	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	0/53	0/50		
09= NSABP B–49	(4**A**$_{60}$**C**$_{q2/q3}$;12**P**$_{80q1}$/4**P**$_{175q2}$)/(6**A**$_{50}$**D**$_{75}$**C**$_{500q3}$) v 6**D**$_{75}$**C**$_{600q3}$	**D**$_{450}$/**P**$_{700–960}$ vs **D**$_{450}$	**A**$_{240–300}$	3/932	0/938	1·5	0·7
09M WSG Plan B	(4**E**$_{90}$**C**$_{600}$;4**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{400}$ vs **D**$_{450}$	**E**$_{360}$	0/1227	0/1222		
10V MASTER, Fudan	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**C**$_{600}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	0/523	0/524		
(b) subtotal				**6/ 3736 (0·2%)**	**1/ 3745 (0·0%)**	**2·5**	**1·7**
(c) Taxane plus anthracycline versus higher taxane ± capecitabine							
00W N–SAS–BC 02 Japan	(4**A**$_{60}$**C**$_{600}$;4**P**$_{175}$ v 8**P**$_{175}$)**q3**	**P**$_{700}$ vs **P**$_{1400}$	**A**$_{240}$	0/263	0/267		
00W N–SAS–BC 02 Japan	(4**A**$_{60}$**C**$_{600}$;4**D**$_{75}$ v 8**D**$_{75}$)**q3**	**D**$_{300}$ vs **D**$_{600}$	**A**$_{240}$	0/265	0/265		
01V Multicentre France	(6**E**$_{100}$**D**$_{75}$ v 8**D**$_{100}$)**q3**	**D**$_{450}$ vs **D**$_{800}$	**E**$_{600}$	*(21 patients)*		*(no data)*	
05] Asan, Seoul	(4**A**$_{60}$**C**$_{600}$;4**D**$_{75}$ v 4**Vrb**$_{25d1,8}$**Cap**$_{2000d1–14}$;4**D**$_{75}$)**q3**‡	**D**$_{300}$ vs **D**$_{300}$	**A**$_{240}$	*(75 patients)*		*(no data)*	
06Z$_3$ MINDACT:EORTC10041	(3**FE**$_{100}$**C**$_{500}$;3**D**$_{100}$ v 6**D**$_{75}$**Cap**$_{1650d1–14}$)**q3**	**D**$_{300}$ vs **D**$_{450}$	**E**$_{300}$	1/194	0/198	0·1	0·1
09[$_2$ Remagus 04, France	(4**FE**$_{100}$**C**; 4**D**$_{100}$ v 6**D**$_{75}$**Cap**)**q3**‡	**D**$_{400}$ vs **D**$_{450}$	**E**$_{400}$	*(100 patients)*		*(no data)*	
11N PUMCH–Breast–TCX	6((**A**$_{50}$/**E**$_{75}$)**D**$_{75}$**C**$_{500}$ v **D**$_{75}$**C**$_{500}$**Cap**$_{950d1–14}$)**q3**	**D**$_{450}$ vs **D**$_{450}$	**A**$_{300}$/**E**$_{450}$	*(400 patients)*		*(no data)*	
(c) subtotal with data §				**1/ 722 (0·1%)**	**0/ 730 (0·0%)**	**0·1**	**0·1**
(d) Taxane plus anthracycline versus higher taxane plus carboplatin (confounded)							
01M BCIRG 006	(4**A**$_{60}$**C**$_{600}$;4**D**$_{100}$ v 6**D**$_{75}$**Cpt**$_{AUC6}$)**q3**+12**Trz**$_{q1}$; **Trz**$_{q3}$ to 1yr	**D**$_{400}$ vs **D**$_{450}$	**A**$_{240}$	2/1074	1/1075	0·5	0·7
06~ CAMS NeoPaclitaxel	6(**P**$_{175}$**E**$_{75}$ v **P**$_{175}$**Cpt**$_{AUC5}$)**q3**	**P**$_{1050}$ vs **P**$_{1050}$	**E**$_{450}$	*(80 patients)*		*(no data)*	
09T TRYPHAENA	6**PtzTrz**+(3**FE**$_{100}$**C**$_{500}$;3**D**$_{75–100}$ v 6**D**$_{75}$**Cpt**$_{AUC6}$)**q3**‡	**D**$_{225–300}$ vs **D**$_{450}$	**E**$_{300}$	*(225 patients)*		*(no data)*	
10U CH–BC–007	(4**E**$_{90}$**C**$_{600}$; 4**D**$_{75}$/**P**$_{175}$ v 6**D**$_{75}$/**P**$_{175}$**Cpt**$_{AUC5}$)**q3**	**D**$_{300}$ v **D**$_{450}$ or **P**$_{700}$ vs **P**$_{1050}$	**E**$_{360}$	*(298 patients)*		*(no data)*	
11M CH–BC–012	(4**E**$_{80}$**C**$_{600}$;4**P**$_{175}$ v 8**P**$_{150}$**Cpt**$_{AUC3}$)**q2**	**P**$_{700}$ vs **P**$_{1200}$	**E**$_{360}$	*(132 patients)*		*(no data)*	
(d) subtotal with data §				**2/ 1074 (0·2%)**	**1/ 1075 (0·1%)**	**0·5**	**0·7**
Total (a + b + c + d)				**12/ 6768 (0·2%)**	**2/ 6783 (0·0%)**	**4·6**	**3·4**



■ 99% or ◁▷ 95% confidence intervals

Heterogeneity between 4 subtotals: χ^2_3 = 0·7; p > 0.1; NS

Heterogeneity within subtotals: χ^2_2 = 0·5; p > 0.1; NS

Heterogeneity between 6 trials: χ^2_5 = 1·1; p > 0.1; NS

‡ Pre–operative chemotherapy

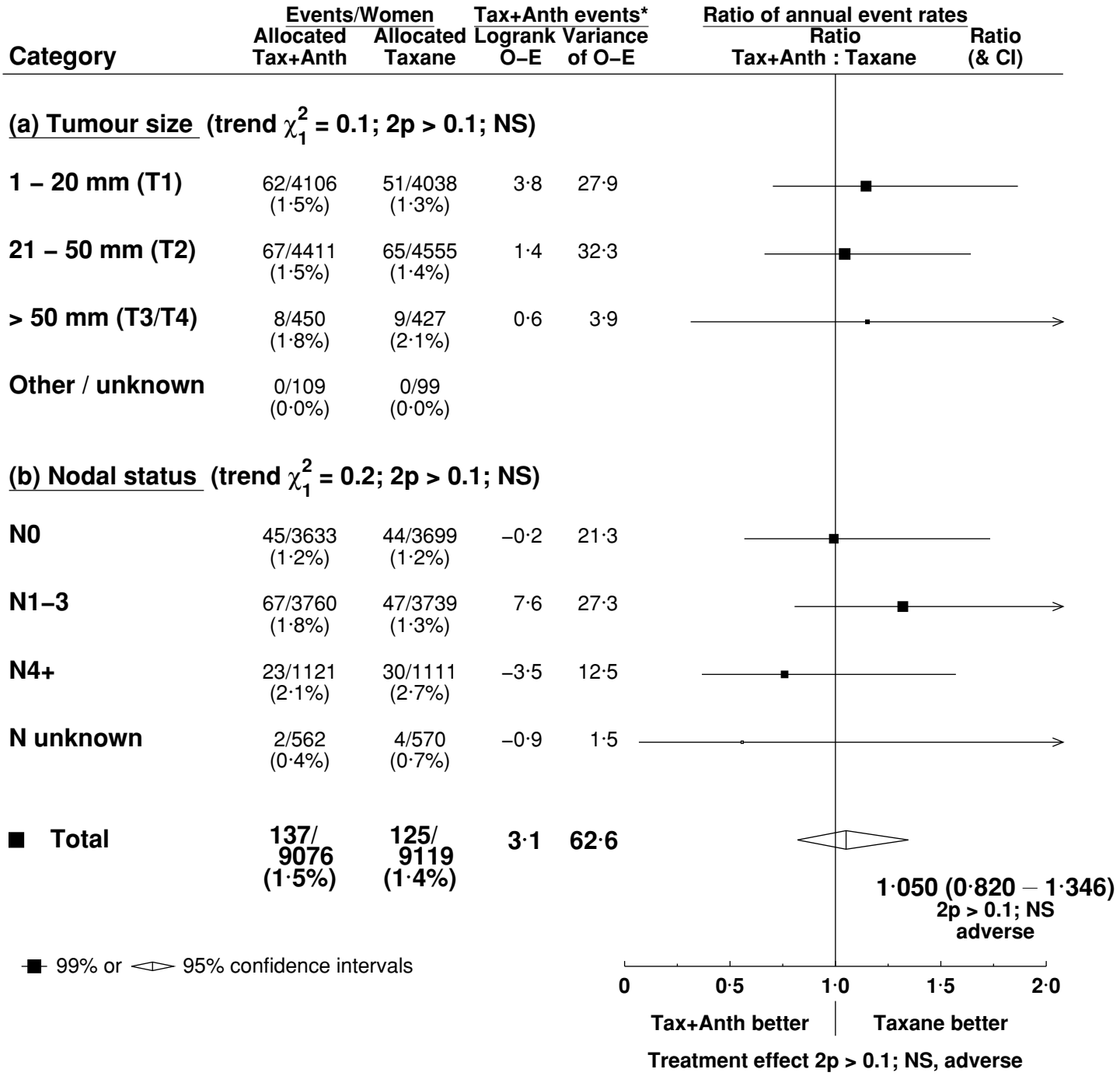
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

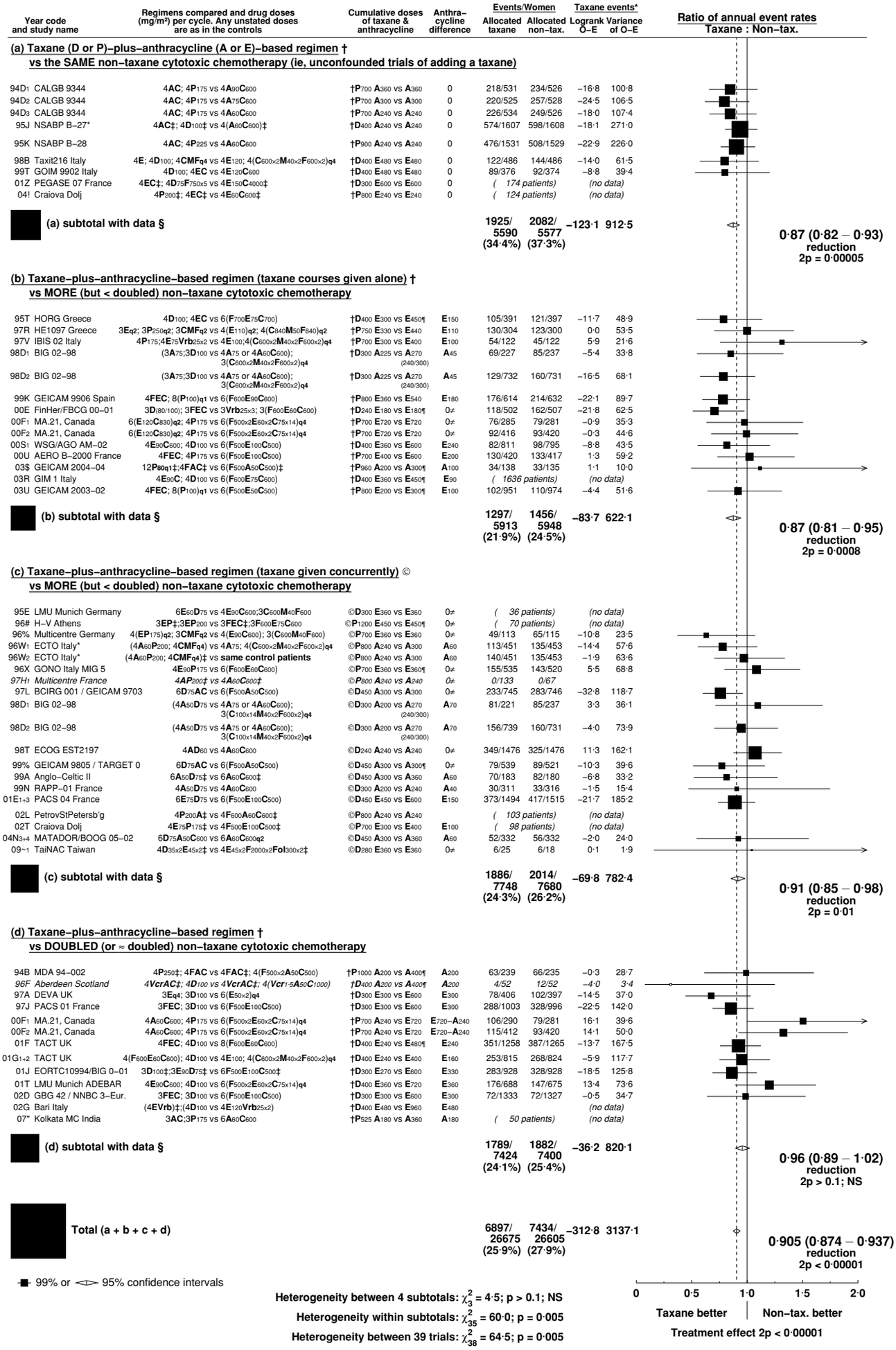
Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Vrb = vinorelbine; Cap = capecitabine; Cpt = carboplatin; Ptz = pertuzumab

P23: Sensitivity analyses for death without recurrence by tumour size and nodal status. All trial comparisons (a)-(d).



P24: Any recurrence in trials of taxane-plus-anthracycline-based regimen vs same, or more (<doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3–way trials versus the same control patients

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre–operative chemotherapy

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

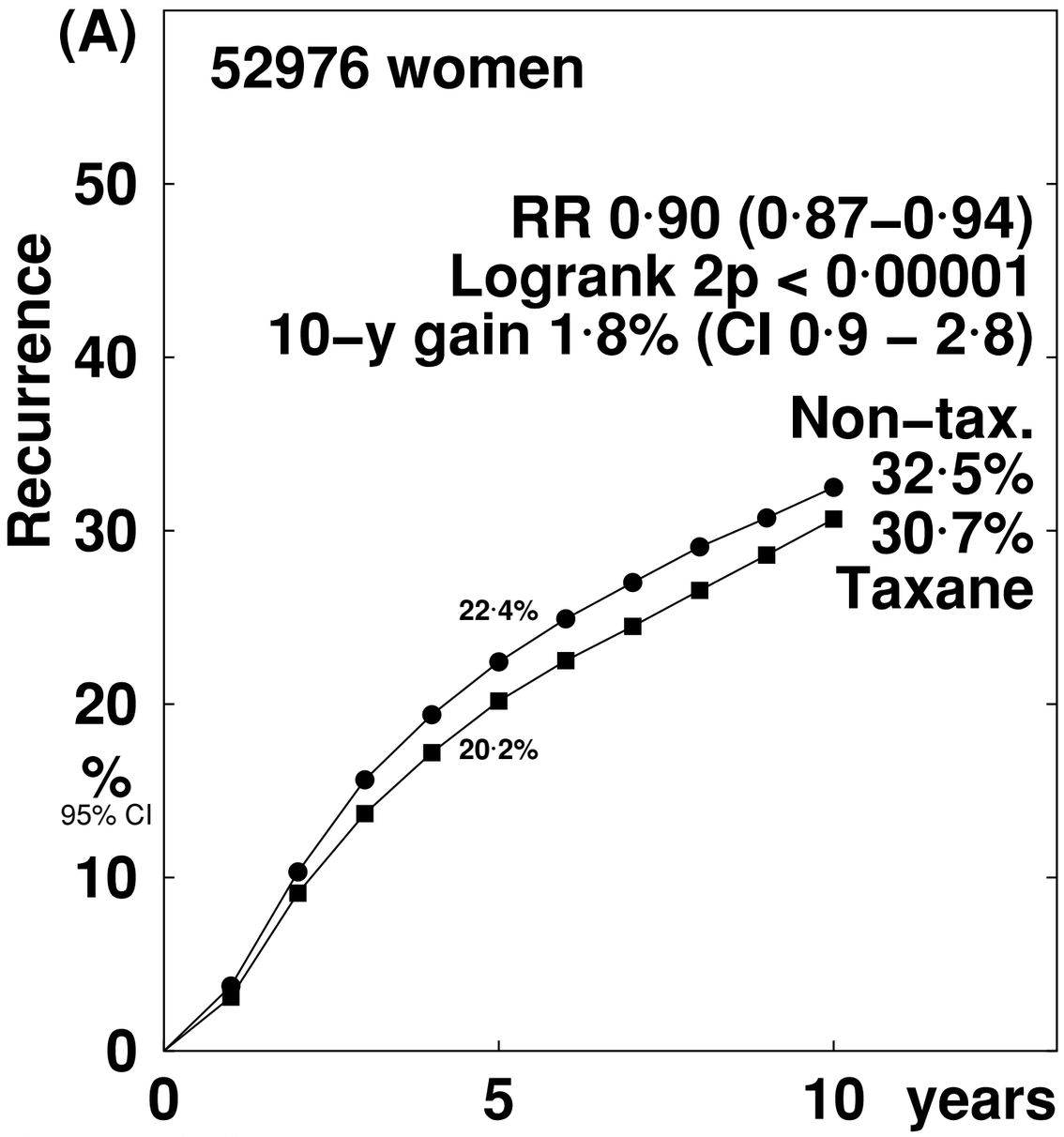
¶ Control anthracycline dose less than E90 or A60 per cycle

Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin. Other agents: C = cyclophosphamide; F = fluorouracil; Fol = folinic acid; M = methotrexate; Vcr = vincristine; Vrb = vinorelbine (Not shown: G–CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1–14 po; ×2 (×3) means d1, d8 (d15) iv

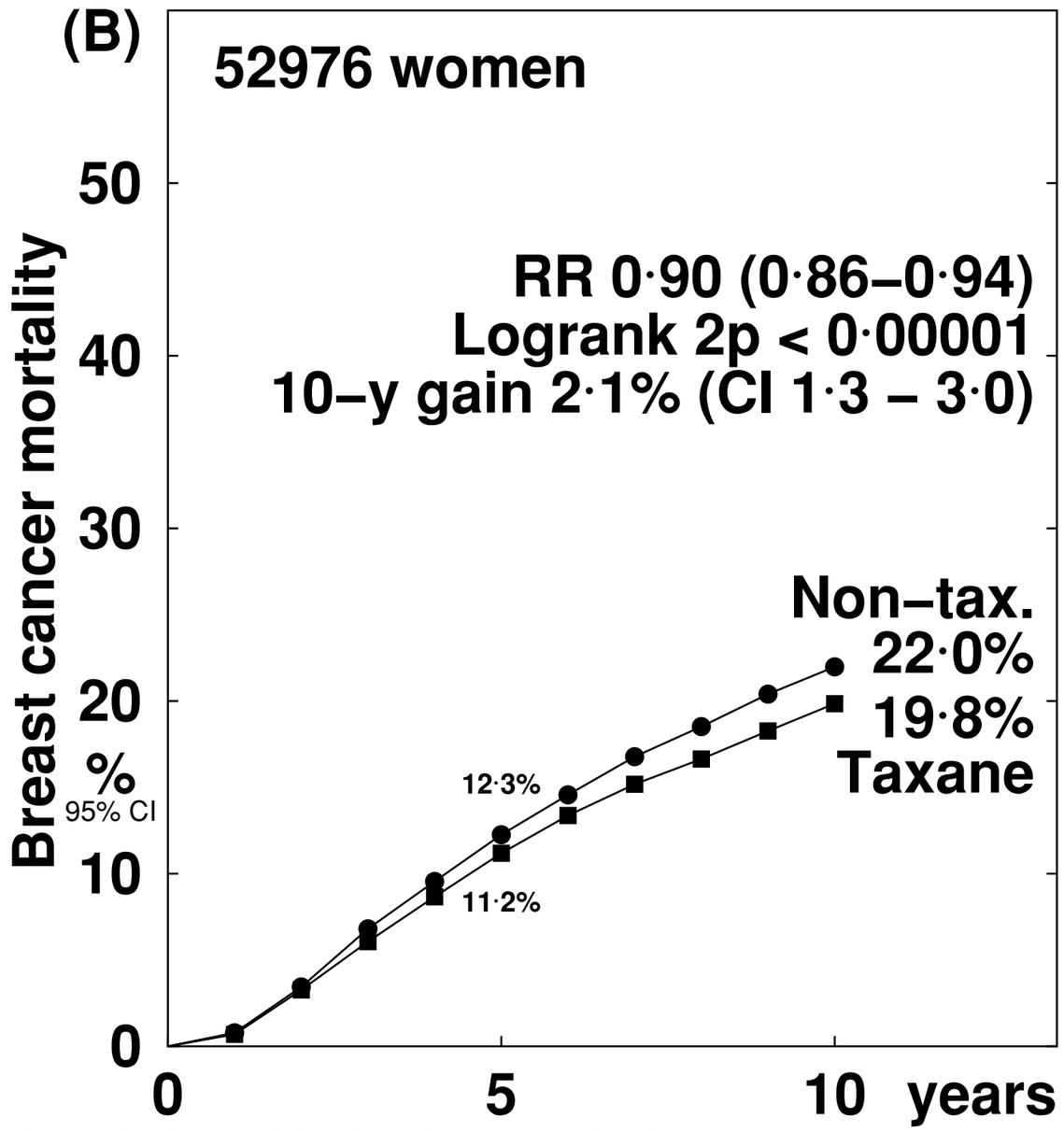
03$ at discretion local investigators could have used epirubicin 100mg/m2 instead of doxorubicin 50mg/m2

P25: 10-year cumulative risk of (A) any recurrence, (B) breast cancer mortality, (C) death without recurrence, (D) all-cause mortality; in trials of taxane-plus-anthracycline-based regimen vs same, or more (<doubled or ~doubled) non-taxane cytotoxic chemotherapy



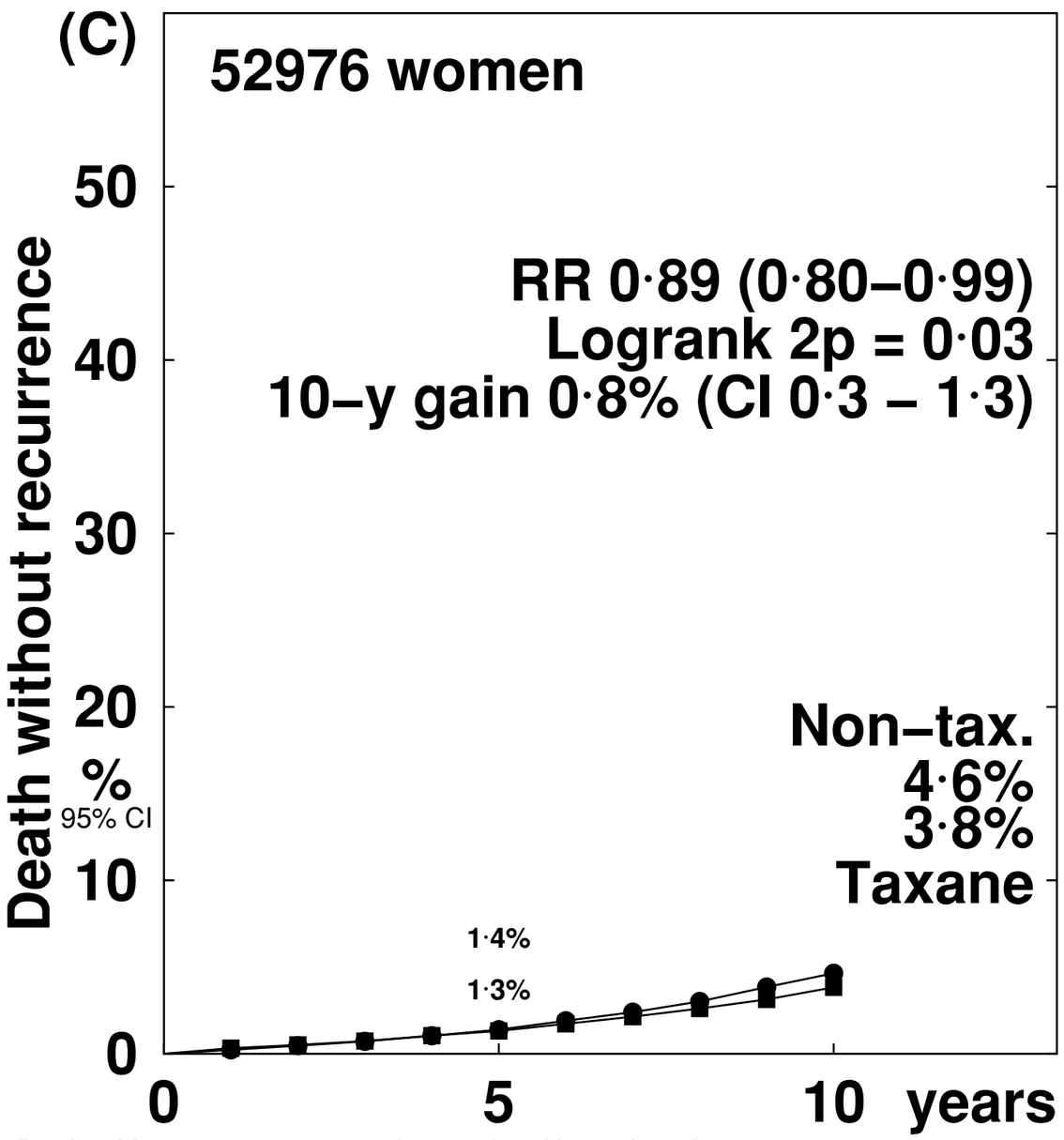
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Taxane	4·53 (5047 / 111389)	2·81 (1609 / 57166)	1·85 (237 / 12790)
Non–tax.	5·14 (5629 / 109489)	2·84 (1554 / 54691)	1·98 (239 / 12041)
Rate ratio, from	0·88 CI 0·85 – 0·92	0·99 CI 0·92 – 1·06	0·89 CI 0·74 – 1·07
(O–E) / V	–303·2 / 2400·4	–8·5 / 743·4	–13·3 / 111·0



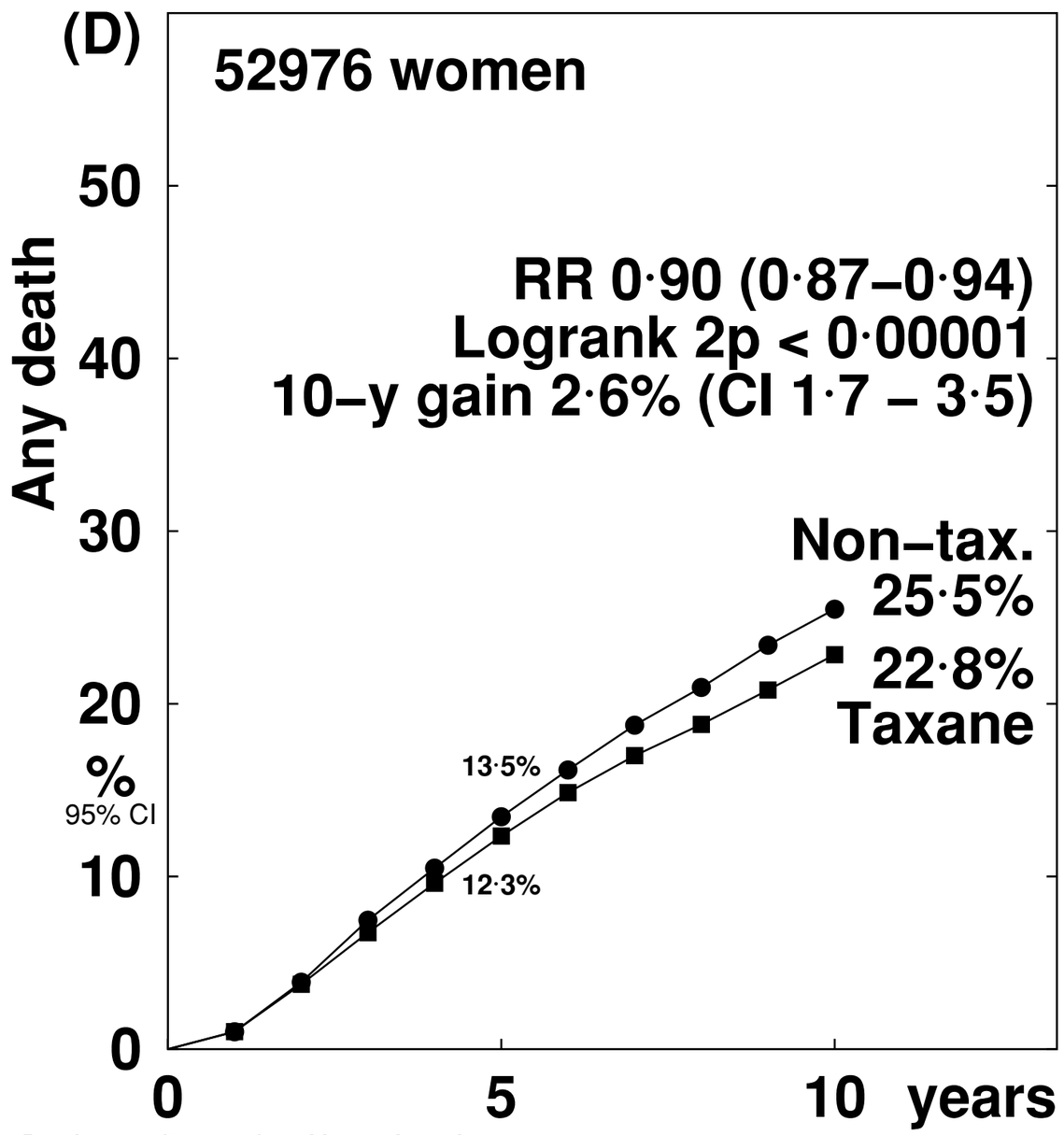
Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Taxane	2·31 CI 2·23 – 2·40	2·12 CI 2·00 – 2·23	1·70 CI 1·49 – 1·90
Non–tax.	2·58 CI 2·49 – 2·67	2·38 CI 2·26 – 2·50	1·54 CI 1·34 – 1·74
Rate ratio, from	0·91 CI 0·86 – 0·95	0·87 CI 0·81 – 0·94	1·09 CI 0·91 – 1·31
(O–E) / V	–133·1 / 1334·2	–95·1 / 679·6	9·9 / 113·4



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

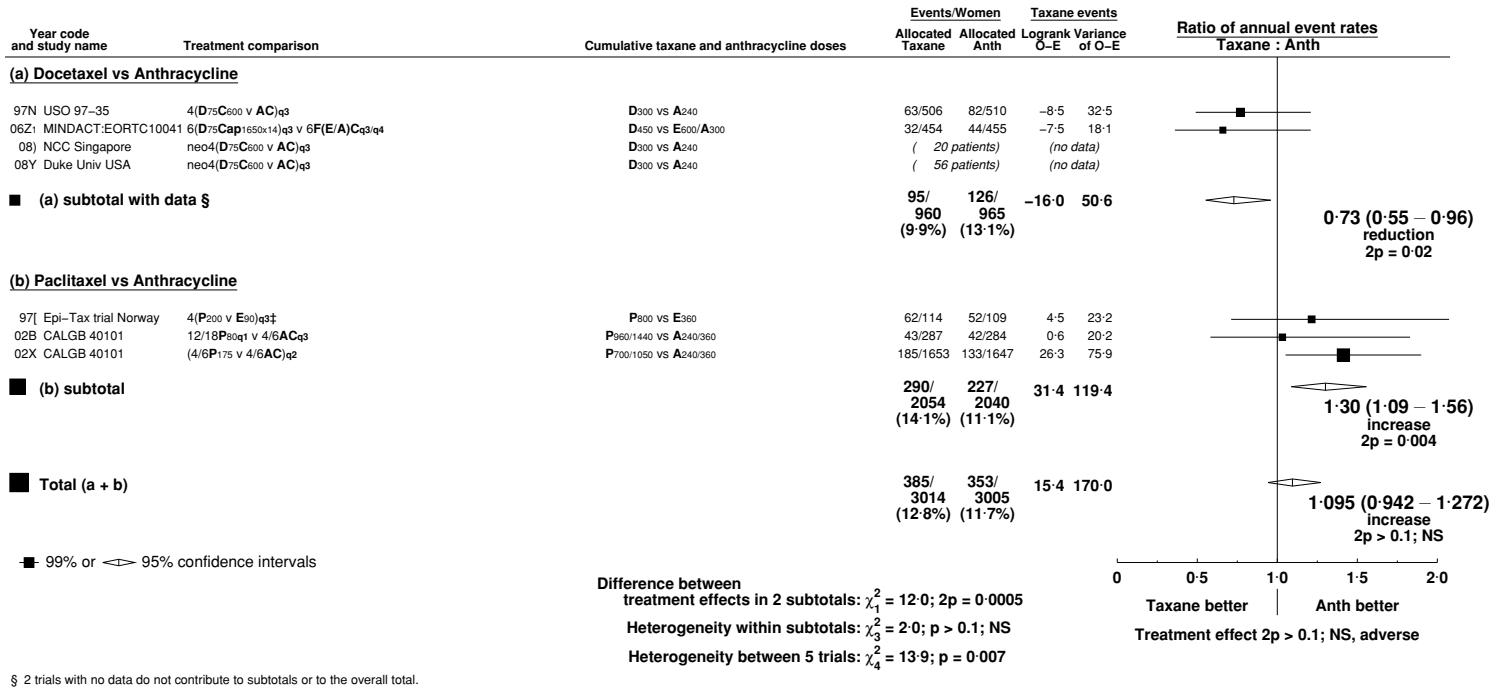
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Taxane	0·26 (293 / 111389)	0·50 (283 / 57166)	1·19 (152 / 12790)
Non–tax.	0·27 (301 / 109489)	0·63 (347 / 54691)	1·16 (140 / 12041)
Rate ratio, from	0·97 CI 0·82 – 1·14	0·77 CI 0·65 – 0·90	1·04 CI 0·82 – 1·33
(O–E) / V	–5·1 / 143·6	–39·3 / 149·2	2·8 / 65·8



Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Taxane	2·57 (3040 / 118173)	2·59 (1663 / 64274)	2·79 (414 / 14837)
Non–tax.	2·85 (3349 / 117405)	3·01 (1878 / 62350)	2·65 (370 / 13967)
Rate ratio, from	0·91 CI 0·87 – 0·96	0·85 CI 0·79 – 0·91	1·07 CI 0·93 – 1·24
(O–E) / V	–138·1 / 1477·8	–134·4 / 828·8	12·7 / 179·2

P26: Any recurrence in trials of taxane-based regimens versus anthracyline-based regimens



§ 2 trials with no data do not contribute to subtotals or to the overall total.

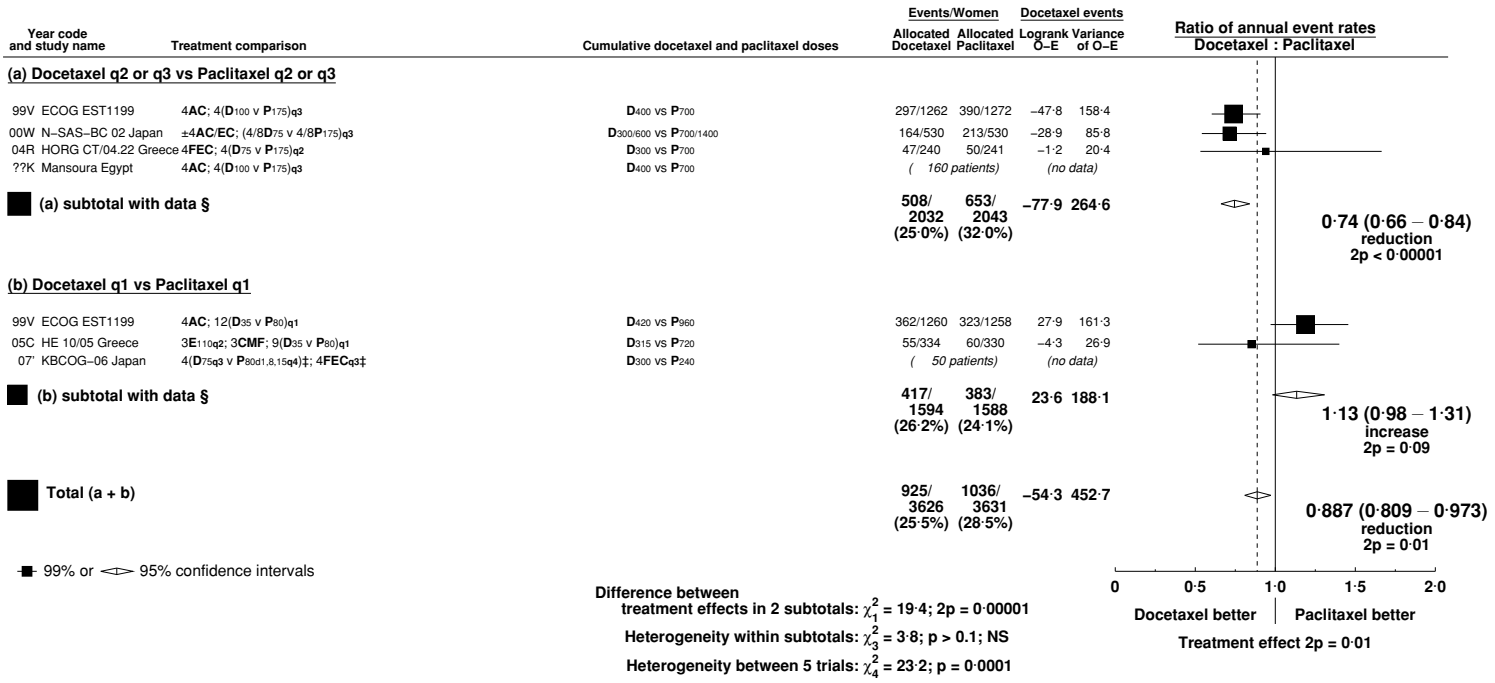
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; Cap = capecitabine

P27: Any recurrence in trials of Docetaxel versus Paclitaxel



§ 2 trials with no data do not contribute to subtotals or to the overall total.

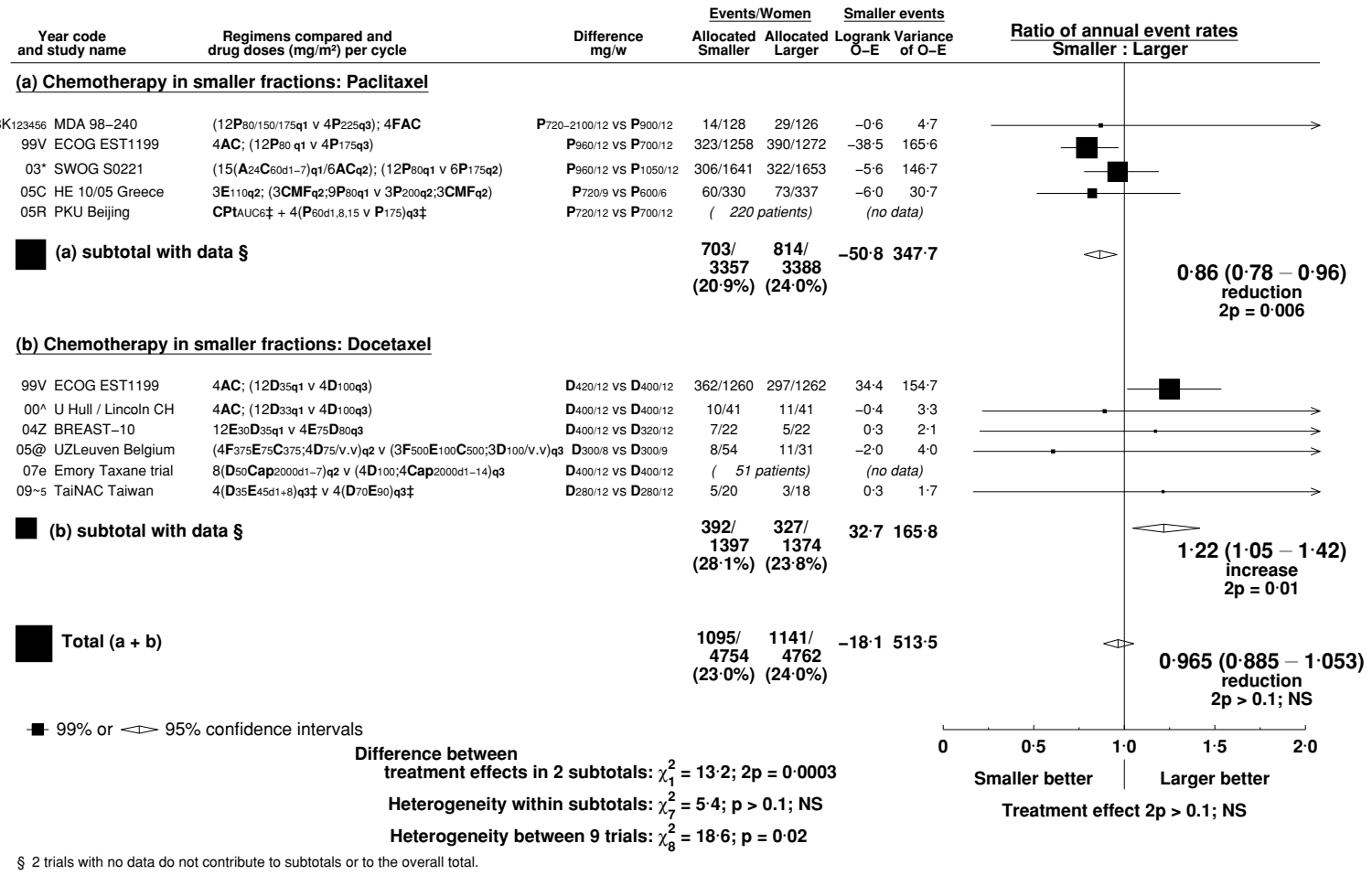
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil

P28: Any recurrence in trials comparing similar cumulative dose taxane chemotherapy delivered in smaller vs larger fractions



§ 2 trials with no data do not contribute to subtotals or to the overall total.

‡ Pre−operative chemotherapy

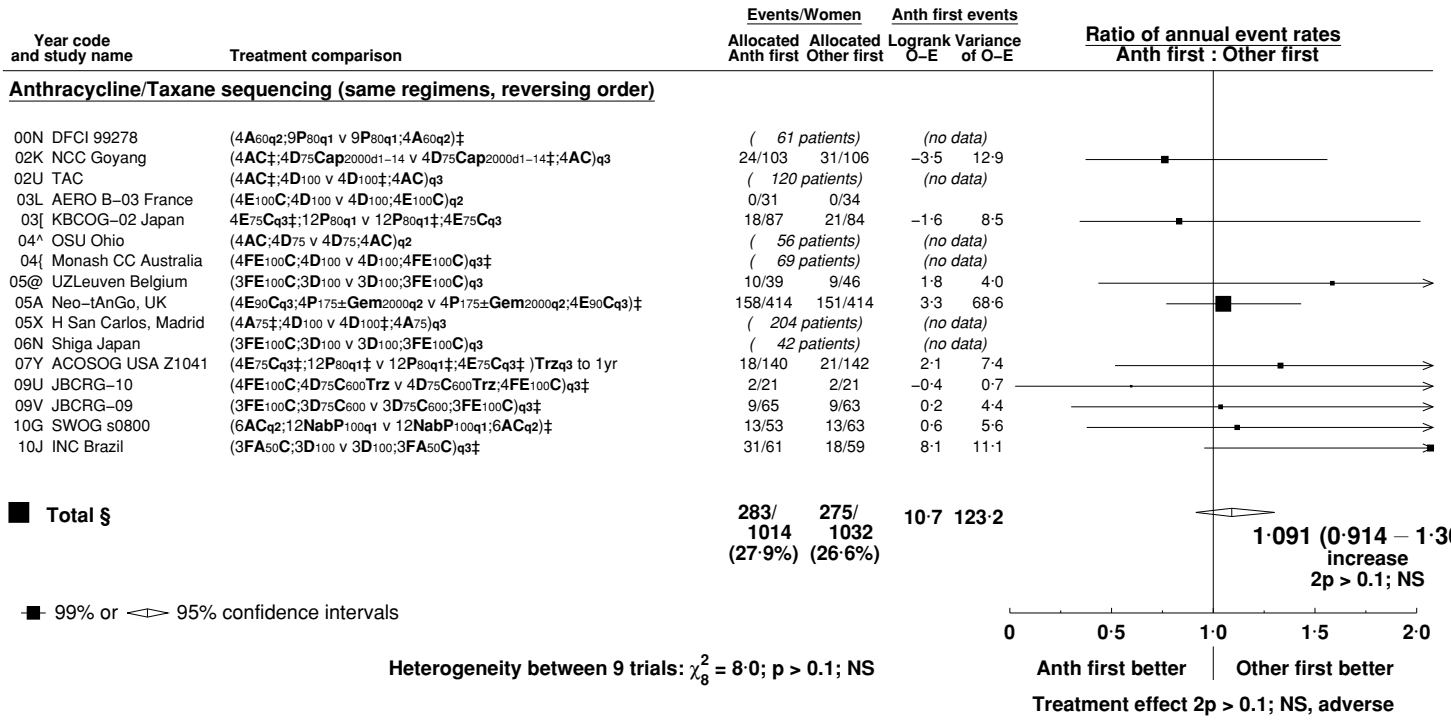
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Cap = capecitabine; Cpt = carboplatin

P29: Any recurrence in trials comparing sequencing order of anthracycline and taxane chemotherapy



§ 6 trials with no data do not contribute to the total.

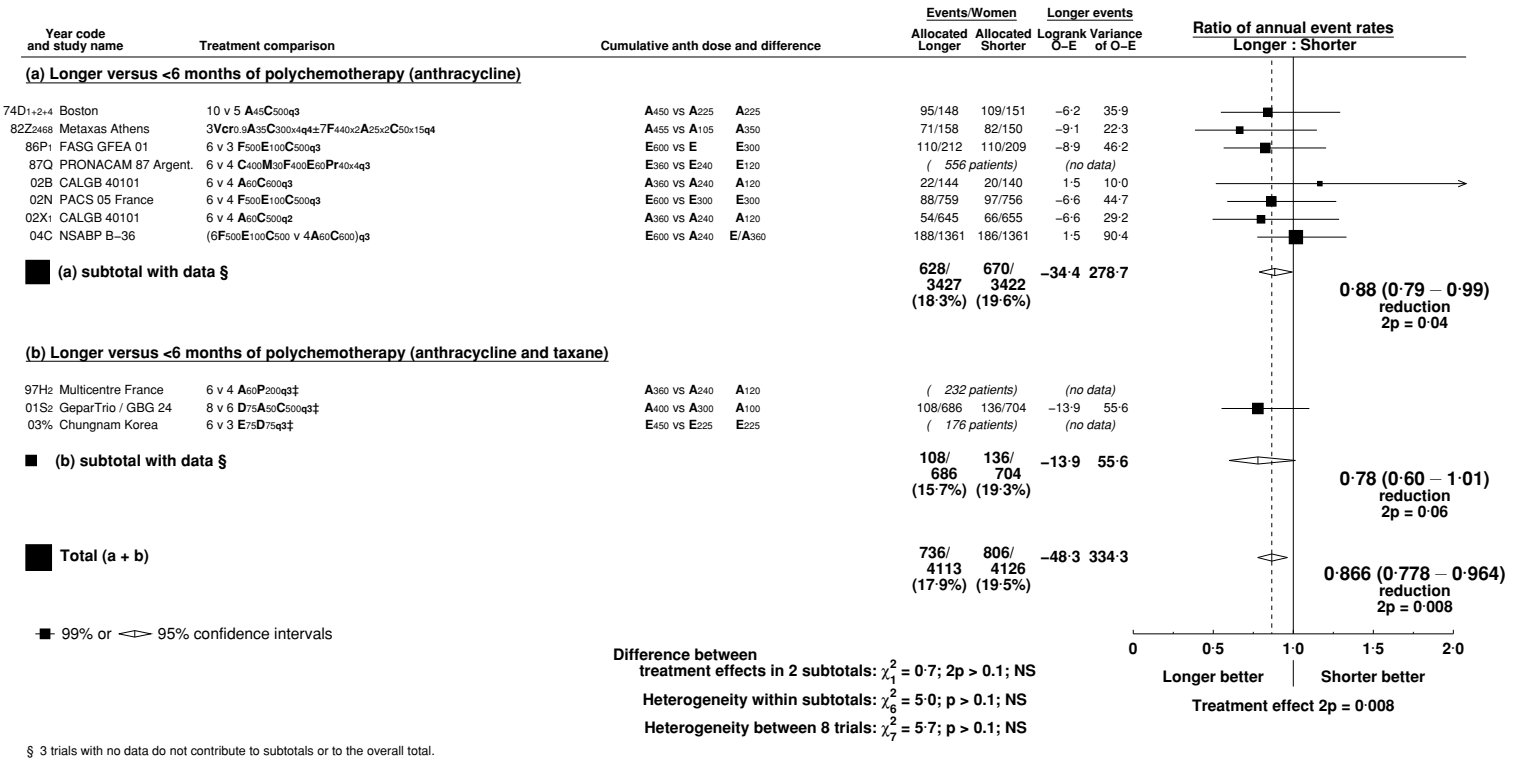
‡ Pre−operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Cap = capecitabine; Gem = gemcitabine; NabP = Nab paclitaxel

P30: Any recurrence in trials of longer versus shorter athracycline/taxane regimens



§ 3 trials with no data do not contribute to subtotals or to the overall total.

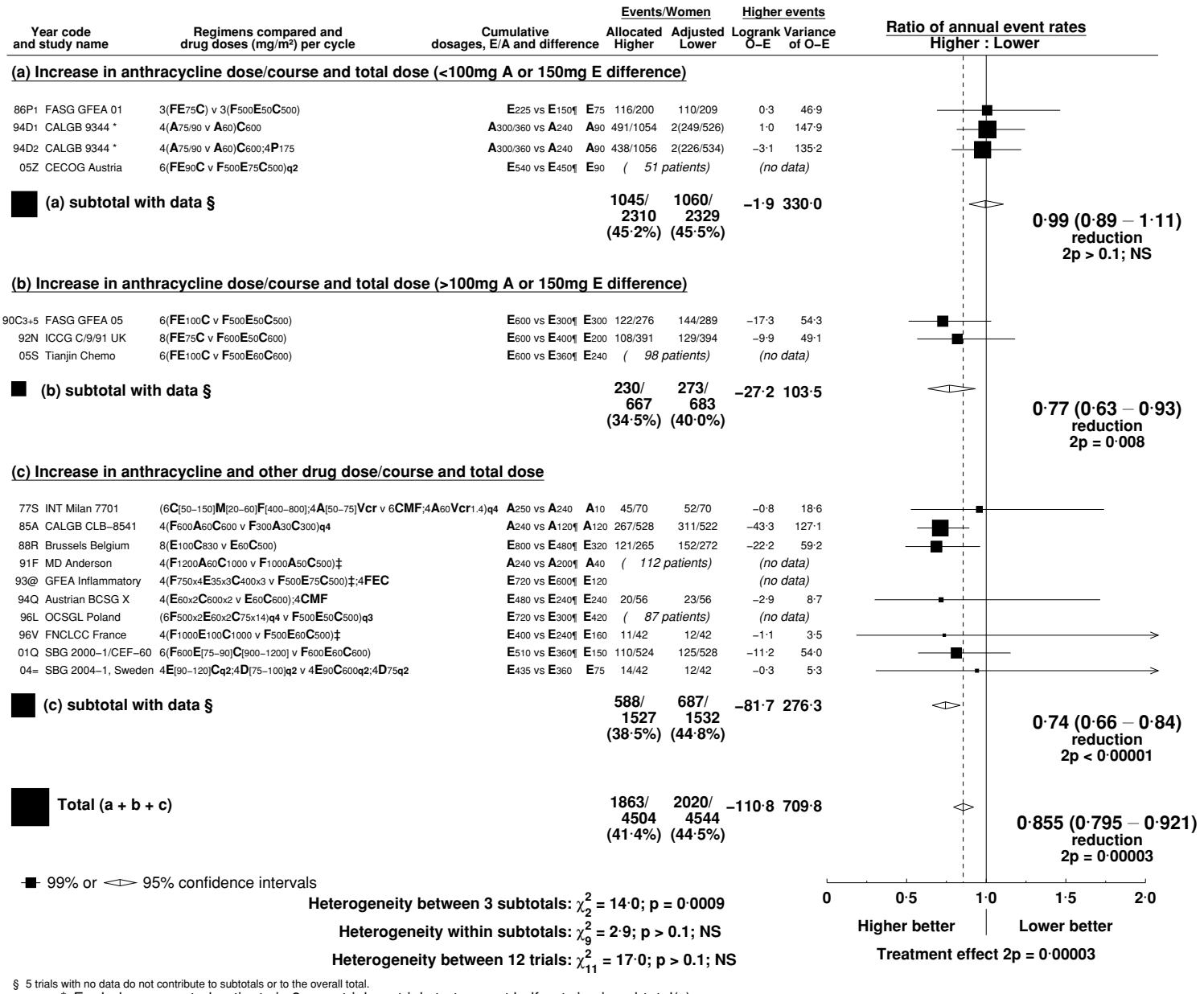
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Pr = prednisone; Vcr = vincristine

P31: Any recurrence in trials of higher versus lower anthracycline dose



§ 5 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of events/patients.

‡ Pre–operative chemotherapy

¶ Control anthracycline dose less than E90 or A60 per cycle

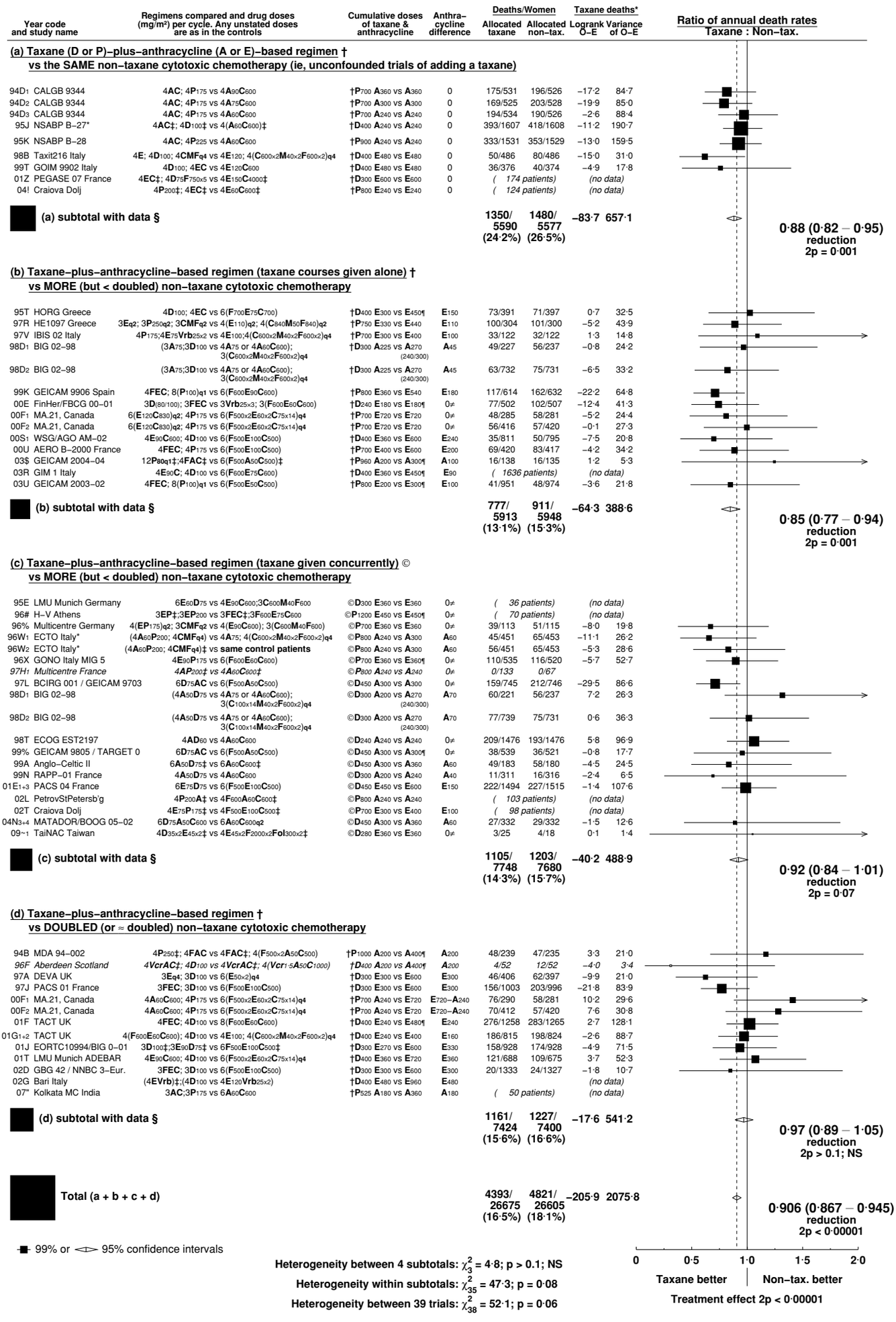
Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin.

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Vcr = vincristine

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1-14 po; ×2 (×3) means d1, d8 (d15) iv

77S in control arm dose for CMF are $C_{100}M_{40}F_{600}$

P32: Breast cancer mortality in trials of taxane-plus-anthracycline-based regimen vs same, or more (<doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3–way trials versus the same control patients

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre–operative chemotherapy

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

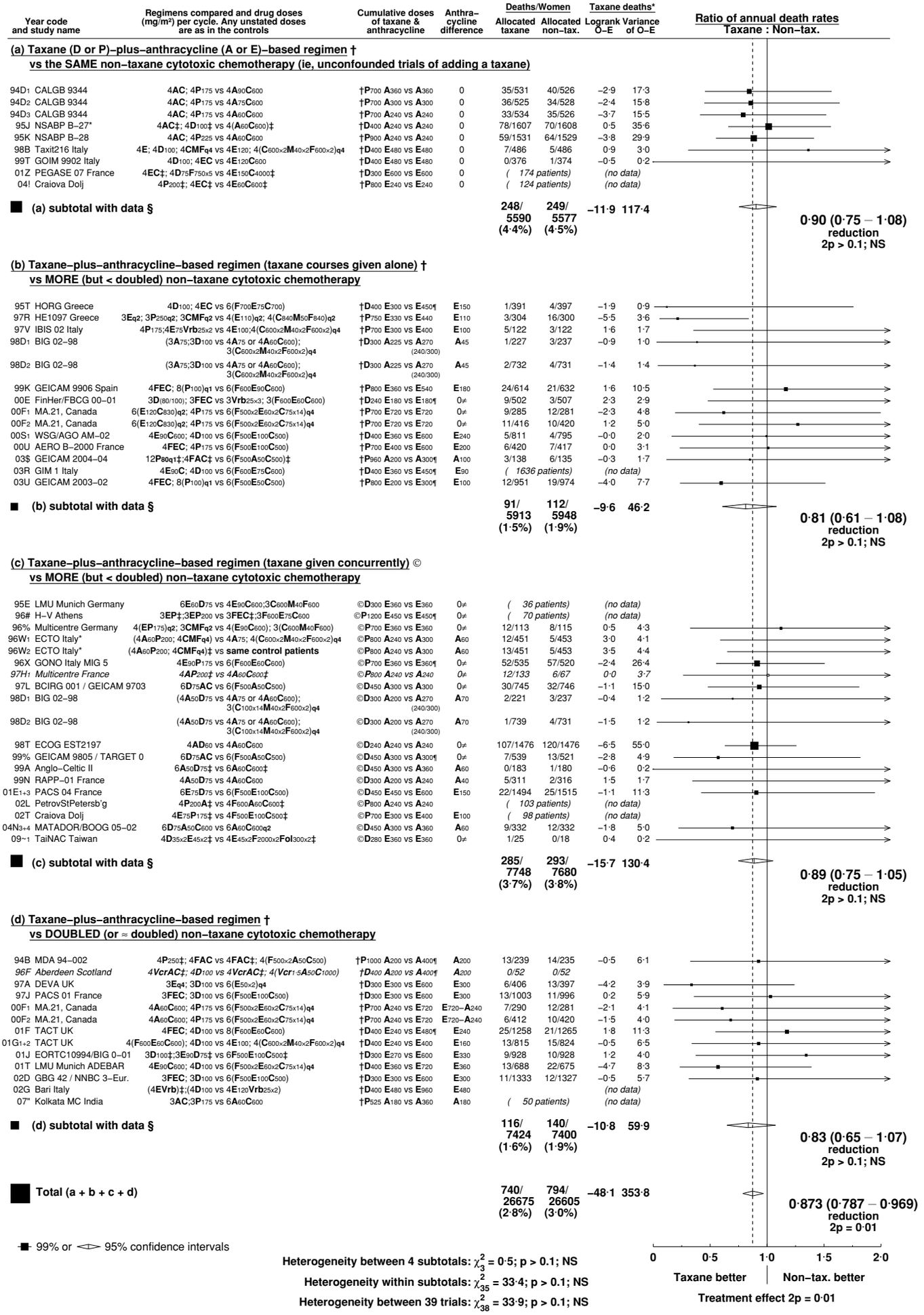
¶ Control anthracycline dose less than E90 or A60 per cycle

Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin. Other agents: C = cyclophosphamide; F = fluorouracil; Fol = folinic acid; M = methotrexate; Vcr = vincristine; Vrb = vinorelbine (Not shown: G–CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1–14 po; ×2 (×3) means d1, d8 (d15) iv

03$ at discretion local investigators could have used epirubicin 100mg/m2 instead of doxorubicin 50mg/m2

P33: Death without recurrence in trials of taxane-plus-anthracycline-based regimen vs same, or more (<doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3–way trials versus the same control patients

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre–operative chemotherapy

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

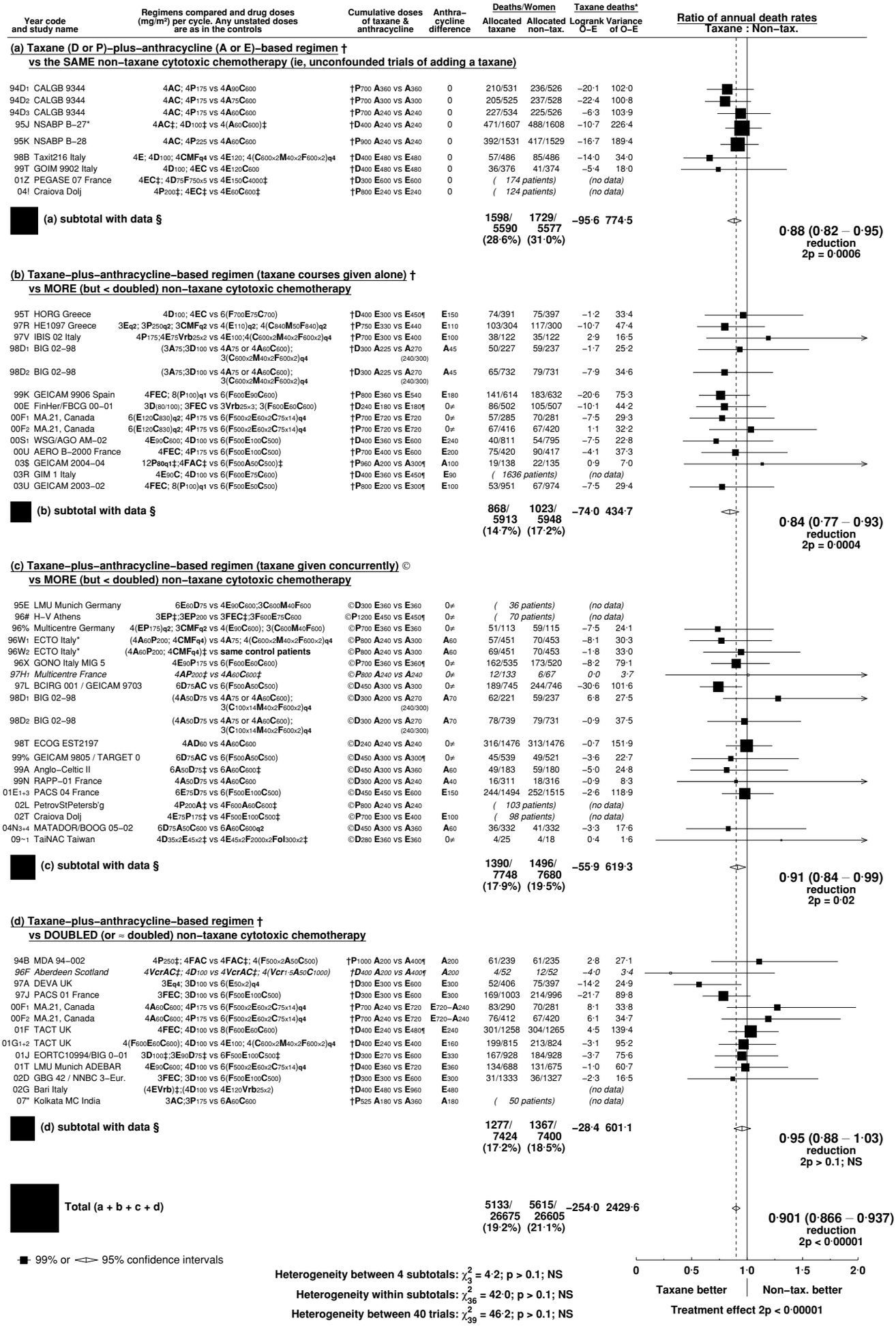
¶ Control anthracycline dose less than E90 or A60 per cycle

Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin. Other agents: C = cyclophosphamide; F = fluorouracil; Fol = folinic acid; M = methotrexate; Vcr = vincristine; Vrb = vinorelbine (Not shown: G–CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1–14 po; ×2 (×3) means d1, d8 (d15) iv

03$ at discretion local investigators could have used epirubicin 100mg/m2 instead of doxorubicin 50mg/m2

P34: All-cause mortality in trials of taxane-plus-anthracycline-based regimen vs same, or more (<doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3–way trials versus the same control patients

† Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased

‡ Pre–operative chemotherapy

© Concurrent treatment with taxane and anthracycline; total chemotherapy duration and number of courses not increased

≠ Same cumulative anthracycline dose, but differences in other drugs

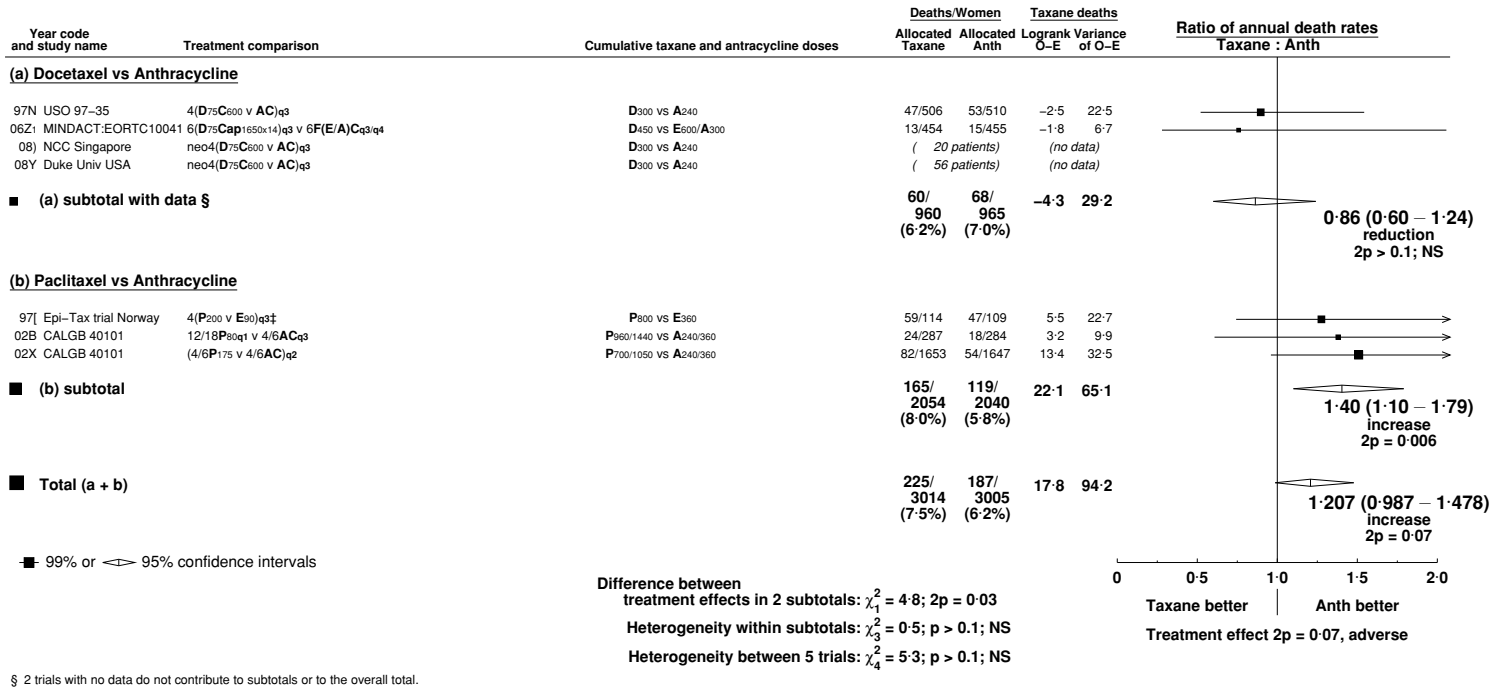
¶ Control anthracycline dose less than E90 or A60 per cycle

Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin. Other agents: C = cyclophosphamide; F = fluorouracil; Fol = folinic acid; M = methotrexate; Vcr = vincristine; Vrb = vinorelbine (Not shown: G–CSF, erythropoietin, trastuzumab, antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1–14 po; ×2 (×3) means d1, d8 (d15) iv

03$ at discretion local investigators could have used epirubicin 100mg/m2 instead of doxorubicin 50mg/m2

P35: Breast cancer mortality in trials of taxane-based regimens versus anthracyline-based regimens



§ 2 trials with no data do not contribute to subtotals or to the overall total.

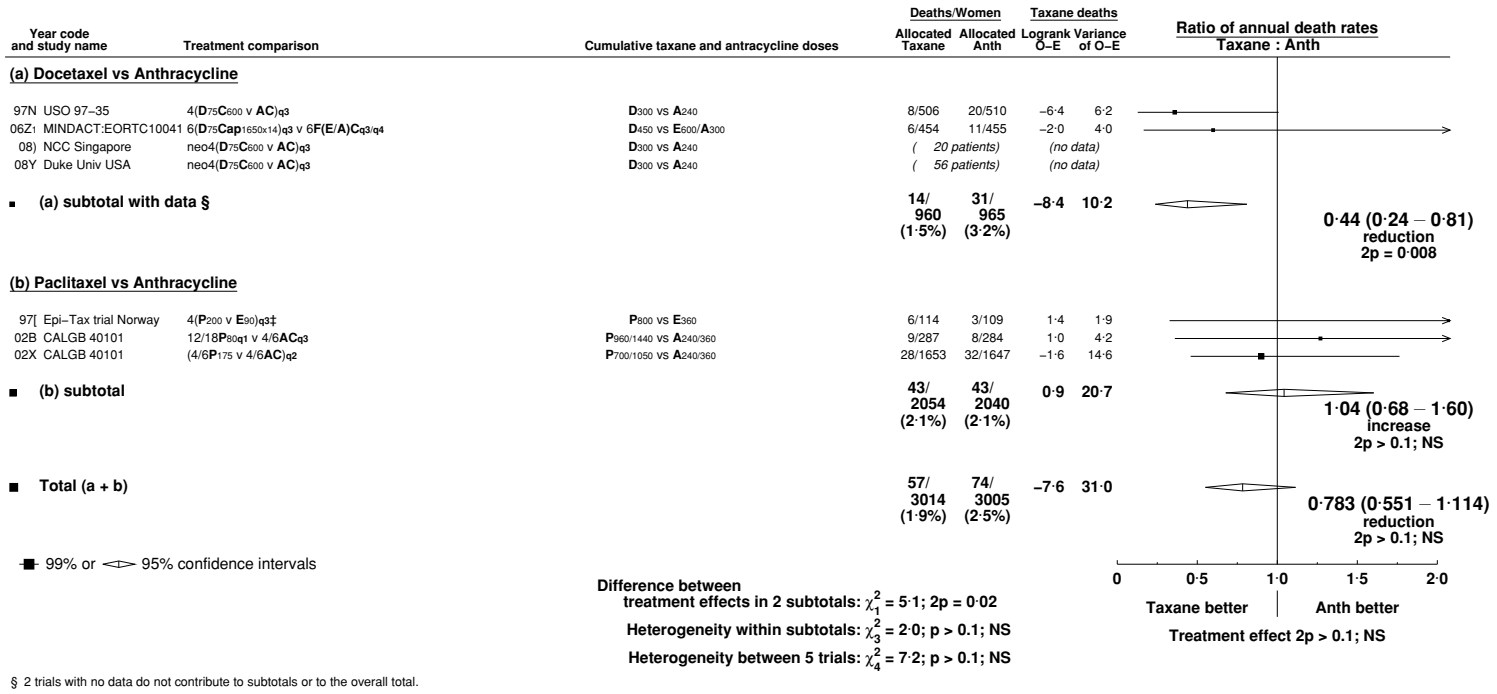
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; Cap = capecitabine

P36: Death without recurrence in trials of taxane-based regimens versus anthracyline-based regimens



§ 2 trials with no data do not contribute to subtotals or to the overall total.

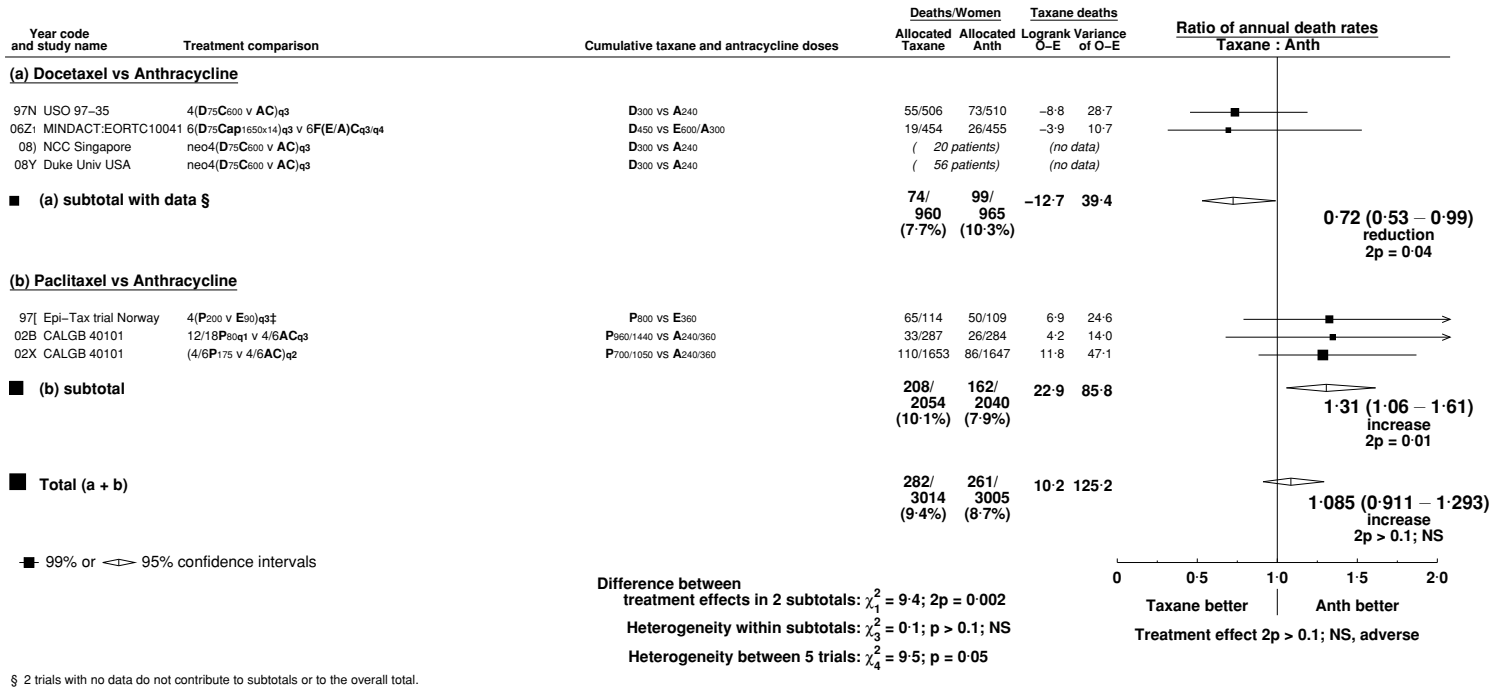
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; Cap = capecitabine

P37: All-cause mortality in trials of taxane-based regimens versus anthracyline-based regimens



§ 2 trials with no data do not contribute to subtotals or to the overall total.

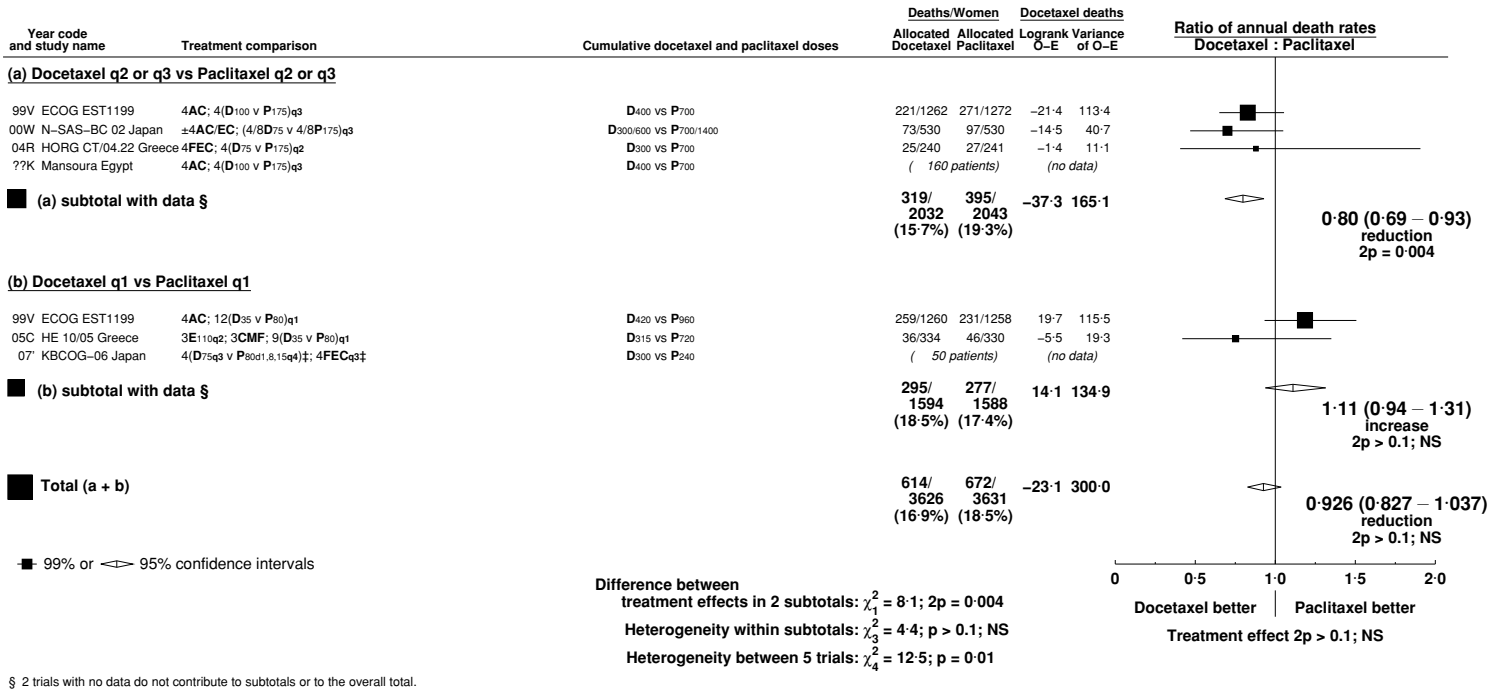
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; Cap = capecitabine

P38: Breast cancer mortality in trials of Docetaxel versus Paclitaxel



§ 2 trials with no data do not contribute to subtotals or to the overall total.

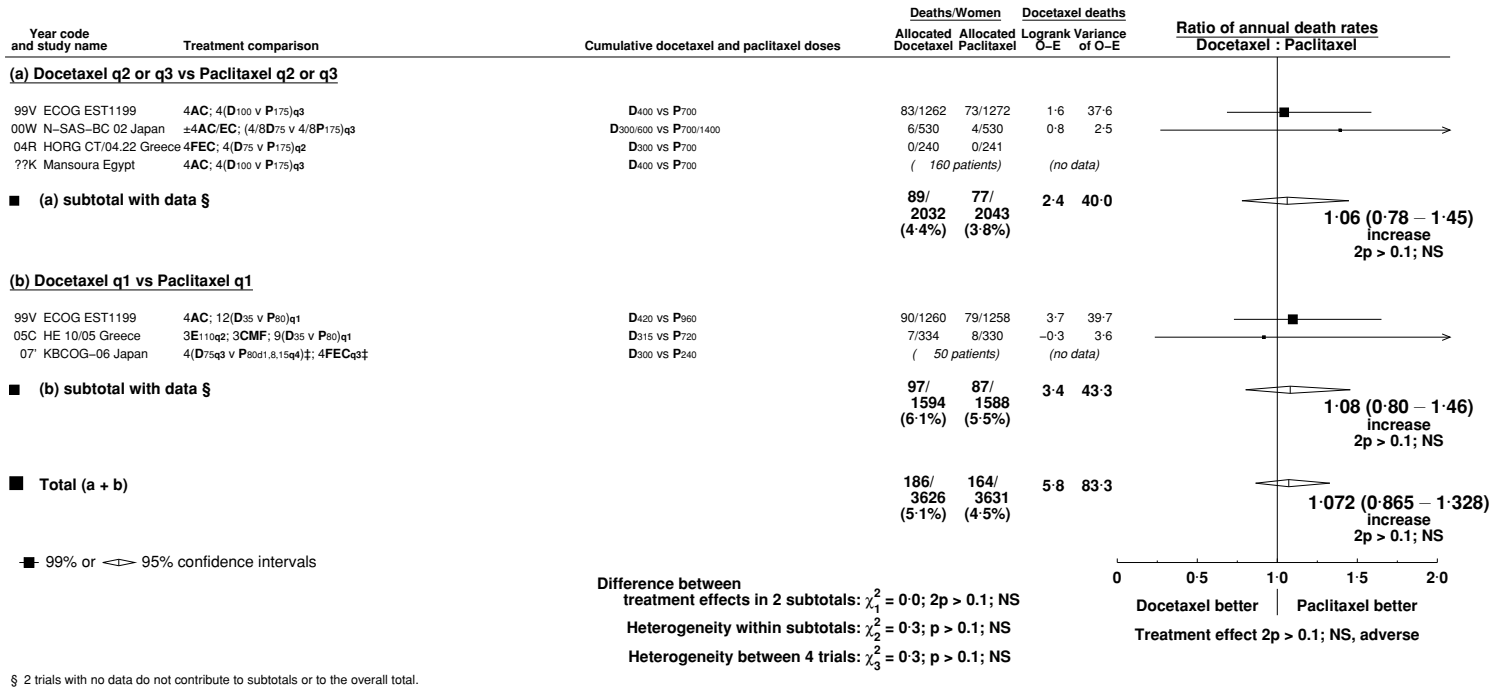
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil

P39: Death without recurrence in trials of Docetaxel versus Paclitaxel



§ 2 trials with no data do not contribute to subtotals or to the overall total.

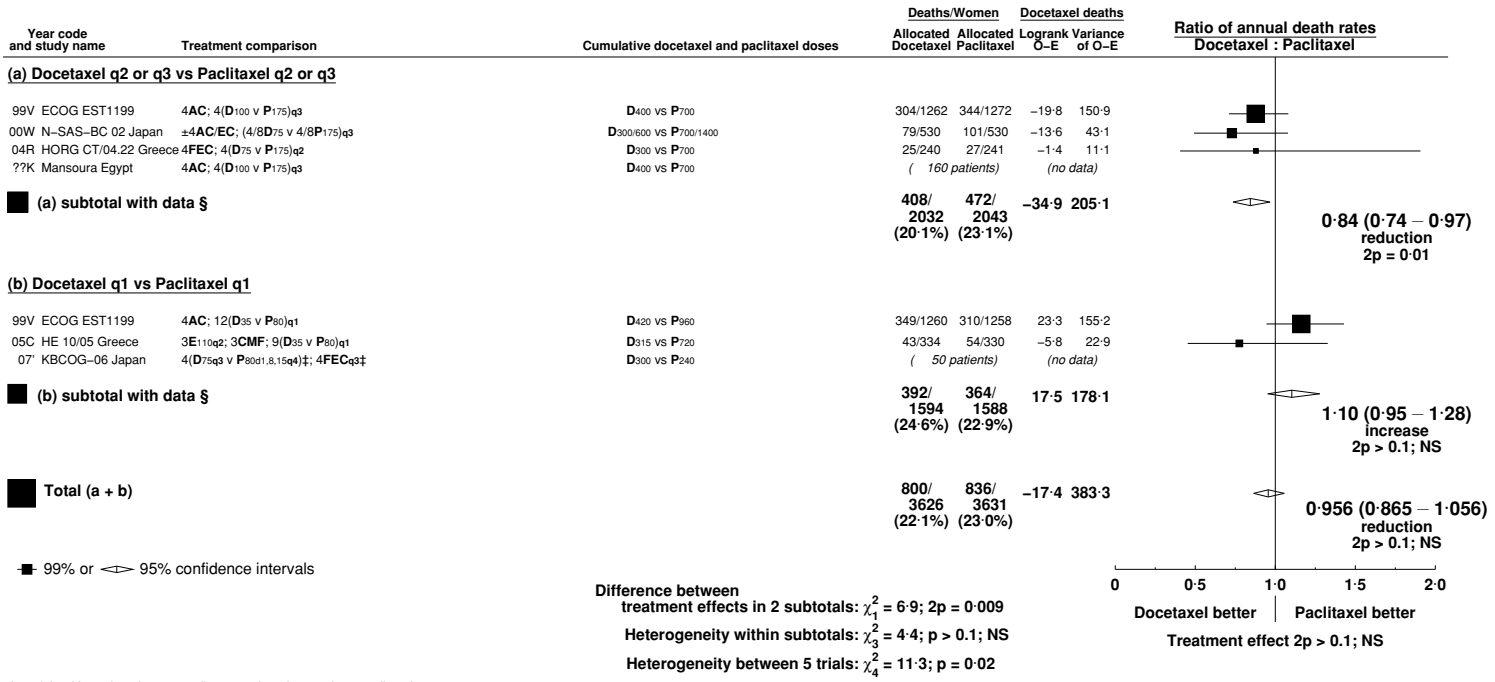
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil

P40: All-cause mortality in trials of Docetaxel versus Paclitaxel



§ 2 trials with no data do not contribute to subtotals or to the overall total.

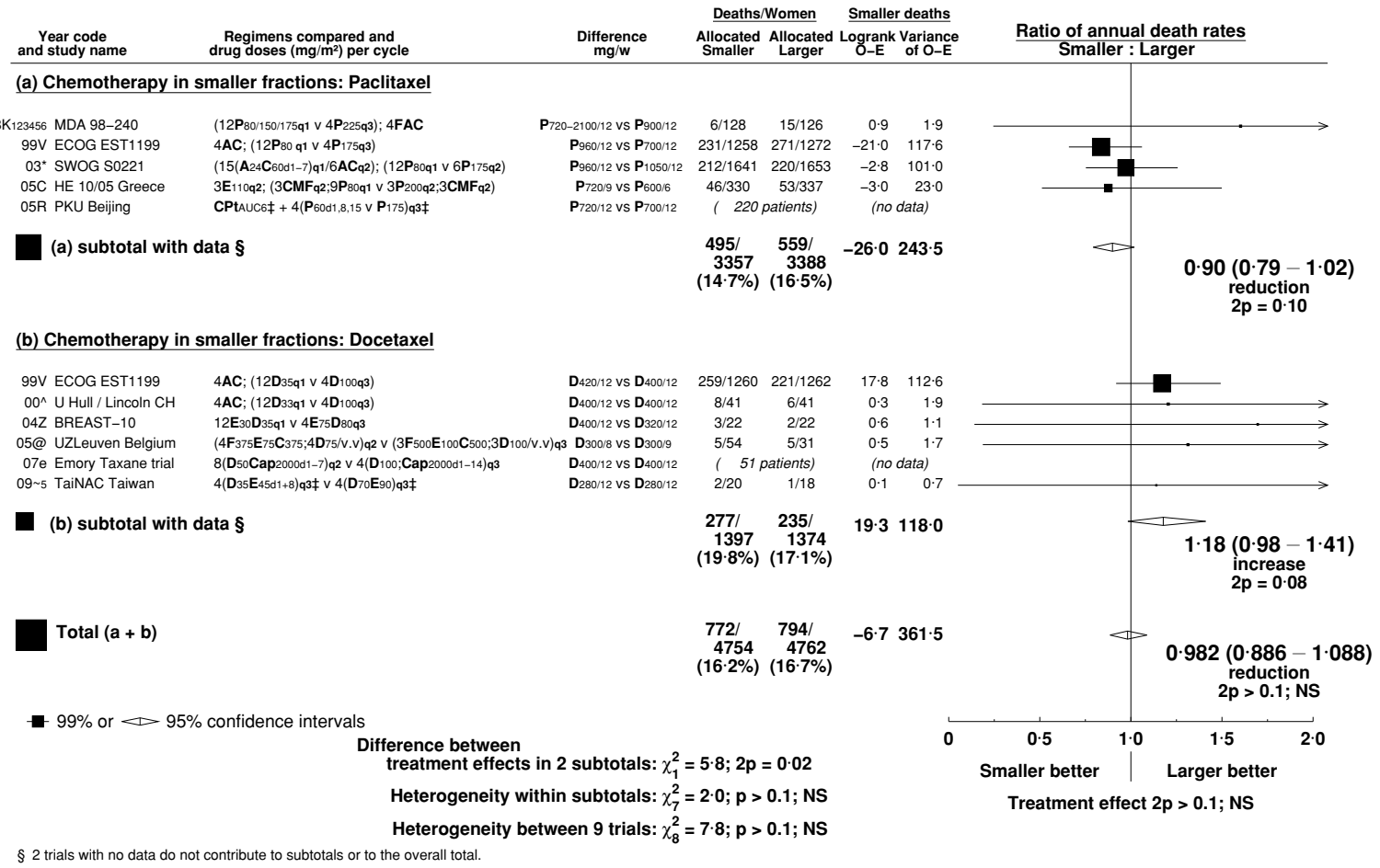
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil

P41: Breast cancer mortality in trials comparing similar cumulative dose taxane chemotherapy delivered in smaller vs larger fractions



§ 2 trials with no data do not contribute to subtotals or to the overall total.

‡ Pre−operative chemotherapy

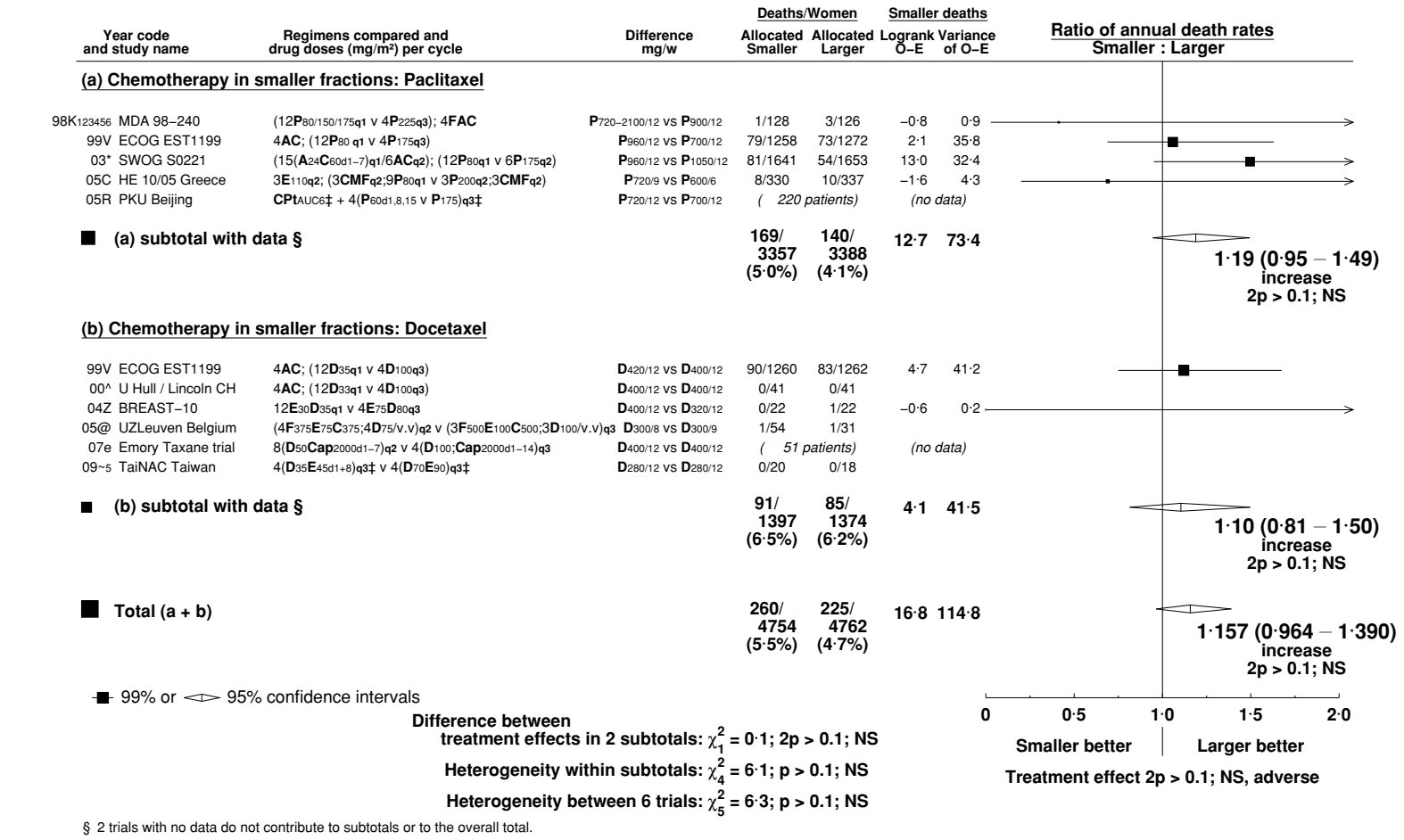
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Cap = capecitabine; Cpt = carboplatin

P42: Death without recurrence in trials comparing similar cumulative dose taxane chemotherapy delivered in smaller vs larger fractions



§ 2 trials with no data do not contribute to subtotals or to the overall total.

‡ Pre–operative chemotherapy

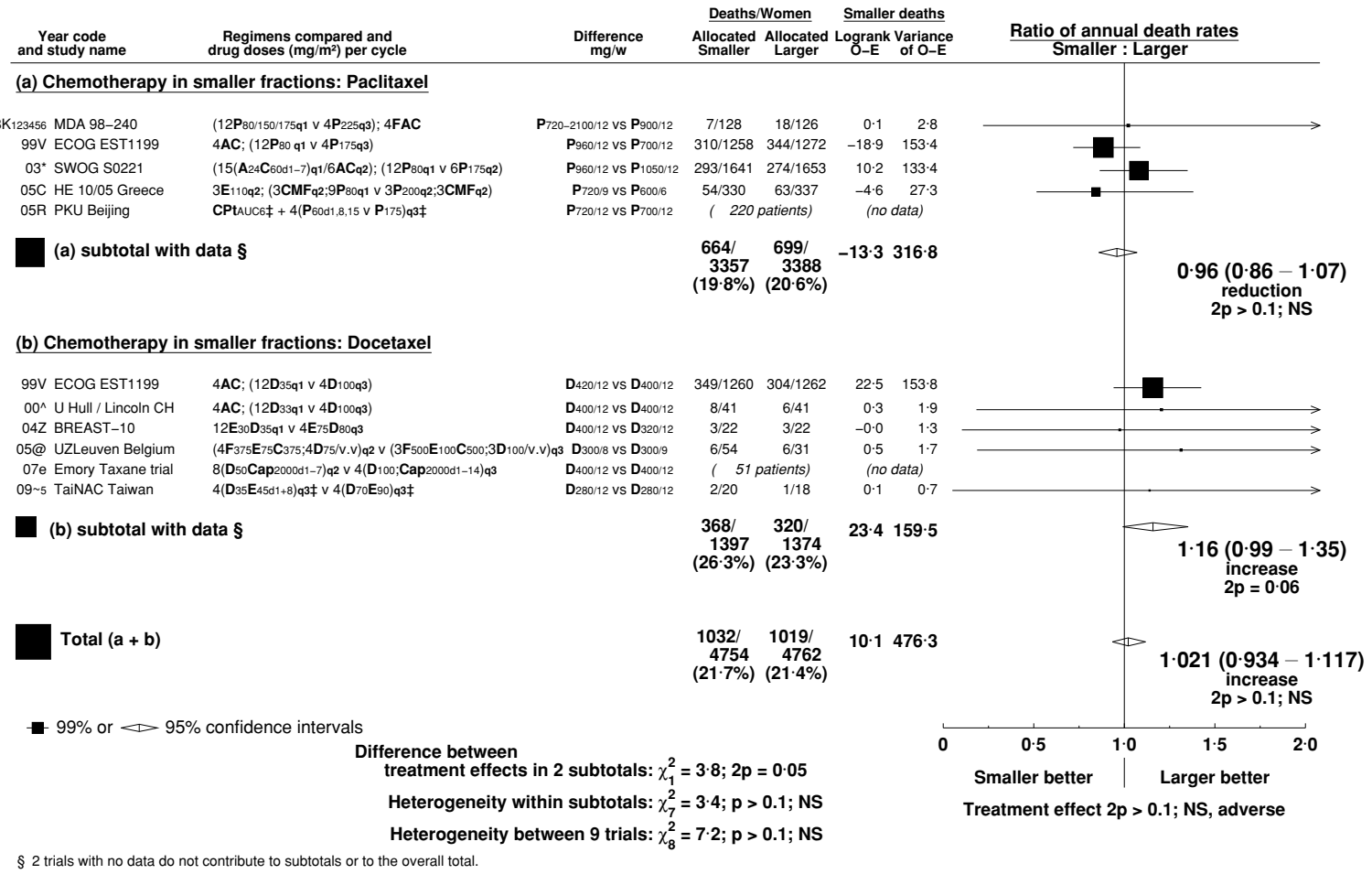
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Cap = capecitabine; Cpt = carboplatin

P43: All-cause mortality in trials comparing similar cumulative dose taxane chemotherapy delivered in smaller vs larger fractions



§ 2 trials with no data do not contribute to subtotals or to the overall total.

‡ Pre–operative chemotherapy

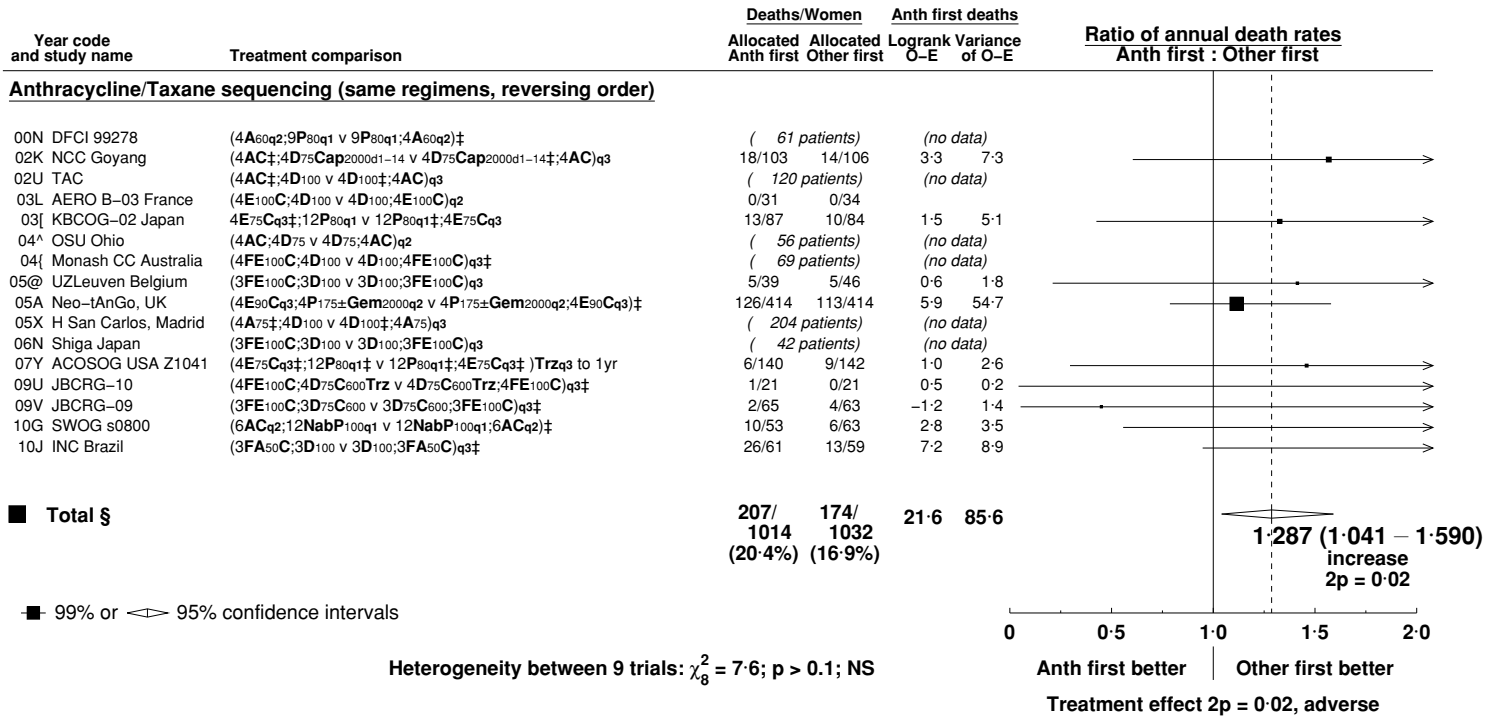
v.v Vice versa

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Cap = capecitabine; Cpt = carboplatin

P44: Breast cancer mortality in trials comparing sequencing order of anthracycline and taxane chemotherapy



§ 6 trials with no data do not contribute to the total.

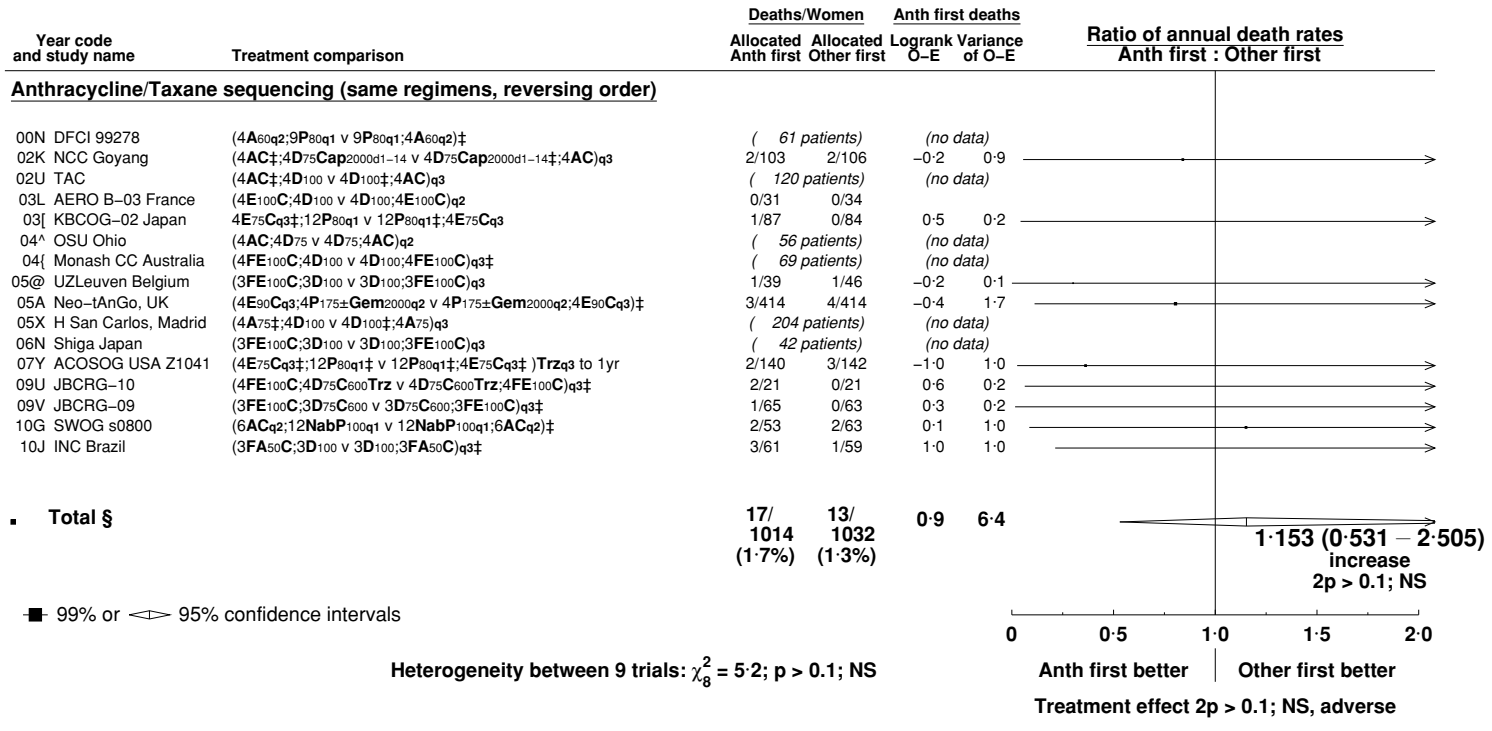
‡ Pre−operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Cap = capecitabine; Gem = gemcitabine; NabP = Nab paclitaxel

P45: Death without recurrence in trials comparing sequencing order of anthracycline and taxane chemotherapy



§ 6 trials with no data do not contribute to the total.

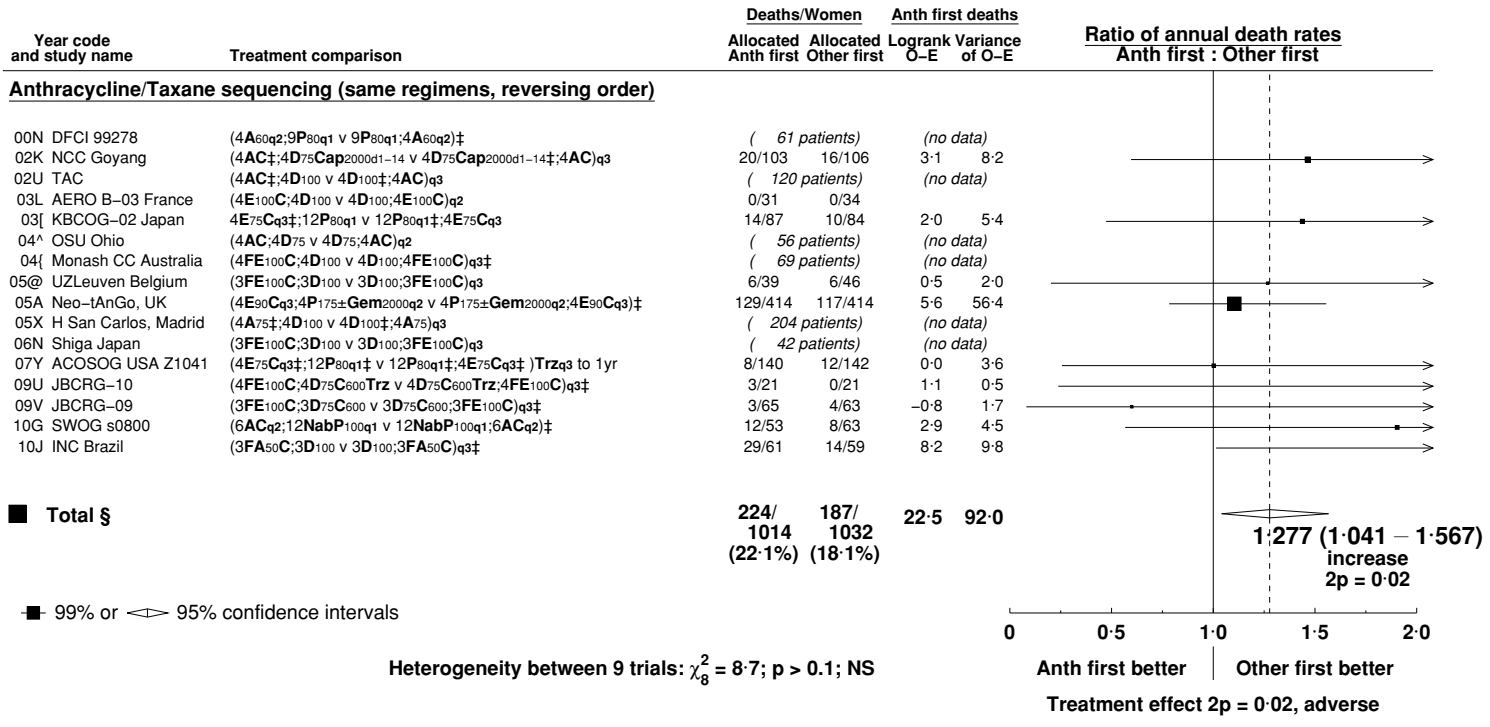
‡ Pre−operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Cap = capecitabine; Gem = gemcitabine; NabP = Nab paclitaxel

P46: All-cause mortality in trials comparing sequencing order of anthracycline and taxane chemotherapy



§ 6 trials with no data do not contribute to the total.

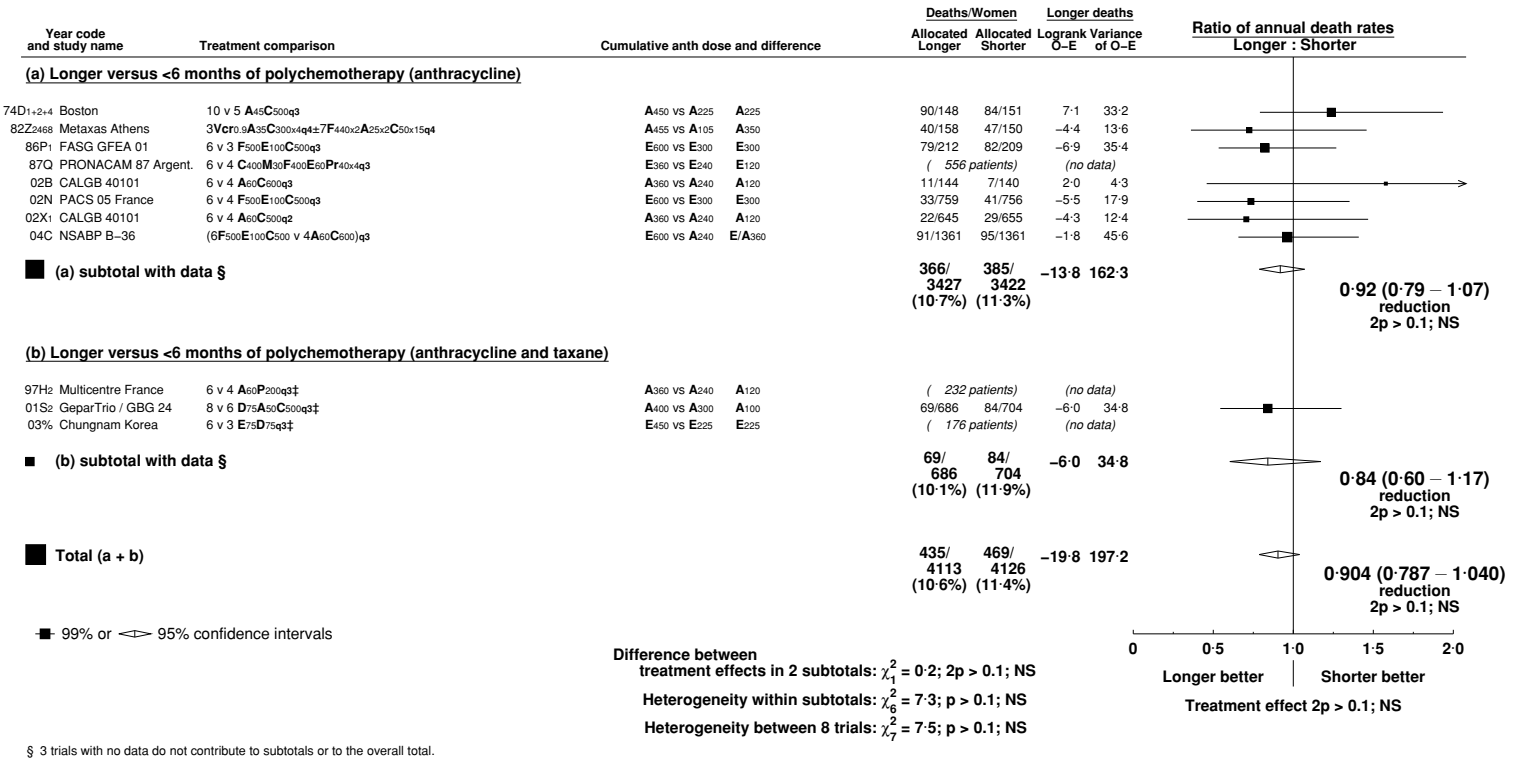
‡ Pre−operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Trz = trastuzumab; Cap = capecitabine; Gem = gemcitabine; NabP = Nab paclitaxel

P47: Breast cancer mortality in trials of longer versus shorter athracycline/taxane regimens



§ 3 trials with no data do not contribute to subtotals or to the overall total.

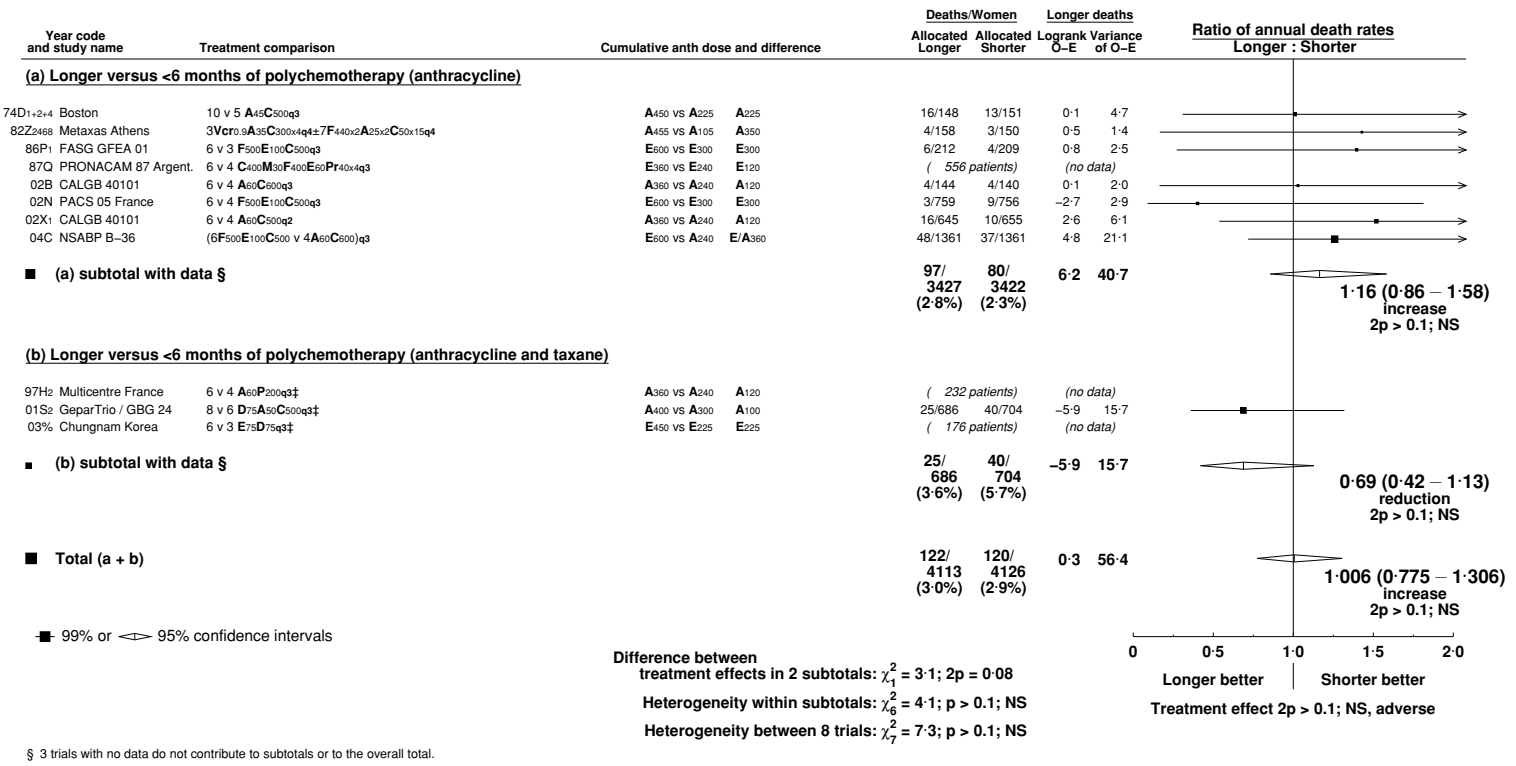
‡ Pre−operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Pr = prednisone; Vcr = vincristine

P48: Death without recurrence in trials of longer versus shorter athracycline/taxane regimens



§ 3 trials with no data do not contribute to subtotals or to the overall total.

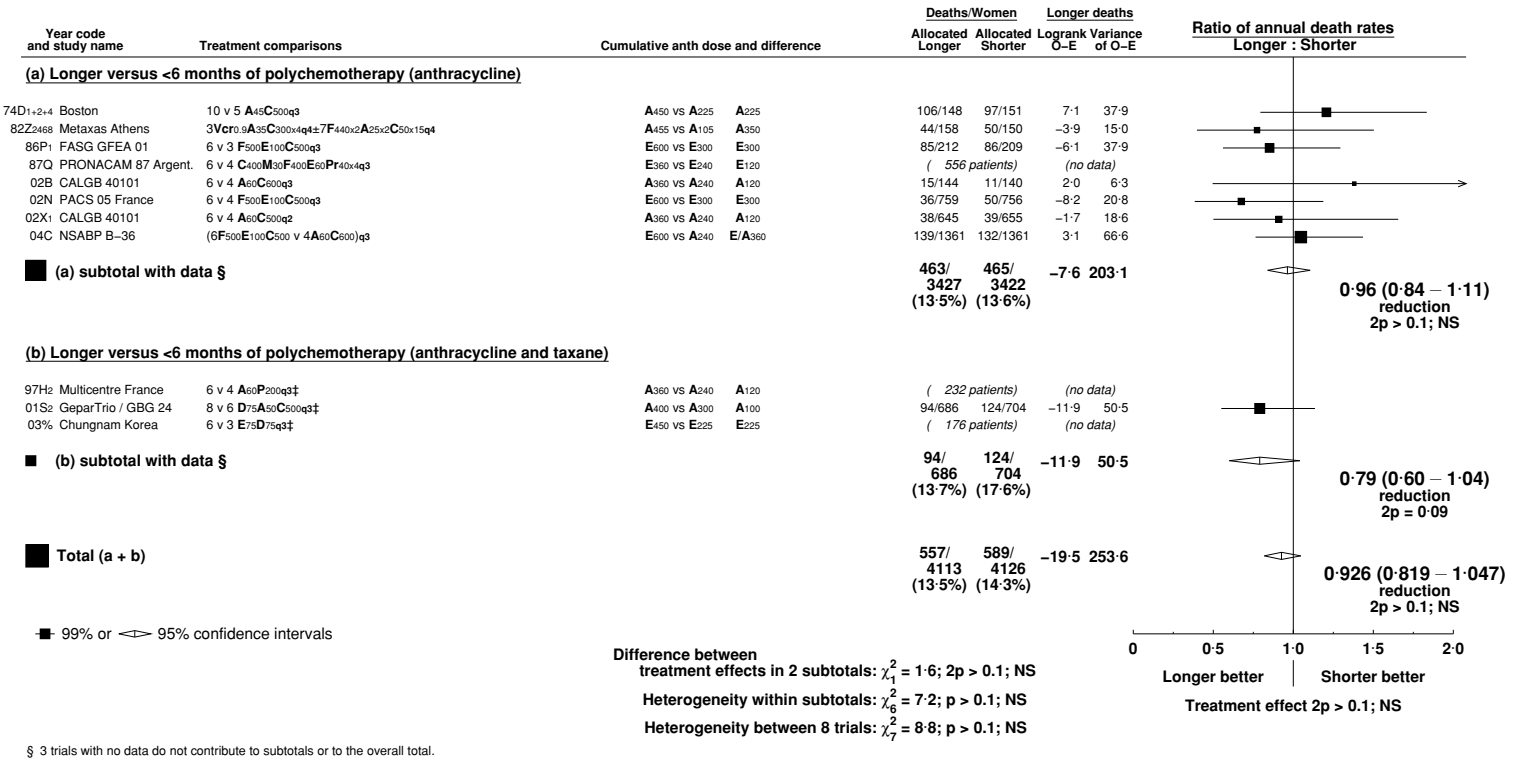
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Pr = prednisone; Vcr = vincristine

P49: All-cause mortality in trials of longer versus shorter athracycline/taxane regimens



§ 3 trials with no data do not contribute to subtotals or to the overall total.

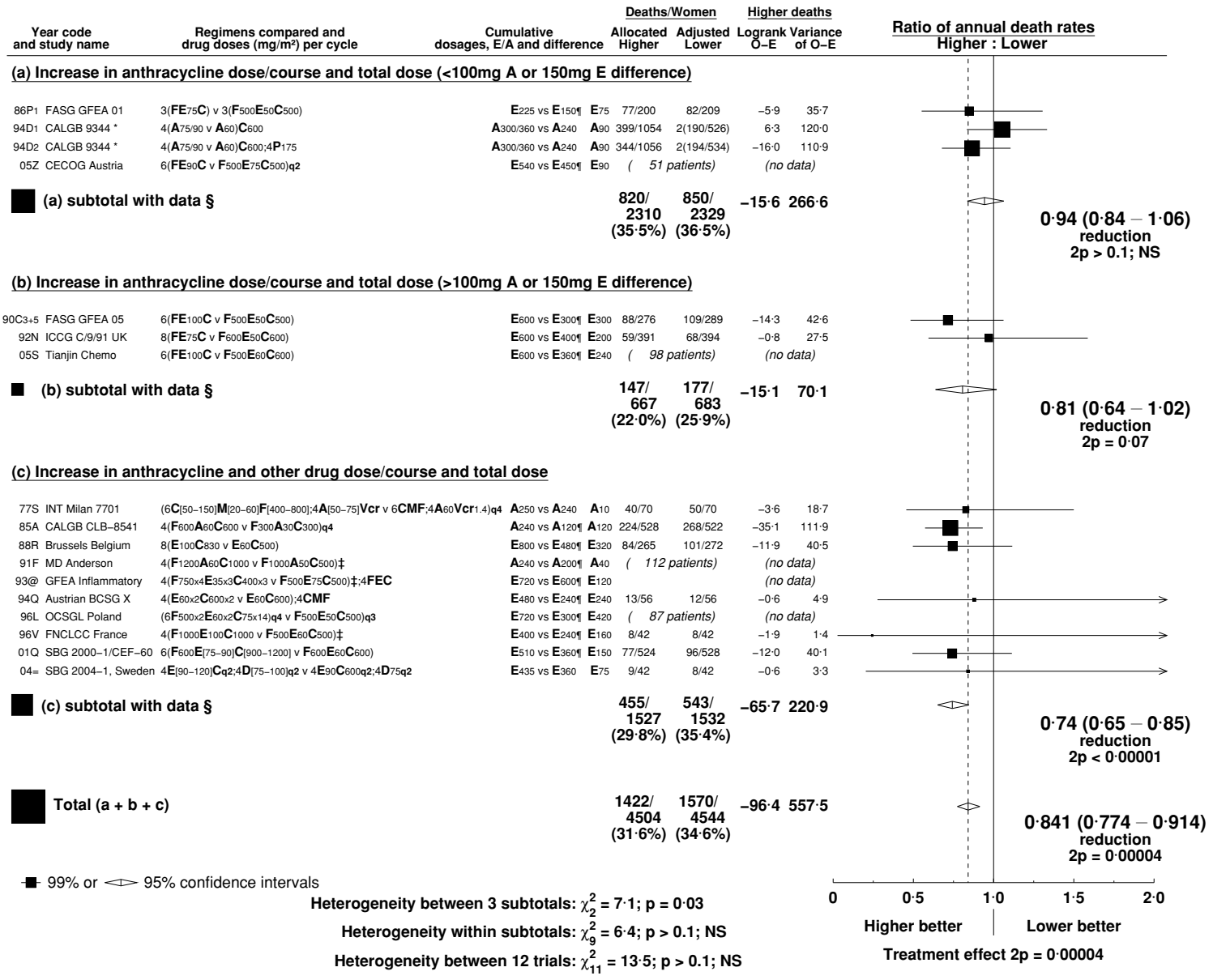
‡ Pre–operative chemotherapy

Taxanes: D = docetaxel; P = paclitaxel

Anthracyclines: A = doxorubicin (Adriamycin); E = epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Pr = prednisone; Vcr = vincristine

P50: Breast cancer mortality in trials of higher versus lower anthracycline dose



§ 5 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.

‡ Pre–operative chemotherapy

¶ Control anthracycline dose less than E90 or A60 per cycle

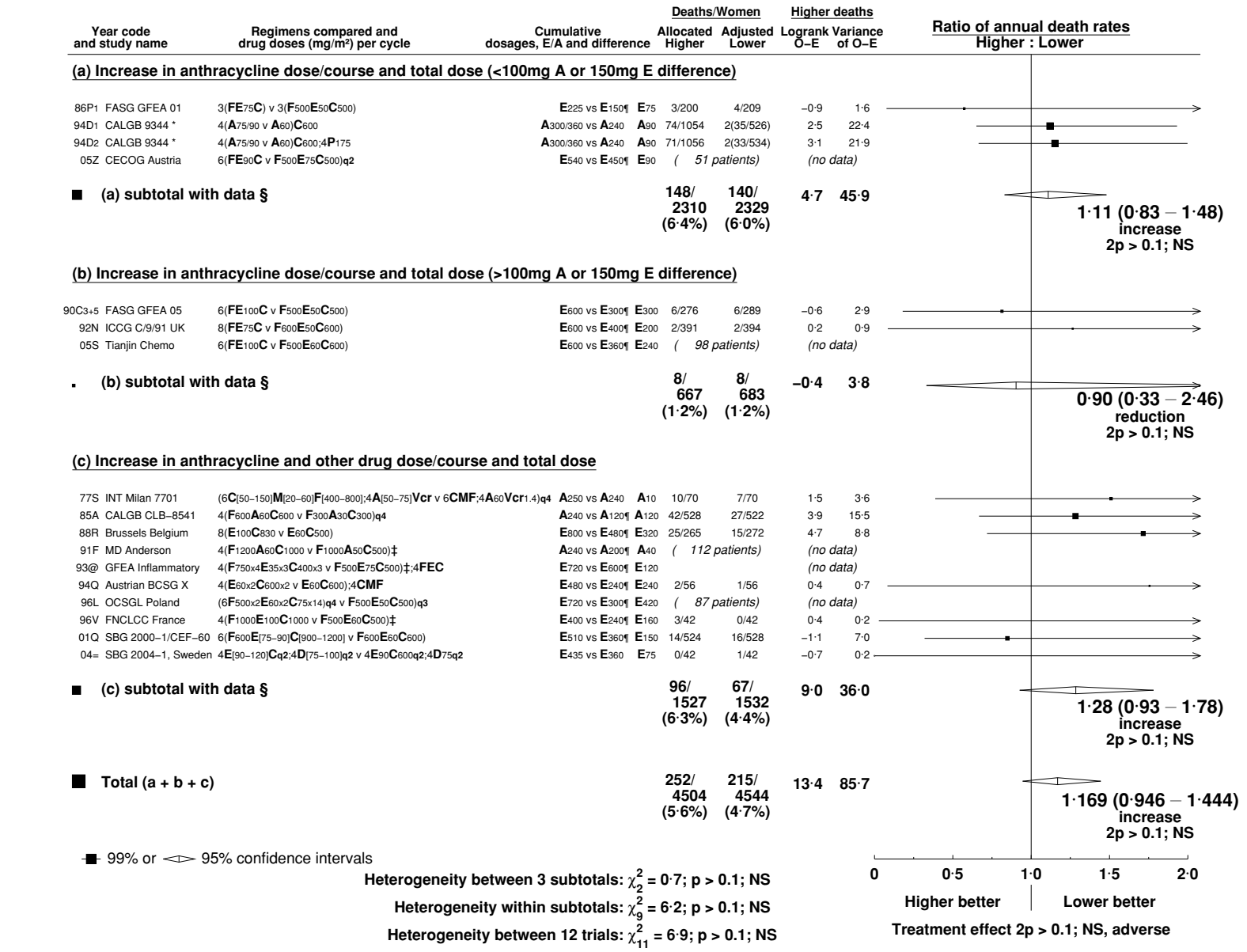
Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin.

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Vcr = vincristine

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1-14 po; ×2 (×3) means d1, d8 (d15) iv

77S in control arm dose for CMF are $C_{100}M_{40}F_{600}$

P51: Death without recurrence in trials of higher versus lower anthracycline dose



§ 5 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.

‡ Pre–operative chemotherapy

¶ Control anthracycline dose less than E90 or A60 per cycle

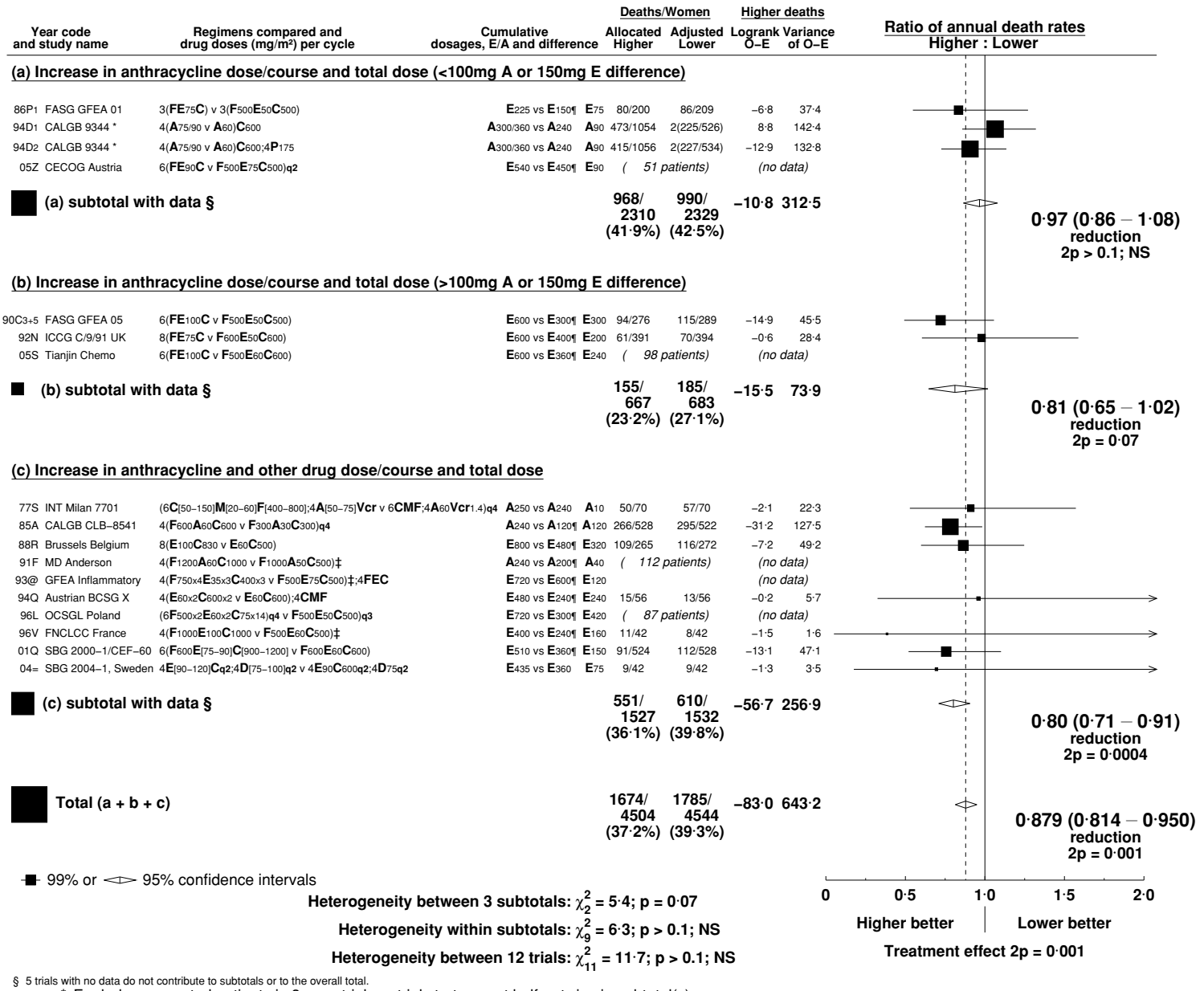
Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin.

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Vcr = vincristine

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1-14 po; ×2 (×3) means d1, d8 (d15) iv

77S in control arm dose for CMF are $C_{100}M_{40}F_{600}$

P52: All-cause mortality in trials of higher versus lower anthracycline dose



§ 5 trials with no data do not contribute to subtotals or to the overall total.

* For balance, control patients in 3–way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.

‡ Pre–operative chemotherapy

¶ Control anthracycline dose less than E90 or A60 per cycle

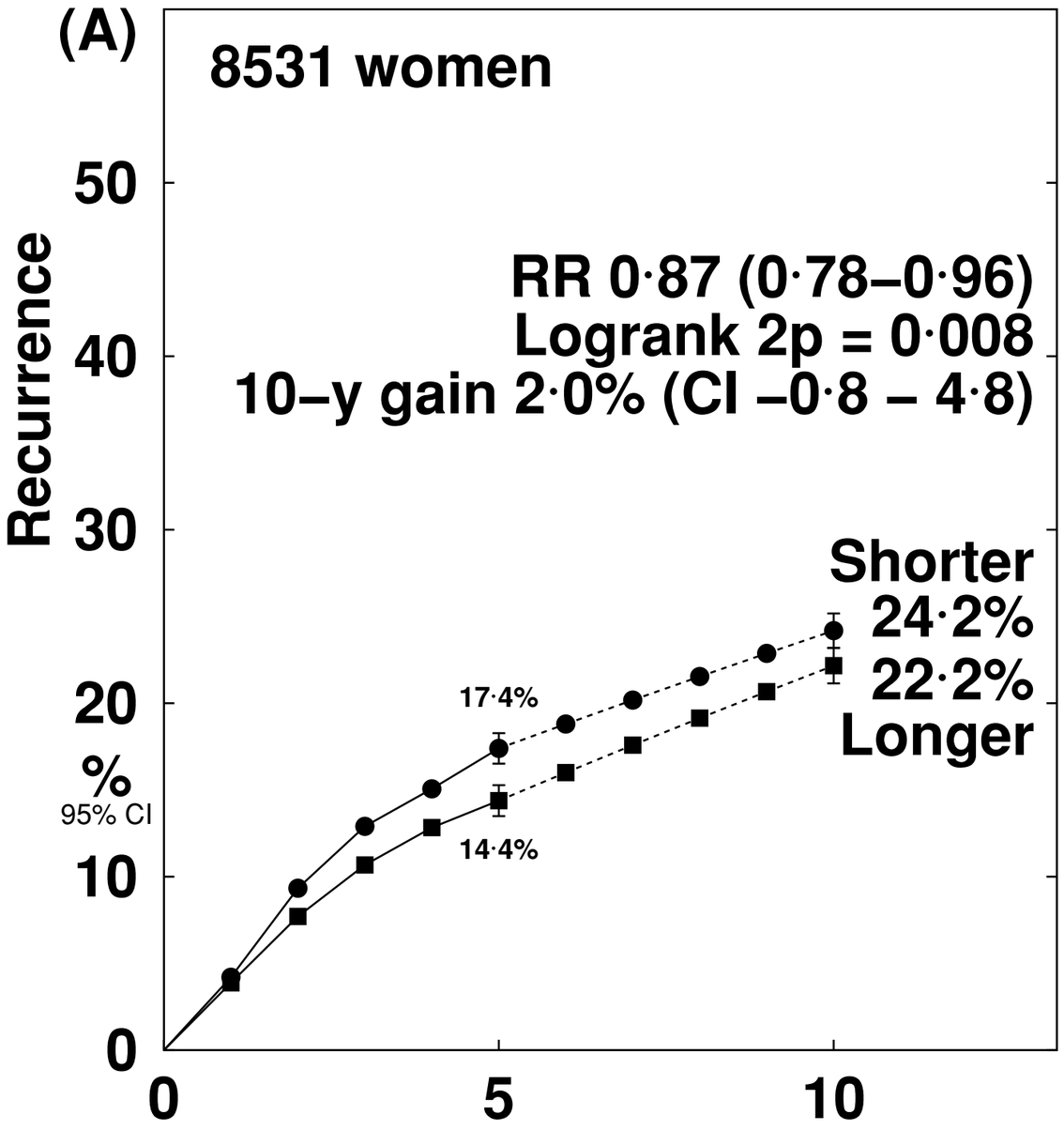
Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin.

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; Vcr = vincristine

All regimens q3week (unless specified as q1, q2 or q4). Semicolon [;] indicates treatment sequence. ×14 means d1-14 po; ×2 (×3) means d1, d8 (d15) iv

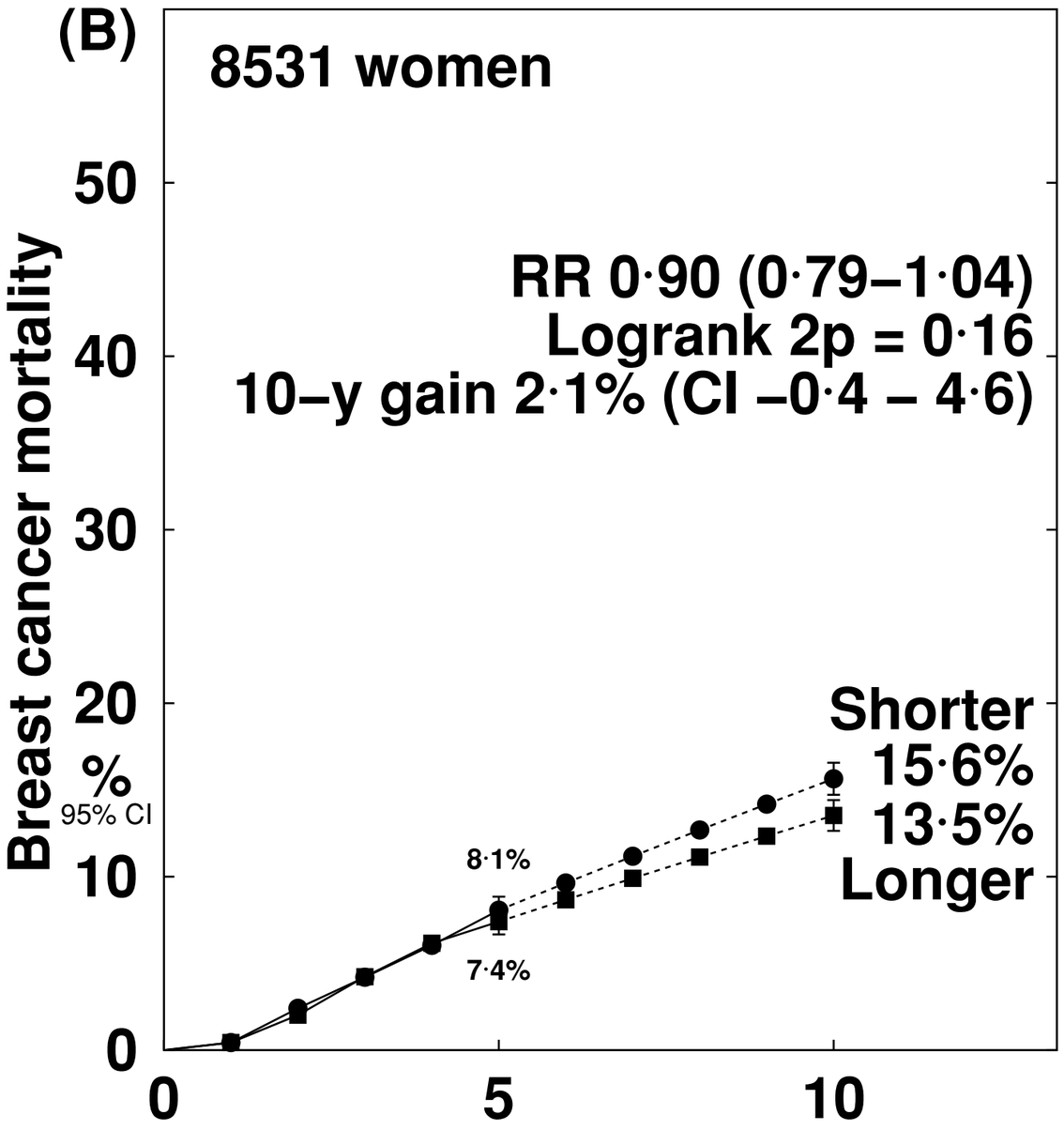
77S in control arm dose for CMF are C100M40F600

P53: 10-year cumulative risk of (A) any recurrence, (B) breast cancer mortality, (C) death without recurrence, (D) all-cause mortality; in trials of longer versus shorted anthracycline/taxane regimen (smoothed after 5 years)



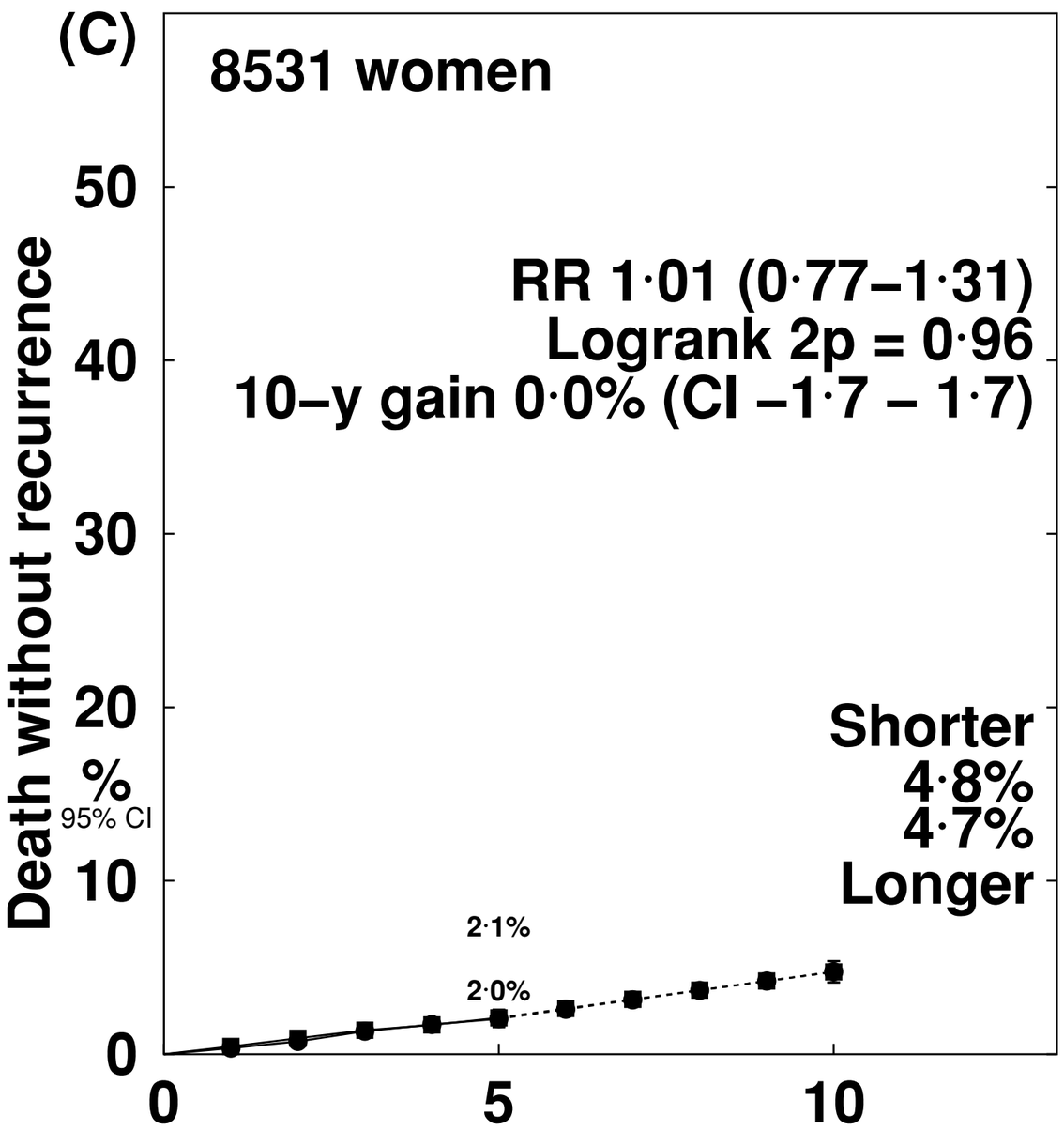
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Longer	3·25 (573 / 17623)	1·91 (148 / 7763)	2·98 (15 / 503)
Shorter	3·83 (667 / 17424)	1·71 (129 / 7538)	2·12 (10 / 472)
Rate ratio, from	0·81 CI 0·72 – 0·92	1·11 CI 0·87 – 1·43	1·03 CI 0·39 – 2·67
(O–E) / V	–54·9 / 268·3	6·5 / 61·9	0·1 / 4·2



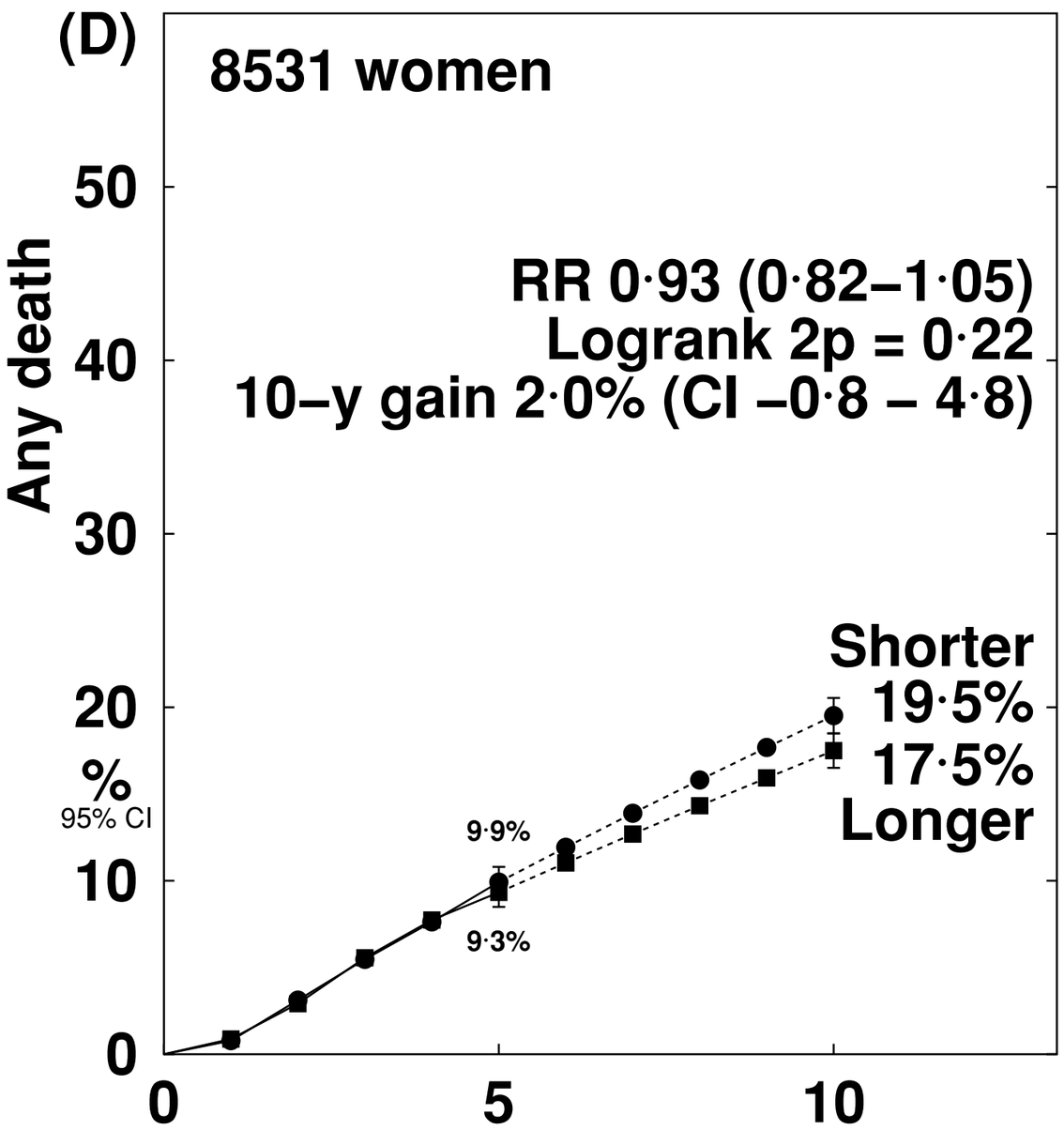
Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Longer	1·53 CI 1·35 – 1·70	1·44 CI 1·19 – 1·70	3·41 CI 1·99 – 4·84
Shorter	1·65 CI 1·46 – 1·83	1·64 CI 1·37 – 1·91	2·44 CI 1·25 – 3·64
Rate ratio, from	0·93 CI 0·78 – 1·10	0·79 CI 0·61 – 1·03	1·67 CI 0·81 – 3·45
(O–E) / V	–10·2 / 131·4	–13·4 / 58·4	3·8 / 7·4



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

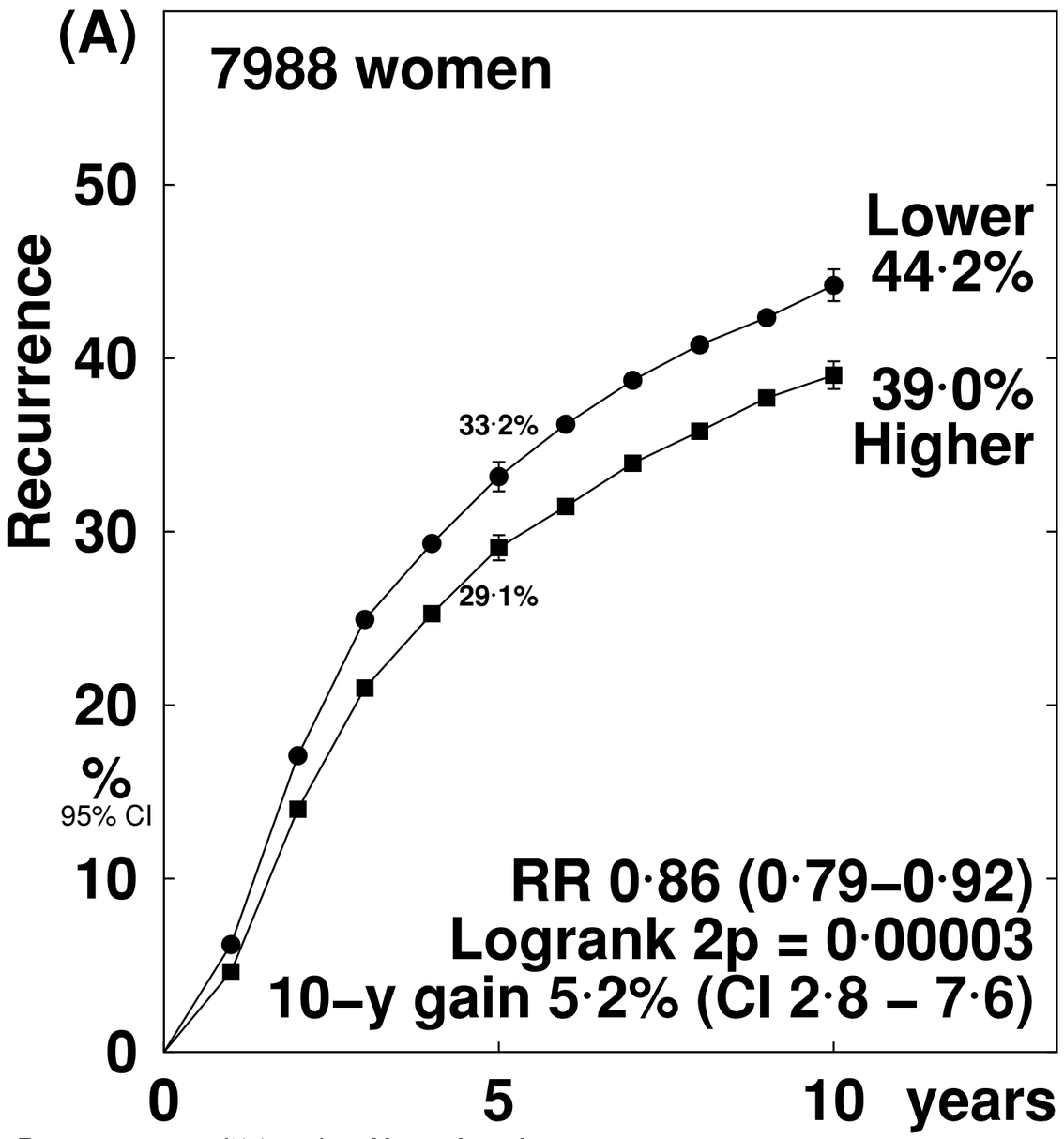
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Longer	0·41 (72 / 17623)	0·57 (44 / 7763)	1·19 (6 / 503)
Shorter	0·43 (75 / 17424)	0·54 (41 / 7538)	0·85 (4 / 472)
Rate ratio, from	1·03 CI 0·74 – 1·44	0·97 CI 0·63 – 1·51	0·83 CI 0·16 – 4·35
(O–E) / V	1·1 / 35·1	–0·5 / 19·9	–0·3 / 1·4



Death rates (% / year) and logrank analyses

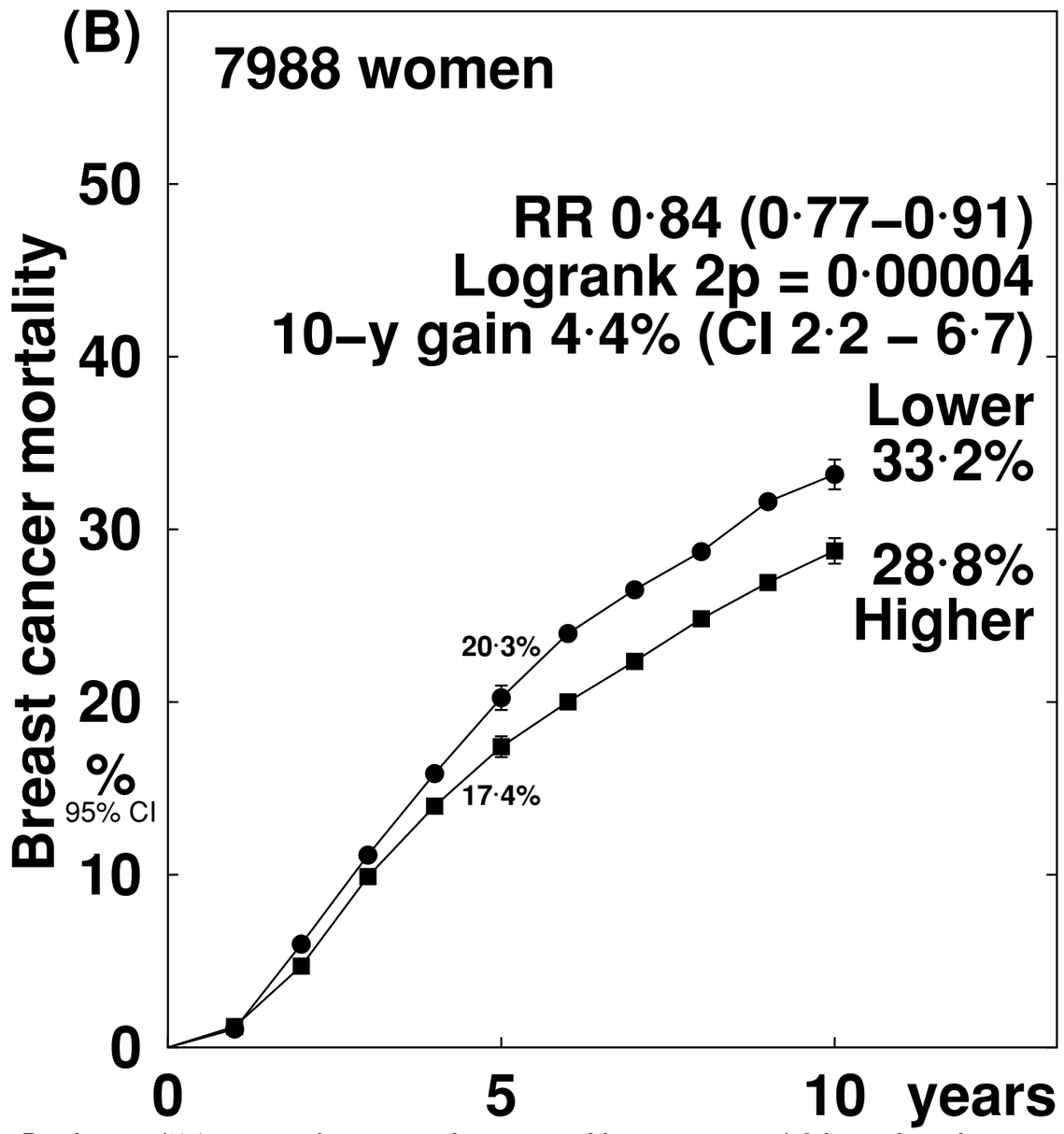
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Longer	1·93 (359 / 18621)	1·98 (170 / 8600)	4·34 (28 / 645)
Shorter	2·07 (386 / 18633)	2·17 (183 / 8449)	3·05 (20 / 655)
Rate ratio, from	0·95 CI 0·81 – 1·10	0·84 CI 0·67 – 1·04	1·50 CI 0·77 – 2·90
(O–E) / V	–9·1 / 166·6	–13·9 / 78·3	3·5 / 8·8

P54: 10-year cumulative risk of (A) any recurrence, (B) breast cancer mortality, (C) death without recurrence, (D) all-cause mortality; in trials of higher versus lower anthracycline dose



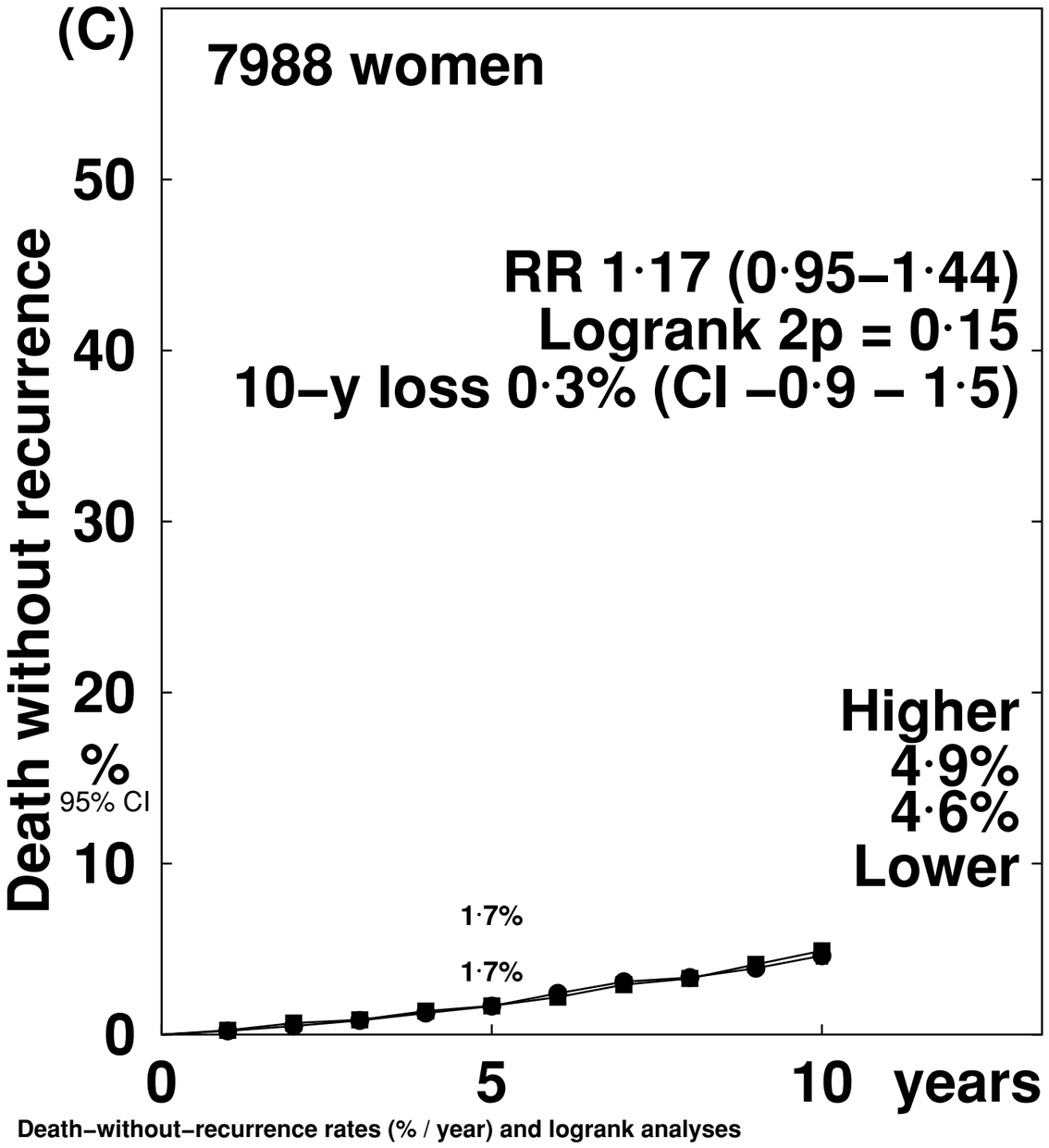
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Higher	7·16 (1306 / 18250)	3·09 (372 / 12039)	2·33 (185 / 7935)
Lower	8·10 (1104 / 13625)	3·77 (326 / 8657)	2·20 (115 / 5234)
Rate ratio, from	0·84 CI 0·77 – 0·92	0·83 CI 0·71 – 0·98	1·06 CI 0·82 – 1·35
(O–E) / V	–86·2 / 493·8	–28·1 / 153·1	3·4 / 62·9



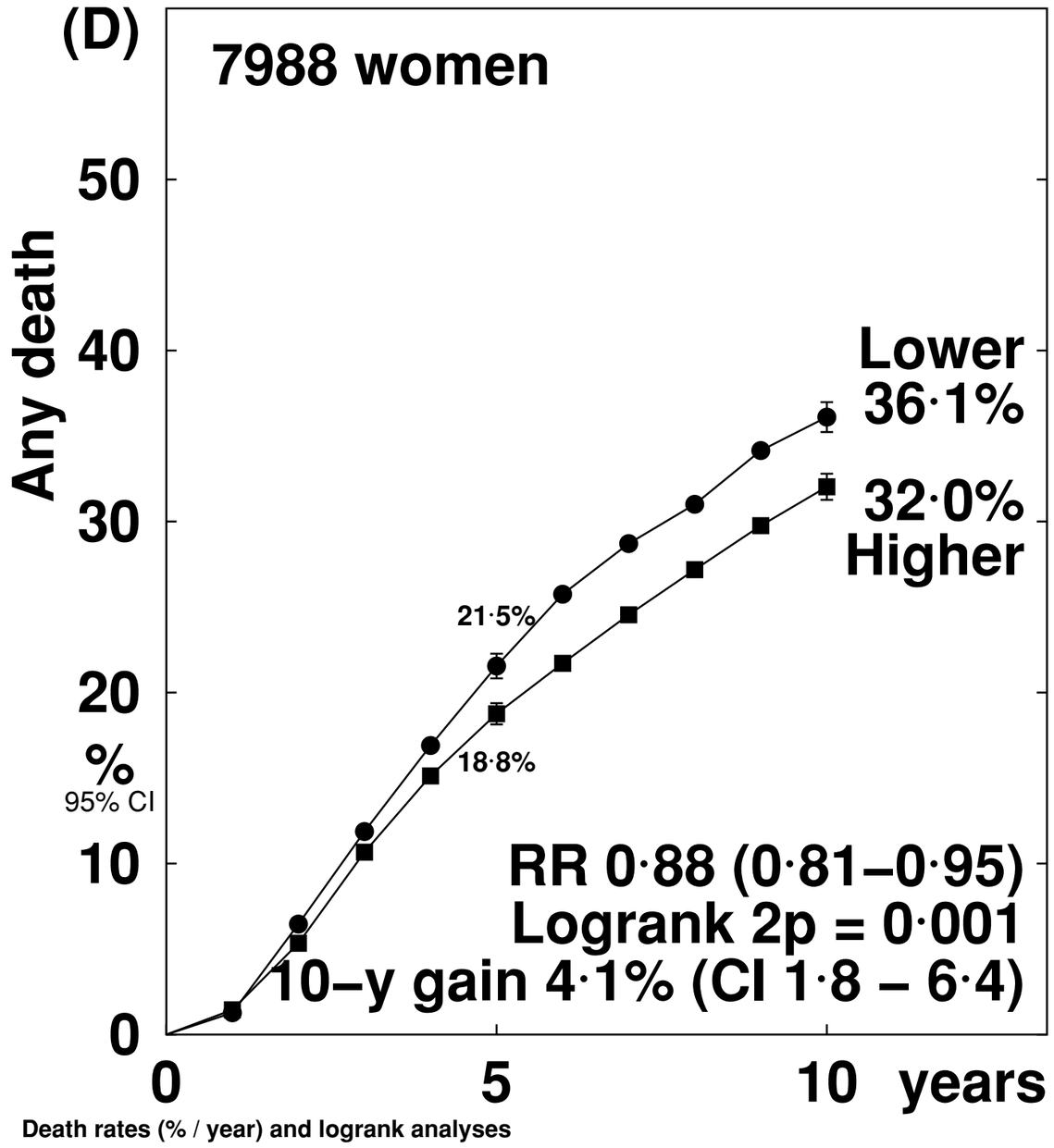
Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Higher	3·92 CI 3·64 – 4·19	3·06 CI 2·78 – 3·35	1·85 CI 1·59 – 2·11
Lower	4·31 CI 3·98 – 4·64	3·60 CI 3·24 – 3·97	2·26 CI 1·90 – 2·62
Rate ratio, from	0·84 CI 0·75 – 0·94	0·83 CI 0·71 – 0·96	0·87 CI 0·69 – 1·09
(O–E) / V	–52·4 / 308·8	–33·8 / 176·1	–10·1 / 72·6



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

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Higher	0·35 (64 / 18250)	0·66 (79 / 12039)	1·37 (109 / 7935)
Lower	0·30 (41 / 13625)	0·60 (52 / 8657)	1·03 (54 / 5234)
Rate ratio, from	1·03 CI 0·68 – 1·54	1·07 CI 0·75 – 1·54	1·38 CI 0·98 – 1·94
(O–E) / V	0·6 / 23·3	2·0 / 29·2	10·8 / 33·2



Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Higher	4·26 (854 / 20036)	3·69 (520 / 14104)	3·12 (300 / 9604)
Lower	4·60 (703 / 15284)	4·14 (427 / 10314)	3·13 (203 / 6479)
Rate ratio, from	0·86 CI 0·77 – 0·95	0·86 CI 0·75 – 0·98	1·01 CI 0·83 – 1·22
(O–E) / V	–51·8 / 332·1	–31·8 / 205·3	0·6 / 105·9

P55-57: Toxicity table 1 – Anthracycline plus taxane versus taxane without anthracycline. Selected reported toxicity data (extracted, where available, from individual trial publications). All columns reported as Taxane plus anthracycline versus Taxane without anthracycline. n= number of patients, (%), NR = not reported

	Trial name	**No. pts**	**All toxicity Grade ≥3 n (%)**	**Cardiac and Vascular events Grade ≥3 n (%)**	**Peripheral Sensory Neuropathy Grade ≥2 n (%)**	**Neutropenia Grade ≥3 n (%)**	**Febrile Neutropenia Grade ≥3 n (%)**	**Fatigue Grade ≥3 n (%)**	**Compliance completed all cycles %**	**Reference**
(a) Concurrent docetaxel + anthracycline vs same dose docetaxel + cyclophosphamide										
07&	**USO 6090/11271** 6($A_{50}D_{75}C_{500}$ vs $D_{75}C_{600}$) q3	1263	350 vs 380 (56.3 vs 59.3)	**Combined:** 25 vs 4 (4.0 vs 0.6) Asystole 1 vs 0 Cardiomyopathy/cardiac failure/MI 11 vs 0 Hypertension 1 vs 0 Tachycardia/arrhythmia 2 vs 2 Thromboembolic (including CVA) 10 vs 2	33 vs 40 (5.3 vs 6.2)	213 vs 268 (29.4 vs 41.8)	49 vs 50 (7.9 vs 7.8)	46 vs 19 (7.4 vs 3.0)	NR	Blum et al J Clin Oncol 2017, 35:2647-55
09J	**NSABP-B46i** 6($A_{50}D_{75}C_{500}$ vs $D_{75}C_{600}$) q3	1055	230 vs 201 (43.7 vs 40.0)	**Combined:** 21 vs 7 (4.0 vs 1.3) Cardiac ischaemia 0 vs 0 Hypertension 1 vs 0 LV dysfunction 5 vs 0 Thromboembolic 10 vs 5 CNS ischaemia 3 v 0 Arrhythmia 3 vs 2	38 vs 47 (7.2 vs 8.9)	76 vs 52 (14.4 vs 9.8)	35 vs 27 (6.7 vs 5.1)	34 vs 23 (6.5 vs 4.4)	NR	Blum et al J Clin Oncol 2017, 35:2647-55
09R	**Shanghai Jiao Tong** 6(A_{50}/$E_{60}D_{75}C_{500}$ vs $D_{75}C_{600}$) q3‡	96	NR	NR	NR	40 vs 24 (78.4 vs 53.3)	3 vs 2 (5.9 vs 4.4)	NR	88.2 vs 71	Chen at al Breast Can Res Treat 2013, 142:549-58 Chen et al Chin J Can Res 2016, 28:561-9
(b) Sequential taxane plus anthracycline versus higher cumulative dose docetaxel + cyclophosphamide										
08L	**DBCG 07 READ** ($3E_{90}C_{600}$;$3D_{100}$ vs $6D_{75}C_{600}$) q3	2012	NR	**Combined:** 8 vs 8 (0.8 vs 0.8) Cardiomyopathy 1 vs 2 Heart failure 7 vs 6	349 vs 297 (35.1 vs 29.5)	NR	102 vs 59 (10.3 vs 5.9)	297 vs 245 (29.9 vs 24.4)	90.7 vs 87.3	Ejlertsen et al J Clin Oncol 2017, 35:2639-46
09&	**Kangawa, Japan** ($3FE_{100}C_{500}$;$3D_{100}$ vs $6D_{75}C_{600}$) q3‡	103	NR	NR	19 vs 19 (36.5 vs 39.6) reported as nerve disorder	46 vs 47 (88.5 vs 97.9)	11 vs 2 (21.2 vs 4.2)	1 vs 1 (1.9 vs 2.1)	94.3 vs 94	Narui et al The Breast 2019, 47:1-9

	Trial name	No. pts	All toxicity Grade ≥3 n (%)	Cardiac and Vascular events Grade ≥3 n (%)	Peripheral Sensory Neuropathy Grade ≥2 n (%)	Neutropenia Grade ≥3 n (%)	Febrile Neutropenia Grade ≥3 n (%)	Fatigue Grade ≥3 n (%)	Compliance completed all cycles %	Reference
09=	**NSABP-B49 (results only as %)** ($4A_{60}Cq2/3;12P_{80}$ q1/$4P_{175}$ q2)/ $6A_{50}D_{75}C_{500}$ q3 vs $6D_{75}C_{600}$ q3	1832	(42 vs 40)	LV dysfunction (<1 vs <1) Hypertension (3 vs 3) Thromboembolic event (G3 1, G4< 1 vs G3 < 1 %) Heart failure 0 vs 0	≥G3 (4 vs 1)	G3 (4 vs <1) G4 (1 vs 1)	G3 (3 vs 7) G4 (<1 vs 1)	(4 vs 4)	NR	Blum et al J Clin Oncol 2017, 35:2647-55
09E	**SUCCESS C^** ($3FE_{100}C_{500};3D_{100}$ vs $6D_{75}C_{600}$) q3	3643	^2245 vs 2089 (76.3 vs 70.1)	NR	^≥G3 45 vs 23 (1.5 vs 0.8)	^1187 vs 1101 (40.3 vs 36.9)	^114 vs 145 (3.9 vs 4.9)	^131 vs 83 (4.4 vs 2.8)	NR	de Gregorio et al Br J Cancer 2022, 126:1715-24
09M	**WSG PLAN-B^** ($4E_{90}C_{600};4D_{100}$ vs $6D_{75}C_{600}$) q3	2449		**Combined:** 5 vs 6 Heart failure 3 vs 3 Cardiac death 2 vs 2 PE 0 vs 1					87.5 vs 93.0	Nitz et al J Clin Oncol 2019, 37:799-808 de Gregorio et al Br J Cancer 2022, 126:1715-24
09U	**JBCRG-10** ($4D_{75}C_{600};4FE_{100}C_{500}$ or vv vs $6D_{75}C_{600}$)Trz q3‡	67 (43 vs 24)	24 vs 11 (55.8 vs 45.8)	Heart failure 1 vs 0 (2.3 vs 0) PE 1 vs 0 (2.3 vs 0)	NR	7 vs 4 (16.2 vs 16.7)	11 vs 4 (25.6 vs 16.7)	0 vs 0 (0 vs 0)	NR	Ueno et al Jpn J Clin Oncol 2020, 50:3-11
09V	**JBCRG-09** ($3D_{75}C_{600};3FE_{100}C_{500}$ or vv vs $6D_{75}C_{600}$) q3‡	195	NR	NR	NR	55 vs 36 (43.0 vs 55.4)	26 vs 9 (20.3 vs 13.8)	1 vs 0 (0.8 vs 0)	95.3 vs 86.1	Ishiguro et al Breast Can Res and Treatment 2020, 180:715-24
10V	**MASTER** ($3FEC_{100}C_{500};3D_{100}$ vs $6D_{75}C_{600}$) q3	1047	NR	**Combined:** 11 vs 4 (2.1 vs 0.8) Decreased ejection fraction 5 vs 1 (0.9 vs 0.2) Ventricular arrhythmia 5 vs 2 (0.9 vs 0.3) Thrombosis 1 vs 1 (0.2 vs 0.2)	≥G3 4 vs 15 (0.8 vs 2.8)	279 vs 290 (53.4 vs 55.3)	9 vs 11 (1.7 vs 2.0)	24 vs 24 (4.5 vs 4.6)	93.5 vs 94.5	Yu et al Lancet Regional Health 2021, 11:100158

	Trial name	No. pts	All toxicity Grade ≥3 n (%)	Cardiac and Vascular events Grade ≥3 n (%)	Peripheral Sensory Neuropathy Grade ≥2 n (%)	Neutropenia Grade ≥3 n (%)	Febrile Neutropenia Grade ≥3 n (%)	Fatigue Grade ≥3 n (%)	Compliance completed all cycles %	Reference
(c) Taxane plus anthracycline versus taxane +/- capecitabine										
00W	**N-SAS-BC 02 Japan (results only as %)** ($4A_{60}C6_{00}$;$4P_{175}$/$4D_{75}$ vs $8P_{175}$/D_{75}) q3	1049	NR	Cardiac arrhythmia: AC-P vs P: (1.0 vs 0.5) AC-D vs D: (0 vs 1.1)	≥G3 AC-P vs P: (4.2 vs 5.7) AC-D vs D: (0.4 vs 3.8)	AC-P vs P: (17.2 vs 1.9) AC-D vs D: (19.5 vs 6.9)	AC-P vs P: (5.7 vs 0.4) AC-D vs D: (11.1 vs 8.1)	AC-P vs P: (3.8 vs 1.9) AC-D vs D: (3.1 vs 1.9)	87 vs 86	Watanabe et al Cancer 2017, 123:759-68
06Z	**MINDACT** ($3FE_{100}C_{500}$;$3D_{100}$ vs $6D_{75}Cap_{1650d1\text{-}14}$) q3	392	NR	NR	NR	NR	NR	NR	NR	Cardoso et al NEJM 2016, 375:717-29 Piccart et al Lancet Oncology 2021, 476-88
(d) Taxane plus anthracycline versus taxane + carboplatin										
01M	**BCIRG 006** ($4A_{60}C_{600}$;$4D_{100}$ vs 6 $D_{75}Cpt_{AUC6}$) q3 +12Trz q1;Trz q3 to 1yr	2149	NR	Congestive heart failure 21 v 4 (2.0 vs 0.4) Hypertension (any grade) 178 vs 190 (16.6 vs 17.7)	Grade ≥1 531 vs 380 (49.7 vs 36.0)	764 vs 696 (71.5 vs 65.9)	116 vs 101 (10.9 vs 9.6)	77 vs 76 (7.2 vs 7.2)	NR	Slamon et al NEJM 2011, 365:1273-83
11R	**PATTERN** $3FE_{100}C_{500}$;$3D_{100}$ q3 vs 6(($P_{80}Cpt_{AUC2}$)$_{d1,8,15}$) q4	647	NR	NR	3 vs 12 (0.9 vs 3.7)	297 vs 283 (92.8 vs 87.9)	30 vs 3 (9.4 vs 0.9)	3 vs 3 (0.9 vs 0.9)	94.7 vs 92.9	Yu et al JAMA oncology 2020, 6:1390-6

^ combined results from joint publication

P58: Toxicity table 2 – Trials of docetaxel versus paclitaxel. Selected toxicity reporting extracted from individual trial publications
Where available results presented as n=number, (%), NR = not reported

	Trial name	No. pts	All toxicity Grade ≥3 n (%)	Peripheral Sensory neuropathy Grade ≥2 n (%)	Neutropenia Grade ≥3 n (%)	Febrile neutropenia Grade ≥3 n (%)	Fatigue Grade ≥3 n (%)	Dose modification n (%)	Compliance % Completed all taxane cycles	Reference
Docetaxel q2 or 3 vs Paclitaxel q2 or 3										
99V	**ECOG E1199 (results only as %)** 4AC;4(D_{100} vs P_{175}) q3	2534	(71 vs 30)	(16 vs 20)	Grade ≥4 (46 vs 4)	Grade ≥4 (16 vs <1)	(9 vs 2)	(28 vs 22)	87 vs 95	Sparano et al. NEJM 2008, 358:1663-71
00W	**N-SAS BC02 (results only as %)** 4AC/EC;4(D_{75} vs P_{175}) q3	525	NR	Grade ≥3 (0.4 vs 4.2)	(19.5 vs 17.2)	(11.1 vs 5.7)	(3.1 vs 3.8)	NR	86.7 vs 86.7	Watanabe et al Cancer 2017, 123:759-68
00W	**N-SAS BC02 (results only as %)** 8(D_{75} vs P_{175}) q3	524	NR	Grade ≥3 (3.8 vs 5.7)	(6.9 vs 1.9)	(8.1 vs 1.9)	(1.9 vs 1.9)	NR	84.7 vs 86.7	Watanabe et al Cancer 2017, 123:759-68
04R	**HORG CT-04** 4FE_{75}C;4(D_{75} vs P_{175}) q2	481	NR	7 vs 11 (2.9 vs 4.6)	74 vs 51 (31 vs 23)	4 vs 3 (1.7 vs 1.2)	18 vs 20 (7.5 vs 8.3)	(1.7 vs 2.8)	96.3 vs 90	Saloustros et al Br Can Res Trt 2014, 148:591-7
Docetaxel q1 vs paclitaxel q1										
99V	**ECOG E1199 (results only as %)** 4AC;12(D_{35} vs P_{80}) q1	2518	(45 vs 28)	(16 vs 27)	≥Grade 4 (3 vs 2)	≥Grade 4 (1 vs 1)	(11 vs 3)	(40 vs 29)	75 vs 88	Sparano et al. NEJM 2008, 358:1663-71
05C	**HE10/05** 3E_{110} q2;3CMF; 9(D_{35} vs P_{80}) q1	664	NR	Grade ≥3 neurology 4 vs 4 (1.3 vs 1.3)	85 vs 85 (26.9 vs 26.6)	14 vs 17 (4.4 vs 5.3)	7 vs 10 (2.2 vs 3.1)	NR	88.3 vs 88	Fountzilas et al. BMC Cancer 2014, 14:515

P59-60: Toxicity table 3 – Trials of paclitaxel or docetaxel in smaller fractions versus larger fractions. Selected toxicity reporting extracted from individual trial publications
Where available results presented as n=number, (%), NR = not reported

	Trial name	No. pts	All toxicity Grade ≥3 n (%)	Peripheral Sensory neuropathy Grade ≥2 n (%)	Neutropenia Grade ≥3 n (%)	Febrile neutropenia Grade ≥3 n (%)	Fatigue Grade ≥3 n (%)	Dose modification n (%)	Compliance (%) Completed all taxane cycles	Reference
Paclitaxel q1 versus Paclitaxel q2 or q3										
98K	**MDA 98-240 (results only as %)** ($12P_{80/150/175}$q1 vs $4P_{225}$ q3);4 FAC q3	254	NR	(36.5* vs 51.2) *80mg/m^2 dose	NR	(1 vs 9.5)	NR	NR	NR	Green et al. J Clin Oncol 2005, 23:5983-92
99V	**ECOG E1199 (results only as %)** 4AC; ($12P_{80}$q1 vs $4P_{175}$ q3)	2530	(28 vs 30)	(27 vs 20)	Grade ≥4 (2 vs 4)	Grade ≥4 (1 vs <1)	(3 vs 2)	(29 vs 22)	88.0 vs 95.0	Sparano et al. NEJM 2008, 358:1663-71
03*	**SWOG S0221** ($15A_{24}C_{60dq1\text{-}7}$/ 6AC)q2; ($12P_{80}$ q1 v $6P_{175}$ q2)	3294	414 vs 412 (36.3 vs 35.5)	Grade ≥3 119 vs 201 (10.5 vs 17.3) (reported as neurology)	139 vs 22 (12.2 vs 1.9)* *GCSF in q2 arm	1 vs 2 (0.1 vs 0.2)	NR	NR	75.0 vs 71.0	Budd et al. J Clin Oncol 2015, 33:58-64
05C	**HE10/05** $3E_{110}$ q2;(3CMF q2; $9P_{80}$q1 vs $3P_{200}$ q2; 3CMF q2)	667	NR	Grade ≥3 4 vs 16 (1.3 vs 4.9) (reported as neurology)	85 vs 99 (26.6 vs 30.4)	17 vs 20 (5.3 vs 6.1)	10 vs 4 (3.1 vs 1.2)	NR	88.0 vs 93.6	Fountzilas et al. BMC Cancer 2014, 14:515
Docetaxel q1 or q2 vs Docetaxel q3										
99V	**ECOG E1199** 4AC; ($12D_{35}$ q1 vs $4D_{100}$ q3)	2522	(45 vs 71)	(16 vs 16)	Grade ≥4 (3 vs 46)	Grade ≥4 (1 vs 16)	(11 vs 9)	(40 vs 28)	75.0 vs 87.0	Sparano et al. NEJM 2008, 358:1663-71
O0^	**U Hull / Lincoln CH** 4AC; ($12D_{33}$ q1 vs $4D_{100}$ q3)	82	NR	0 vs 16 (0 vs 38.2) Grade not reported	5/82 overall (6)	4/82 (5)	4 vs 7 (10 vs 17) Grade not reported	NR	91.1 vs 93.2	Walker et al. BMC Cancer 2011, 11:179
04Z	**BREAST-10** $12E_{30}D_{35}$ q1 vs $4E_{75}D_{80}$ q3 *reported for whole trial (n=135) including patients	135 (44 in outcomes analysis)	NR	2 vs 1 (3 vs 1.4)	11 vs 45 (16.7 vs 65.2)	0 vs 2 (0 vs 2.9)	1 vs 0 (1.4 vs 0)	NR	NR	Nuzzo et al. BMC Cancer 2011, 11:75

	with metastatic disease									
05@	**UZ Leuven Belgium** ($4F_{375}E_{75}C_{375}$;$4D_{75}$ or vv) q2 vs ($3F_{500}E_{100}C_{500}$; $3D_{100}$ or vv) q3	85	24 vs 15 (30.7 vs 38.4)	NR	5 vs 8 (6.4 vs 21)	0 vs 2 (0 vs 5.1)	8 vs 0 (7.7 vs 0)	10 vs 3 (12.8 vs 7.9)	94.8 vs 97.4	Wildiers et al Breast Can Res Trt 2009, 114:103-12

Statistical Analysis Plan for a Meta-Analysis of randomised trials comparing anthracycline and taxane containing chemotherapy regimens for early breast cancer

This meta-analysis aims to compare the long-term benefits and risks of different anthracycline and taxane containing chemotherapy regimens for early breast cancer

Cohort definitions

The current list of trials contributing to these 8 cohorts are shown in Appendix 1.

Cohort 1. Taxane with and without anthracycline: randomised trials that compare any taxane plus anthracycline regimen versus any taxane regimen without anthracycline.

Cohort 2. Anthracycline with taxane versus anthracycline regimens without taxane: randomised trials that compare any anthracycline plus taxane regimen versus any anthracycline regimen without taxane.

Cohort 3. Taxane versus anthracycline: randomised trials that compare any taxane regimen wihout anthracycline versus any anthracycline regimen without taxane.

Cohort 4. Head-to-head taxane comparisons: randomised trials with head-to-head comparisons between different taxanes (docetaxel versus paclitaxel).

Cohort 5. Dose fractionation: randomised trials that compare taxane regimens with similar cumulative doses but different scheduling (i.e. small more frequent versus larger less frequent).

Cohort 6. Sequencing of sequential anthracycline and taxane chemotherapy: randomised trials of anthracycline then taxane versus the same drug regimens in the opposite order.

Cohort 7. Longer versus shorter duration of anthracycline: randomised trials comparing longer versus shorter duration of anthracycline based chemotherapy.

Cohort 8. Higher versus lower dose of anthracycline: randomised trials comparing higher versus lower doses of anthracycline chemotherapy.

Analysis population

The analysis population will be women with early stage (i.e. operable) or locally advanced breast cancer where treatment is administered with curative intent. Data will be sought from all relevant randomised trials with greater than 10 women randomised, irrespective of primary outcome measure.

Data checking

The usual EBCTCG quality assurance checks for range, consistency and balance between randomisation arms will be undertaken prior to analysis. The dependence of deaths without recorded recurrence and of second cancers (overall and by site) on TN status will also be investigated with any association used to estimate what proportion might actually have been from breast cancer. Checks will be undertaken to compare the incidence of death without recurrence and of second cancers (overall and by site) by age group in each trial to characterise whether these might include miscoded breast cancer events.

Analyses

Primary analyses will be by Intention to Treat (ITT), including all randomised patients irrespective of treatment compliance.

The data variables to be requested from each trial are detailed in Appendix 2.

Primary outcomes

The main endpoint definitions and methods are those used in previous EBCTCG reports.

1. Time to recurrence: includes distant recurrence, invasive loco-regional recurrence and new second primary invasive breast cancer (ipsilateral or contralateral), and the definitions of these will be as in each trial.

2. Breast cancer mortality: information about mortality rates without recurrence will be subtracted from information about overall mortality rates, estimated by log-rank subtraction (as in previous EBCTCG reports). The same statistical methods will be used to construct Kaplan-Meier graphs that estimate breast cancer mortality (i.e. the pattern of

mortality that would have been seen if it had been possible to avoid all deaths before or after recurrence from causes other than breast cancer).

3. Death without recurrence: i.e. without the EBCTCG secretariat having any record of recurrence. The quality of the recurrence data in these trials is likely to be reasonably good, deaths from wholly unknown cause without recorded recurrence will be treated as death from an unknown cause that was not breast cancer.

4. All-cause mortality

Exploratory endpoints

1. Time to first distant recurrence: includes distant recurrence and ignores any prior loco-regional or contralateral recurrences.

2. Time to loco-regional recurrence as first event: includes ipsilateral breast, chest wall and loco-regional lymph nodes (axilla and SCF).

3. Time to new contralateral recurrence

4. AML incidence

5. Incidence and site of second cancers: Information on the site of other non-breast second primary before any recurrence of breast cancer will be collected. Categorisation of sites will include but is not limited to: haematological, lung, colorectal, GI, gynaecological, urological.

6. Safety – Data on other non-fatal adverse events (e.g. ischaemic heart disease, stroke, pulmonary embolus, DVT) will be sought and analysed.

Subgroup Analyses

Pre-specified subgroup analyses will be undertaken but, given the well-known hazards of subgroup analysis, will be interpreted appropriately cautiously. Investigation of potential interactions between tumour or patient characteristics and treatment efficacy will be undertaken with breast cancer recurrence as primary outcome.

Subgroup Analyses of Recurrence Forest plots for subgroup analyses by:

- Site of first recurrence (distant metastasis, invasive loco-regional recurrence or contralateral breast cancer)
- Period of follow-up (years 0-1, 2-4, 5-9, and 10+ after randomisation)
- Age (<45, 45-54, 55-64, 65+);
- ER status (ER-, ER+, ER unknown);
- ER/PR status (ER+/PR- vs ER+/PR+)
- Nodal status (N0/N-, N1-3, N4+, N unknown);
- Tumour size (T1, T2, T3/T4);
- Tumour grade (well-differentiated, moderately differentiated, poorly differentiated);
- Proliferation index (%Ki-67 0-9, 10-19, 20-49, 50+)
- HER2 status (HER2-, HER2+, unknown)
- Tumour histology (ductal, lobular, other, unknown)
- BMI (<20, 20-<25, 25-<30, 30+)

Statistical analyses

If a log-rank statistic (observed [o]-expected [e]) have variance v, then defining z=(o-e)/sqrt(v) and b=(o-e)/v, where b has variance 1/v, the outcome RR is estimated as exp(b) with SE=(RR-1)/z. 95% CIs and 99% CIs for RRs are derived from those for b (by normal approximations). Two-sided significance with p values of less than 0.05 were considered significant for analyses of the primary and secondary outcomes, and to compensate for multiple investigations, p values of less than 0.01 were considered significant for subgroup analyses.

Tests of heterogeneity and of trend

First calculate the log-rank statistic (o-e) and its variance v in each separate stratum, and add these up to get the overall logrank (O-E) and it variance V (i.e. the sum of the separate variances). Delete any uninformative strata (i.e. those for which v is zero), and number the remaining strata from 1 to n. A χ^2 test (on n-1 degrees of freedom) for

heterogeneity between the treatment effects in different strata can be obtained by subtracting $(O-E)^2/V$ from the sum of the separate values, one per stratum, of $(o-e)^2/v$.

Alternatively, a χ^2 test for trend (i.e. for whether the treatment effect changes progressively from one stratum to the next) will be calculated as follows: if the stratum numbered s has logrank statistics (o-e) and v then define m, the mean stratum number, to be the sum, one term per stratum, of sv/V and define T to be the sum, one term per stratum, of (s-m)(o-e). The variance of T, var(T), is then the sum, one term per stratum, of $(s-m)^2v$, and the χ^2 test (on 1 degree of freedom) for trend is $T^2/var(T)$. If there are only two strata then the tests for trend and heterogeneity are identical.

Appendix 1. Taxane trial list, updated to November 2019

Cohort1: Taxane + Anthracycline vs Taxane without Anthracycline

Trial & year code	Trial name	Comparisons	N	Received	Published
(a) Concurrent docetaxel plus anthracycline versus same dose docetaxel plus cyclophosphamide					
34206 2007&	USO 06090 / 11271, USA	(Docetaxel [75 mg/m2 iv] d1 + Doxorubicin [50 mg/m2 iv] d1 + Cyclophosphamide [600 mg/m2 iv] d1) q3wk × 6 vs (Docetaxel [75 mg/m2 iv] d1 + Cyclophosphamide [600 mg/m2 iv] d1) q3wk × 6	1296	Yes	✓ 2017[1]
4772 2009J1	NSABP B-46-I, USA	Docetaxel [75 mg/m2 iv] + Doxorubicin [50 mg/m2 iv] + Cyclophosphamide [500 mg/m2] + pegfilgrastim [6 mg sc d2] q21d × 6 vs Docetaxel [75 mg/m2 iv] + Cyclophosphamide [600 mg/m2] q21d × 6	1077	Yes	✓ 2017[1]
46701 2009R	NATT / NCT00912444, Shanghai Jiao Tong University School of Medicine, China	(Docetaxel [75mg/m2 iv] + (Doxorubicin [50mg/m2 iv] or Epirubicin [60 mg/m2 iv]) + Cyclophosphamide [500 mg/m2 iv] + G-CSF) q3wk × 6 preoperative vs (Docetaxel [75mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv] + G-CSF) q3wk × 6 preoperative	96	Yes	✓ 2016[2]
(b) Sequential taxane plus anthracycline versus higher cumulative dose docetaxel plus cyclophophamide					
38406 2007I	HORG CT/07.17, Greece	(5-fluorouracil [500mg/m2] + Epirubicin [75mg/m2] + Cyclophosphamide [500mg/m2]) q3wk × 4 then Docetaxel [75mg/m2]q2wk × 4 vs (Docetaxel [75mg/m2] + Cyclophosphamide [500mg/m2]) q2wk × 6	650	Yes - ineligible	✓2016[116]
2225 2008L	DBCG 07 READ, Denmark	(Epirubicin [90 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 3 then docetaxel [100 mg/m2 iv] q3wk × 3 vs (Cyclophosphamide [600 mg/m2 iv] + Docetaxel [75 mg/m2 iv]) q3wk × 6	2012	Yes	✓ 2017[3]
50702 2008]	Shiga Anthracycline trial	Docetaxel [100mg/m2] q3wk × 3 then (5-Fluorouracil [500 mg/m2] + Epirubicin [100 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3 vs (Docetaxel [75mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 6	42	No - ineligible	✓ 2013[4]
51701 2009&	Kanagawa Japan	(5-Fluorouracil [500 mg/m2 iv d1] + Epirubicin [100 mg/m2 d1] + Cyclophosphamide [500 mg/m2 iv d1]) q21d × 3 then Docetaxel [100mg/m2 iv d1] q21d × 3 preoperative vs (Cyclophosphamide [600mg/m2 iv d1] + Docetaxel [75 mg/m2]) q21d × 6 preoperative	103	Yes	✓ 2019[5]
4774 2009J2	NSABP B-49, USA	((Docetaxel [75 mg/m2] + doxorubicin [50 mg/m2] + cyclophosphamide [500 mg/m2 iv]) q3wk × 6) or ((Doxorubicin [60 mg/m2] + cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then paclitaxel [80 mg/m2 iv] qwk × 12) or ((Doxorubicin [60 mg/m2] + cyclophosphamide [600 mg/m2 iv]) q2wk × 4 then paclitaxel [80 mg/m2 iv] qwk × 12) or ((Doxorubicin [60 mg/m2] + cyclophosphamide [600 mg/m2 iv]) q2wk × 4 then paclitaxel [175 mg/m2 iv] q2wk × 4) vs Docetaxel [75 mg/m2 iv] + Cyclophosphamide [600 mg/m2] q21d × 6	1870	Yes	✓ 2017[1]
33810 2009E1	SUCCESS C, Ludwig-Maximilians University, Germany	(5-Fluorouracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) q3wk × 3 then Docetaxel [100 mg/m2 iv] q3wk × 3 vs (Docetaxel [75 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 6	3643	Yes	✓ 2018[6]

30906 2009M	WSG Plan B, Germany	(Epirubicin [90 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 4 then Docetaxel [100 mg/m2] q3wk × 4 vs (Docetaxel [75 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 6	2449	Yes	✓ 2019[7]
48102 2009U	JBCRG-10, Japan Breast Cancer Research Group	(5-fluorouracil [500mg/m2] + epirubicin [100mg/m2] + cyclophosphamide [500mg/m2] q3wk) × 4 then (docetaxel [75mg/m2] + cyclophosphamide [600mg/m2] q3wk + trastuzumab [4mg/kg loading dose then 2mg/kg thereafter] qwk or [8mg/kg loading dose then 6mg/kg thereafter q3wk]) × 4 preoperative or (docetaxel [75mg/m2] + cyclophosphamide [600mg/m2] q3wk + trastuzumab [4mg/kg loading dose then 2mg/kg thereafter] qwk or [8mg/kg loading dose then 6mg/kg thereafter q3wk]) × 4 then (5-fluorouracil [500mg/m2] + epirubicin [100mg/m2] + cyclophosphamide [500mg/m2] q3wk) × 4 preoperative vs (docetaxel [75mg/m2] + cyclophosphamide [600mg/m2] q3wk + trastuzumab [4mg/kg loading dose then 2mg/kg thereafter] qwk or [8mg/kg loading dose then 6mg/kg thereafter q3wk]) × 4 then (5-fluorouracil [500mg/m2] + epirubicin [100mg/m2] + cyclophosphamide [500mg/m2] q3wk) × 4 preoperative	67	Yes	✓ 2020[8]
48103 2009V	JBCRG-09, Japan Breast Cancer Research Group	(5-Fluoro-Uracil [500 mg/m2] + Epirubicin [100 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3 then (Docetaxel [75 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 3 preoperative or (Docetaxel [75 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 3 then (5-Fluoro-Uracil [500 mg/m2] + Epirubicin [100 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3 preoperative vs (Docetaxel [75 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 6 preoperative	195	Yes	✓ 2020[9]
36509 2010V	Fudan BC MASTER / NCT01314833, Fudan University, Shanghai, China	(Cyclophosphamide [500 mg/m2 d1] + Epirubicin [90-100 mg/m2 d1] + Fluorouracil [500 mg/m2 d1]) q21d × 3 then Docetaxel [100 mg/m2 d1] q21d × 3 vs (Cyclophosphamide [600 mg/m2 d1] + Docetaxel [75 mg/m2 d1]) q21d × 6	1047	Yes	✓ 2021[10]
(c) Taxane plus anthracycline versus taxane ± capecitabine					
35901 2000W	N-SAS BC 02, Japan	((Doxorubicin [60mg/m²] or Epirubicin [75mg/m2]) + Cyclophosphamide [600mg/m²]) q3wk × 4 then (Paclitaxel [175mg/m²] or Docetaxel [75mg/m²]) q3wk × 4 vs (Paclitaxel [175mg/m²] or Docetaxel [75mg/m²]) q3wk × 8	1060	Yes	✓ 2017[11]
36901 2001V	Multicentre France Neoadjuvant Trial, France	(Epirubicin[100mg/m²] + Docetaxel [75mg/m²] + filgrastim) q3wk × 6 maximum preoperative vs Docetaxel [100mg/m²] q3wk × 8 maximum preoperative	21	No	✓ 2004[12]
54201 2005]	Asan Neoadjuvant Capecitabine trial, University of Ulsan College of Medicine, Seoul, Korea	(Doxorubicin [60 mg/m2 d1] + Cyclophosphamide [600 mg/m2 d1]) q3wk × 4 then Docetaxel [75 mg/m2] q3wk × 4 preoperative vs (Capecitabine [2000 mg/m2 d1-14] + Vinorelbine [25 mg/m2 d1,8]) q 3wk × 4 then Docetaxel [75 mg/m2] q3wk × 4 preoperative	75	No	✓ 2015[13]
6332 2006Z1&3	EORTC 10041 / BIG 3-04 / MINDACT, Belgium	(Fluorouracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) d1 q3wk × 3; Docetaxel [?? mg/m2 iv d1] q3wk × 3 vs Docetaxel [75 mg/m2 iv d1] + Capecitabine [1650 mg/m2 po d1-14] q3wk × 6	392	Yes	✓ 2021[14]
37004 2009[2	Remagus 04, France	FEC × 4 then Docetaxel × 4 preoperative vs Docetaxel-capecitabine × 6 preoperative	100	No	2012[15]
52106 2009~6	TaiNAC, Taiwan	(Docetaxel [35 mg/m2 iv] + Epirubicin [45 mg/m2 iv]) d1+8 × 4 preoperative vs (Docetaxel [35 mg/m2] + 5-Fluorouracil [2000mg/m2] + Leucovorin [300 mg/m2]) d1+8 × 4 preoperative	10	Yes – ineligible	No

2630 2011K	ABCSG-32, Austria	(Docetaxel [100 mg/m2 iv] + Pegfilgrastim [6mg sc d2] + Trastuzumab [8mg/kg loading dose then 6mg/kg iv]) + non-pegylated liposomal Doxorubicin [50mg/m2 iv] q21d × 6 preoperative or (Docetaxel [100 mg/m2 iv] + Pegfilgrastim [6mg sc d2] + Trastuzumab [8mg/kg loading dose then 6mg/kg iv] + non-pegylated liposomal Doxorubicin [50mg/m2 iv] + Bevacizumab [15 mg/kg]) q21d × 6 preoperative vs (Docetaxel [100 mg/m2 iv] + Pegfilgrastim [6mg sc d2] + Trastuzumab [8mg/kg loading dose then 6mg/kg iv] + non-pegylated liposomal Doxorubicin [50mg/m2 iv] + Bevacizumab [15 mg/kg]) q21d × 6 preoperative or (Docetaxel [100 mg/m2 iv] + Pegfilgrastim [6mg sc d2] + Trastuzumab [8mg/kg loading dose then 6mg/kg iv] + Bevacizumab [15 mg/kg]) q21d × 6 preoperative	100	Yes - ineligible	✓ Abstract 2015[16]
54101 2011N	PUMCH-Breast-TCX / NCT01354522, Beijing	Docetaxel [75 mg/m2 iv d1] + (Doxorubicin [50 mg/m2 iv d1] or Epirubicin [75 mg/m2 iv d1]) + Cyclophosphamide [500 mg/m2 iv d1] q3wk × 6 vs Docetaxel [75 mg/m2 iv d1] + Cyclophosphamide [500 mg/m2 iv d1] + Capecitabine [950 mg/m2 bid po d1-14] q3wk × 6	400	No	No
(d) Taxane plus anthracycline versus taxane plus carboplatin (confounded)					
33505 2001M	BCIRG 006, TRIO (formerly Breast Cancer International Research Group)	(Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then (Docetaxel [100mg/m²] q21d × 4 + Trastuzumab [4-2mg/kg/wk] qwk × 12) then Trastuzumab [6mg/kg] q21d until 1 yr vs (Docetaxel [75mg/m²] + (Cis-Platinum [75mg/m²] or Carboplatin [AUC 6])) q21d × 6 + Trastuzumab [4-2mg/kg/wk] qwk × 18 then Trastuzumab [6mg/kg] q21d until 1 yr	2149	Yes	✓ 2011[18]
22311 2006~	CAMS Neoadjuvant Paclitaxel trial, Beijing, China	(Paclitaxel [175 mg/m2 iv d1] + Epirubicin [75 mg/m2 iv d1]) q21d × 2-6 cycles preoperative vs (Paclitaxel [175 mg/m2 iv d1] + carboplatin [AUC 5 iv d2]) q21d × 2-6 cycles preoperative	80	No	✓ 2016[19]
43903 2009T	TRYPHAENA, Basel, Switzerland	(Pertuzumab [840 mg then 420 mg iv q3wk] + Trastuzumab [8mg/kg iv then 6mg/kg q3wk iv]) × 6 + ((5-Fluoro-Uracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) for cycles 1-3 then Docetaxel [75 mg/m2 iv then 100 mg/m2 iv q3wk] for cycles 4-6) preoperative then Trastuzumab [6mg/kg iv] q3wk to 1 yr vs (Trastuzumab [8mg/kg iv then 6mg/kg iv] + Pertuzumab [840 mg then 420 mg iv] + Carboplatin [AUC6] + Docetaxel [75 mg/m2]) q3w × 6 preoperative then Trastuzumab [6mg/kg iv] q3wk to 1 yr	225	No	✓ 2013[20]
52107 2009~7	TaiNAC, Taiwan	(Docetaxel [35 mg/m2 iv] + Epirubicin [45 mg/m2 iv]) d1+8 × 4 preoperative vs (Docetaxel [35 mg/m2] + Cisplatin [35 mg/m2 iv]) d1+8 × 4 preoperative	8	Yes – ineligible	No
22309 2010U	CH-BC-007 / NCT01150513, Beijing, China	Epirubicin [90 mg/m2 d1] + Cyclophosphamide [600 mg/m2 d1] q3wk × 4 then Docetaxel [100 mg/m2 d1] q3wk × 4 vs Docetaxel [75 mg/m2 d1] + Carboplatin [AUC 5 d1] q3wk × 6	298	No	✓ 2016[21]
36505 2011H	Fudan Pay/NCT01428414, Fudan University, Shanghai, China	(Trastuzumab [4 mg/kg loading dose then 2 mg/kg iv] + paclitaxel [75 mg/m2]) qwk × 3 + epirubicin [75 mg/m2] q3wk × 4 or 6 cycles preoperative vs (Trastuzumab [4 mg/kg loading dose then 2 mg/kg iv] + paclitaxel [75 mg/m2] + carboplatin [AUC 2]) qwk × 12 or 18 preoperative	100	No	2015[22]
22310 2011M	CH-BC-012 / NCT01378533, Beijing, China	(Epirubicin [80 mg/m2 iv d1 or divided over 2d] + Cyclophosphamide [600 mg/m2 iv d1] + G-CSF [3 mcg/kg d5-9]) q14d × 4 then (Paclitaxel [175 mg/m2 iv d1] + G-CSF [3 mcg/kg d5-9]) q14d × 4 vs (Paclitaxel [150 mg/m2 iv d1] + Carboplatin [AUC=3 iv d2] + G-CSF [3 mcg/kg d5-9]) q14d × 8	132	No	✓ Abstract 2019[17]

36510 2001R	Fudan PATTERN / NCT01216111, Fudan University, Shanghai, China	Cyclophosphamide [500mg/m2] + Epirubicin [100mg/m2] + Fluorouracil [500mg/m2] q3wk × 3 then Docetaxel [100mg/m2wk] q3wk × 3 vs Paclitaxel [80mg/m2 d1,8,16] + Carboplatin [AUC = 2 d1,8,16] q4wk × 6	647	Yes	✓ 2020[23]

Cohort 2: Anthracycline with taxane versus anthracycline regimens without taxane

Trial & year code	Trial name	Comparisons	N	Received	Published
(a) Taxane plus anthracycline based regimen vs the SAME non-taxane cytotoxic chemotherapy					
8316 1994D	CALGB Study 9344 / Intergroup 0148	(Cyclophosphamide [600mg/m²] + Doxorubicin [90mg/m²] + filgrastim [5 or 10µg/kg/d sc d2-12]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4 vs (Cyclophosphamide [600mg/m²] + Doxorubicin [90mg/m²] + filgrastim [5 or 10µg/kg/d sc d2-12]) q3wk × 4 Or (Cyclophosphamide [600mg/m²] + Doxorubicin [75mg/m²]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4 vs (Cyclophosphamide [600mg/m²] + Doxorubicin [75mg/m²]) q3wk × 4 Or (Cyclophosphamide [600mg/m²] + Doxorubicin [60mg/m²]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4 vs (Cyclophosphamide [600mg/m²] + Doxorubicin [60mg/m²]) q3wk × 4	3170	Yes	✓ 2003[24]
4747 1995J	NSABP B-27, USA	((Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 preoperative then Docetaxel [100mg/m²] q21d × 4 preoperative then (Lumpectomy + RT) or Mastectomy) + Tamoxifen [20mg/d] × 5yr or ((Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 preoperative then (Lumpectomy + RT) or Mastectomy) then Docetaxel [100mg/m²] q21d × 4 + Tamoxifen [20mg/d] × 5yr vs ((Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 preoperative then (Lumpectomy + RT) or Mastectomy) + Tamoxifen [20mg/d] × 5yr	2411	Yes	✓ 2003[25]
4748-50 1995K	NSABP B-28, USA	(Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then Paclitaxel [225mg/m²] q21d × 4 then Tamoxifen [20mg/d] × 5yr vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then Tamoxifen [20mg/d] × 5yr Or (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then Paclitaxel [225mg/m²] q21d × 4 vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 Or (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then Paclitaxel [225mg/m²] q21d × 4 then Tamoxifen [20mg/d] × 5yr vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then Tamoxifen [20mg/d] × 5yr	3060	Yes	✓ 2005[26]

4312 1998B	Taxit216, Italy	Epirubicin[120mg/m² iv d1] q21d × 4 then Docetaxel [100mg/m² iv d1] q21d × 4 then (Cyclophosphamide [600mg/m² iv d1,8] + Methotrexate [40mg/m² ivd1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 4 vs Epirubicin[120mg/m² iv d1] q21d × 4 then (Cyclophosphamide [600mg/m² iv d1,8] + Methotrexate [40mg/m² ivd1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 4	972	Yes	✓ Abstract 2008[27]
34301 1999T	GOIM 9902, Italy	Docetaxel [100mg/m² iv d1] q21d × 4 then (Epirubicin[120mg/m² iv d1] + Cyclophosphamide [600mg/m² iv d1]) q21d × 4 vs (Epirubicin[120mg/m² iv d1] + Cyclophosphamide [600mg/m² iv d1]) q21d × 4	750	Yes	✓ 2012[28]
30403 2001Z	Pegase 07, France	Epirubicin [150 mg/m2 d1] + (Cyclophosphamide [4000 mg/m2 d1] + Mesna + filgrastim [10mcg/kg d5 until last cytapheresis (c1) then 5mcg/kg d3 until neutrophils >500/mm^3 (c2-4)]) q3wk × 4 preoperative then Mastectomy + Axillary Lymph Node Dissection then Radiotherapy + (Docetaxel [75mg/m2 d1] + 5-Fluoro-Uracil [750 mg/m2/day iv d1-d5]) q3wk × 4 +/- Tamoxifen [20 mg/d] × 5yr postoperative vs (Epirubicin [150 mg/m2 d1] + Cyclophosphamide [4000 mg/m2 d1] + Mesna + filgrastim [10mcg/kg d5 until last cytapheresis (c1) then 5mcg/kg d3 until neutrophils >500/mm^3 (c2-4)]) q3wk × 4 preoperative then Mastectomy + Axillary Lymph Node Dissection then Radiotherapy +/- Tamoxifen [20 mg/d] × 5yr postoperative	174	No	✓ 2015[29]
44802 2004!	Craiova Dolj Taxane trial, Romania	(Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2] + Paclitaxel [200 mg/m2]) q21d × 2-4 cycles preoperative vs (Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2]) q21d × 2-4 cycles preoperative	124	No	✓ Abstract 2009[30]
(b) Taxane plus anthracycline based regimen (taxane course given alone) vs MORE (but < doubled) non-taxane chemotherapy					
38401-02 1995T	HORG Docetaxel trial, Greece	Docetaxel [100mg/m² iv] q3wk × 4 then (Epirubicin[75mg/m² iv] + Cyclophosphamide [700mg/m² iv]) q3wk × 4 vs (5-Fluoro-Uracil [700mg/m² iv] + Epirubicin[75mg/m² iv] + Cyclophosphamide [700mg/m² iv]) q3wk × 6 Or Docetaxel [100mg/m² iv] q3wk × 4 then (Epirubicin[75mg/m² iv] + Cyclophosphamide [700mg/m² iv]) q3wk × 4 + Tamoxifen [20mg/d po] × 5yr vs (5-Fluoro-Uracil [700mg/m² iv] + Epirubicin[75mg/m² iv] + Cyclophosphamide [700mg/m² iv]) q3wk × 6 + Tamoxifen [20mg/d po] × 5yr	788	Yes	✓ 2010[31]
24604 1997R	HE1097, Greece	(Epirubicin[110mg/m²] + filgrastim [5µg/kg d3-10]) q14d × 3 then (Paclitaxel [250mg/m² over 3h] + filgrastim [5µg/kg d3-10]) q14d × 3 then (Cyclophosphamide [840mg/m²] + Methotrexate [50mg/m²] + 5-Fluoro-Uracil [840mg/m²] + filgrastim [5µg/kg d3-10]) q14d × 3 vs (Epirubicin[110mg/m²] + filgrastim [5µg/kg d3-10]) q14d × 4 then (Cyclophosphamide [840mg/m²] + Methotrexate [50mg/m²] + 5-Fluoro-Uracil [840mg/m²] + filgrastim [5µg/kg d3-10]) q14d × 4	604	Yes	✓ 2005[32]
28507 1997V	IBIS 02, Italy	Paclitaxel [175mg/m² iv d1] q3wk × 4 then (Epirubicin[75mg/m² iv d1] + Vinorelbine [25mg/m² iv d1,8]) q3wk × 4 vs Epirubicin[100mg/m² iv d1] q3wk × 4 then (Cyclophosphamide [600mg/m² iv d1,8] + Methotrexate [40mg/m² iv d1,8] + 5-Fluoro-Uracil [600mg/m² d1,8]) q4wk × 4	244	Yes	✓ 2010[33]
35403-04 1998D	BIG 02-98, Belgium	Doxorubicin [75mg/m² iv] q3wk × 3 then Docetaxel [100mg/m² iv] q3wk × 3 then (Cyclophosphamide [100mg/m² po d1-14] + Methotrexate [40mg/m² d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 3 vs Doxorubicin [75mg/m² iv]	1927	Yes	✓ 2013[34]

		q3wk × 4 then (Cyclophosphamide [100mg/m² po d1-14] + Methotrexate [40mg/m² d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 3 or (Doxorubicin [60mg/m² iv] + Cyclophosphamide [600mg/m² iv]) q3wk × 4 then (Cyclophosphamide [100mg/m² po d1-14] + Methotrexate [40mg/m² d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 3			
29607 1999K	GEICAM 9906, Spain	(5-Fluoro-Uracil [600mg/m² d1] + Epirubicin[90mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q3wk × 4 then Paclitaxel [100mg/m²] qwk × 8 vs (5-Fluoro-Uracil [600mg/m² d1] + Epirubicin[90mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q3wk × 6	1246	Yes	✓ 2008[35]
28902-03 2000E	FinHer/FBCG 00-01, Finland	Docetaxel [80/100mg/m² d1] q21d × 3 then (5-Fluorouracil [600mg/m² d1] + Epirubicin[60mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q21d × 3 vs Vinorelbine [25mg/m² d1, 8, 15] q21d × 3 then (5-Fluorouracil [600mg/m² d1] + Epirubicin[60mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q21d × 3 Or Docetaxel [80/100mg/m² d1] q21d × 3 then (5-Fluorouracil [600mg/m² d1] + Epirubicin[60mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q21d × 3 vs Vinorelbine [25mg/m² d1,8,15] q21d × 3 then (5-Fluorouracil [600mg/m² d1] + Epirubicin[60mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q21d × 3	1009	Yes	✓ 2009[36]
26109/13 2000F	MA.21, Canada	Radiotherapy then (Epirubicin[120mg/m² iv d1] + Cyclophosphamide [830mg/m² iv d1] + filgrastim [5µg/kg/d sc d2-13]) q14d × 6 + Erythropoietin [150µg/kg sc q3d/wk] then Paclitaxel [175mg/m² iv q3wk] × 4 (after 3wk delay) vs Radiotherapy then (5-Fluoro-Uracil [500mg/m² iv d1,8] + Epirubicin[60mg/m² iv d1,8] + Cyclophosphamide [75mg/m² po d1-14]) q28d × 6 + (Co-trimoxazole [480mg po bd] / Ciprofloxacin [500mg po bd])	1402	Yes	✓ 2010[37]
30903 2000S	WSG/AGO AM-02, Germany	(Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4 then Docetaxel [100mg/m²] q3wk × 4 vs (Cyclophosphamide [500mg/m²] + Epirubicin[100mg/m²] + 5-Fluoro-Uracil [500mg/m²]) q3wk × 6	1606	Yes	✓ 2014[38]
36601 2000U	AERO B-2000, France	(5-Fluoro-Uracil [500mg/m²] + Epirubicin[100mg/m²] + Cyclophosphamide [500mg/m²]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4 vs (5-Fluoro-Uracil [500mg/m²] + Epirubicin[100mg/m²] + Cyclophosphamide [500mg/m²]) q3wk × 6	837	Yes	✓ 2014[39]
1140 2003$	GEICAM 2004-04	Paclitaxel [80mg/m² iv] qwk × 12 then ((5-Fluoro-Uracil [500mg/m² iv d1] + Doxorubicin [50mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1]) q3wk × 4 / (5-Fluoro-Uracil [500mg/m² iv d1] + Epirubicin[100mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1]) q3wk × 4) preoperative vs ((5-Fluoro-Uracil [500mg/m² iv d1] + Doxorubicin [50mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1]) q3wk × 6 / (5-Fluoro-Uracil [500mg/m² iv d1] + Epirubicin[100mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1]) q3wk × 6) preoperative	273	Yes	✓ 2010[40]
37804 2003R	GIM 1, Italy	(Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then Docetaxel [100mg/m²] q21d × 4 vs (5-Fluoro-Uracil [600mg/m²] + Epirubicin[75mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 6	1636	No	No
29610-12 2003U	GEICAM 2003-02, Spain	(5-Fluoro-Uracil [500mg/m²] + Doxorubicin [50mg/m²] + Cyclophosphamide [500mg/m²]) q3wk × 4 then Paclitaxel [100mg/m²] qwk × 8 vs (5-Fluoro-Uracil	1925	Yes	✓ 2013[41]

		[500mg/m²] + Doxorubicin [50mg/m²] + Cyclophosphamide [500mg/m²]) q3wk × 6			
(c) Taxane plus anthracycline (taxane given concurrently) vs MORE (but < doubled) non-taxane chemotherapy					
33801 1995E	LMU Munich, Germany	(Docetaxel [75mg/m²] + Epirubicin[60mg/m²]) q21d × 6 vs (Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m²]) q21d × 4 then (Cyclophosphamide [600mg/m²] + Methotrexate [40mg/m²] + 5-Fluoro-Uracil [600mg/m²]) q21d × 3	36	No	✓ 2000[42]
31101-02 1996#	Helena-Venizelou Chemotherapy Trial, Greece	(Epirubicin[75mg/m² iv d1] + Paclitaxel [200mg/m² over 3h d1]) q21d × 3 preoperative then (Epirubicin[75mg/m² iv d1] + Paclitaxel [200mg/m² over 3h d1]) q21d × 3 postoperative + Radiotherapy [to chest wall] then Tamoxifen × 5yr vs (5-Fluoro-Uracil [600mg/m² d1] + Epirubicin[75mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q21d × 3 preoperative then (5-Fluoro-Uracil [600mg/m² d1] + Epirubicin[75mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q21d × 3 postoperative + Radiotherapy [to chest wall] then Tamoxifen × 5yr	70	No	✓ Abstract 1998[43]
30801 1996%	Multicentre Germany Chemotherapy Trial	(Epirubicin[90mg/m² iv d1] + Paclitaxel [175mg/m² iv d1]) q14d × 4 + filgrastim [5mcg/kg sc d5-13] then (Cyclophosphamide [600mg/m² iv d1] + Methotrexate [40mg/m² iv d1] + 5-Fluoro-Uracil [600mg/m² iv d1]) q14d × 3 vs (Epirubicin[90mg/m² iv d1] + Cyclophosphamide [600mg/m² iv d1]) q21d × 4 then (Cyclophosphamide [600mg/m² iv d1] + Methotrexate [40mg/m² iv d1] + 5-Fluoro-Uracil [600mg/m² iv d1]) q21d × 3	228	Yes	✓ 2006[44]
3521 1996Q	European Cooperative Trial in Operable Breast Cancer (ECTO)	(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-Fluoro-Uracil [600mg/m² iv d1,8]) q4wk × 4 then Tamoxifen [20mg/d] × 5yr or (Epirubicin[60mg/m² iv] then Paclitaxel [200mg/m² iv over 3h]) q3wk × 4 preoperative then (Cyclophosphamide [600mg/m² iv d1,8] + Methotrexate [40mg/m² iv d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q4wk × 4 preoperative then Tamoxifen [20mg/d] × 5yr vs Epirubicin[75mg/m² iv] q3wk × 4 then (Cyclophosphamide [600mg/m² iv d1,8] + Methotrexate [40mg/m² iv d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q4wk × 4 then Tamoxifen [20mg/d] × 5yr	1355	Yes	✓ 2009[45]
31401 1996X	GONO-MIG 5, Italy	(Epirubicin[90mg/m² iv d1] + Paclitaxel [175mg/m² iv over 3h d1]) q3wk × 4 vs (5-Fluoro-Uracil [600mg/m² iv d1] + Epirubicin[60mg/m² iv d1] + Cyclophosphamide [600mg/m² iv d1]) q3wk × 6	1055	Yes	✓ 2016[46]
33102 1997H1	Multicentre France Neoadjuvant Chemotherapy Trial	(Doxorubicin [60mg/m² iv] + Paclitaxel [200mg/m² iv]) q3wk × 4 preoperative vs (Doxorubicin [60mg/m² iv] + Cyclophosphamide [600mg/m² iv]) q3wk × 4 preoperative	200	Synthetic	✓ 2004[47]
33501 1997L	BCIRG 001 / GEICAM 9703	(Doxorubicin [50mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1] + Docetaxel [75mg/m² iv d1]) q21d × 6 vs (Doxorubicin [50mg/m² iv d1] + 5-Fluoro-Uracil [500mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1]) q21d × 6	1491	Yes	✓ 2013[48]
35403-04 1998D	BIG 02-98, Belgium	(Doxorubicin [50mg/m² iv] + Docetaxel [75mg/m² iv]) q3wk × 4 then (Cyclophosphamide [100mg/m² po d1-14] + Methotrexate [40mg/m² d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 3 vs Doxorubicin [75mg/m² iv] q3wk	1928	Yes	✓ 2013[34]

		× 4 then (Cyclophosphamide [100mg/m² po d1-14] + Methotrexate [40mg/m² d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 3 or (Doxorubicin [60mg/m² iv] + Cyclophosphamide [600mg/m² iv]) q3wk × 4 then (Cyclophosphamide [100mg/m² po d1-14] + Methotrexate [40mg/m² d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q28d × 3			
7520 1998T	ECOG EST2197, USA	(Doxorubicin [60mg/m²] + Docetaxel [60mg/m²]) q3wk × 4 vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4	2952	Yes	✓ 2008[49]
29603-06 1999%	GEICAM 9805 / TARGET 0, Spain	(Docetaxel [75mg/m² d1] + Doxorubicin [50mg/m² d1] + Cyclophosphamide [500mg/m² d1]) q3wk × 6 vs (5-Fluoro-Uracil [500mg/m² d1] + Doxorubicin [50mg/m² d1] + Cyclophosphamide [500mg/m² d1]) q3wk × 6	1060	Yes	✓ 2010[50]
27402 1999A	Anglo-Celtic II (Primary Medical Therapy Trial IIA), UK	(Doxorubicin [50mg/m²] + Docetaxel [75mg/m²]) q3wk × 6 primary preoperative vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 6 primary preoperative	363	Yes	✓ 2010[51]
20603 1999N	RAPP-01, France	(Doxorubicin [50mg/m²] + Docetaxel [75mg/m²]) q3wk × 4 postoperative vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4 postoperative	627	Yes	✓ 2005[52]
33202/04 2001E1+3	PACS 04, France	(Epirubicin[75mg/m² iv d1] + Docetaxel [75mg/m² iv d1]) q3wk × 6 + Radiotherapy vs (5-Fluoro-Uracil [500mg/m² iv d1] + Epirubicin[100mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1]) q3wk × 6 + Radiotherapy	3009	Yes	✓ 2009[53]
8727 2002L	St Petersburg Neoadjuvant trial, Russia	(Paclitaxel [200 mg/m2] + Doxorubicin [60 mg/m2]) q3wk × 4 preoperative vs (5-Fluorouracil [600 mg/m2] + Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 4 preoperative	103	No	✓ Abstract 2002[54]
38913-14 2004N	MATADOR / BOOG 2005-02 / CKTO 2004-04	(Docetaxel [75mg/m iv d1] + Doxorubicin [50mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1] + Pegfilgrastim [6mg sc 1d after chemo]) q3wk × 6 vs (Doxorubicin [60mg/m² iv d1] + Cyclophosphamide [600mg/m² iv d1] + Pegfilgrastim [6mg sc 1d after chemo]) q2wk × 6	664	Yes	✓ 2018[55]
40302 2007”	Kolkata Chemotherapy trial, India	Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2] q3wk × 6 then Paclitaxel [175 mg/m2] q3wk × 3 vs Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2] q3wk × 6	50	No	✓2012[56]
(d) Taxane plus anthracycline vs DOUBLED non-taxane cytotoxic chemotherapy					
1122-24, 27-29 1994B	Protocol 94-002 MDA	Paclitaxel [250mg/m² 24h infusion] q3wk × 4 then (5-Fluoro-Uracil [500mg/m² iv d1,4] + Doxorubicin [50mg/m² 72h infusion] + Cyclophosphamide [500mg/m² iv d1]) q3wk × 4 then Radiotherapy vs (5-Fluoro-Uracil [500mg/m² iv d1,4] + Doxorubicin [50mg/m² 72h infusion] + Cyclophosphamide [500mg/m² iv d1]) q3wk × 8 then Radiotherapy	474	Yes	✓ 2011[57]
34001 1996F	Aberdeen Trial, Scotland	(Cyclophosphamide [1000mg/m²] + Doxorubicin [50mg/m²] + Vincristine [1·5mg/m²] + Prednisolone [40mg]) q21d × 4 preoperative then (Prednisolone [100mg po] + Docetaxel [100mg/m²]) q21d × 4 postoperative vs (Cyclophosphamide [1000mg/m²] + Doxorubicin [50mg/m²] + Vincristine [1·5mg/m²] + Prednisolone [40mg]) q21d × 4 preoperative then (Cyclophosphamide [1000mg/m²] + Doxorubicin [50mg/m²] + Vincristine [1·5mg/m²] + Prednisolone [100mg po]) q21d × 4 postoperative	104	Synthetic	✓ Abstract 2003[58]

20008-09 1997A	DEVA, UK	(Epirubicin[50mg/m² d1,8] q4wk × 3 then Docetaxel [100mg/m² d1] q3wk × 3) + Tamoxifen [20 mg/d] × 5yr concurrent vs Epirubicin[50mg/m² d1,8] q4wk × 6 + Tamoxifen [20 mg/d] × 5yr concurrent	803	Yes	✓ 2011[59]
33201 1997J	PACS 01, France	(5-Fluoro-Uracil [500mg/m² d1] + Epirubicin[100mg/m² d1] + Cyclophosphamide [500mg/m² d1]) q21d × 3 then Docetaxel [100mg/m² d1] q21d × 3 vs (5-Fluoro-Uracil [500mg/m² d1] + Epirubicin[100mg/m² d1] + Cyclophosphamide [500mg/m² d1]) q21d × 6	1999	Yes	✓ 2012[60]
26109/13 2000F	MA.21, Canada	Radiotherapy then (Doxorubicin [60mg/m² iv d1] + Cyclophosphamide [600mg/m² iv d1]) q21d × 4 then Paclitaxel [175mg/m² iv q3wk] × 4 (after 3wk delay) vs Radiotherapy then (5-Fluoro-Uracil [500mg/m² iv d1,8] + Epirubicin[60mg/m² iv d1,8] + Cyclophosphamide [75mg/m² po d1-14]) q28d × 6 + (Co-trimoxazole [480mg po bd] / Ciprofloxacin [500mg po bd])	1403	Yes	✓ 2010[37]
24016/18 2001F	TACT, UK	(5-Fluoro-Uracil [600mg/m² iv] + Epirubicin[60mg/m² iv] + Cyclophosphamide [600mg/m² iv]) q3wk × 4 then Docetaxel [100mg/m² iv d1] q3wk × 4 vs (5-Fluoro-Uracil [600mg/m² iv] + Epirubicin[60mg/m² iv] + Cyclophosphamide [600mg/m² iv]) q3wk × 8	2523	Yes	✓ 2009[61]
24017/19 2001G1+2	TACT, UK	(5-Fluoro-Uracil [600mg/m² iv] + Epirubicin[60mg/m² iv] + Cyclophosphamide [600mg/m² iv]) q3wk × 4 then Docetaxel [100mg/m² iv d1] q3wk × 4 vs Epirubicin[100mg/m² iv] q3wk × 4 then (Cyclophosphamide [100mg/m² po d1-14 / 600mg/m² iv d1,8] + Methotrexate [40mg/m² iv d1,8] + 5-Fluoro-Uracil [600mg/m² iv d1,8]) q4wk × 4	1639	Yes	✓ 2009[61]
6320-21 2001J	E.O.R.T.C. Trial 10994	Docetaxel [100mg/m² iv] q3wk × 3 then (Epirubicin[90mg/m² iv] + Docetaxel [75mg/m² iv]) q3wk × 3 preoperative vs ((5-Fluoro-Uracil [500mg/m² iv] + Epirubicin[100mg/m² iv] + Cyclophosphamide [500mg/m² iv]) q3wk × 6) / ((5-Fluoro-Uracil [iv d1,8] + Epirubicin[iv d1,8] + Cyclophosphamide [po d1-14]) q4wk × 6) / ((5-Fluoro-Uracil [iv d1] + Epirubicin[iv d1] + Cyclophosphamide [iv d1] + Filgrastim [sc d2-15]) q3wk × 6) preoperative	1856	Yes	✓ 2014[62]
33804 2001T	ADEBAR Study, Germany	Radiotherapy + (Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m²]) q21d ×4 then Docetaxel [100mg/m²] q21d × 4 vs Radiotherapy + (Epirubicin[60mg/m² d1,8] + 5-Fluoro-Uracil [500mg/m² d1,8] Cyclophosphamide [75mg/m² d1-14]) q4wk × 6	1363	Yes	✓ 2016[63]
35009-10 2002D	GBG 42, Germany	(5-Fluoro-Uracil [500mg/m²] + Epirubicin[100mg/m²] + Cyclophosphamide [500mg/m²]) q3wk × 3 then Docetaxel [100mg/m²] q3wk × 3 vs (5-Fluoro-Uracil [500mg/m²] + Epirubicin[100mg/m²] + Cyclophosphamide [500mg/m²]) q3wk × 6	2660	Yes	✓ Abstract[64] 2012
28403-08 2002G	Bari Inflammatory Breast Cancer with Surgery, Italy	(Epirubicin[120mg/m² d1] + Vinorelbine [25mg/m² d1,8]) × 4 preoperative then Surgery/Radiotherapy then Docetaxel [100mg/m²] q3wk × 4 vs (Epirubicin[120mg/m² d1] + Vinorelbine [25mg/m² d1,8]) × 4 preoperative then Surgery/Radiotherapy then (Epirubicin[120mg/m² d1] + Vinorelbine [25mg/m² d1,8]) q3wk × 4	56	No	✓ Abstract 2008[65]

Cohort 3: Taxane vs Anthracycline

Trial & year code	Trial name	Comparisons	N	Received	Published
(a) Docetaxel vs anthracycline					
34201&03 1997N1&2	U.S. Oncology Trial 97-35, USA	(Docetaxel [75mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4 vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4	1016	Yes	✓ 2005[66]
6328 2006Z2	MINDACT/ EORTC 10041 / BIG 3-04, Belgium	Docetaxel [75 mg/m2 iv d1] + Capecitabine [825 mg/m2 po bd d1-14] q3wk × 6 vs (Fluorouracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) d1 q3wk × 6 (or various other anthracycline based regimens)	909	Yes	✓ 2017[67]
51901 2008)	Singapore-NCC0705	(Cyclophosphamide [iv d1] + Docetaxel [iv d1]) q3wk × 4 preoperative vs (Cyclophosphamide [iv d1] + Doxorubicin [iv d1]) q3wk × 4 preoperative	20	No	No
48301 2008Y	Duke Taxane trial/NCT00636441, USA	(Docetaxel [75 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 4 preoperative vs (Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 4 preoperative	56	No	✓ 2010[68]
(b) Paclitaxel vs anthracycline					
44701&02 1997[1&2	Epi-Tax trial, Norway	Paclitaxel [200 mg/m2] q3wk × 4 preoperative vs Epirubicin [90 mg/m2] q3wk × 4 preoperative	223	Yes	✓ 2011[69]
8322 2002B1	CALGB 40101, USA	(Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4 or × 6 vs Paclitaxel [80mg/m²] qwk × 12 or × 18	570	Yes	✓ 2014[70]
8323 2002B2	CALGB 40101, USA	(Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q2wk × 4 or × 6 vs Paclitaxel [175mg/m²] q2wk × 4 or × 6	2622	Yes	✓ 2014[70]
8324 2002B3	CALGB 40101, USA	(Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q2wk × 4 vs Paclitaxel [175mg/m²] q2wk × 4	679	Yes	✓ 2014[70]

Cohort 4: Head-to-Head Taxanes

Trial code	Trial name	Comparisons	N	Received	Published
(a) Docetaxel 2-weekly or 3-weekly vs paclitaxel 2-weekly or 3-weekly					
7521-22 1999V	E1199/Intergroup Trial, ECOG, USA	(Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Docetaxel [100 mg/m2 iv over 1h] q3wk × 4 vs (Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Paclitaxel [175 mg/m2 iv over 3h] q3wk × 4	2534	Yes	✓ 2015[71]

35901 2000W	N-SAS BC 02, Japan	((Doxorubicin [60mg/m²] or Epirubicin [75mg/m2]) + Cyclophosphamide [600mg/m²]) q3wk × 4 then Docetaxel [75mg/m²] q3wk × 4 then Tam/AIs × 5yr if ER+/PR+ vs ((Doxorubicin [60mg/m²] or Epirubicin [75mg/m2]) + Cyclophosphamide [600mg/m²]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4 then Tam/AIs × 5yr if ER+/PR+ Or Docetaxel [75mg/m²] q3wk × 8 then Tam/AIs × 5yr if ER+/PR+ vs Paclitaxel [175mg/m²] q3wk × 8 then Tam/AIs × 5yr if ER+/PR+	1060	Yes	✓ 2017[11]
38404 2004R	CT/04.22, HORG, Greece	(5-fluorouracil [700mg/m2 iv] d1 + epirubicin [75mg/m2 iv d1,15] + cyclophosphamide [700mg/m2 iv d1]) q4w × 4 then (Docetaxel [75mg/m2 iv] q2w × 4 vs Paclitaxel [175mg/m2 iv] q2w × 4)	481	Yes	✓ 2014[73]
42201	Mansoura Taxane trial, Egypt	(Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 4 then Docetaxel [100 mg/m2] q3wk × 4 vs (Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2]) q3wk × 4 then Paclitaxel [175 mg/m2] q3wk × 4	160	No	✓ Abstract 2011[73]
(b) Docetaxel weekly vs paclitaxel weekly					
7521-22 1999V	E1199/Intergroup Trial, ECOG, USA	(Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Docetaxel [35 mg/m2 iv over 1h] qwk × 12 vs (Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Paclitaxel [80 mg/m2 iv over 1h] qwk × 12	2518	Yes	✓ 2015[71]
24610 2005C	HE 10/05, HECOG, Greece	Epirubicin [110mg/m2] q2wk × 3 then (Cyclophosphamide [840mg/m2] + Methotrexate [57mg/m2] + 5-Fluorouracil [840mg/m2]) q2wk × 3 then Docetaxel [35mg/m2] qwk × 9 vs Epirubicin [110mg/m2] q2wk × 3 then (Cyclophosphamide [840mg/m2] + Methotrexate [57mg/m2] + 5-Fluorouracil [840mg/m2]) q2wk × 3 then Paclitaxel [80mg/m2] qwk × 9	664	Yes	✓ 2014[75]
38302 2007'	KBCOG-06, Japan	Docetaxel [75mg/m2] q3wk × 4 then (5-Fluoro-Uracil + Epirubicin + Cyclophosphamide) preoperative vs Paclitaxel [80mg/m2 d1,8,15] q4wk × 4 then (5-Fluoro-Uracil + Epirubicin + Cyclophosphamide) preoperative	50	No	No

Cohort 5: Dose fractionation

Trial & year code	Trial name	Comparisons	N	Received	Published
(a) Chemotherapy in smaller fractions: Paclitaxel					
1125-26, 1134-37 1998K	MDA 98-240, USA	Paclitaxel [80mg/m²] qwk × 12 + (5-Fluoro-Uracil [500mg/m² d1,4] + Cyclophosphamide [500mg/m² d1] + Doxorubicin [50mg/m² over 72h]) q3wk × 4 preoperative then Local Therapy vs Paclitaxel [225mg/m² over 24h] q3wk × 4 + (5-Fluoro-Uracil [500mg/m² d1,4] + Cyclophosphamide [500mg/m² d1] + Doxorubicin [50mg/m² over 72h]) q3wk × 4 preoperative then Local Therapy Or	254	Yes	✓ 2005[76]

		Paclitaxel [150/175mg/m²] qwk × 12 + (5-Fluoro-Uracil [500mg/m² d1,4] + Cyclophosphamide [500mg/m² d1] + Doxorubicin [50mg/m² over 72h]) q3wk × 4 preoperative then Local Therapy vs Paclitaxel [225mg/m² over 24h] q3wk × 4 + (5-Fluoro-Uracil [500mg/m² d1,4] + Cyclophosphamide [500mg/m² d1] + Doxorubicin [50mg/m² over 72h]) q3wk × 4 preoperative then Local Therapy			
7521-22 1999V	E1199/Intergroup Trial, ECOG, USA	(Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Paclitaxel [80 mg/m2 iv over 1h] qwk × 12 vs (Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Paclitaxel [175 mg/m2 iv over 3h] q3wk × 4	2530	Yes	✓ 2015[71]
1215/19 2003*	SWOG S0221, USA	(Doxorubicin [24mg/m²/wk] + Cyclophosphamide [60mg/m²/d po] + filgrastim [5mcg/kg/d sc d2-7]) qwk × 15wk then Paclitaxel [80mg/m²] qwk × 12 or (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²] + Pegfilgrastim [6mg sc d2]) q2wk × 6 then Paclitaxel [80mg/m²] qwk × 12 vs (Doxorubicin [24mg/m²/wk iv] + Cyclophosphamide [60mg/m²/d po] + filgrastim [5mcg/kg/d sc d2-7]) qwk × 15wk then (Paclitaxel [175mg/m²] + Pegfilgrastim [6mg sc d2]) q2wk × 6 or (Doxorubicin [60mg/m² d1] + Cyclophosphamide [600mg/m² iv d1] + Pegfilgrastim [6mg sc d2]) q2wk × 6 then (Paclitaxel [175mg/m²] + Pegfilgrastim [6mg sc d2]) q2wk × 6	3294	Yes	✓ 2015[77]
24610 2005C	HE 10/05, HECOG, Greece	Epirubicin [110mg/m2] q2wk × 3 then (Cyclophosphamide [840mg/m2] + Methotrexate [57mg/m2] + 5-Fluorouracil [840mg/m2]) q2wk × 3 then Paclitaxel [80mg/m2] qwk × 9 vs Epirubicin [110mg/m2] q2wk × 3 then Paclitaxel [200mg/m2] q2wk × 3 then (Cyclophosphamide [840mg/m2] + Methotrexate [57mg/m2] + 5-Fluorouracil [840mg/m2]) q2wk × 3	667	Yes	✓ 2012[75]
51801 2005R	PKU Paclitaxel trial, Beijing China	(Carboplatin [AUC 6 d1] + Paclitaxel [60 mg/m2 d1,8,15]) q3wk × 4 preoperative vs (Carboplatin [AUC 6 d1] + Paclitaxel [175 mg/m2 d1]) q3wk × 4 preoperative	220	No	Abstract 2010[78]
(b) Chemotherapy in smaller fractions: Docetaxel					
7521-22 1999V	E1199/Intergroup Trial, ECOG, USA	(Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Docetaxel [35 mg/m2 iv over 1h] qwk × 12 vs (Doxorubicin [60 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 4 then Docetaxel [100 mg/m2 iv over 1h] q3wk × 4	2886	Yes	✓ 2015[71]
45201-02 2000^	Hull Neoadjuvant trial, UK	(Doxorubicin [60mg/m2 iv] + Cyclophosphamide [600mg/m² iv] q3wk) × 4 then Docetaxel [33mg/m² iv] qwk × 12 (with a 2 week break between cycles 6 and 7) preoperative vs (Doxorubicin [60mg/m2 iv] + Cyclophosphamide [600mg/m² iv] q3wk) × 4 then Docetaxel [100mg/m2 iv] q3wk × 4 preoperative	82	Yes	✓ 2011[79]
38803 2004Z	BREAST-10, Italy	Epirubicin [30mg/m2 d1,8,15] + Docetaxel [35mg/m2 d1,8,15] q4wk × 3 preoperative vs Epirubicin [75mg/m2 d1] + Docetaxel [80mg/m2 d1] q3wk × 4 preoperative	44	Yes	✓ 2011[80]
46401 2005@	UZLeuven Chemotherapy trial, Belgium	((5-fluorouracil [375 mg/m2] + Epirubicin [75 mg/m2] + Cyclophosphamide [375 mg/m2]) q10-11d × 4 then Docetaxel [75 mg/m2] q2wk × 4) + pegfilgrastim [6mg sc] d2 of each cycle vs (5-fluorouracil [500 mg/m2] +	85	Yes	✓ 2009[81]

		Epirubicin [100 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3 then Docetaxel [100 mg/m2] q3wk × 3 Or (Docetaxel [75 mg/m2] q2wk × 4 then (5-fluorouracil [375 mg/m2] + Epirubicin [75 mg/m2] + Cyclophosphamide [375 mg/m2]) q10-11d × 4) + pegfilgrastim [6mg sc] d2 of each cycle vs Docetaxel [100 mg/m2] q3wk × 3 then (5-fluorouracil [500 mg/m2] + Epirubicin [100 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3			
45504 2007e	Emory Induction trial / NCT00209092, USA	(Docetaxel [50 mg/m2 iv d1] + Capecitabine [2000 mg/m2 po d1-7]) q2wk × 8 vs Docetaxel [100 mg/m2 iv d1] q3wk × 4 then Capecitabine [2000 mg/m2 po d1-14] q3wk × 4 preoperative	51	No	✓ 2016[83]

Cohort 6: Sequencing of sequential anthracycline and taxane chemotherapy

Trial & year code	Trial name	Comparisons	N	Received	Published
6607 2000N	DFCI 99278, USA	Doxorubicin [60mg/m² iv] q2wk × 4 preoperative then Paclitaxel [80mg/m² iv] qwk × 9 preoperative/postoperative vs Paclitaxel [80mg/m² iv] qwk × 9 preoperative then Doxorubicin [60mg/m² iv] q2wk × 4 preoperative/postoperative	62	No	✓ 2005[82]
40801 2002K	Goyang Neoadjuvant Crossover Trial, South Korea	(Doxorubicin [60mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q3wk × 4 preoperative then (Docetaxel [75mg/m² d1] + Capecitabine [1000mg/m² bd d1-14]) q3wk × 4 postoperative vs (Docetaxel [75mg/m² d1] + Capecitabine [1000mg/m² bd d1-14]) q3wk × 4 preoperative then (Doxorubicin [60mg/m² d1] + Cyclophosphamide [600mg/m² d1]) q3wk × 4 postoperative	209	Yes	✓ 2008[84]
45101 2002U	Mount Vernon & Baylor College TAC, UK	(Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2]) × 4 preoperative then Docetaxel [100 mg/m2] × 4 postoperative vs Docetaxel [100 mg/m2] × 4 preoperative then (Doxorubicin [60 mg/m2] + Cyclophosphamide [600 mg/m2]) × 4 postoperative	120	No	✓ Abstract 2007[86]
36602 2003L	AERO-B03, France	(Epirubicin[100mg/m²] + Cyclophosphamide [600mg/m²] + Pegfilgrastim [d2]) q2wk × 4 then (Docetaxel [100mg/m²] + Pegfilgrastim [6mg d2]) q2wk × 4 vs (Docetaxel [75mg/m²] + Epirubicin[75mg/m²] + Cyclophosphamide [500mg/m²] + Pegfilgrastim [6mg d2]) q3wk × 6	65	Yes	✓ 2007[85]
38301 2003[	KBCOG-02, Japan	(Epirubicin[75mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4 preoperative then Paclitaxel [80mg/m²] qwk × 12 postoperative vs Paclitaxel [80mg/m²] qwk × 12 preoperative then (Epirubicin[75mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4 postoperative	171	Yes	✓ Abstract 2008[87]
50601 2004^	OSU Chemotherapy Sequencing, USA	(Doxorubicin [60mg/m2 iv] + cyclophosphamide [600 mg/m2 iv]) q2wk × 4 then docetaxel [75mg/m2 iv] q2wk × 4 then pegfilgrastim [6mg sc] following each chemotherapy cycle vs Docetaxel [75mg/m2 iv] q2wk × 4 then	56	No	✓ 2008[88]

		(doxorubicin [60mg/m2 iv] + cyclophosphamide [600 mg/m2 iv]) q2wk × 4 then pegfilgrastim [6mg sc] following each chemotherapy cycle			
53101 2004{	SETUP / ACTRN12605000588695, Australia	(5-fluorouracil [500mg/m2 iv] + Epirubicin [100mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q3wk × 4 then Docetaxel [100mg/m2 iv] preoperative vs Docetaxel [100mg/m2 iv] then (5-fluorouracil [500mg/m2 iv] + Epirubicin [100mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q3wk × 4 preoperative	69	No	✓ 2014[89]
46401 2005@	UZLeuven Chemotherapy trial	(5-fluorouracil [500 mg/m2] + Epirubicin [100 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3 then Docetaxel [100 mg/m2] q3wk × 3 vs Docetaxel [100 mg/m2] q3wk × 3 then (5-fluorouracil [500 mg/m2] + Epirubicin [100 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3 Or ((5-fluorouracil [375 mg/m2] + Epirubicin [75 mg/m2] + Cyclophosphamide [375 mg/m2]) q10-11d × 4 then Docetaxel [75 mg/m2] q2wk × 4) + pegfilgrastim [6mg sc] d2 of each cycle vs (Docetaxel [75 mg/m2] q2wk × 4 then (5-fluorouracil [375 mg/m2] + Epirubicin [75 mg/m2] + Cyclophosphamide [375 mg/m2]) q10-11d × 4) + pegfilgrastim [6mg sc] d2 of each cycle	85	Yes	✓ 2009[81]
1812 2005A	Neo-tAnGo Trial, UK	(Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m² d1]) q3wk × 4 preoperative then Paclitaxel [175mg/m² d1] q2wk × 4 preoperative vs Paclitaxel [175mg/m² d1] q2wk × 4 preoperative then (Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m² d1]) q3wk × 4 preoperative Or (Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m² d1]) q3wk × 4 preoperative then (Paclitaxel [175mg/m² d1] + Gemcitabine [2g/m² d1]) q2wk × 4 preoperative vs (Paclitaxel [175mg/m² d1] + Gemcitabine [2g/m² d1]) q2wk × 4 preoperative then (Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m² d1]) q3wk × 4 preoperative	828	Yes	✓ 2014[90]
24903 2005X	NCT00123929 H San Carlos Madrid, Spain	Doxorubicin [75 mg/m2] q3wk × 4 preoperative then surgery then Docetaxel [100 mg/m2] q3wk × 4 + Radiotherapy + Tam/AIs if ER+/PR+ vs Docetaxel [100 mg/m2] q3wk × 4 preoperative then surgery then Doxorubicin [75mg/m2] q3wk × 4 + Radiotherapy + Tam/AIs if ER+/PR+	204	No	✓ 2011[91]
50701 2006N	Shiga Chemotherapy Sequencing, Japan	(5-Fluorouracil [500 mg/m2] + Epirubicin [110 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3 then Docetaxel [100mg/m2] q3wk × 3 vs Docetaxel [100mg/m2] q3wk × 3 then (5-Fluorouracil [500 mg/m2] + Epirubicin [110 mg/m2] + Cyclophosphamide [500 mg/m2]) q3wk × 3	42	No	✓ 2013[92]
32502 2007Y	ACOSOG Z1041, USA	5-Fluorouracil [500 mg/m2 iv] + Epirubicin [75 mg/m2 iv] + Cyclophosphamide [500 mg/m2] d1 q3wk × 4 then (Paclitaxel [80 mg/m2] + Trastuzumab [4 mg/kg loading dose and 2 mg/kg weekly dose] d1, d8, d15) q3wk × 4 preoperative then surgery then Trastuzumab [6 mg/kg] d1 q21d for up to 52 wks vs Paclitaxel [80 mg/m2] + Trastuzumab [4 mg/kg loading dose and 2 mg/kg weekly dose] d1, d8, d15 q3wk × 4 then 5-Fluorouracil [500 mg/m2 iv] + Epirubicin [75 mg/m2 iv] + Cyclophosphamide [500	282	Yes	✓ 2019[93]

		mg/m2] d1 q3w × 4 + Trastuzumab [2 mg/kg] d1, d8, d15 q3wk × 4 concurrently preoperative then surgery then Trastuzumab [6 mg/kg] d1 q21d for up to 52 wks			
48102 2009U	JBCRG-10, Japan	(5-fluorouracil [500mg/m2] + Epirubicin [100mg/m2] + Cyclophosphamide [500mg/m2] q3wk) × 4 then (Docetaxel [75mg/m2] + Cyclophosphamide [600mg/m2] q3wk + Trastuzumab [4mg/kg loading dose then 2mg/kg thereafter] qwk or [8mg/kg loading dose then 6mg/kg thereafter q3wk]) × 4 preoperative vs (Docetaxel [75mg/m2] + Cyclophosphamide [600mg/m2] q3wk + Trastuzumab [4mg/kg loading dose then 2mg/kg thereafter] qwk or [8mg/kg loading dose then 6mg/kg thereafter q3wk]) × 4 then (5-fluorouracil [500mg/m2] + Epirubicin [100mg/m2] + Cyclophosphamide [500mg/m2] q3wk) × 4 preoperative	42	Yes	✓ Abstract 2020[8]
48103 2009V	JBCRG-09, Japan	(5-Fluoro-Uracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) q3wk × 3 then (Docetaxel [75 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 3 preoperative vs (Docetaxel [75 mg/m2 iv] + Cyclophosphamide [600 mg/m2 iv]) q3wk × 3 then (5-Fluoro-Uracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) q3wk × 3 preoperative	128	Yes	✓ 2020[9]
1223 2010G	SWOG S0800, USA	(Doxorubicin [60 mg/m2 iv d1] + cyclophosphamide [600mg/m2 iv d1] + pegfilgrastim [6mg sc d2]) q2wk × 6 then Nab-paclitaxel [100mg/m2 iv d1] qwk × 12 preoperative vs Nab-paclitaxel [100mg/m2 iv] qwk × 12 then (doxorubicin [60 mg/m2 iv d1] + cyclophosphamide [600mg/m2 iv d1] + pegfilgrastim [6mg sc d2]) q2wk × 6 preoperative	116	Yes	✓ 2016[94]
29902 2010J	NeoSAMBA, Brazil	(5-Fluoro-Uracil [500mg/m2 iv] + Doxorubicin [50mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q21d × 3 then Docetaxel [100mg/m2 iv] q21d × 3 preoperative vs Docetaxel [100mg/m2 iv] q21d × 3 then (5-Fluoro-Uracil [500mg/m2 iv] + Doxorubicin [50mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q21d × 3 preoperative	120	Yes	✓ 2020[95]

Cohort 7: Longer vs shorter duration of anthracycline

Trial & year code	Trial name	Comparisons	N	Received	Published
(a) Longer versus shorter less than 6 months of polychemotherapy (anthracycline)					
6601-02, 6604	Adjuvant Breast 74-063 A, USA	(Cyclophosphamide [500 mg/m2 iv] + Doxorubicin [45 mg/m2 iv]) q3wk × 10 vs (Cyclophosphamide [500 mg/m2 iv] + Doxorubicin [45 mg/m2 iv]) q3wk × 5	299	Yes	1987[96]
1974D	Adjuvant Breast 75-122 B				
19305, 07, 09, 11 1982Z	Metaneira B Stage II and III, Greece	Oophorectomy + (Vincristine [0.9 mg/m2 iv d1] + Doxorubicin [35 mg/m2 iv d1] + Cyclophosphamide [100 mg po tds d1-4]) qm × 3 + (5-Fluoro-Uracil [440 mg/m2 iv d1,8] + Doxorubicin [25 mg/m2 iv d1,8] + Cyclophosphamide [50 mg po tds d1-15]) × 7 vs Oophorectomy + (Vincristine [0.9 mg/m2 iv d1]	308	Yes	No

		+ Doxorubicin [35 mg/m2 iv d1] + Cyclophosphamide [100 mg po tds d1-4]) qm × 3			
13001 1986P1	FASG GFEA 01, France	(Epirubicin[50mg/m² iv] + 5-Fluoro-Uracil [500mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q21d × 3 then Radiotherapy then (Epirubicin[50mg/m² iv] + 5-Fluoro-Uracil [500mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q21d × 3 vs (Epirubicin[50mg/m² iv] + 5-Fluoro-Uracil [500mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q21d × 3 then Radiotherapy	421	Yes	✓ 2003[97]
28001 1987Q	PRONACAM 87, Argentina	(Cyclophosphamide [400mg/m²] + Methotrexate [30mg/m²] + 5-Fluoro-Uracil [400mg/m²] + Epirubicin[60mg/m²] + Prednisone [40mg/m² po] × 4d) q21d × 6 vs (Cyclophosphamide [400mg/m²] + Methotrexate [30mg/m²] + 5-Fluoro-Uracil [400mg/m²] + Epirubicin[60mg/m²] + Prednisone [40mg/m² po] × 4d) q21d × 4	556	No	✓ Abstract 1995[98]
8322 2002B	CALGB 40101, USA	(Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 6 vs (Doxorubicin [60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 4	282	Yes	✓ 2012[70]
33206 2002N	PACS 05, France	(5-Fluorouracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) q3wk × 6 vs (5-Fluorouracil [500 mg/m2 iv] + Epirubicin [100 mg/m2 iv] + Cyclophosphamide [500 mg/m2 iv]) q3wk × 4	1515	Yes	✓ 2017[99]
8323 2002X1	CALGB 40101, USA	(Doxorubicin [60mg/m² iv over 10-15min d1] + Cyclophosphamide [600mg/m² iv bolus d1]) q2wk × 6 vs (Doxorubicin [60mg/m² iv over 10-15min d1] + Cyclophosphamide [600mg/m² iv bolus d1]) q2wk × 4	1300	Yes	✓ 2012[70]
4762/78 2004C	NSABP B-36, USA	(5-Fluoro-Uracil [500mg/m2] + Epirubicin[100mg/m2] + Cyclophosphamide [500mg/m2]) q21d × 6 then celecoxib placebo [bid po] × 3yr vs (Doxorubicin [60mg/m2] + Cyclophosphamide [600mg/m2]) q21d × 4 then celecoxib placebo [bid po] × 3yr Or (5-Fluoro-Uracil [500mg/m2] + Epirubicin[100mg/m2] + Cyclophosphamide [500mg/m2]) q21d × 6 then celecoxib [bid po] × 3yr vs (Doxorubicin [60mg/m2] + Cyclophosphamide [600mg/m2]) q21d × 4 then celecoxib [bid po] × 3yr Or (5-Fluoro-Uracil [500mg/m2] + Epirubicin[100mg/m2] + Cyclophosphamide [500mg/m2]) q21d × 6 vs (Doxorubicin [60mg/m2] + Cyclophosphamide [600mg/m2]) q21d × 4	2722	No	✓ 2022[72]
(b) Longer versus shorter <6 months of polychemotherapy (anthracycline and taxane)					
33103 1997H2	Multicentre France Phase II Neoadjuvant Chemotherapy Trial	(Doxorubicin [60mg/m² iv] + Paclitaxel [200mg/m² iv]) q3wk × 6 preoperative vs (Doxorubicin [60mg/m² iv] + Paclitaxel [200mg/m² iv]) q3wk × 4 preoperative	232	No	✓ Abstract 2002[100]

2619 1999M	ABCSG-14, Austria	(Epirubicin[75mg/m² d1] + Docetaxel [75mg/m² d1] + filgrastim [5mcg/kg sc d3-10]) q3wk × 6 preoperative vs (Epirubicin[75mg/m² d1] + Docetaxel [75mg/m² d1] + filgrastim [5mcg/kg sc d3-10]) q3wk × 3 preoperative	292	Yes - ineligible	✓ 2007[101]
35003 2001S2	GeparTrio / GBG 24, Germany	(Doxorubicin [50mg/m² d1] + Cyclophosphamide [500mg/m² d1] + Docetaxel [75mg/m² d1]) q21d × 2 then (Doxorubicin [50mg/m² d1] then Cyclophosphamide [500mg/m² d1] + Docetaxel [75mg/m² d1]) q21d × 6 preoperative vs (Doxorubicin [50mg/m² d1] + Cyclophosphamide [500mg/m² d1] + Docetaxel [75mg/m² d1]) q21d × 2 then (Doxorubicin [50mg/m² d1] then Cyclophosphamide [500mg/m² d1] + Docetaxel [75mg/m² d1]) q21d × 4 preoperative	1390	Yes	✓ 2010[102]
53501 2003%	Chungnam Neoadjuvant trial, South Korea	(Epirubicin [75 mg/m2] + Docetaxel [75 mg/m2]) q3wk × 6 preoperative vs (Epirubicin [75 mg/m2] + Docetaxel [75 mg/m2]) q3wk × 4 preoperative	176	No	2009[103]

Cohort 8: Higher vs lower dose anthracycline

Trial & year code	Trial name	Comparisons	N	Received	Published
(a) Increase in anthracycline dose/course and total dose (<100mg A or 150mg E difference)					
13001 1986P1	GFEA 01, France	(Epirubicin[75mg/m² iv] + 5-Fluoro-Uracil [500mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q21d × 3 then Radiotherapy vs (Epirubicin[50mg/m² iv] + 5-Fluoro-Uracil [500mg/m2 iv] + Cyclophosphamide [500mg/m2 iv]) q21d × 3 then Radiotherapy	409	Yes	✓ 2003[97]
8316 1994D1	CALGB 9344, USA	(Cyclophosphamide [600mg/m²] + Doxorubicin [75mg/m²]) q3wk × 4 or (Cyclophosphamide [600mg/m²] + Doxorubicin [90mg/m²] + filgrastim [5 or 10µg/kg/d sc d2-12]) q3wk × 4 vs (Cyclophosphamide [600mg/m²] + Doxorubicin [60mg/m²]) q3wk × 4	1580	Yes	✓ 2003[24]
8316 1994D2	CALGB 9344, USA	(Cyclophosphamide [600mg/m²] + Doxorubicin [75mg/m²]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4 or (Cyclophosphamide [600mg/m²] + Doxorubicin [90mg/m²] + filgrastim [5 or 10µg/kg/d sc d2-12]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4 vs (Cyclophosphamide [600mg/m²] + Doxorubicin [60mg/m²]) q3wk × 4 then Paclitaxel [175mg/m²] q3wk × 4	1590	Yes	✓ 2003[24]
46301 2005Z	CECOG/BREAST.2.2.005, Austria	(5-Fluorouracil [500 mg/m² iv] + Epirubicin [90mg/m² iv] + Cyclophosphamide [500mg/m² iv] d1 + pegfilgrastim [6mg sc] d2) q14d × 6 vs (5-Fluorouracil [500 mg/m² iv] + Epirubicin [75mg/m² iv] + Cyclophosphamide [500mg/m² iv] d1 + pegfilgrastim [6mg sc] d2) q14d × 6	50	No	✓ 2008[104]
(b) Increase in anthracycline dose/course and total dose (>100mg A or 150mg E difference)					
13006, 13008 1990C3+5	GFEA 05, France	(Epirubicin[100mg/m²] + 5-Fluoro-Uracil [500mg/m²] + Cyclophosphamide [500mg/m²]) × 6 vs (Epirubicin[50mg/m²] + 5-Fluoro-Uracil [500mg/m²] + Cyclophosphamide [500mg/m²]) × 6	565	Yes	✓ 2005[105]

20006-07 1992N	C/9/91 / HMFEC, UK	(Cyclophosphamide [600mg/m² d1] + Epirubicin[75mg/m² d1] + 5-Fluoro-Uracil [600mg/m² d1]) q3wk × 8 vs (Cyclophosphamide [600mg/m² d1] + Epirubicin[50mg/m² d1] + 5-Fluoro-Uracil [600mg/m² d1]) q3wk × 8 Or (Cyclophosphamide [600mg/m² d1] + Epirubicin[75mg/m² d1] + 5-Fluoro-Uracil [600mg/m² d1]) q3wk × 8 + Tamoxifen [20mg/d] × 5yr vs (Cyclophosphamide [600mg/m² d1] + Epirubicin[50mg/m² d1] + 5-Fluoro-Uracil [600mg/m² d1]) q3wk × 8 + Tamoxifen [20mg/d] × 5yr Or	785	Yes	✓ 2016[106]
12911 2005S	Tianjin Chemotherapy trial, China	(Cyclophosphamide [600 mg/m2] + Epirubicin [100 mg/m2] + 5-Fluorouracil [500 mg/m2]) q21d × 6 vs (Cyclophosphamide [600 mg/m2] + Epirubicin [60 mg/m2] + 5-Fluorouracil [500 mg/m2] q21d × 6)	98	No	✓ Abstract 2007[107]
(c) Increase in anthracycline and other drug dose/course and total dose					
3504 0977S	B1/ Protocol 7701, Italy	(Cyclophosphamide [50-100-150 mg/m2 po d1-14] + Methotrexate [20-40-60 mg/m2 iv d1,8] + 5-Fluoro-Uracil [400-600-800 mg/m2 iv d1,8] + Prednisolone [40 mg/m2 im d1-14]) q4w × 6 then (Doxorubicin [50-75 mg/m2 iv d1,8] + Vincristine [1.4 mg/m2 iv d1,8]) q4wk × 4 [intensification every 2 cycles] vs (Cyclophosphamide [100 mg/m2 po d1-14] + Methotrexate [40 mg/m2 iv d1,8] + 5-Fluoro-Uracil [600 mg/m2 iv d1,8] + Prednisolone [40 mg/m2 im d1-14]) q4wk × 6 then (Doxorubicin [60 mg/m2 iv d1,8] + Vincristine [1.4 mg/m2 iv d1,8]) q4wk × 4	140	Yes	✓ Abstract 1985[108]
8307 1985A	CALGB Study CLB-8541, USA	(Cyclophosphamide [600 mg/m2 iv d1] + Doxorubicin [60 mg/m2 iv d1] + 5-Fluoro-Uracil [600 mg/m2 iv d1,8]) q4w × 4 vs (Cyclophosphamide [300 mg/m2 iv d1] + Doxorubicin [30 mg/m2 iv d1] + 5-Fluoro-Uracil [300 mg/m2 iv d1,8]) q4w × 4	1050	Yes	✓ 1994[110]
25701 1988R	Jules Bordet Classical CMF Versus EC Standard Dose Versus EC High Dose in Node Positive Breast Cancer, Belgium	(Epirubicin[100mg/m² iv d1] + Cyclophosphamide [830mg/m² iv] d1) q21d × 8 vs (Epirubicin[60mg/m² iv d1] + Cyclophosphamide [500mg/m² iv d1]) q21d × 8	537	Yes	✓ 2009[109]
1132 1991F	MD Anderson Neoadjuvant Trial, USA	(5-Fluoro-Uracil [1200mg/m²] + Doxorubicin [60mg/m²] + Cyclophosphamide [1000mg/m²] + G-CSF [5µg/kg/d d4-17]) q18d × 4 preoperative vs (5-Fluoro-Uracil [1000mg/m²] + Doxorubicin [50mg/m²] + Cyclophosphamide [500mg/m²]) q21d × 4 preoperative	112	No	✓ Abstract 1999[111]
13013 1993@	GFEA Inflammatory BC trial, France	(5-Fluoro-Uracil [750 mg/m2 iv d1-4] + Epirubicin [35 mg/m2 iv d2-4] + Cyclophosphamide [400 mg/m2 iv d2-4] + lenograstim) preoperative then (Radiotherapy or Surgery) then (5-Fluoro-Uracil [500 mg/m2 iv d1] + Epirubicin [75 mg/m2 iv d1] + Cyclophosphamide [500 mg/m2 iv d1]) × 4 postoperative vs (5-Fluoro-Uracil [500 mg/m2 iv d1] + Epirubicin [75 mg/m2 iv d1] + Cyclophosphamide [500 mg/m2 iv d1]) preoperative then (Radiotherapy or Surgery) then (5-Fluoro-Uracil [500 mg/m2 iv d1] + Epirubicin [75 mg/m2 iv d1] + Cyclophosphamide [500 mg/m2 iv d1]) × 4 postoperative	Not known	No	

2616 1994Q	ABCSG Trial X, Austria	(Epirubicin[60mg/m2 iv d1,d2] + Cyclophosphamide [600mg/m2 iv d1,d2] + Uromitexan + filgrastim [5mcg/kg sc d3-13]) q3wk × 4 then (Cyclophosphamide [600mg/m2] + Methotrexate [40mg/m2] + 5-Fluoro-Uracil [600mg/m2]) q3wk × 4 vs (Epirubicin[60mg/m2 iv d1] + Cyclophosphamide [600mg/m2 iv d1]) q3w × 4 then (Cyclophosphamide [600mg/m2] + Methotrexate [40mg/m2] + 5-Fluoro-Uracil [600mg/m2]) q3wk × 4	112	Yes	No
21102 1996L	OCSGL Trial, Poland	(Cyclophosphamide [75mg/m² po d1-14] + Epirubicin[60mg/m² iv d1,8] + 5-Fluoro-Uracil [500mg/m² iv d1,8]) q28d × 6 then Tamoxifen × 3yr vs (5-Fluoro-Uracil [500mg/m² iv] + Epirubicin[50mg/m² iv] + Cyclophosphamide [500mg/m² iv]) q21d × 6 then Tamoxifen × 3yr	87	No	✓ 2003[112]
16213 1996V	Gustave-Roussy Neoadjuvant Chemotherapy Trial, France	(5-Fluoro-Uracil [1000mg/m² d1] + Cyclophosphamide [1000mg/m² d1] + Epirubicin[100mg/m² d1 iv]) q21d × 4 + G-CSF [5µg/m² sc d6-11] preoperative vs (5-Fluoro-Uracil [500mg/m² d1] + Cyclophosphamide [500mg/m² d1] + Epirubicin[60mg/m² d1 iv]) q21d × 4 preoperative	84	Yes	✓ Abstract 2003[113]
21611 2001Q	SBG 2000-1 / SBG CEF-60, Sweden	(5-Fluoro-Uracil [600mg/m²] + Epirubicin[75-90mg/m²] + Cyclophosphamide [900-1200mg/m²]) q3wk × 6 vs (5-Fluoro-Uracil [600mg/m²] + Epirubicin[60mg/m²] + Cyclophosphamide [600mg/m²]) q3wk × 6	1052	Yes	✓ 2018[114]
2024 2004=	SBG 2004-1 Phase II Feasibility, Sweden	(Epirubicin[start 90mg/m²] + Cyclophosphamide [start 600mg/m²]) escalating q2wk × 4 then Docetaxel [start 75mg/m²] escalating q2wk × 4 + lenograstim [5mcg/kg d4-11] or pegfilgrastim [6mg d2] + Ciprofloxacin vs (Epirubicin[90mg/m²] + Cyclophosphamide [600mg/m²]) q2wk × 4 then Docetaxel [75mg/m²] q2wk × 4 + lenograstim [5mcg/kg d4-11] or pegfilgrastim [6mg d2] + Ciprofloxacin	84	Yes	✓ 2018[115]

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Appendix 2 – EBCTCG seventh cycle: List of variables for taxane trials

Either using the codes we suggest below or using your own codes, please extract from your dataset the variables that correspond most closely to the items listed below and send them to us. Please provide one record for each woman ever randomised (including anyonewho was randomised and then was later categorised as ineligible, withdrawn, unevaluable, lost or "protocol deviant" – but, please tell us in question 9 which patients your group's preferred analyses would exclude, and why).

For trials where a dataset has previously been sent to the EBCTCG it is probably easiest and most reliable to update by re-sending all variables. If, however, this would cause difficulties then you can send only the additional variables; let us know if you want a file of the data you previously sent and we will provide it.

If any variable is not available or not applicable, please omit it and send only the remaining variables. If you have any of the requested variables in your records in a form that would require substantial additional work to supply (eg computerisation, or manual coding), please feel free to omit them for now, but in your cover document please tell us of their existence.

- Please send your data in a separate Excel spreadsheet for each separate trial, if possible.
- Please send a cover document giving all your coding conventions (including your format for dates).
- Please send your data to: bc.overview@ctsu.ox.ac.uk with your research group's name (and/or the EBCTCG number for your research group) and your group's name for the trial in the subject line.

If you have any questions about this data request, please contact the EBCTCG secretariat on bc.overview@ndph.ox.ac.uk (tel: +44-1865-743852). All data supplied to the secretariat will be held securely and treated confidentially, in accordance with UK Medical Research Council data security policies.

CORE VARIABLES - BASELINE (Q1-28)

A) RANDOMISATION AND PATIENT CHARACTERISTICS (Q1-9)

1. **Your patient identifier** *(preferably specifying uniquely which trial as well as which patient)*
2. **Date of randomisation** *(specify your format for dates [in your covering document])*
3. **Allocated treatment** *(specify your codes)*
4. **Age** at randomisation *(years)* **NB Here & everywhere else, leaving an item Blank means Not Known**
5. **Height** at randomisation *(m)*
6. **Weight** at randomisation *(kg)*
7. **Menopausal status** at randomisation *(1=pre-, 2=peri-, 3=postmenopausal with intact ovaries & uterus, 4=ovarian ablation, 5=hysterectomy, 6=both [ie, 4 and 5])*
8. **Did chemotherapy cause apparently permanent cessation of menses?** *(1=no/not applicable, 2=yes)*
9. **Would your group's preferred analyses exclude this patient?** NB A few trial patients may be randomised in error, otherwise ineligible, lost with no follow-up, unevaluable or withdraw consent. *(1=no known reason for exclusion, 2=yes [specify main reason(s) for preferring exclusion, if known])*

B) SURGICAL DETAILS (Q10-12; OR, DEFINE AND USE YOUR OWN CODES)

10. **Date of surgery** *Please provide date patient received surgery if known.*
11. **Breast surgery** *(1=none, 2=only lumpectomy or wide local excision, 3=quadrantectomy or sector resection, 4=partial mastectomy, 5=simple or total mastectomy, 6=radical mastectomy)*
12. **Axillary surgery** *(1=none, 2=sentinel node biopsy only, 3=axillary sampling, 4=surgical clearance of less than levels I & II, 5=full clearance of axillary levels I & II, 6=clearance of more than levels I & II, 7=axillary clearance, but levels cleared unspecified)*

C) NODAL STATUS (Q13-14; OR, USE YOUR OWN CODES [EG, TNM])

13. **Sentinel node biopsy** *(1=not done, 2=done and negative for cancer, 3= isolated tumour cells [≤0.2 mm], 4=micrometastasis, 5=macroscopic nodal deposit [>2 mm], 6=positive, size unknown)*
14. **Axillary status** *(specify codes, or: 1=N- histologically, 2=N- other/unknown method, 3=1-3 positive nodes, 4=4-9 [or 4+] positive, 5=10+ positive, 6=N+ histologically, unknown number, 7=N+ other/unknown method)*

D) TUMOUR CHARACTERISTICS (Q15-19; OR, USE YOUR OWN CODES [EG, TNM])

15. **Method first detected** *(1=mammographic screening, 2=incidental, 3=symptomatic, 4=other)*
16. **Laterality** *(1=left, 2=right, 3=bilateral)*
17. **Pathological grade** *(1=well differentiated, 2=moderately,3=poorly)*
18. **Histological type** *(1=invasive, not otherwise specified, 2=ductal, 3=lobular, 4=other, 5=mixed)*
19. **Tumour diameter in mm:** largest diameter of excised primary *(mm)*

E) RECEPTOR STATUS (Q20-28; OR, USE YOUR OWN CODES)

20. **Summary of Estrogen Receptor (ER) status of primary tumour** *(1=ER-poor, 2=ER+, 3=ER++ [define in cover document, unless ER-poor is <10 fm/mg and ER++ is ER definitely ≥100 fm/mg])*
21. **Quantitative ER measurement** *(measured in central/reference lab if possible, otherwise best available)*
22. **Units for ER** *(1=fm/mg, 2=% +ve by IHC, 3=Allred score [category score], 4=H-score, 9=other [specify]*)

23. **Summary of Progesterone Receptor (PR) status of primary tumour** *(1=PR-poor, 2=PR+, 3=PR++ [define in cover document, unless PR-poor is <10 fm/mg and PR++ is PR definitely ≥100 fm/mg])*
24. **Quantitative PR measurement** *(done in central/reference lab if possible, otherwise best available)*
25. **Units for PR** *(coded as Q21)*

26. **Summary of HER2 status of primary** *(1=negative/normal, 2=positive/over-expressing)*
27. **Quantitative HER2 measurement** *(done in central/reference lab if possible, otherwise best available)*
28. **Units for HER2** *(1=IHC [% staining], 2=IHC score [0, 1+, 2+, 3+], 3=FISH [# copies], 4=FISH [HER2:CEP17 ratio], 5=CISH [# copies], 6=CISH [HER2:CEP17], 9=other [please specify])*

CORE VARIABLES – FOLLOW-UP (Q29-47)

F) ADJUVANT TREATMENT (Q29-33; OR, USE YOUR OWN CODES)

29. **Chemotherapy given** *(1=No, 2=Yes, 3=Unknown)*
30. **Date of start of endocrine therapy (***Please provide date patient started endocrine therapy if known, else date of surgery.)*
31. **Date Endocrine therapy stopped**
32. **Any substantial deviation from trial treatment allocation (before any breast cancer recurrence)?** *(1=no, 2=never started, 3=discontinued, 4=switched to opposite trial group, 5=other [specify])*
33. **Date of first such deviation from allocated treatment** *(ignore deviations after recurrence)*

G) CANCER RECURRENCE AND SECOND CANCERS (Q34-44; OR, USE YOUR OWN CODES)

34. **Any recurrence of invasive breast cancer (ie, locoregional, contralateral or distant)?** NB Includes any occurrence of new ipsilateral or contralateral breast cancer *(1=no, 2=yes)*
35. **<u>If no:</u> Date patient last known to be free of such recurrence; <u>If yes:</u> Date of first such recurrence**

36. **Site of first distant recurrence (ie, possibly distant; not just locoregional/contralateral)** *(1=no distant recurrence, 2=recurrence, unknown if distant, 3=distant recurrence, unknown/multiple sites, 4=only in distant soft tissue, 5=only in distant nodes, 6=only in bone, 7=only visceral, 8=only in CNS)*
37. **Date of first distant recurrence** NB Locoregional recurrence can precede first distant recurrence

38. **Site of first locoregional recurrence** *(1=no locoregional recurrence recorded, 2=multiple or unspecified locoregional sites 3=only in breast [new or recurrent cancer] or chest wall, 4=only in axilla, 5=only in other locoregional nodes [eg, supraclavicular or internal mammary])*
39. **Date of first locoregional recurrence**

40. **Contralateral breast cancer?** *(1=no, 2=yes: new invasive cancer thought to have arisen during follow-up in the contralateral breast)*
41. **Date of first contralateral breast cancer**

NB If patient had more than one second malignancy during follow-up, <u>repeat</u> variables 38-40 for each.

42. **Site of any second malignancy *[except breast cancer]* during follow-up** *(Describe ALL sites. Use and specify your own codes; if you use ICD codes specify revision, eg ICD-9 or ICD-10)*
43. **Date of this second malignancy**
44. **MIGHT this have been a breast cancer metastasis?** *(1=no, 2=possibly/not yet certain [eg, possible lung, liver, bone or brain metastasis: please do not report definite breast metastases as second cancers])*

H) SURVIVAL (Q45-47)

45. **Is patient known to have died?** *(1=no, 2=yes)*
46. **<u>If no:</u> Date patient last known to be alive; <u>If yes:</u> Date of death**
47. **<u>If yes:</u> Cause of death** *(use and specify your own codes; if you use ICD codes specify which version, eg ICD-9 or ICD-10)*

ADDITIONAL VARIABLES (Q48-58)

I) ADDITIONAL TUMOUR MARKER DATA (Q48-56; OR, USE YOUR OWN CODES)

Note: If tests of gene expression or special tests of IHC quantitation were done on the excised primary then please send a separate file in your own format with the fully detailed set of results on each individual.

48. Summary of gene-expression status of primary tumour *(1=low risk, 2=intermediate risk, 3=high risk):* NB Please also provide the fully detailed gene expression results for each patient as a separate dataset.

49. Quantitative gene-expression prognostic score *(best available single numerical measure)*

50. Prognostic score used to quantify gene expression profile *(use own code, or: 1=OncotypeDx prognostic score, 2=Mammaprint prognostic score, 9=other [please specify])*

51. Summary of Topo-isomerase II alpha (TOPO2A) status of primary tumour *(1= normal [ie, no gene over-expression or deletion], 2=positive/over-expressing, 3=deleted)*

52. Quantitative TOPO2A measurement *(done in central/reference laboratory if possible)*

53. Units for TOPO2A *(1=IHC [% staining], 2=IHC score [0, 1+, 2+, 3+], 3=FISH [number of copies], 4=FISH [TOPO:CEP17 ratio], 5=CISH [# copies], 6=CISH [TOPO:CEP17], 9=other [please specify])*

54. Summary of Proliferation Index of primary tumour *(1=low, 2=intermediate, 3=high)*

55. Quantitative Proliferation Index *(best available single numerical measure, in central/ ref lab if possible)*

56. Factor measured for Proliferation Index *(1=S-phase fraction [%], 2=thymidine labelling index [%], 3=Ki-67 by IHC [% staining], 9=other [please specify]*)

J) BONE FRACTURES AND CARDIOVASCULAR EVENTS BEFORE RECURRENCE (Q57-58; OMIT IF NOT SOUGHT)

Some trial treatments may cause or prevent bone fractures or cardiovascular events. Please describe all such events (eg, hip fracture, spinal fracture, myocardial infarction, stroke, pulmonary embolus, episode of cardiac failure) if, but only if, such events were sought and recorded systematically for the trial.

If more than one bone fracture or cardiovascular event was recorded, repeat variables 55-56 for each.

57. Nature of event *(use your own codes; if you use ICD codes, specify which version, eg ICD-9 or ICD-10, and if you use CTC Adverse Event codes, please specify version number, eg CTCAE-3 or CTCAE-4)*

58. Date of event

P92-94: Search strategies

Assessment of treatment effects in EBCTCG meta-analyses involves identification of all available randomised data, wherever possible, including not only published but also unpublished trial results (with follow-up updated, where records permit, beyond the last available publication). The searches and updating are both important because trial results that do not show significant treatment effects initially, or that become less promising with longer follow-up, may be less likely to be published, or have updates published, than other trial results.

To achieve unbiased ascertainment of the randomised evidence, the EBCTCG secretariat remains in regular contact with all known trials that still have an active investigator (or an active successor), and has for decades been seeking both published and unpublished trials by interactions with all known trialists as well as by electronic searches and scans of potentially relevant reference lists. Hence, the unbiasedness of the meta-analyses in EBCTCG reports depends not on whether there would have been *publication* bias if the EBCTCG dataset was restricted to published data (for it has no such restriction), but whether, despite all efforts, any material *ascertainment* bias remains.

Formal statistical tests for publication bias or ascertainment bias are so weak that appreciable bias might escape them, scientifically reliable assessment of the potential for such bias should chiefly be based on an understanding of EBCTCG procedures for identifying trials and obtaining and updating the results according to the randomly allocated treatment (with no potentially biased exclusions, regardless of what the trial publications excluded). These EBCTCG methods are described below.

The EBCTCG secretariat request regular data updates from trialists, and include the latest available data in meta-analyses. Where only certain trial arms or patient groups of a particular trial are relevant to a given question, they are also included.

The need to include all available eligible randomised data has led to the development of comprehensive methods of identifying published and unpublished trials. The EBCTCG has existed for more than 30 years and the methods for identifying studies have developed over this period. The search strategy is comprehensive and labour-intensive. It involves a team of six research assistants who search databases and conference proceedings, and assess the search results.

i) Database searches

The EBCTCG secretariat has been performing methodical literature searches since the 1980s and the search strategy has developed over this period. Initially trials were sought through

literature searches, contact with research groups worldwide and with pharmaceutical companies. Later, this was extended over a wider range of databases, trial registers, conference proceedings and adverts/surveys.

In recent years database searches of MEDLINE, Embase and the Cochrane Library are conducted on a regular basis using the following search terms:

1 random$.af.
2 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).af.
3 (phase III or phase 3 or phase IV or phase 4).af.
4 controlled clinical trial$.af.
5 placebo$.af.
6 (meta?analys$ or (meta adj1 analys$)).af.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp breast neoplasms/
9 (breast$ adj5 (neoplas$ or carcinom$ or cancer$ or tumor$ or tumour$)).af.
10 (advanced or metastatic or inoperable).ti.
11 locally advanced.af. or (neoadjuvant or adjuvant or early or operable).ti.
12 10 not 11
13 (8 or 9) not 12
14 7 and 13
15 Human$/
16 Animal$/
17 16 not (15 and 16)
18 14 not 17
19 18

Search results are screened manually. Further information is sought for any search results which indicate a possible eligible trial.

ii) Conference proceedings

Lists of titles and abstracts of cancer conferences are searched systematically. Research assistants read all titles and abstracts from each conference listed below. Further information is sought for any search results which indicate a possible eligible trial.

- San Antonio Breast Cancer Congress
- American Society of Clinical Oncology
- European Cancer Organisation
- European Society of Medical Oncology

iii) EBCTCG Steering Committee

These searches are supplemented by input from breast cancer trialists' around the world. The EBCTCG's Steering Committee includes 56 individuals from 17 countries. The committee meet annually to discuss progress. They review lists of included trials in ongoing meta-

analyses. Committee members are invited to consider whether any eligible trials have been omitted and, if so, to provide contacts for any missing trials.

iv) EBCTCG Collaborative Group

The EBCTCG Collaborative group includes >500 individuals representing >200 trial groups from >30 countries. Each draft manuscript is circulated to the collaborative group before submission, giving further opportunity for any unpublished trials to be identified.

These methods have led to the compilation of a database of some 40,000 articles of relevance to EBCTCG overviews (by 1.1.2023), which continues to be populated on a regular basis, with additional targeted updates for any meta-analyses prior to submission for publication.

Methods to assess integrity of individual trial data

For each meta-analysis, a study protocol is developed by the EBCTCG secretariat in conjunction with leads of the trials which may contribute to the analysis. A data request, outlining the variables required, is sent to each contributing trial group. Received data are standardised and added to the EBCTCG database enabling various tests of internal integrity. Data are then checked against published reports and assessed for valid randomisation sequence, balance of baseline variables and follow-up dates across the intervention groups. A summary report is sent back to the trialist, and any queries resolved. Issues relating to the non-availability of data, for example because they are not supplied for unpublished studies, are discussed in each EBCTCG report.