

THE LANCET

Supplementary webappendix

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

Supplement to: Early Breast Cancer Trialists' Collaborative Group (EBCTCG).
Comparisons between different polychemotherapy regimens for early breast cancer:
meta-analyses of long-term outcome among 100 000 women in 123 randomised trials.
Lancet 2011; published online Dec 6. DOI:10.1016/S0140-6736(11)61625-5.

Webappendix: Supplementary figures and tables for “Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials”

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Taxanes: Taxane-plus-anthracycline-based regimen vs the same, or more, non-taxane chemotherapy
Anth vs Δ CMF: Any anthracycline-based regimen vs standard CMF (or near-standard CMF)
Anth vs nil: Any anthracycline-based regimen vs no adjuvant chemotherapy
 Δ CMF vs nil: Standard CMF (or near-standard CMF) vs no adjuvant chemotherapy

Pp 2-6: Main subgroup analyses: splits x regimen, age, nodes, ER, grade

Results just for breast cancer mortality (ie, mortality with recurrence, as calculated by logrank subtraction)

- 2 Taxanes (as text-figure 2)
- 3 Anth vs Δ CMF (as text-figure 4)
- 4 Anth vs nil (as text-figure 6)
- 5 Δ CMF vs nil
- 6 Anth or Δ CMF vs nil

Pp 7-14: More detailed subgroup analyses (with ER and FU duration further split)

Results both for recurrence and for breast cancer mortality; compressed for highly magnified online viewing

- 7-8 Taxanes
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- 13-14 Δ CMF vs nil

Pp 15-17: 8-year or 10-year Kaplan-Meier-related graphs for 6 selected subgroups (age <55 / 55-69 years, ER-poor / ER+, poorly differentiated / not)

Results for breast cancer mortality, 6 subgroups / page

- 15 Taxanes
- 16 Anth vs nil
- 17 Δ CMF vs nil

Pp 18-20: Kaplan-Meier-related graphs contrasting selected treatment effects

(i) recurrence, (ii) breast cancer mortality, (iii) overall mortality: 3 outcomes x 2 effects (as text figures 1, 3, 5)

- 18 Taxanes (left, control = SAME non-taxane chemo; right, control = MORE non-taxane chemo)
- 19 Anth vs Δ CMF (left, dose/cycle \geq A60/E90 & total dose $>$ A240/E360 [eg CAF/CEF]; right, Anth=4A60C)
- 20 Anth vs nil or Δ CMF vs nil (left, Anth [NB on average, the effect is like that of 4A60C]; right, Δ CMF)

Pp 21-62: 42 forest plots, one line per trial, for 6 different endpoints (Grey square = data last sent before 2001) Results for early recurrence (years 0-4), any recurrence, breast cancer mortality, death without recurrence in year 0, death without recurrence, overall mortality: 1 outcome / page = 6 endpoints x 7 comparisons

- 21-26 Taxanes
- 27-32 Anth vs Δ CMF
- 33-38 Anth vs nil
- 39-44 Anth vs nil or Δ CMF vs nil
- 45-50 One anthracycline-based regimen vs another (6 trials)
- 51-56 Δ CMF vs nil and any other CMF regimen (with lower dose/cycle than Δ CMF) vs nil
- 57-62 Any prolonged ($>$ 1 cycle) polychemotherapy regimen vs nil

Page 63: Table of non-breast-cancer mortality without recurrence during the first year after randomisation, by age for various chemotherapy comparisons

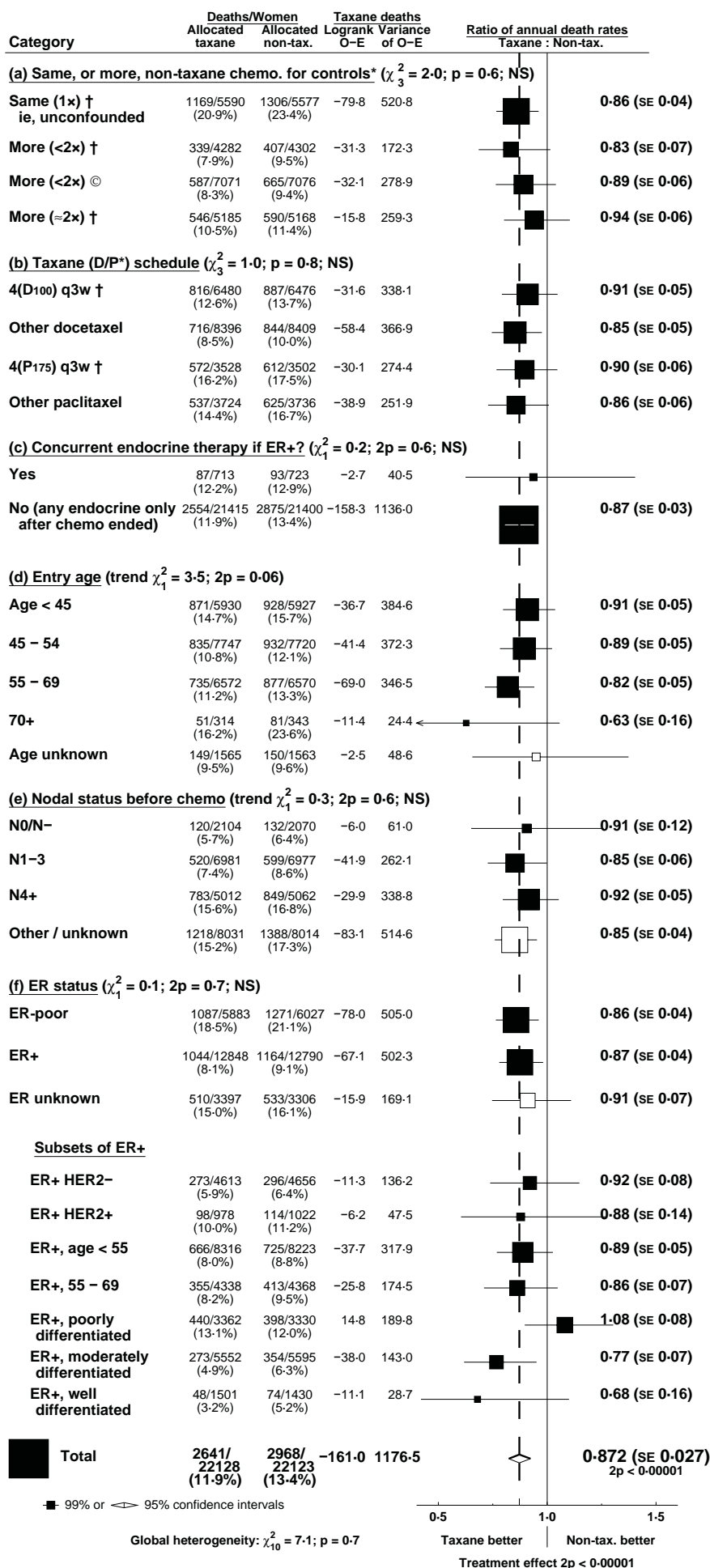
Pp 64-68: One or more references for each trial in the forest plots on pp 21-50 of breast cancer mortality (in the same order as in those forest plots)

Pp 69-110 (end): Powerpoint-format presentation of selected figures or parts of figures
([Download powerpoint presentation from EBCTCG website](#))

Notes on statistical methods: Annual breast cancer mortality rates are by subtraction of mortality rates among women without recurrence from those among all women. Likewise, breast cancer mortality rate ratios (RR \pm 1SE, newer treatment vs control) derive from logrank subtraction (ie, subtraction of logrank analyses of mortality without recurrence from logrank analyses of overall mortality).

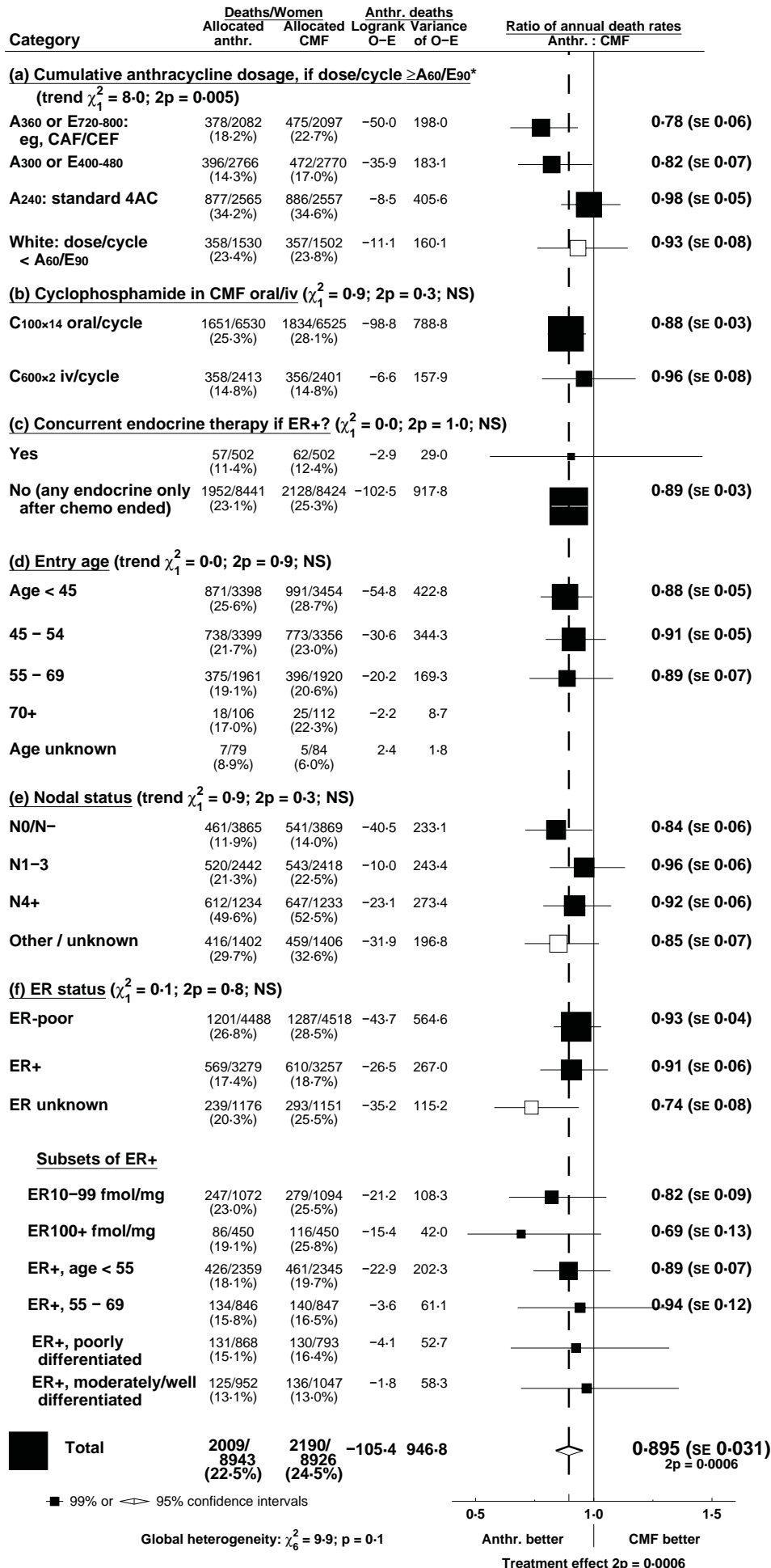
Forest plots of recurrence (or of mortality without recurrence) give woman-years before first recurrence, those of overall mortality give woman-years before death and those of mortality without recurrence give numbers randomised. Numbers of women randomised, woman-years and first events generally double-count controls in 2:1 comparisons (and triple-count those in 3:1 comparisons), but calculations of the logrank statistic (O-E) and its variance V are unaffected by this, and do not double- or triple-count controls. If a logrank statistic (O-E) has variance V, then, defining $z=(O-E)/\sqrt{V}$ and $b=(O-E)/V$, $RR=\exp(b)$ is the event rate ratio, and is taken to have $SE=(RR-1)/z$ and 95% CI $\exp(b\pm 1.96/\sqrt{V})$. P-values (all of which are two-sided) are obtained by comparing z with a standard normal distribution (so $z=1.96$ yields $2p=0.05$). In calculating p-values for side-effects (before recurrence), a continuity correction of 0.5 is applied to (O-E).

P 2: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy NB First four subgroups are as in forest plots*.



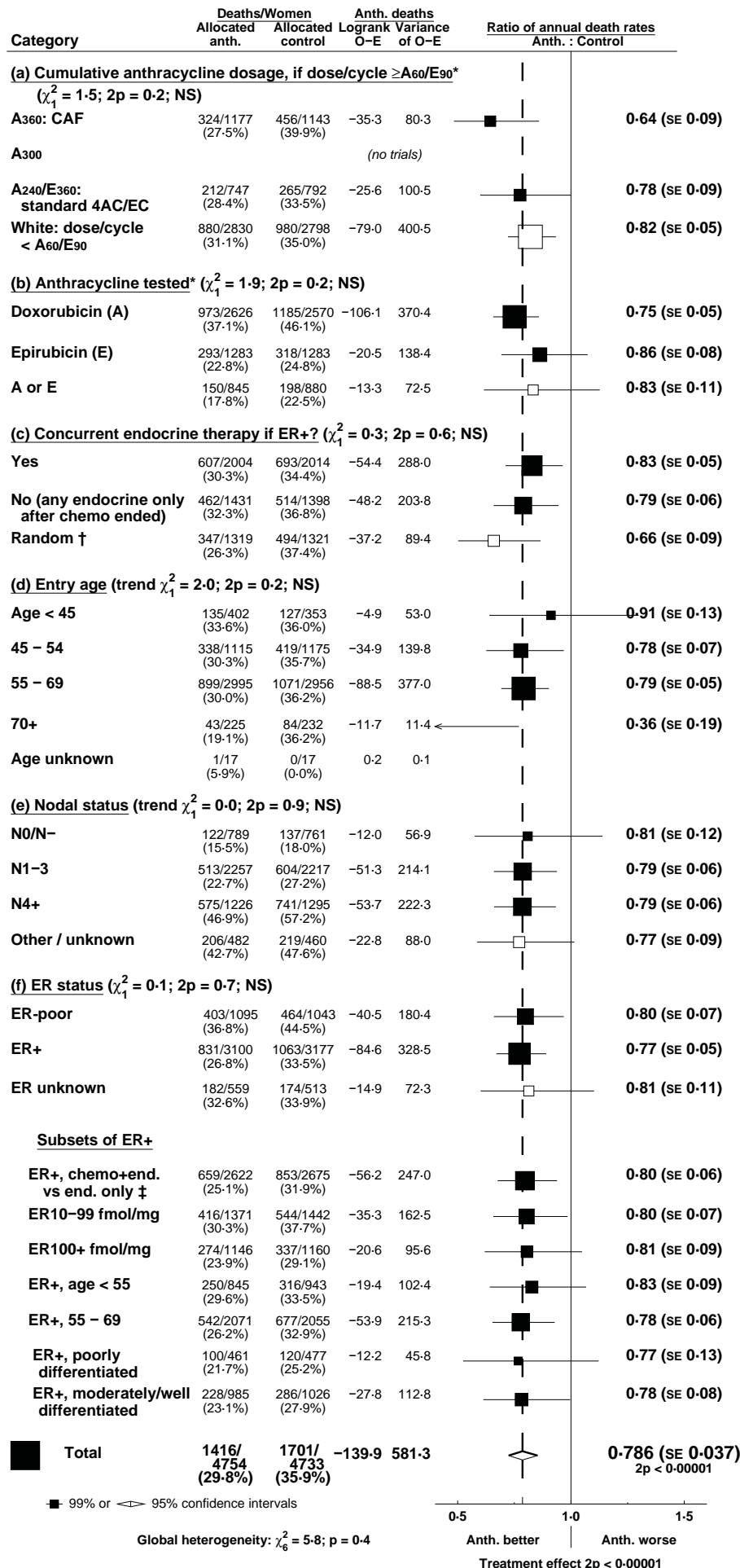
* Forest plots (webappendix pp 21-26) give details of each trial's cytotoxic regimens
D = docetaxel; P = paclitaxel; 4(D100) q3w means 4 doses of docetaxel 100 mg/m² at intervals of 3 weeks
† Taxane courses do not overlap other chemotherapy courses
© Taxane given concurrently with anthracycline

P 3: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), any anthracycline-based regimen vs. standard CMF (or near-standard CMF).
 NB First four subgroups are as in forest plots*.



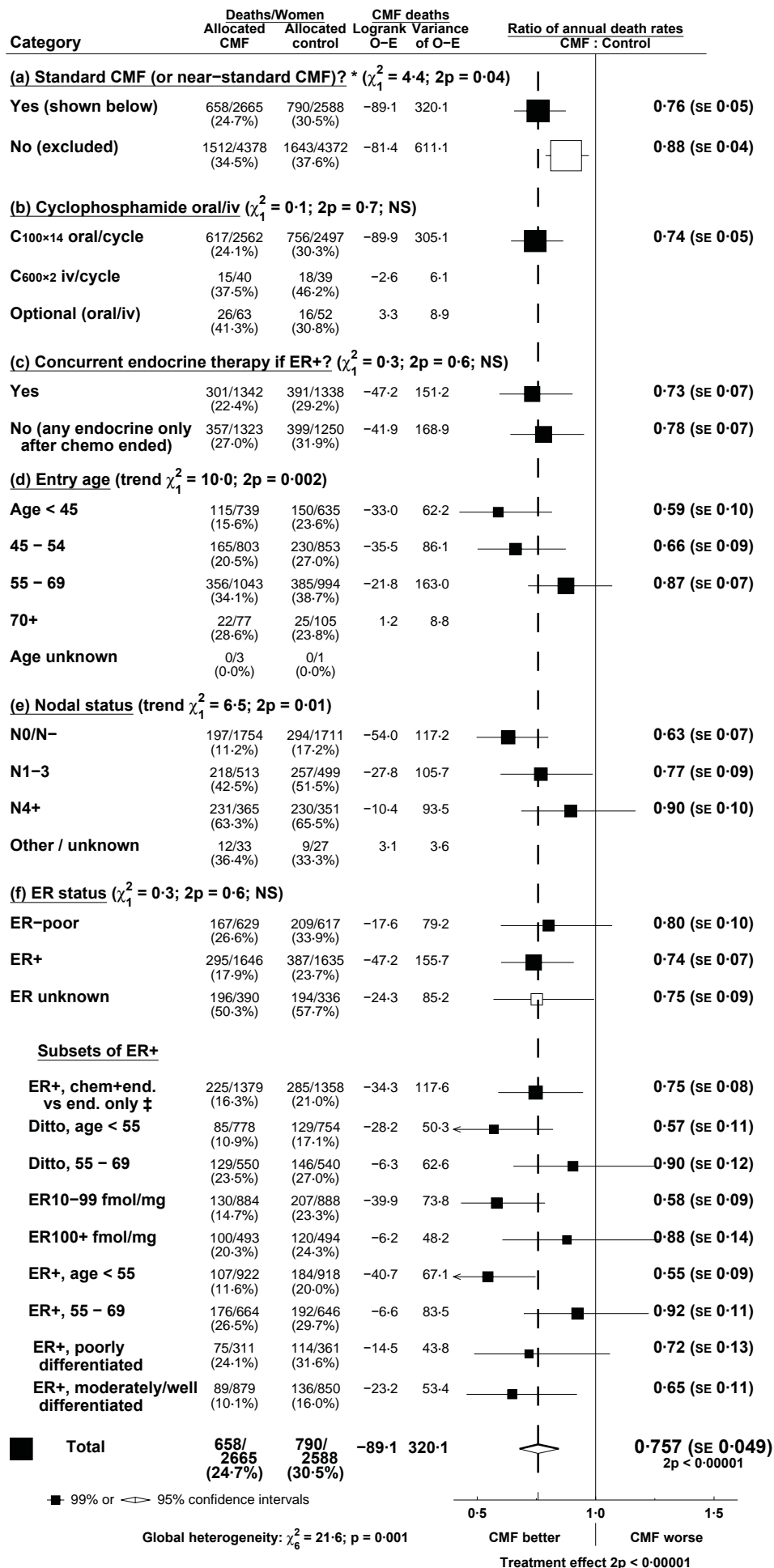
* Forest plots (webappendix pp 27-32) give details of each trial's cytotoxic regimens
 Anthracyclines: A = doxorubicin (Adriamycin), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil
 Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; A60/E90 means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin

P 4: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), any anthracycline-based regimen vs No chemotherapy
 NB First four subgroups are as in forest plots*



* Forest plots (webappendix pp 33-38) give details of each trial's cytotoxic regimens
 Anthracyclines: A = doxorubicin (Adriamycin), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil
 Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; A₆₀/E₉₀ means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
 † In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
 ‡ chem+end. = chemo-endocrine therapy

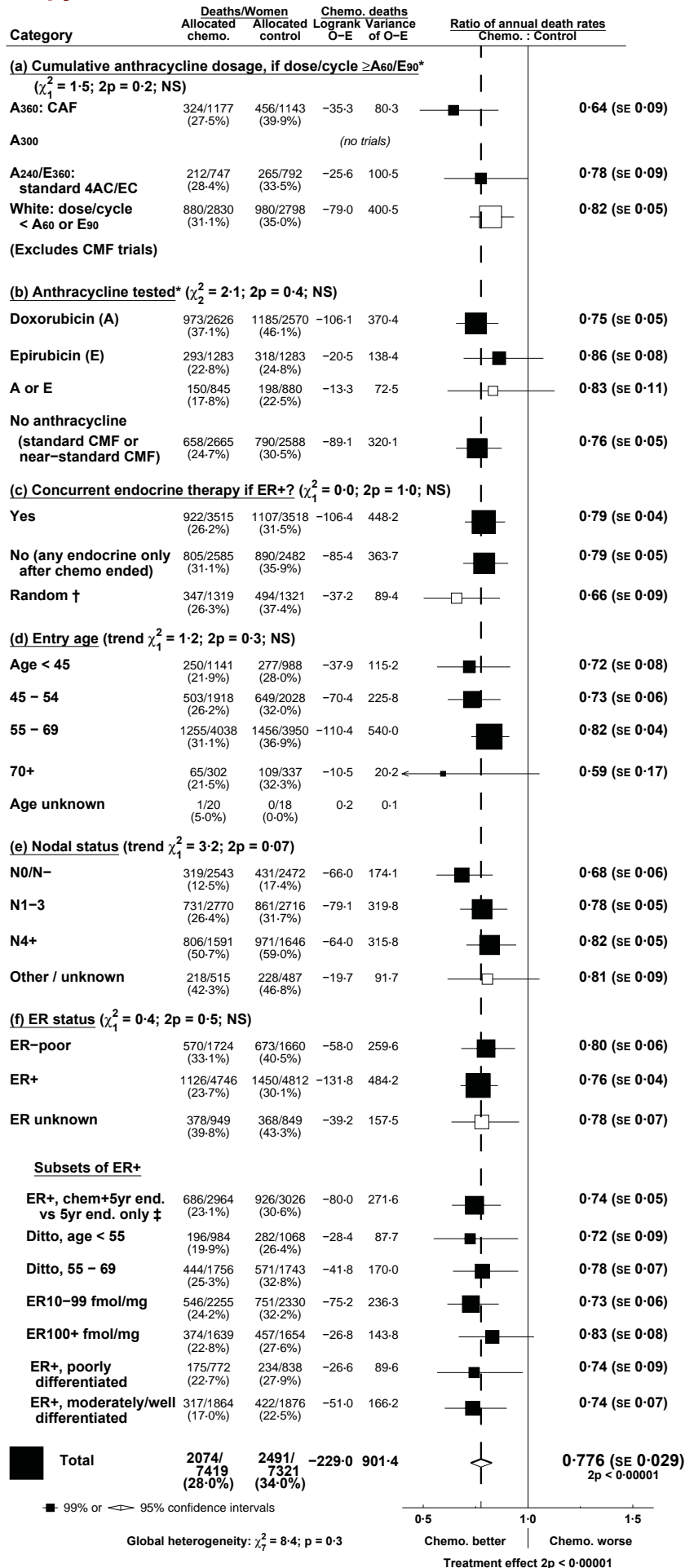
P 5: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence), standard CMF (or near-standard CMF)* vs. No chemotherapy



* See forest plots (webappendix pp 51-56) for details of regimens tested. Except in the first section, all analyses are of standard CMF (or near standard CMF). Trials of other CMF regimens (all with lower dose/cycle of at least one drug) are shown only in the first section (as a white square), and are then excluded.

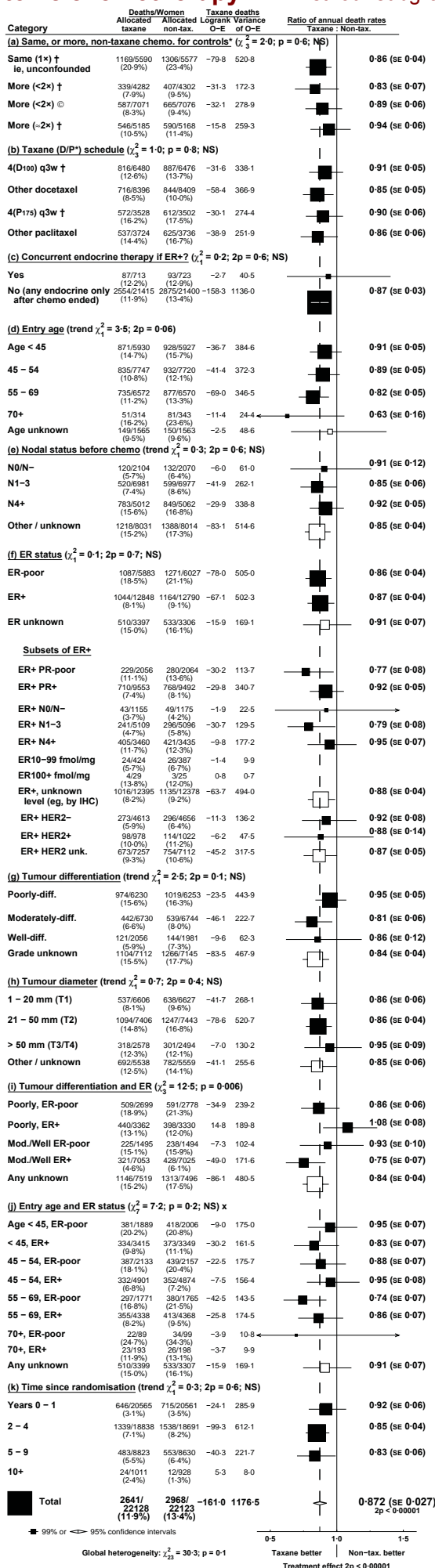
‡ chem+end. = chemo-endocrine therapy

P 6: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence), anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy



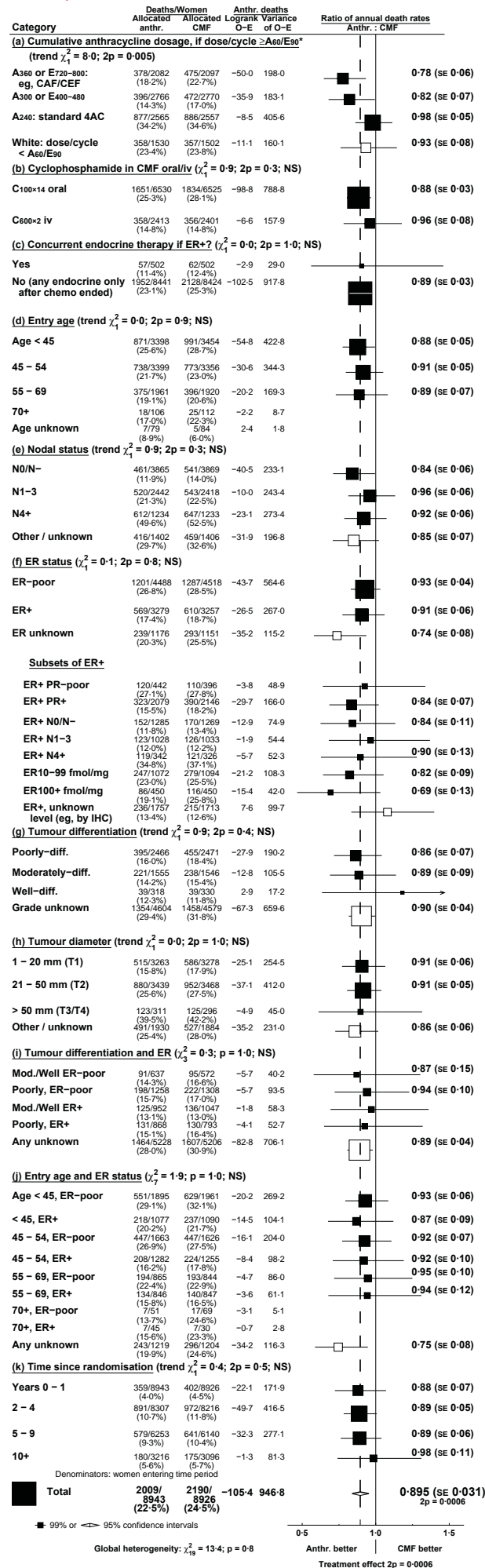
* Forest plots (webappendix pp 39-44) give details of each trial's cytotoxic regimens
Anthracyclines: A = doxorubicin (Adriamycin), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil
Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; A₆₀/E₉₀ means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
† In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
‡ chem+end. = chemo-endocrine therapy; 5yr end. = 5 years of tamoxifen (or, in part of one trial, toremifene)

P 8: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy NB First four subgroups are as in forest plots*.



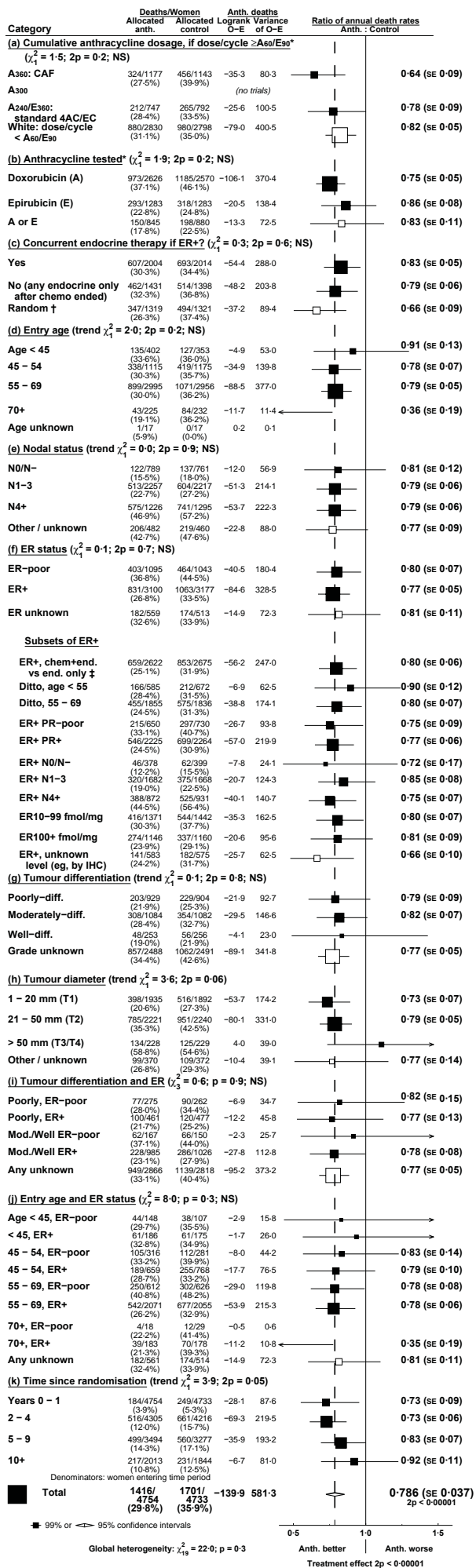
* Forest plots (webappendix pp 21-26) give details of each trial's cytotoxic regimens
D = docetaxel; P = paclitaxel; 4(D100) q3w means 4 doses of docetaxel 100 mg/m² at intervals of 3 weeks
† Taxane courses do not overlap other chemotherapy courses
© Taxane given concurrently with anthracycline

P 10: Subgroup analyses of BREAST CANCER MORTALITY (mortality with recurrence, by logrank subtraction), any anthracycline-based regimen vs. standard CMF (or near-standard CMF).
 NB First four subgroups are as in forest plots*.



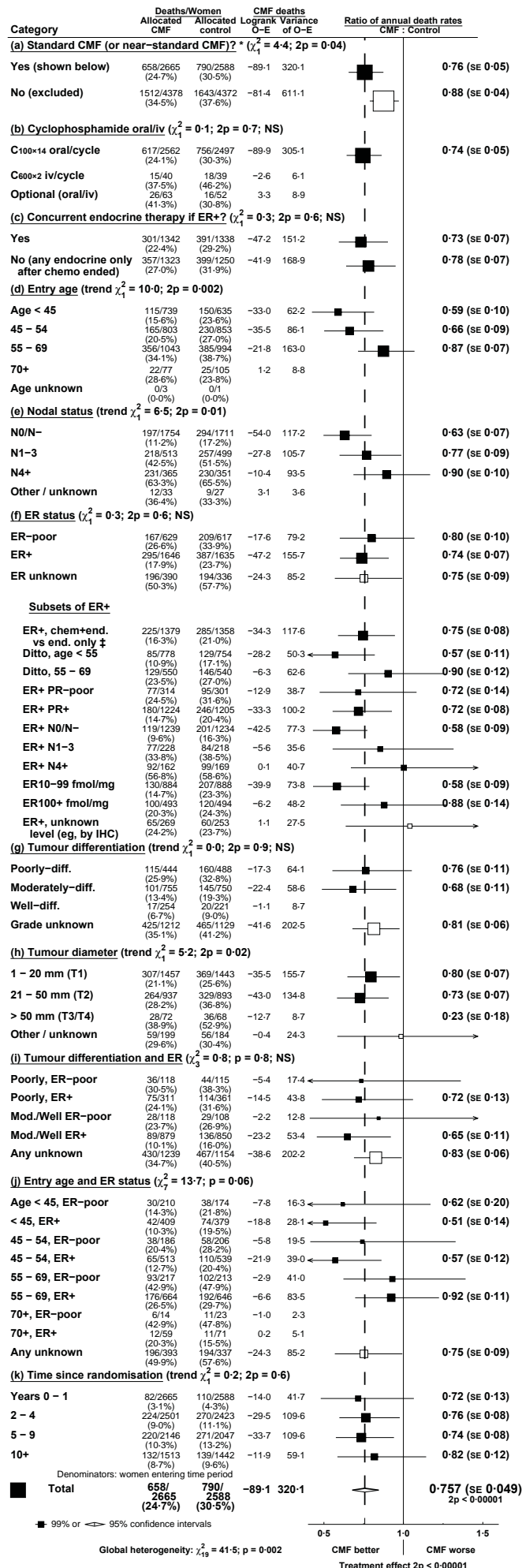
* Forest plots (webappendix pp 27-32) give details of each trial's cytotoxic regimens
 Anthracyclines: A = doxorubicin (Adriamycin), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil
 Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; A50/E50 means 50 mg/m² of doxorubicin or 50 mg/m² of epirubicin

P 12: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of any anthracycline-based regimen (eg, standard 4AC) vs. No chemotherapy



* Forest plots (webappendix pp 33-38) give details of each trial's cytotoxic regimens
 Anthracyclines: A = doxorubicin (Adriamycin), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil
 Dose/cycle (and cumulative dosage) is given after the drug name in mg/m². A60/E90 means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin
 † In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.
 ‡ chem+end. = chemo-endocrine therapy

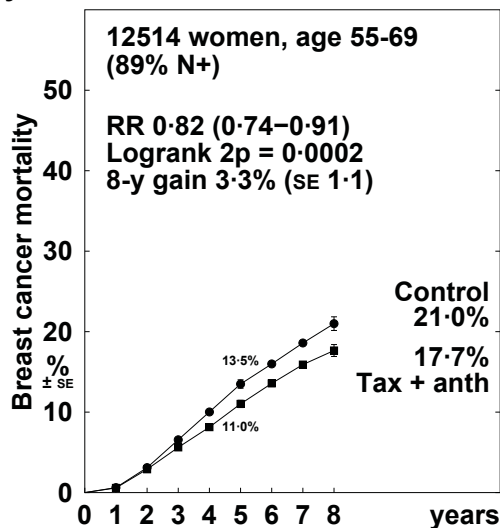
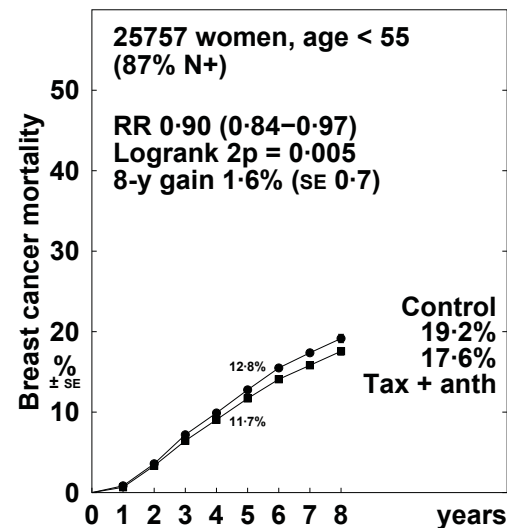
P 14: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of standard CMF (or near-standard CMF)* vs. No chemotherapy



* See forest plots (webappendix pp 51-56) for details of regimens tested. Except in the first section, all analyses are of standard CMF (or near standard CMF). Trials of other CMF regimens (all with lower dose/cycle of at least one drug) are shown only in the first section (as a white square), and are then excluded.
‡ chemo+end. = chemo-endocrine therapy

P 15: Any taxane-plus-anthracycline-based regimen vs control with the SAME or MORE non-taxane chemotherapy (all trials combined): subgroup analyses of 8-year breast cancer mortality RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Entry age <55 or 55-69 years

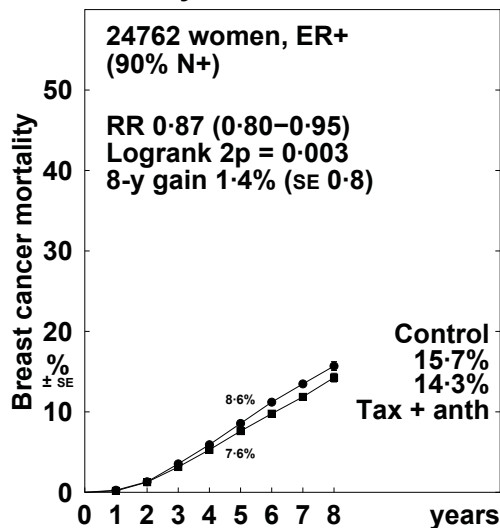
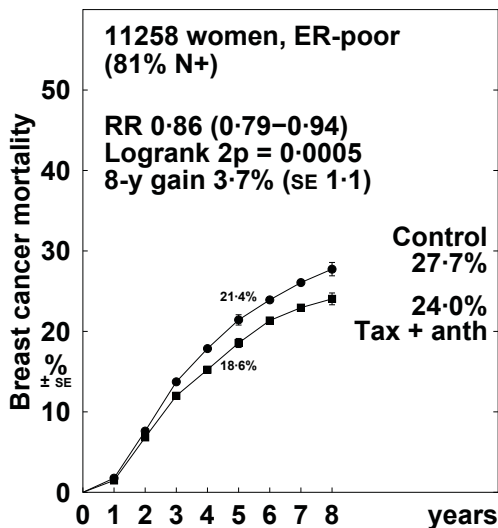


Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Year 5+
Tax + anth	2.42 SE 0.07	2.36 SE 0.13
Control	2.62 SE 0.07	2.63 SE 0.15
Rate ratio	0.91 SE 0.04	0.88 SE 0.08
(O-E) / V	-58.4 / 604.0	-19.6 / 152.8

Years 0 - 4	Year 5+
2.21 SE 0.09	2.64 SE 0.21
2.69 SE 0.11	3.14 SE 0.25
0.81 SE 0.05	0.85 SE 0.11
-57.7 / 275.4	-11.4 / 71.0

ER status, mainly by immunohistochemistry

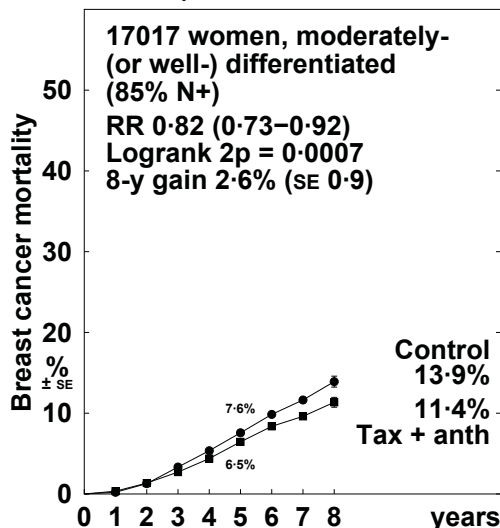
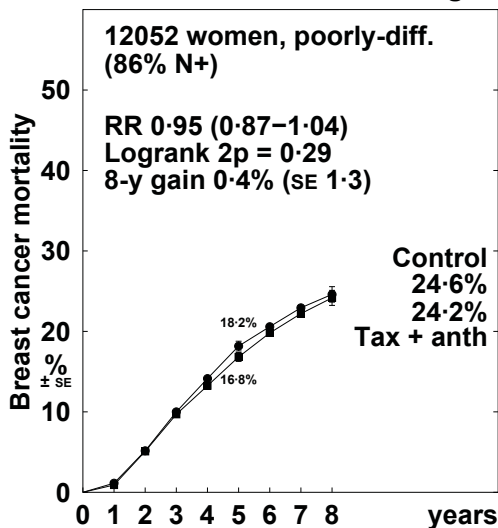


Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Year 5+
Tax + anth	4.00 SE 0.13	2.44 SE 0.20
Control	4.86 SE 0.15	2.67 SE 0.23
Rate ratio	0.85 SE 0.04	0.91 SE 0.12
(O-E) / V	-71.7 / 438.8	-6.2 / 66.1

Years 0 - 4	Year 5+
1.45 SE 0.05	2.51 SE 0.15
1.62 SE 0.06	2.87 SE 0.16
0.89 SE 0.05	0.85 SE 0.08
-44.3 / 365.5	-22.8 / 136.8

Tumour grade (few were well-differentiated)



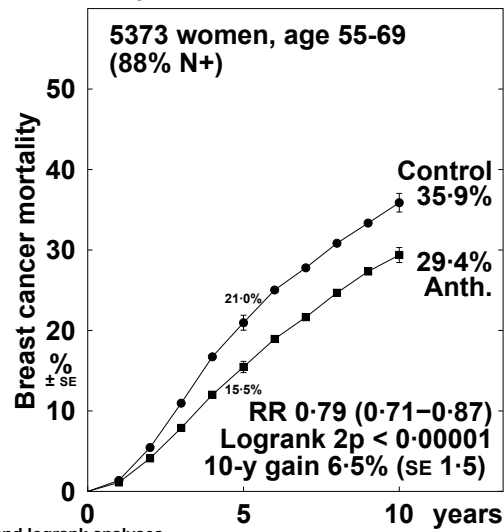
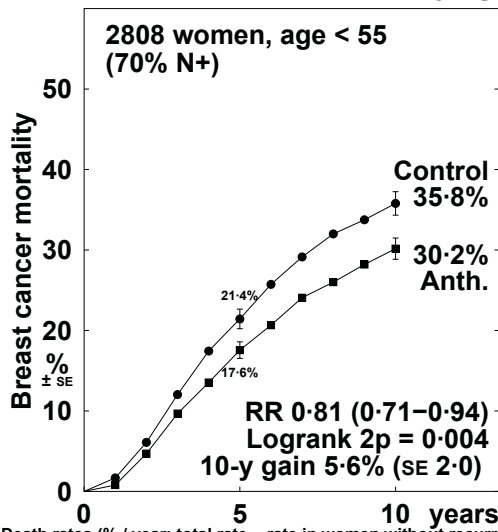
Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Year 5+
Tax + anth	3.53 SE 0.12	3.07 SE 0.28
Control	3.79 SE 0.13	2.69 SE 0.28
Rate ratio	0.93 SE 0.05	1.16 SE 0.15
(O-E) / V	-29.3 / 390.0	7.3 / 49.1

Years 0 - 4	Year 5+
1.22 SE 0.06	1.85 SE 0.17
1.45 SE 0.07	2.37 SE 0.19
0.84 SE 0.06	0.75 SE 0.11
-37.5 / 216.0	-19.0 / 64.9

P 16: At least 4 cycles of any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy: subgroup analyses of 10-year breast cancer mortality by age, ER status and tumour grade RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Entry age <55 or 55-69 years

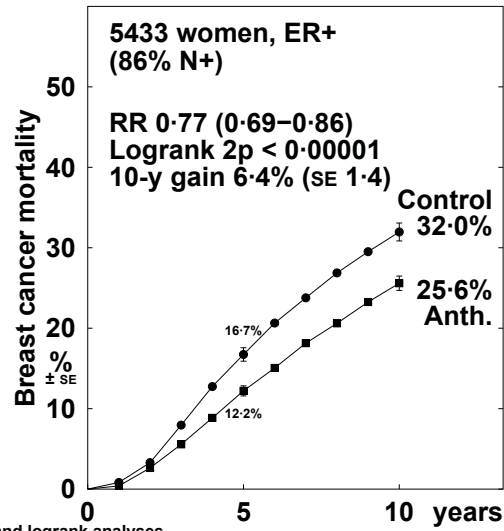
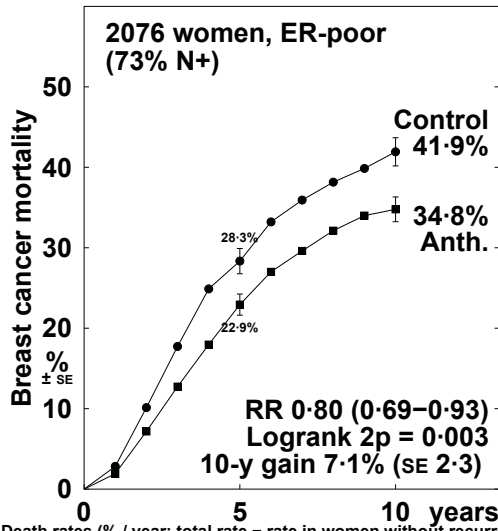


Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	3.81 SE 0.24	3.53 SE 0.28	1.85 SE 0.25
Control	4.77 SE 0.29	4.11 SE 0.34	2.01 SE 0.28
Rate ratio	0.79 SE 0.09	0.81 SE 0.11	0.96 SE 0.21
(O-E) / V	-25.5 / 108.4	-13.5 / 63.4	-0.9 / 21.0

Years 0 - 4	Years 5 - 9	Year 10+
3.26 SE 0.16	3.63 SE 0.20	3.43 SE 0.28
4.79 SE 0.22	4.40 SE 0.27	3.65 SE 0.33
0.71 SE 0.06	0.86 SE 0.08	0.94 SE 0.13
-65.9 / 193.2	-19.2 / 125.4	-3.5 / 58.3

ER status

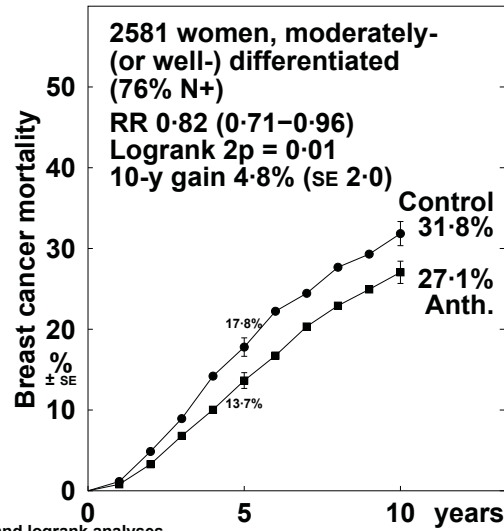
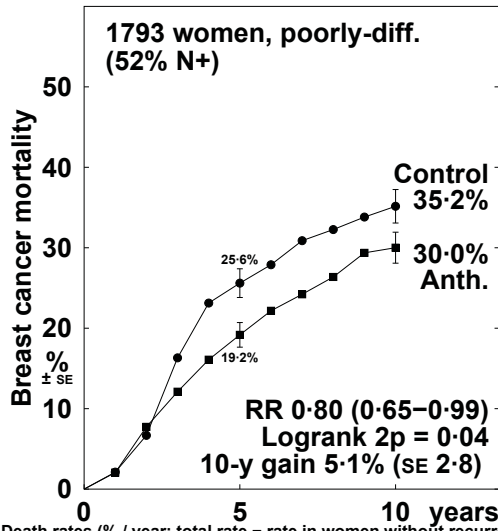


Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	4.96 SE 0.32	3.50 SE 0.33	2.64 SE 0.36
Control	6.84 SE 0.41	4.47 SE 0.42	2.92 SE 0.41
Rate ratio	0.76 SE 0.08	0.80 SE 0.13	0.98 SE 0.20
(O-E) / V	-29.2 / 107.7	-10.8 / 48.7	-0.5 / 24.1

Years 0 - 4	Years 5 - 9	Year 10+
2.60 SE 0.14	3.40 SE 0.19	3.09 SE 0.26
3.63 SE 0.19	4.17 SE 0.25	3.14 SE 0.30
0.71 SE 0.07	0.81 SE 0.08	0.92 SE 0.14
-54.3 / 156.2	-26.4 / 123.3	-4.0 / 48.9

Tumour grade (few were well-differentiated)



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

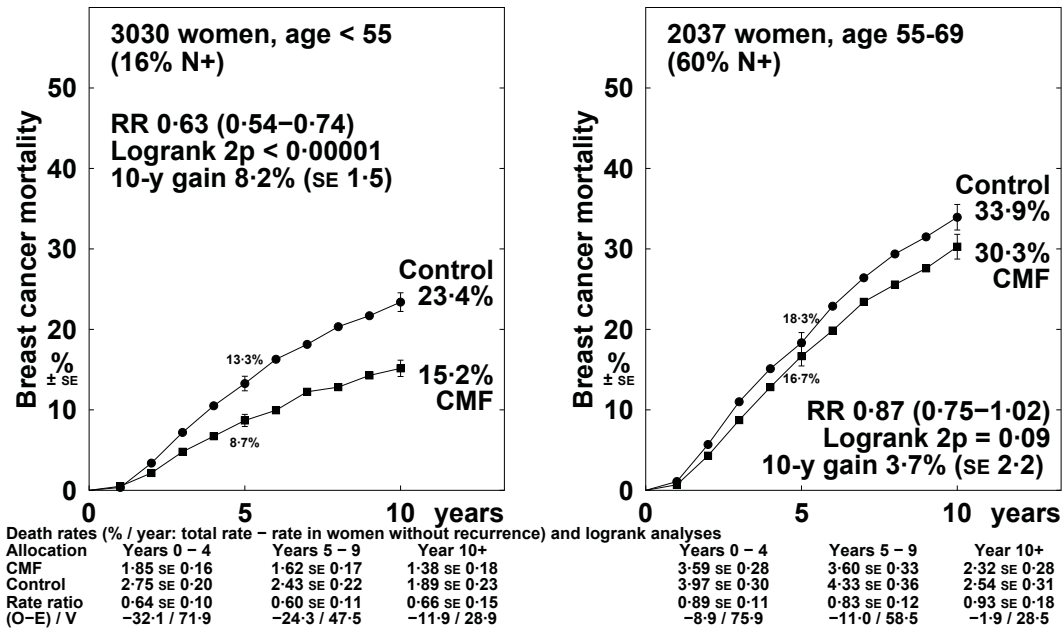
Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	4.31 SE 0.36	2.98 SE 0.40	0.76 SE 0.31
Control	5.73 SE 0.44	2.88 SE 0.43	0.58 SE 0.29
Rate ratio	0.73 SE 0.11	1.05 SE 0.22	1.07 SE 0.78
(O-E) / V	-20.6 / 65.5	1.0 / 22.1	0.1 / 1.7

Years 0 - 4	Years 5 - 9	Year 10+
2.85 SE 0.22	3.45 SE 0.30	2.51 SE 0.36
3.89 SE 0.26	3.91 SE 0.34	2.67 SE 0.40
0.74 SE 0.09	0.89 SE 0.12	1.02 SE 0.23
-25.7 / 86.4	-6.5 / 58.5	0.4 / 20.1

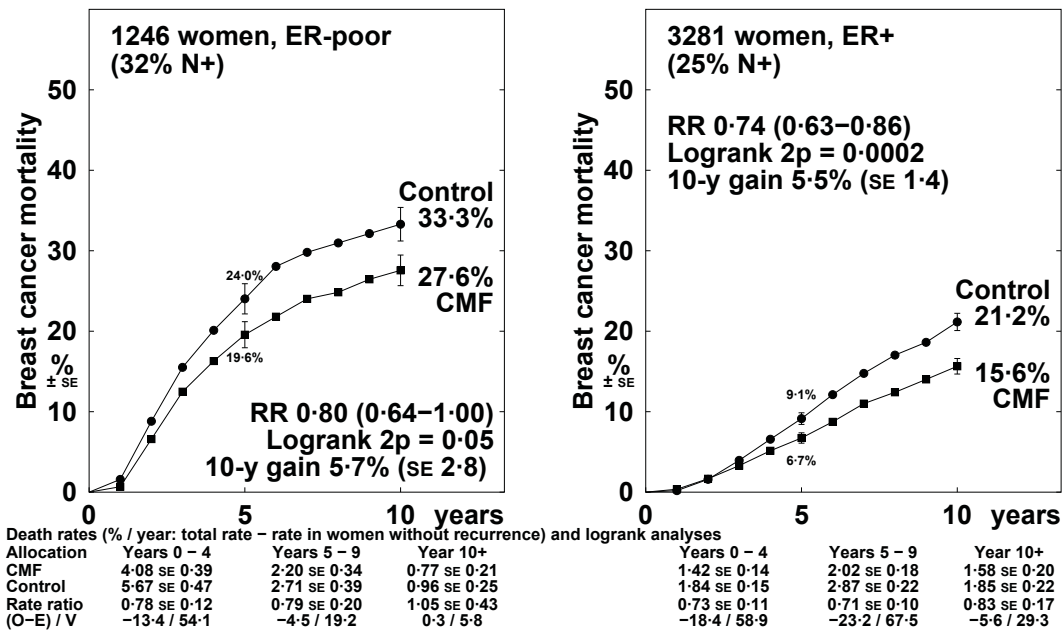
P 17: Standard CMF (or near-standard CMF) vs no adjuvant chemotherapy: subgroup analyses of 10-year breast cancer mortality by age, ER status and tumour grade

RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

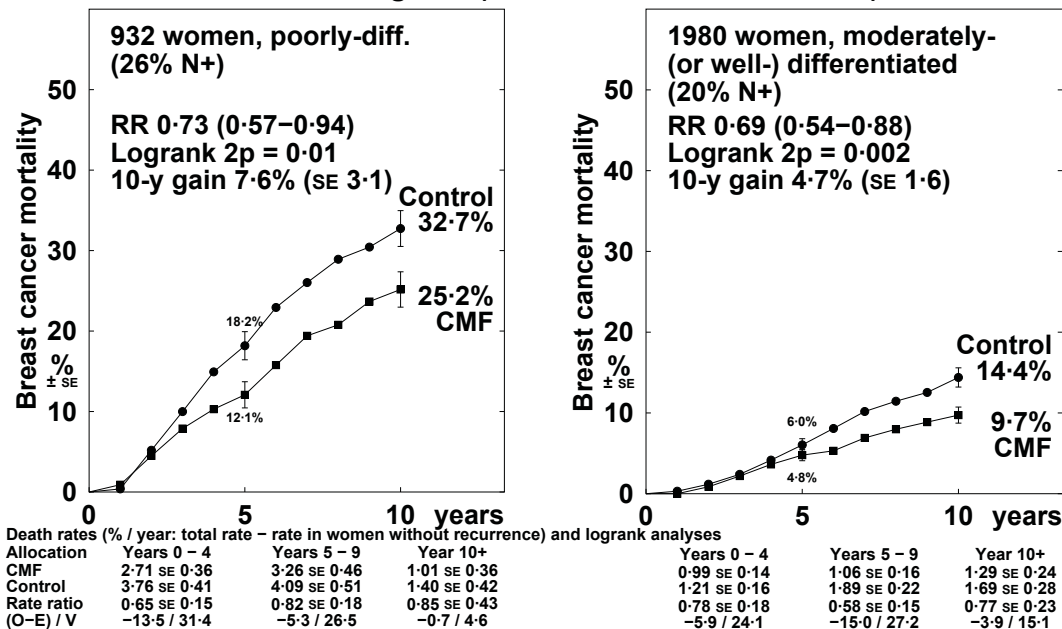
Entry age <55 or 55-69 years



ER status



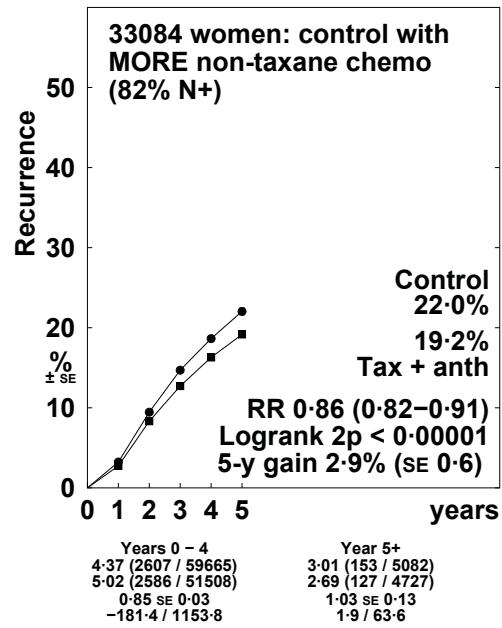
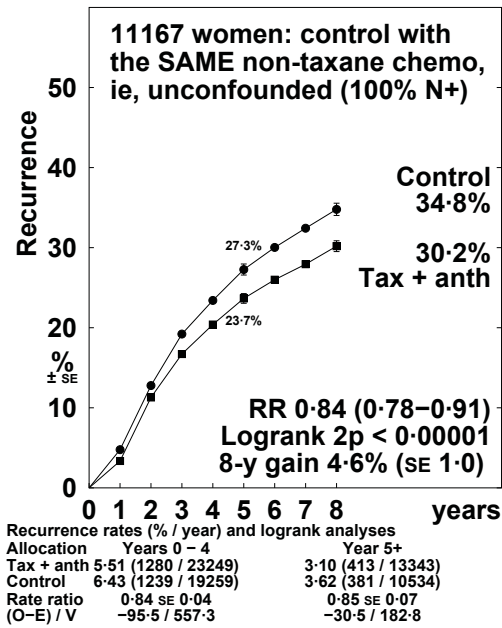
Tumour grade (few were well-differentiated)



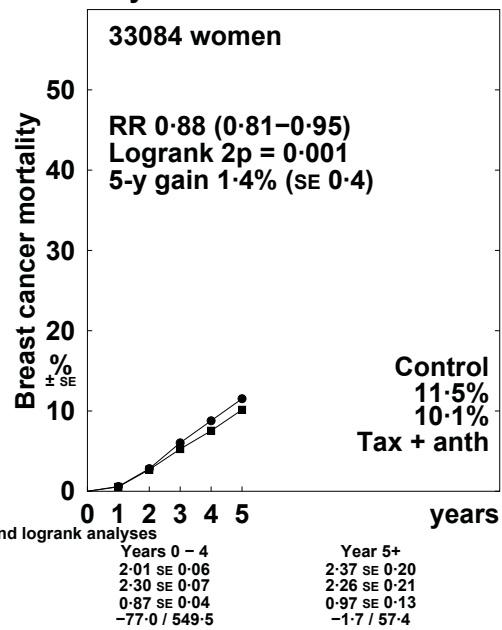
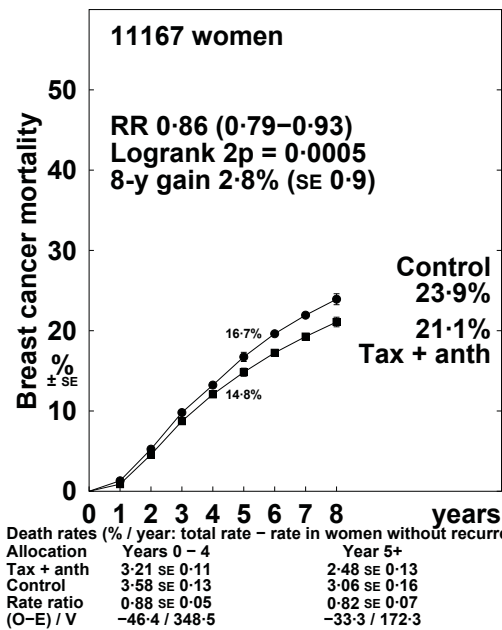
P 18: Taxane-plus-anthracycline-based regimen vs control with Left: the SAME, or Right: MORE, non-taxane chemotherapy

Time to recurrence, breast cancer mortality and overall mortality. Trials vs the SAME non-taxane chemotherapy (usually 4AC) just added 4 extra taxane-only cycles. RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

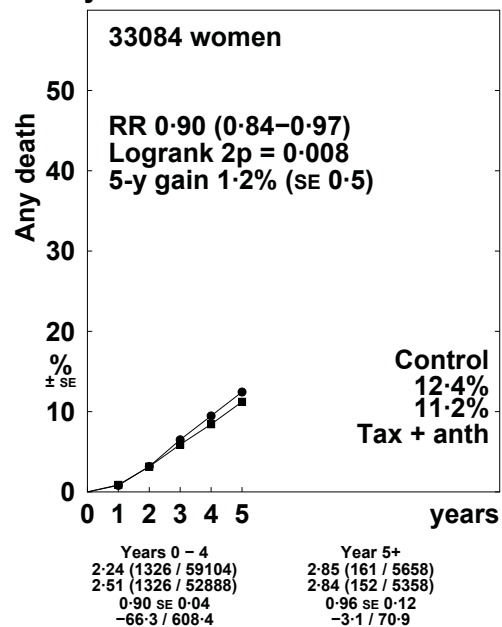
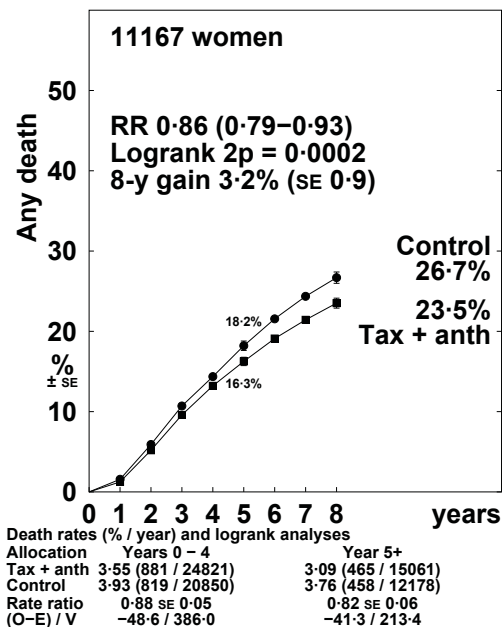
Recurrence



Breast cancer mortality



Overall mortality

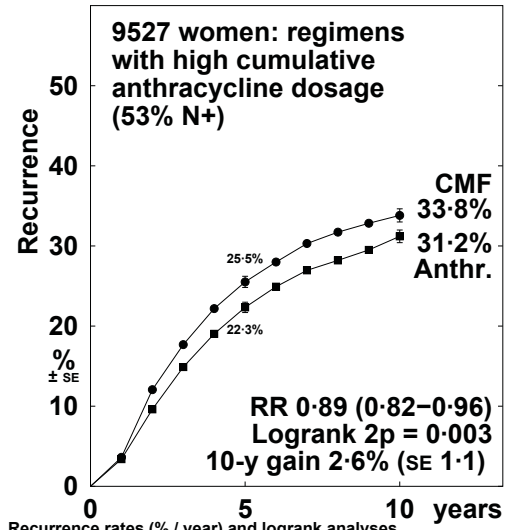


P 19: Selected anthracycline-based regimens vs standard CMF (or near-standard CMF)
Left: regimens with cumulative dosage > 240 mg/m² doxorubicin or 360 mg/m² epirubicin (eg, CAF or CEF), Right: standard 4AC (cumulative dosage 240 mg/m² doxorubicin)

(All graphs exclude regimens with < 60 mg/m² doxorubicin or 90 mg/m² epirubicin per cycle)

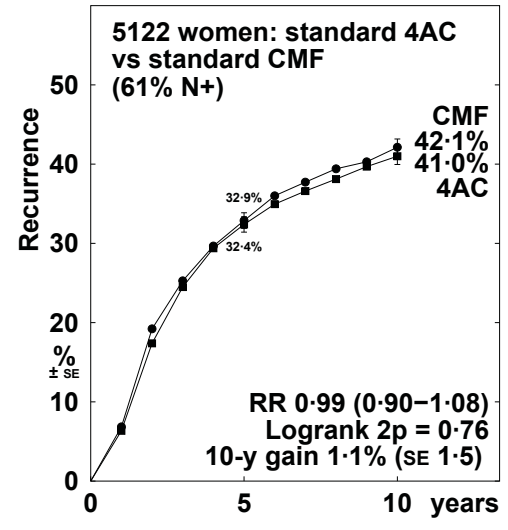
Time to recurrence, breast cancer mortality and overall mortality. RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Recurrence



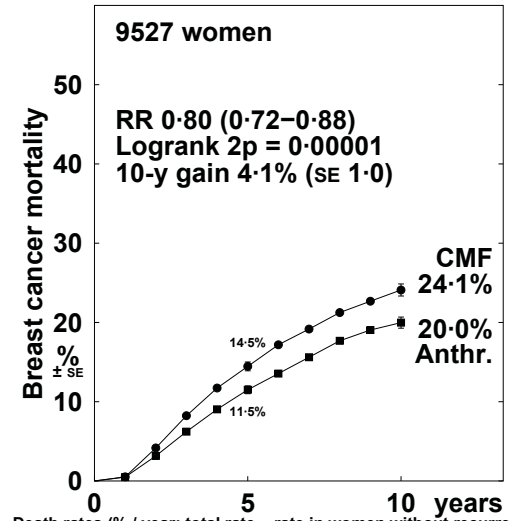
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anthr.	5.05 (989 / 19575)	2.45 (238 / 9723)	1.64 (65 / 3973)
CMF	6.01 (1104 / 18377)	2.57 (237 / 9236)	1.35 (54 / 4007)
Rate ratio (O-E) / V	0.85 SE 0.04 -74.9 / 457.0	1.00 SE 0.10 0.1 / 106.9	1.12 SE 0.21 1.2 / 26.4



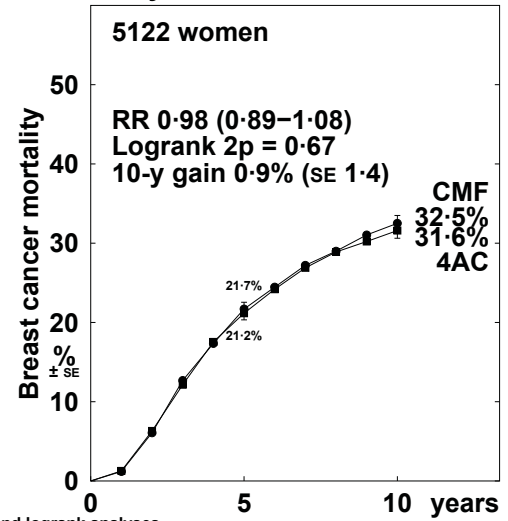
Years 0 - 4	Years 5 - 9	Year 10+
7.97 (820 / 10292) 8.21 (830 / 10108) 0.98 SE 0.05 -8.7 / 355.5	2.86 (194 / 6795) 2.99 (199 / 6658) 0.91 SE 0.10 -8.5 / 92.1	2.36 (100 / 4237) 1.87 (76 / 4054) 1.28 SE 0.17 10.4 / 42.3

Breast cancer mortality



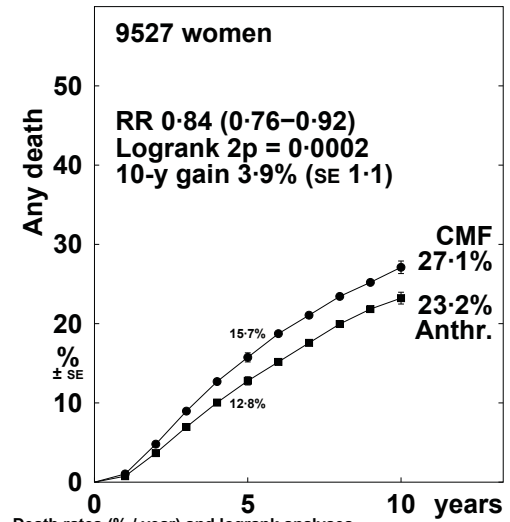
Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anthr.	2.39 SE 0.11	2.08 SE 0.14	0.91 SE 0.14
CMF	3.06 SE 0.12	2.50 SE 0.15	1.11 SE 0.16
Rate ratio (O-E) / V	0.78 SE 0.06 -62.9 / 248.9	0.84 SE 0.09 -19.3 / 111.5	0.84 SE 0.20 -3.5 / 20.8



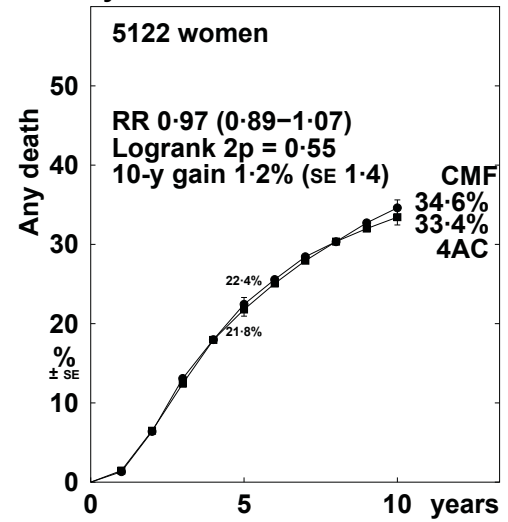
Years 0 - 4	Years 5 - 9	Year 10+
4.65 SE 0.20 4.81 SE 0.21 0.97 SE 0.06 -6.3 / 245.2	2.94 SE 0.19 3.04 SE 0.20 0.97 SE 0.09 -3.7 / 111.6	2.06 SE 0.20 1.96 SE 0.20 1.03 SE 0.15 1.5 / 48.9

Overall mortality



Death rates (% / year) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anthr.	2.67 (561 / 20977)	2.60 (290 / 11151)	1.99 (90 / 4528)
CMF	3.36 (669 / 19894)	2.99 (319 / 10661)	1.92 (87 / 4523)
Rate ratio (O-E) / V	0.79 SE 0.05 -65.0 / 277.4	0.88 SE 0.08 -17.8 / 137.2	1.06 SE 0.16 2.5 / 40.9



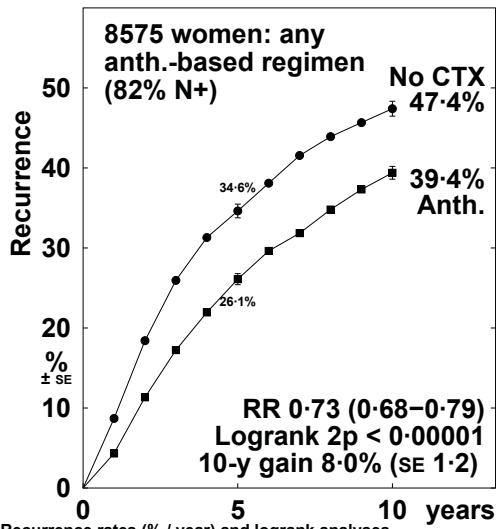
Years 0 - 4	Years 5 - 9	Year 10+
4.81 (551 / 11458) 5.00 (567 / 11351) 0.97 SE 0.06 -8.1 / 254.9	3.33 (266 / 7994) 3.48 (274 / 7883) 0.96 SE 0.09 -5.3 / 127.6	2.67 (141 / 5281) 2.57 (131 / 5106) 1.01 SE 0.13 0.8 / 64.2

P 20: Chemotherapy vs no adjuvant chemotherapy (no CTX)

Left: ≥ 4 cycles of any anthracycline-based regimen, eg standard 4AC,
 Right: standard CMF (or near-standard CMF)

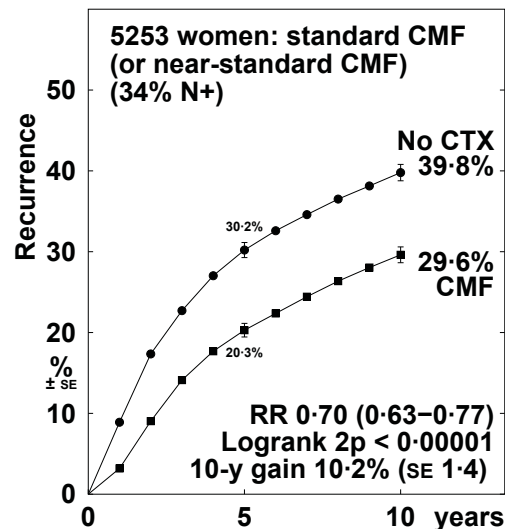
Time to recurrence, breast cancer mortality and overall mortality. RR (and its 95% CI): event rate ratio, from summed logrank statistics for all time periods. Gain (and its SE): absolute difference between ends of graphs.

Recurrence



Recurrence rates (% / year) and logrank analyses

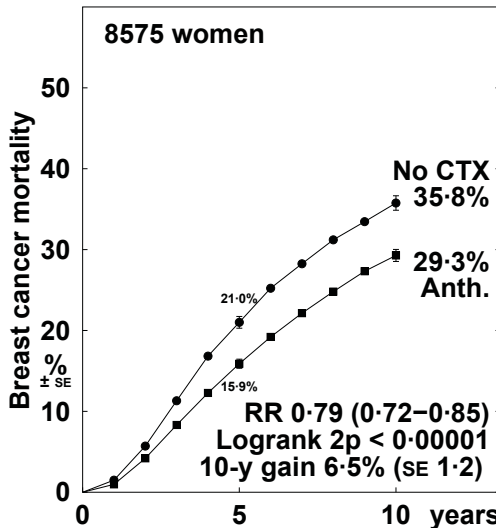
Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	6.14 (1179 / 19190)	4.06 (487 / 11981)	2.91 (161 / 5530)
No CTX	9.06 (1259 / 13899)	4.56 (365 / 8011)	3.87 (159 / 4104)
Rate ratio (O-E) / V	0.69 SE 0.04 -185.2 / 489.8	0.89 SE 0.07 -20.0 / 174.7	0.72 SE 0.11 -21.2 / 65.5



Recurrence rates (% / year) and logrank analyses

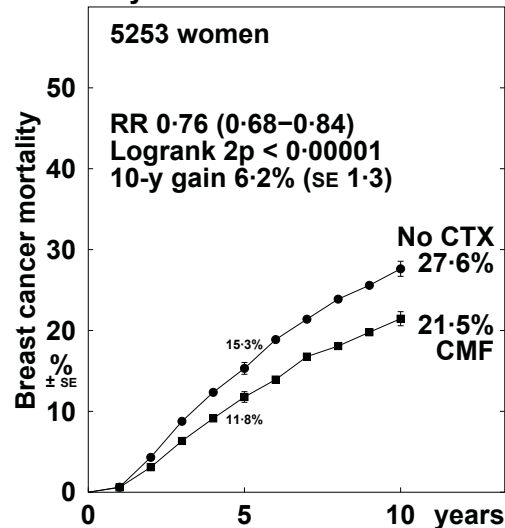
Allocation	Years 0 - 4	Years 5 - 9	Year 10+
CMF	4.83 (549 / 11357)	2.58 (207 / 8038)	1.88 (116 / 6155)
No CTX	7.20 (748 / 10385)	2.93 (210 / 7158)	1.90 (100 / 5260)
Rate ratio (O-E) / V	0.61 SE 0.05 -135.5 / 277.0	0.84 SE 0.09 -16.9 / 95.9	0.99 SE 0.14 -0.7 / 48.7

Breast cancer mortality



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

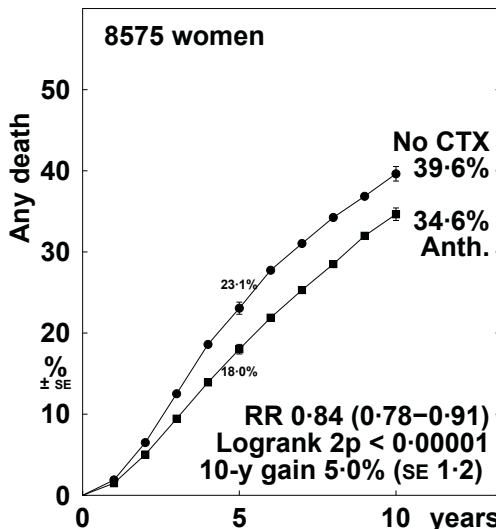
Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	3.38 SE 0.13	3.57 SE 0.16	2.83 SE 0.19
No CTX	4.77 SE 0.17	4.31 SE 0.21	2.98 SE 0.22
Rate ratio (O-E) / V	0.73 SE 0.05 -97.5 / 307.0	0.83 SE 0.07 -35.9 / 193.2	0.92 SE 0.11 -6.7 / 81.0



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

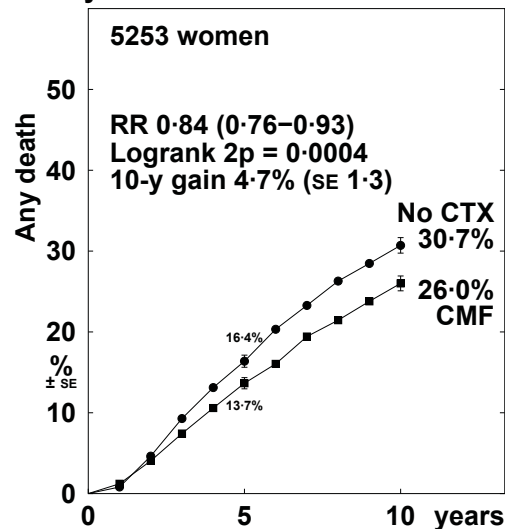
Allocation	Years 0 - 4	Years 5 - 9	Year 10+
CMF	2.51 SE 0.14	2.42 SE 0.16	1.80 SE 0.16
No CTX	3.23 SE 0.17	3.14 SE 0.19	2.10 SE 0.18
Rate ratio (O-E) / V	0.75 SE 0.07 -43.5 / 151.3	0.74 SE 0.08 -33.7 / 109.6	0.82 SE 0.12 -11.9 / 59.1

Overall mortality



Death rates (% / year) and logrank analyses

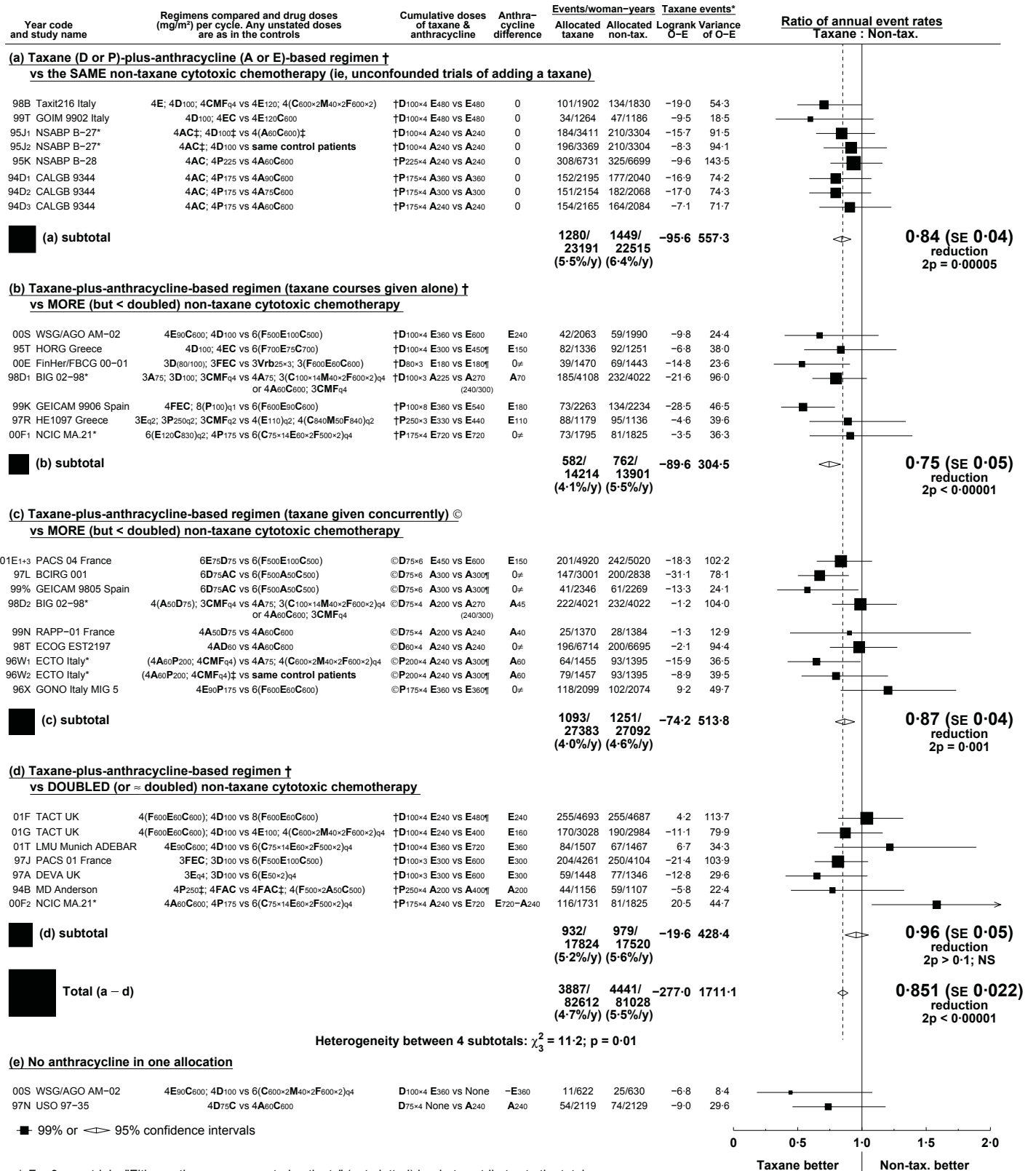
Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	3.91 (811 / 20718)	4.62 (645 / 13969)	4.39 (337 / 7680)
No CTX	5.25 (834 / 15889)	4.93 (492 / 9975)	4.34 (259 / 5969)
Rate ratio (O-E) / V	0.75 SE 0.05 -99.0 / 346.4	0.92 SE 0.06 -19.1 / 234.6	1.00 SE 0.09 -0.1 / 120.2



Death rates (% / year) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
CMF	2.93 (357 / 12167)	3.15 (286 / 9091)	3.14 (230 / 7318)
No CTX	3.49 (410 / 11756)	3.78 (326 / 8617)	3.39 (224 / 6612)
Rate ratio (O-E) / V	0.82 SE 0.07 -33.6 / 170.7	0.81 SE 0.08 -28.5 / 137.2	0.91 SE 0.10 -8.8 / 96.2

P 21: EARLY RECURRENCE (first 5 years) in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3-way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.

For 95J NSABP B-27, this (O-E) is -16.5 with variance V = 120.8; 96W ECTO Italy (O-E) = -16.1, V = 48.4;

98D BIG 02-98 (O-E) = -15.0, V = 131.9; 00F MA.21 (O-E) = 11.2; V = 56.3

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

‡ Pre-operative chemotherapy: all patients in these trials were analysed as unknown nodal status

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

‡ Same cumulative anthracycline dose, but differences in other drugs

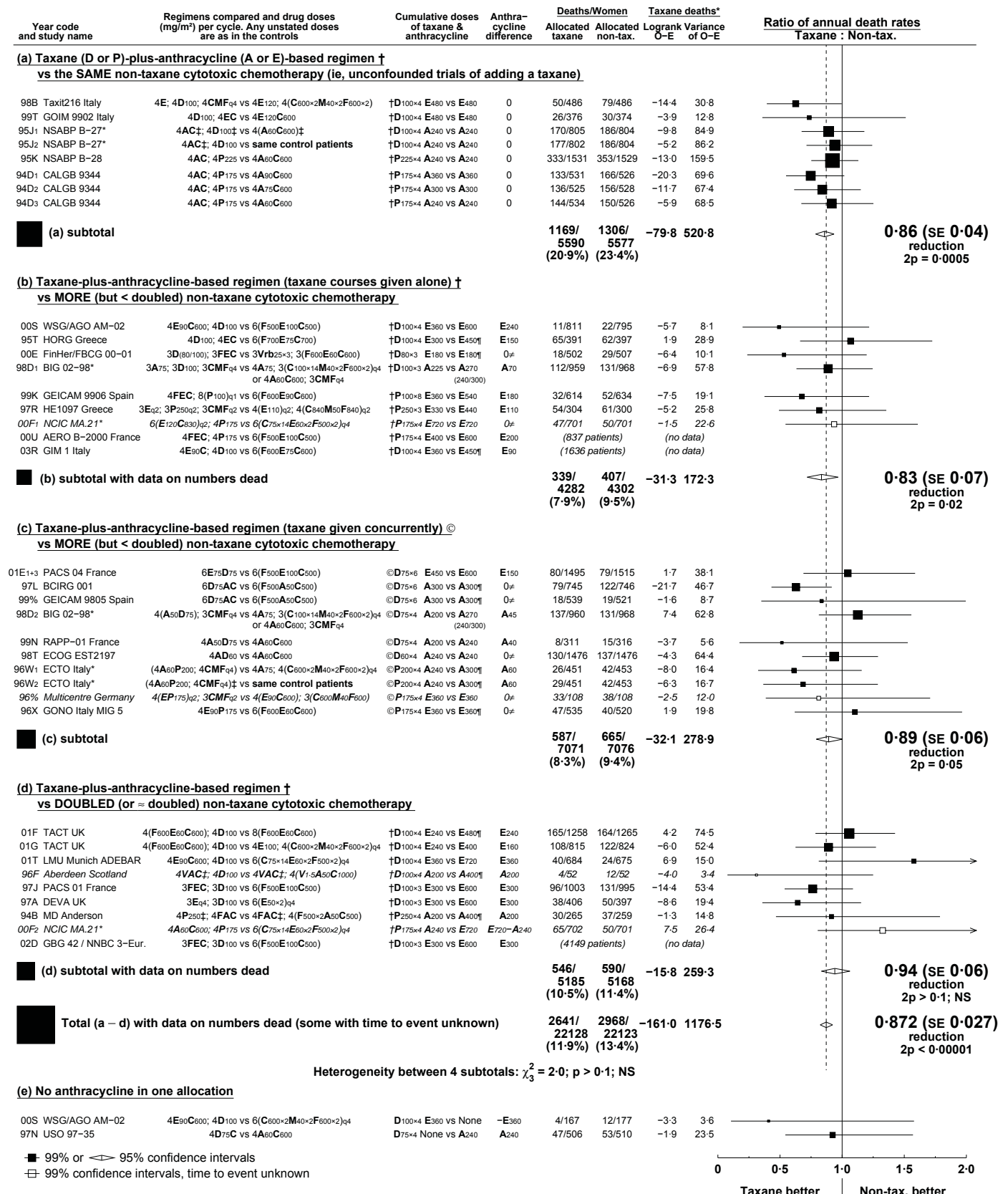
¶ Control anthracycline dose less than E90 or A60 per cycle

Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin
Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; V = 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.

x14 means d1-14 po; x2 (x3) means d1, d8 (d15) iv (except that in trial 94B, F500x2 was d1, d4 iv and in trial 01F, C600x2 could be C100x14).

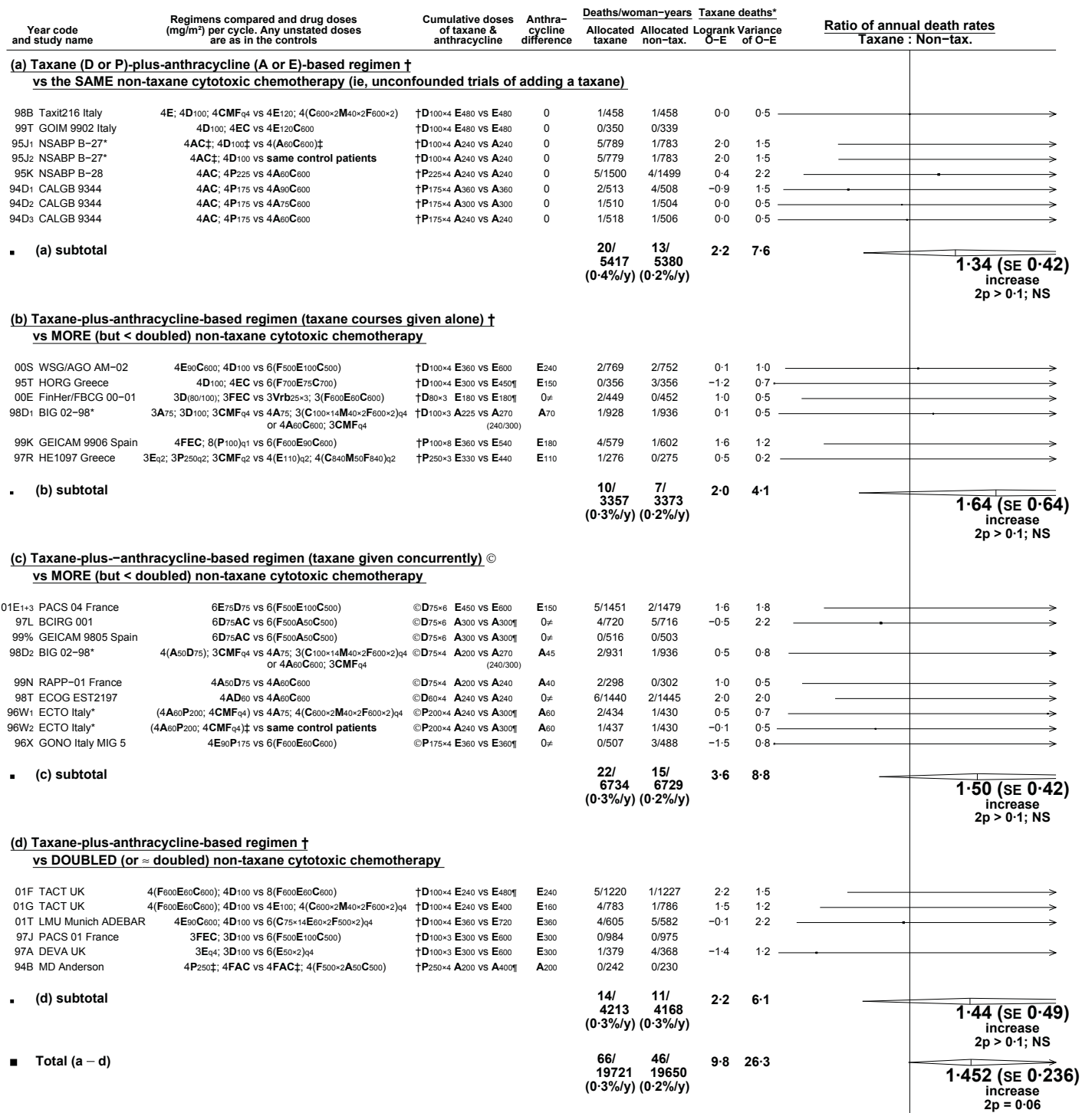
P 23: Breast cancer mortality (mortality with recurrence, by logrank subtraction), any taxane-plus-anthracycline-based regimen vs control with the SAME, or MORE (<doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3-way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
 † For 95J NSABP B-27, this (O-E) is -10.5 with variance V = 112.2; 96W ECTO Italy (O-E) = -9.3, V = 20.8; 98D BIG 02-98 (O-E) = 0.4, V = 81.5; 00F MA.21 (O-E) = 4.0; V = 33.2
 ‡ Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased
 § Pre-operative chemotherapy: all patients in these trials were analysed as unknown nodal status
 © 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; M = methotrexate; V = 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 (except that in trial 94B, F500x2 was d1, d4 iv and in trial 01F, C600x2 could be C100x14).

P 24: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy

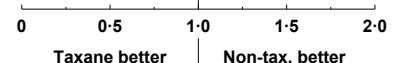


Heterogeneity between 4 subtotals: $\chi^2_3 = 0.1$; $p > 0.1$; NS

(e) No anthracycline in one allocation

00S WSG/AGO AM-02	4E90C600; 4D100 vs 6(C600x2M40x2F600x2)q4	D100x4 E360 vs None	-E360	0/154	0/164					
97N USO 97-35	4D75C vs 4A60C600	D75x4 None vs A240	A240	3/482	1/487	0.9	1.0			

■ 99% or ◁ 95% confidence intervals



* For 3-way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.

For 95J NSABP B-27, this (O-E) is 2.7 with variance $V = 2.4$; 96W ECTO Italy (O-E) = 0.3, $V = 0.9$;

98D BIG 02-98 (O-E) = 0.4, $V = 0.9$; 00F MA.21 (O-E) = 0.0; $V = 0.0$

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

‡ Pre-operative chemotherapy: all patients in these trials were analysed as unknown nodal status

© 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

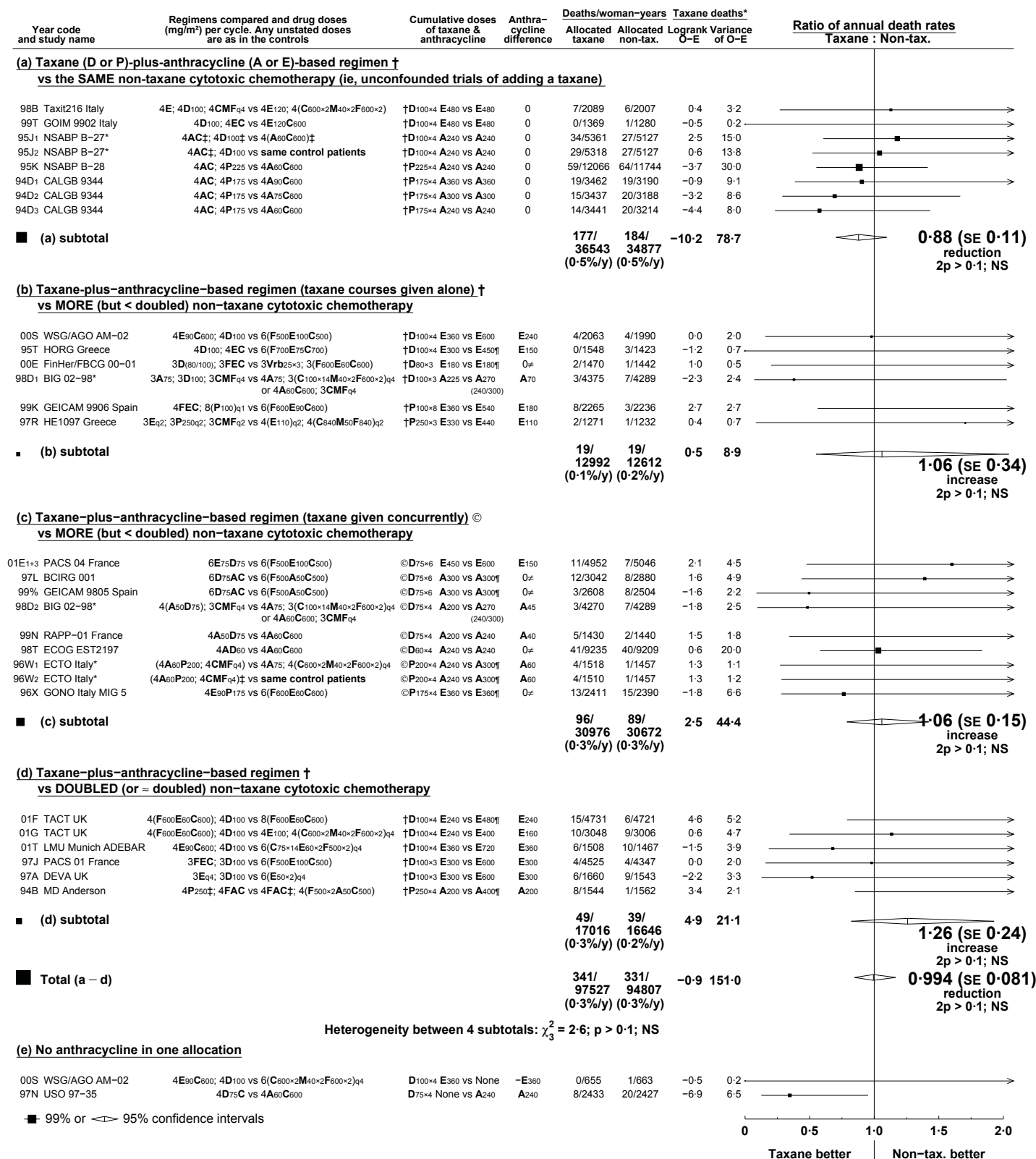
Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; V = vincristine; Vrb = vinorelbine

(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.

x14 means d1-14 po; x2 (x3) means d1, d8 (d15) iv (except that in trial 94B, F500x2 was d1, d4 iv and in trial 01F, C600x2 could be C100x14).

P 25: MORTALITY 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, "Either active vs same control patients" (not plotted) is what contributes to the total.
 For 95J NSABP B-27, this (O-E) is 2.1 with variance V = 19.5; 96W ECTO Italy (O-E) = 1.8, V = 1.9;
 98D BIG 02-98 (O-E) = -2.8, V = 2.8; 00F MA.21 (O-E) = 0.0; V = 0.0

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

‡ Pre-operative chemotherapy: all patients in these trials were analysed as unknown nodal status

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

≠ Same cumulative anthracycline dose, but differences in other drugs

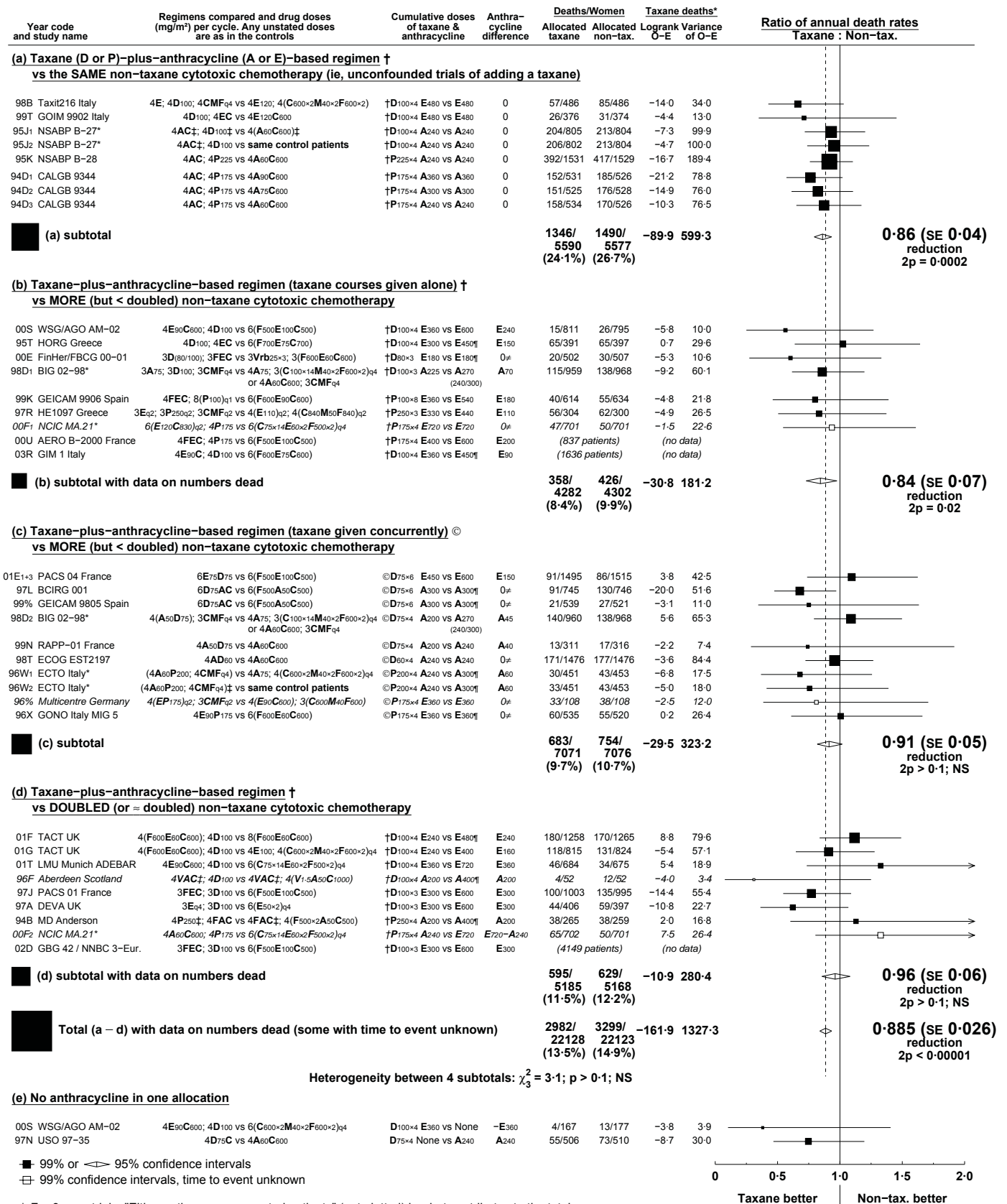
¶ Control anthracycline dose less than E90 or A60 per cycle

Taxanes: D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin
 Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; V = 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 (except that in trial 94B, F500x2 was d1, d4 iv and in trial 01F, C600x2 could be C100x14).

P 26: OVERALL MORTALITY in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy



* For 3-way trials, "Either active vs same control patients" (not plotted) is what contributes to the total.
 † For 95J NSABP B-27, this (O-E) is -8.4 with variance V = 131.6; 96W ECTO Italy (O-E) = -7.5, V = 22.7; 98D BIG 02-98 (O-E) = -2.3, V = 84.2; 00F MA.21 (O-E) = 4.0; V = 33.2
 ‡ Taxane courses do not overlap with any other chemotherapy courses; hence, total chemotherapy duration is increased
 § Pre-operative chemotherapy; all patients in these trials were analysed as unknown nodal status
 © 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; M = methotrexate; V = 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 (except that in trial 94B, F500×2 was d1, d4 iv and in trial 01F, C600×2 could be C100×14).

P 27: EARLY RECURRENCE (first 5 years) in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)

Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosage, E/A	Events/woman-years		Anthr. events O-E	Variance of O-E	Ratio of annual event rates Anthr. : CMF
			Allocated anthr.	Adjusted CMF			
(a) Anthracycline dose/cycle ≥ A60 or E90							
i. Cumulative anthracycline dosage A360 or E720-800							
88R Brussels Belgium	8E100C830 vs 6(C100×14M40×2F600×2)q4	E800	64/1131	82/1073	-11.5	31.6	
89R NCIC MA.5	6(C75×14E60×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4	E720	135/1373	168/1278	-19.8	65.2	
89Bz SWOG 8897	6(C100×14A30×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4	A360	182/6725	223/6687	-19.6	97.5	
Subtotal i			381/9229 (4.1%/y)	473/9038 (5.2%/y)	-50.9	194.3	0.77 (SE 0.06) reduction 2p = 0.0003
ii. Cumulative anthracycline dosage A300 or E400-480							
86S GOCCNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E480	47/363	54/334	-3.7	20.6	
97G FM Italy GMB1	4E120; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E480	36/940	45/925	-3.2	18.8	
90Z GOIRC SANG 2 Italy	16(E30)q1 vs 6(C600×2M40×2F600×2)q4	E480	47/688	51/740	-1.2	21.2	
84K1 GUN-3 Naples	3(CMFq4; [E75×2V1.4×2]q3) vs 6(C100×14M40×2F600×2)q4	E450	57/320	60/360	3.6	21.4	
96N GOCSI MAM2 Italy	4E110; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E440	91/2019	85/2030	1.9	40.2	
96A NEAT, UK	4E100; 4CMFq4 vs 6(C100×14M40×2F600×2)q4	E400	188/3481	225/3316	-20.6	91.8	
97U1+2 IBIS 03 Italy *	4E100; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E400	76/1682	2(38/795)	-0.5	23.0	
91Q GOCSI MAM1 Italy	4A75; 6CMFq4 vs 6(C100×14M40×2F600×2)q4	A300	66/701	73/702	-0.3	25.8	
Subtotal ii			608/10194 (6.0%/y)	669/9997 (6.7%/y)	-24.0	262.7	
iii. Cumulative anthracycline dosage A240							
84B1 NSABP B-15	4A60C600 vs 6(C100×14M40×2F600×2)q4	A240	350/2843	347/2799	0.4	146.4	
84B2 NSABP B-15	4(A60C600)q3; 3CMFq4 vs 6(C100×14M40×2F600×2)q4	A240	326/2907	347/2799	-13.3	141.7	
91H NSABP B-23	4A60C600 vs 6(C100×14M40×2F600×2)q4	A240	144/4524	136/4492	4.2	67.3	
Subtotal iii			820/10274 (8.0%/y)	830/10090 (8.2%/y)	-8.7	355.5	0.98 (SE 0.05) reduction 2p > 0.1; NS
Subtotal (i + ii + iii)			1809/29697 (6.1%/y)	1972/29125 (6.8%/y)	-83.6	812.5	0.90 (SE 0.03) reduction 2p = 0.003
Trend between 3 subtotals: $\chi^2_1 = 6.7$; $2p = 0.010$							
(b) Anthracycline dose/cycle < A60 or E90							
78L2 ONCOFRANCE	12(F400×4A30C300×4V1)q4 vs 12(C100×14M40×2F600×2)q4	A360¶	48/537	54/385	-11.5	21.4	
88R Brussels Belgium	8E60C500 vs 6(C100×14M40×2F600×2)q4	E480¶	94/1064	82/1073	4.4	35.7	
94J1+2+3 GOIRC SANG 2B R1	6(C§M§F§V1.4E40×2)q4 vs 6(C600×2M40×2F600×2)q4	E480¶	40/1105	38/1092	0.0	17.6	
84L ICCG C/2/84 UK	8(FE50C)q4 vs 8(C600×2M40×2F600×2)q4	E400¶	136/1465	142/1403	-7.0	61.3	
80C1 SE Sweden BCG A	8A40C200×4 vs 8(C100×14M40×2F600×2)q4	A320¶	7/77	8/79	0.6	2.2	
84N ICCG C/6/89 UK	6FE50Cq4 vs 6(C600×2M40×2F600×2)q4	E300¶	73/1946	65/1989	3.6	32.8	
(b) subtotal			398/6194 (6.4%/y)	389/6021 (6.5%/y)	-10.0	170.9	
Total (a + b)			2207/35891 (6.1%/y)	2361/35146 (6.7%/y)	-93.6	983.5	0.909 (SE 0.030) reduction 2p = 0.003

■ 99% or ◊ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 7.4$; $p = 0.06$

Heterogeneity within subtotals: $\chi^2_{16} = 13.9$; $p > 0.1$; NS

Heterogeneity between 20 trials: $\chi^2_{19} = 21.3$; $p > 0.1$; NS

* 97U was (4E; 4CMF) vs (4CMF; 4E) vs (6CMF), and its controls count twice in subtotal and in total of events/woman-years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

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

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

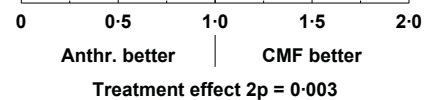
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence

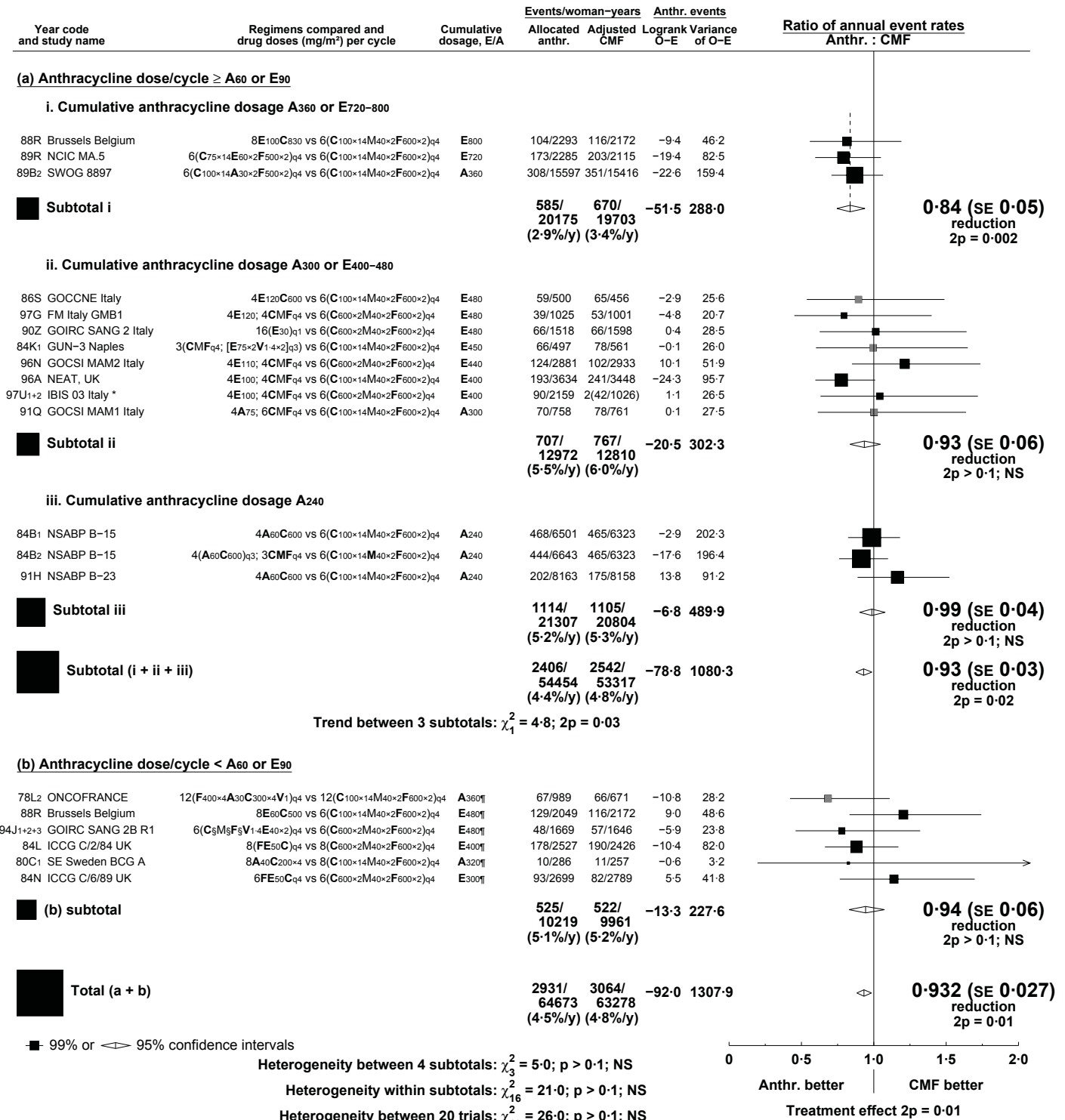
×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than E90 or A60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted C, M or F respectively on cycles (3, 2 or 1) and (6, 5 or 4)



P 28: RECURRENCE in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 5.0$; p > 0.1; NS

Heterogeneity within subtotals: $\chi^2_{16} = 21.0$; p > 0.1; NS

Heterogeneity between 20 trials: $\chi^2_{19} = 26.0$; p > 0.1; NS

* 97U was (4E; 4CMF) vs (4CMF; 4E) vs (6CMF), and its controls count twice in subtotal and in total of events/woman-years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

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

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

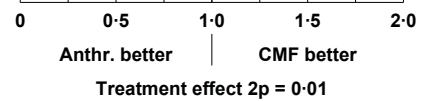
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence

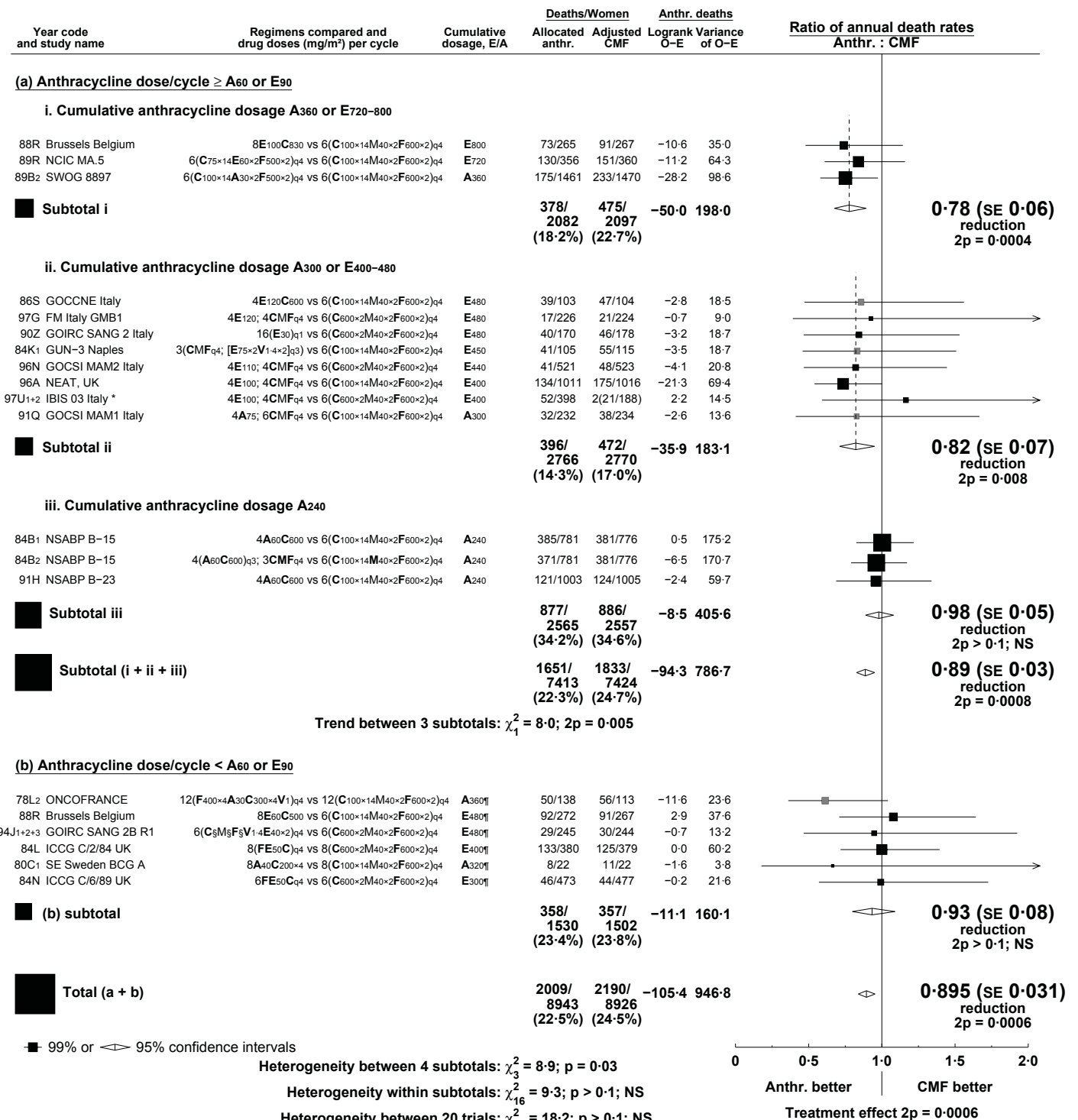
×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than E90 or A60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted C, M or F respectively on cycles (3, 2 or 1) and (6, 5 or 4)



P 29: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 8.9$; p = 0.03

Heterogeneity within subtotals: $\chi^2_{16} = 9.3$; p > 0.1; NS

Heterogeneity between 20 trials: $\chi^2_{19} = 18.2$; p > 0.1; NS

* 97U was (4E; 4CMF) vs (4CMF; 4E) vs (6CMF), and its controls count twice in subtotal and in total of deaths/women; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

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

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

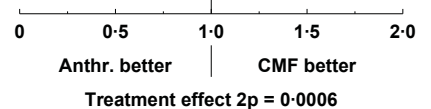
(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon ; indicates treatment sequence

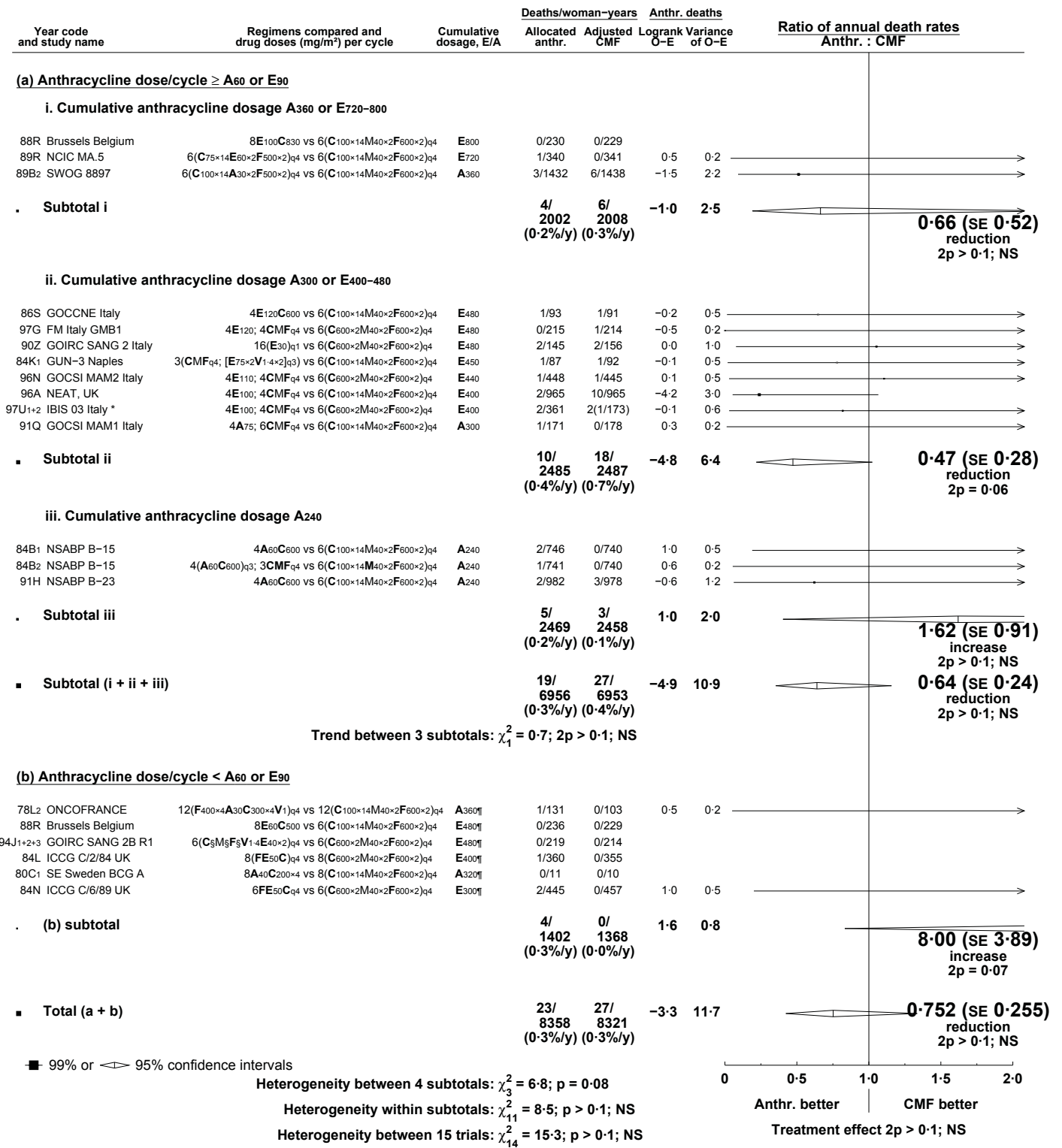
×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than E90 or A60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted C, M or F respectively on cycles (3, 2 or 1) and (6, 5 or 4)



P 30: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



* 97U was (4E; 4CMF) vs (4CMF; 4E) vs (6CMF), and its controls count twice in subtotal and in total of deaths/woman-years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

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

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

(Not shown: antibiotic, hormonal, local or steroid therapies)

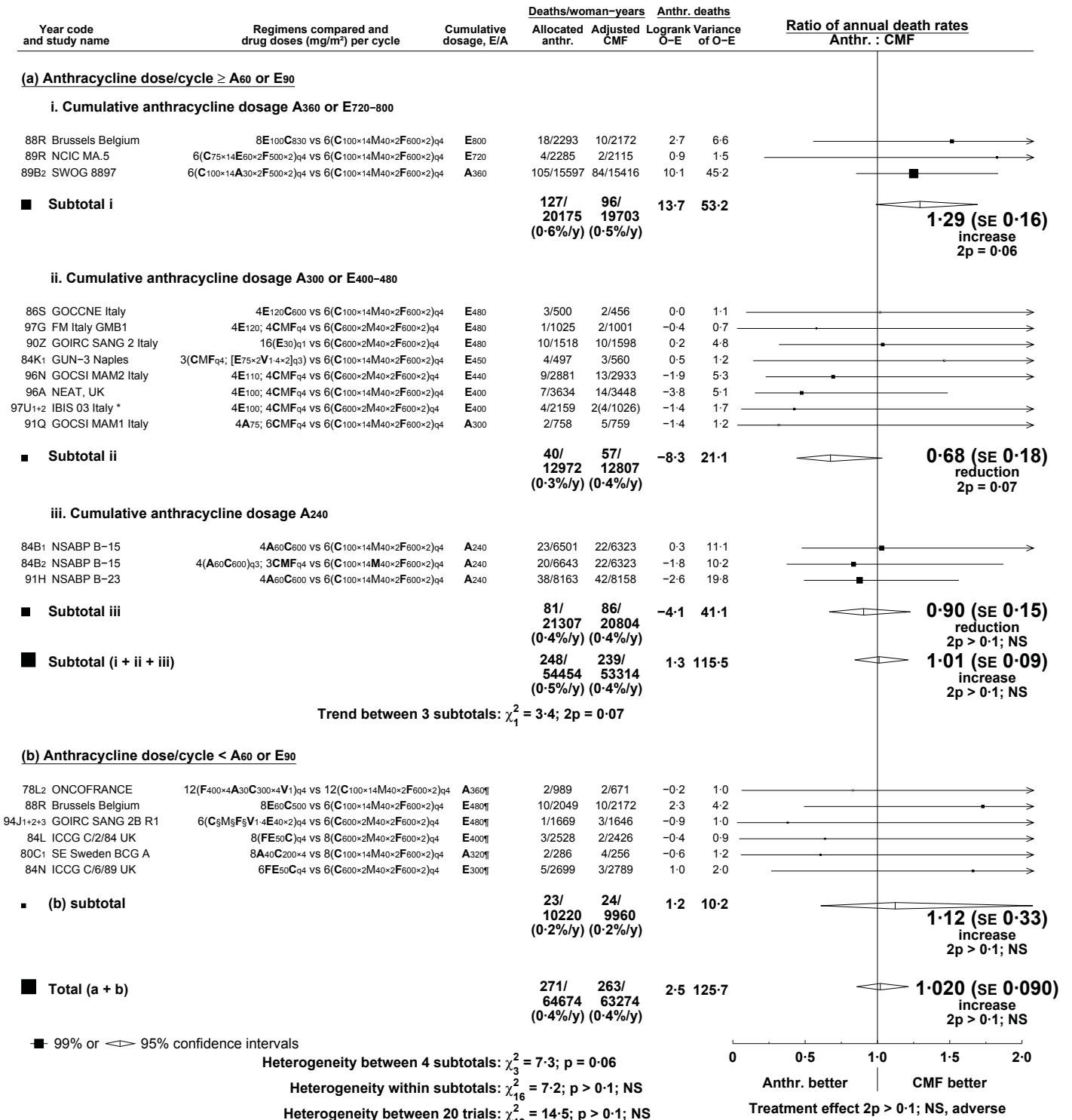
All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence

×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than E90 or A60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted C, M or F respectively on cycles (3, 2 or 1) and (6, 5 or 4)

P 31: MORTALITY WITHOUT RECURRENCE in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 7.3$; $p = 0.06$

Heterogeneity within subtotals: $\chi^2_{16} = 7.2$; $p > 0.1$; NS

Heterogeneity between 20 trials: $\chi^2_{19} = 14.5$; $p > 0.1$; NS

* 97U was (4E; 4CMF) vs (4CMF; 4E) vs (6CMF), and its controls count twice in subtotal and in total of deaths/woman-years; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

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

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

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence

×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than E90 or A60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted C, M or F respectively on cycles (3, 2 or 1) and (6, 5 or 4)

0 0.5 1.0 1.5 2.0
Anthr. better | CMF better
Treatment effect $2p > 0.1$; NS, adverse

P 32: OVERALL MORTALITY in trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF)

Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosage, E/A	Deaths/Women		Anthr. deaths		Ratio of annual death rates Anthr. : CMF
			Allocated anthr.	Adjusted CMF	Logrank O-E	Variance of O-E	
(a) Anthracycline dose/cycle ≥ A60 or E90							
i. Cumulative anthracycline dosage A360 or E720-800							
88R Brussels Belgium	8E100C830 vs 6(C100×14M40×2F600×2)q4	E800	91/265	101/267	-7.8	41.6	
89R NCIC MA.5	6(C75×14E60×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4	E720	134/356	153/360	-10.3	65.8	
89B2 SWOG 8897	6(C100×14A30×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4	A360	280/1461	317/1470	-18.1	143.7	
Subtotal i			505/2082 (24.3%)	571/2097 (27.2%)	-36.2	251.2	0.87 (SE 0.06) reduction 2p = 0.02
ii. Cumulative anthracycline dosage A300 or E400-480							
86S GOCCNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E480	42/103	49/104	-2.8	19.6	
97G FM Italy GMB1	4E120; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E480	18/226	23/224	-1.1	9.7	
90Z GOIRC SANG 2 Italy	16(E30)q1 vs 6(C600×2M40×2F600×2)q4	E480	50/170	56/178	-3.0	23.5	
84K1 GUN-3 Naples	3(CMFq4; [E75×2V1.4×2]q3) vs 6(C100×14M40×2F600×2)q4	E450	45/105	58/115	-3.0	19.9	
96N GOCSI MAM2 Italy	4E110; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E440	50/521	61/523	-6.0	26.1	
96A NEAT, UK	4E100; 4CMFq4 vs 6(C100×14M40×2F600×2)q4	E400	141/1011	189/1016	-25.1	74.5	
97U1+2 IBIS 03 Italy *	4E100; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E400	56/398	2(25/188)	0.8	16.1	
91Q GOCSI MAM1 Italy	4A75; 6CMFq4 vs 6(C100×14M40×2F600×2)q4	A300	34/232	43/234	-4.0	14.8	
Subtotal ii			436/2766 (15.8%)	529/2770 (19.1%)	-44.2	204.3	0.81 (SE 0.06) reduction 2p = 0.002
iii. Cumulative anthracycline dosage A240							
84B1 NSABP B-15	4A60C600 vs 6(C100×14M40×2F600×2)q4	A240	408/781	403/776	0.8	186.4	
84B2 NSABP B-15	4(A60C600)q3; 3CMFq4 vs 6(C100×14M40×2F600×2)q4	A240	391/781	403/776	-8.4	180.8	
91H NSABP B-23	4A60C600 vs 6(C100×14M40×2F600×2)q4	A240	159/1003	166/1005	-5.1	79.5	
Subtotal iii			958/2565 (37.3%)	972/2557 (38.0%)	-12.6	446.7	0.97 (SE 0.05) reduction 2p > 0.1; NS
Subtotal (i + ii + iii)			1899/7413 (25.6%)	2072/7424 (27.9%)	-93.1	902.1	0.90 (SE 0.03) reduction 2p = 0.002
Trend between 3 subtotals: $\chi^2_1 = 2.9$; 2p = 0.09							
(b) Anthracycline dose/cycle < A60 or E90							
78L2 ONCOFRANCE	12(F400×4A30C300×4V1)q4 vs 12(C100×14M40×2F600×2)q4	A360¶	52/138	58/113	-11.7	24.6	
88R Brussels Belgium	8E60C600 vs 6(C100×14M40×2F600×2)q4	E480¶	102/272	101/267	5.1	41.9	
94J1+2+3 GOIRC SANG 2B R1	6(C5M5F5V1.4E40×2)q4 vs 6(C600×2M40×2F600×2)q4	E480¶	30/245	33/244	-1.7	14.1	
84L ICCG C/2/84 UK	8(FE50C)q4 vs 8(C600×2M40×2F600×2)q4	E400¶	136/380	127/379	-0.4	61.1	
80C1 SE Sweden BCG A	8A40C200×4 vs 8(C100×14M40×2F600×2)q4	A320¶	10/22	15/22	-2.1	5.0	
84N ICCG C/6/89 UK	6FE50Cq4 vs 6(C600×2M40×2F600×2)q4	E300¶	51/473	47/477	0.8	23.6	
(b) subtotal			381/1530 (24.9%)	381/1502 (25.4%)	-10.0	170.3	
Total (a + b)			2280/8943 (25.5%)	2453/8926 (27.5%)	-103.0	1072.4	0.908 (SE 0.029) reduction 2p = 0.002

■ 99% or ◊ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 5.8$; p > 0.1; NS

Heterogeneity within subtotals: $\chi^2_{16} = 10.0$; p > 0.1; NS

Heterogeneity between 20 trials: $\chi^2_{19} = 15.9$; p > 0.1; NS

* 97U was (4E; 4CMF) vs (4CMF; 4E) vs (6CMF), and its controls count twice in subtotal and in total of deaths/women; the study included women with highly proliferative disease, and slightly updated results from it have recently been published (webappendix p66)

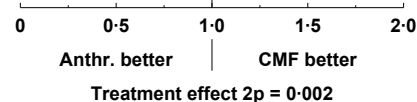
Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; V = vincristine (Not shown: antibiotic, hormonal, local or steroid therapies)

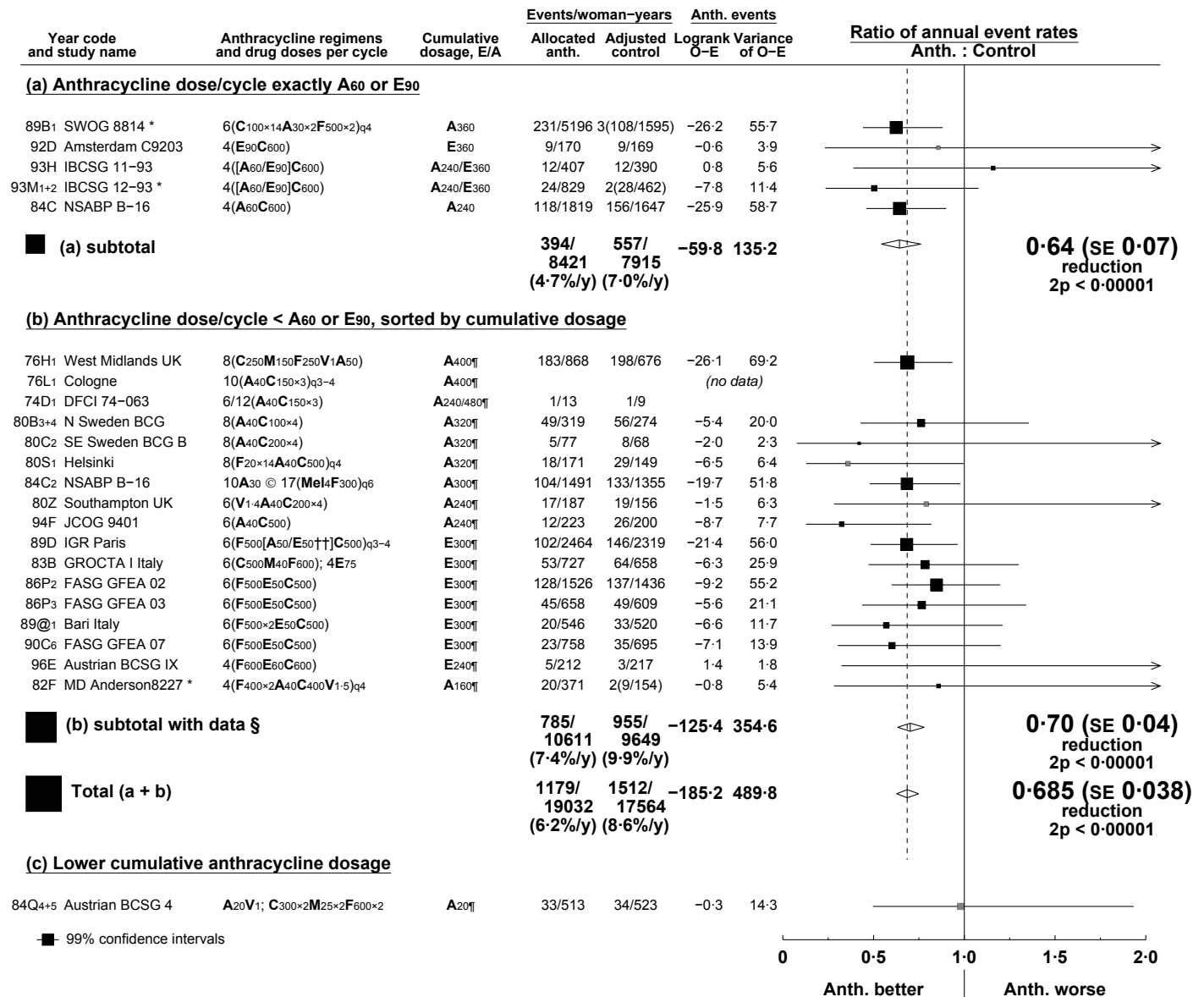
All regimens q3week (unless specified as q4). Semicolon ; indicates treatment sequence ×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than E90 or A60 per cycle of anthracycline

§ 94J interwoven drug schedule: anthracycline group omitted C, M or F respectively on cycles (3, 2 or 1) and (6, 5 or 4)



P 33: EARLY RECURRENCE (first 5 years) in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

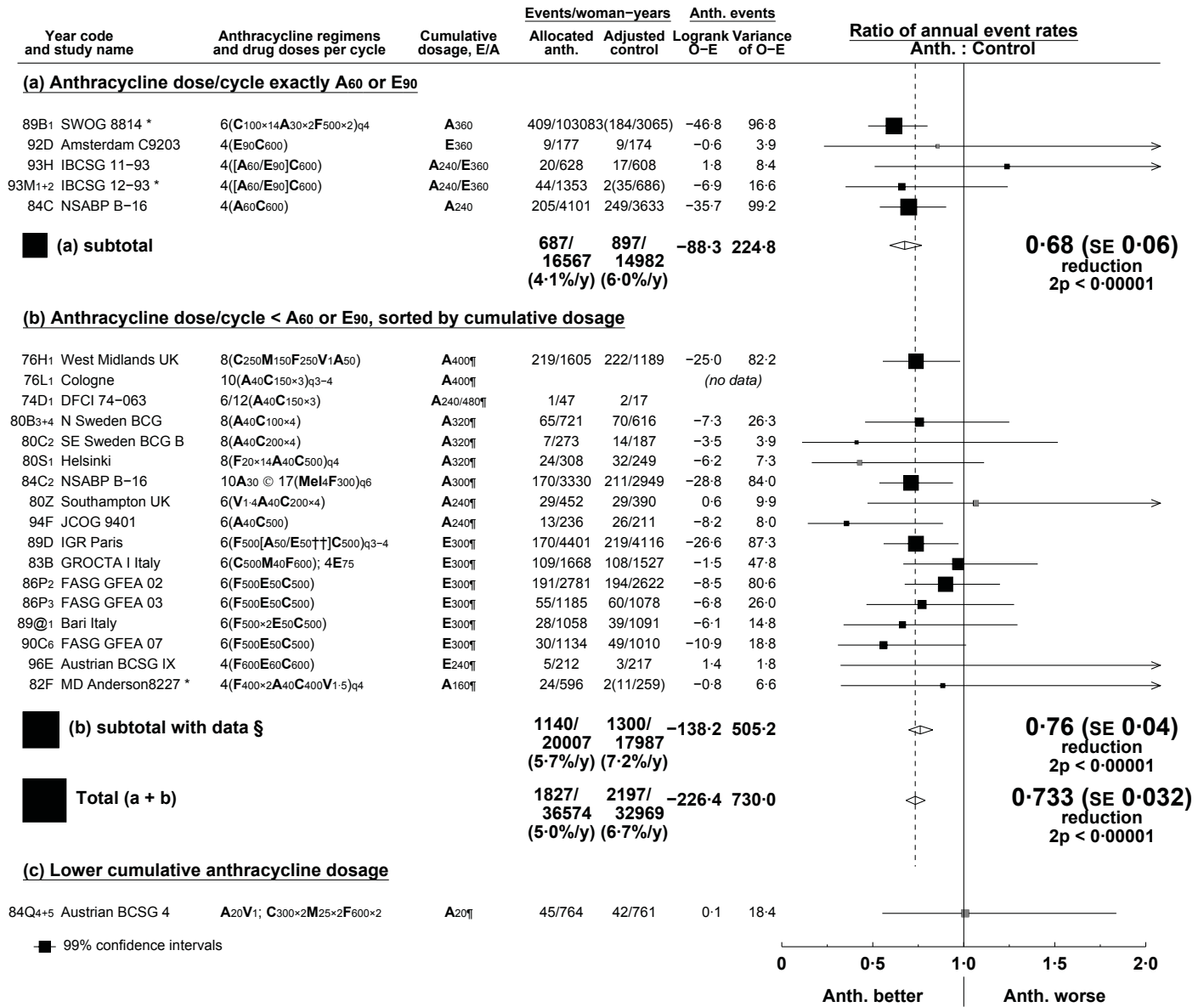
All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

P 34: RECURRENCE in trials of any anthracycline-based regimen vs. No chemotherapy



■ 99% confidence intervals

§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

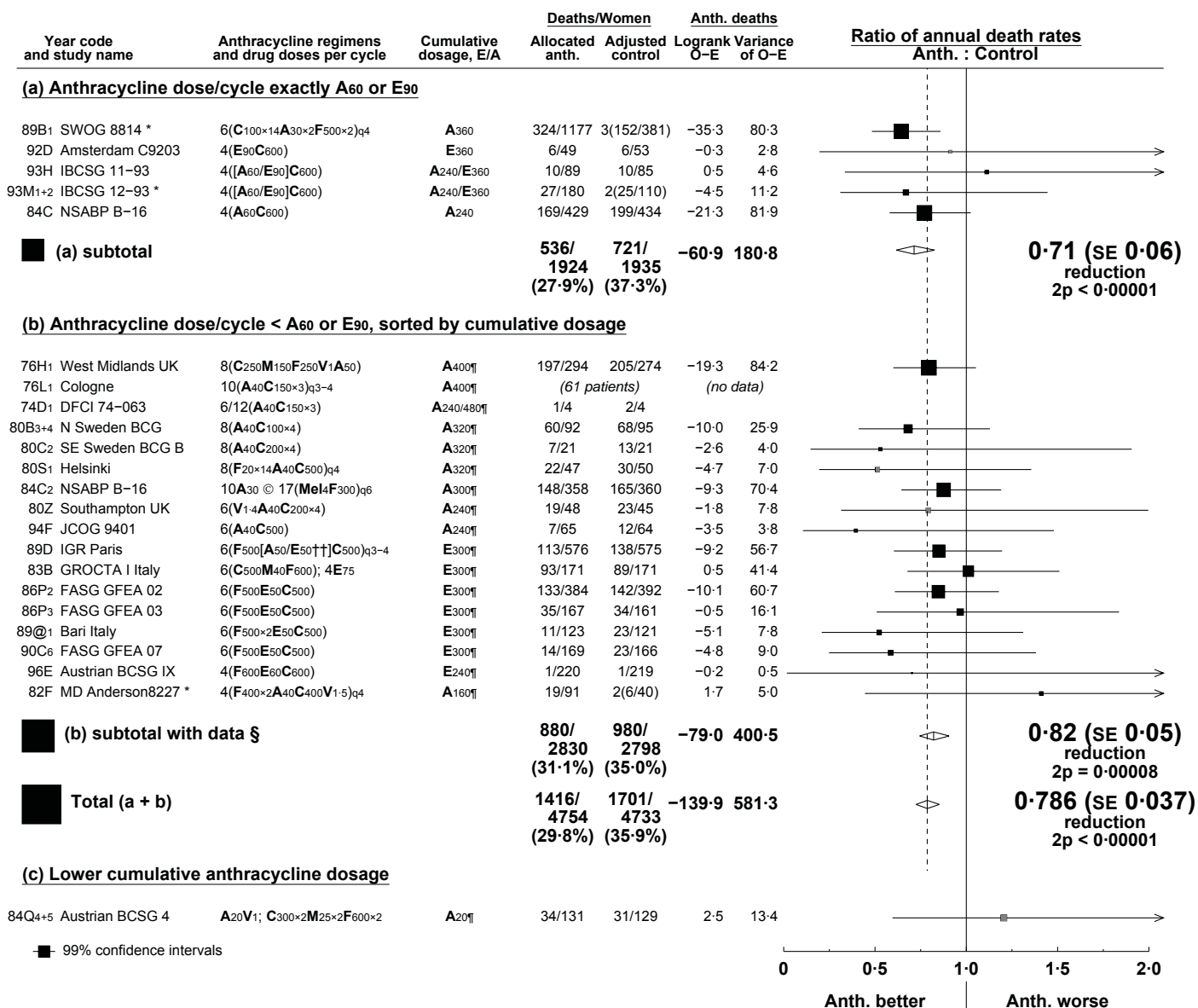
All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

P 35: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

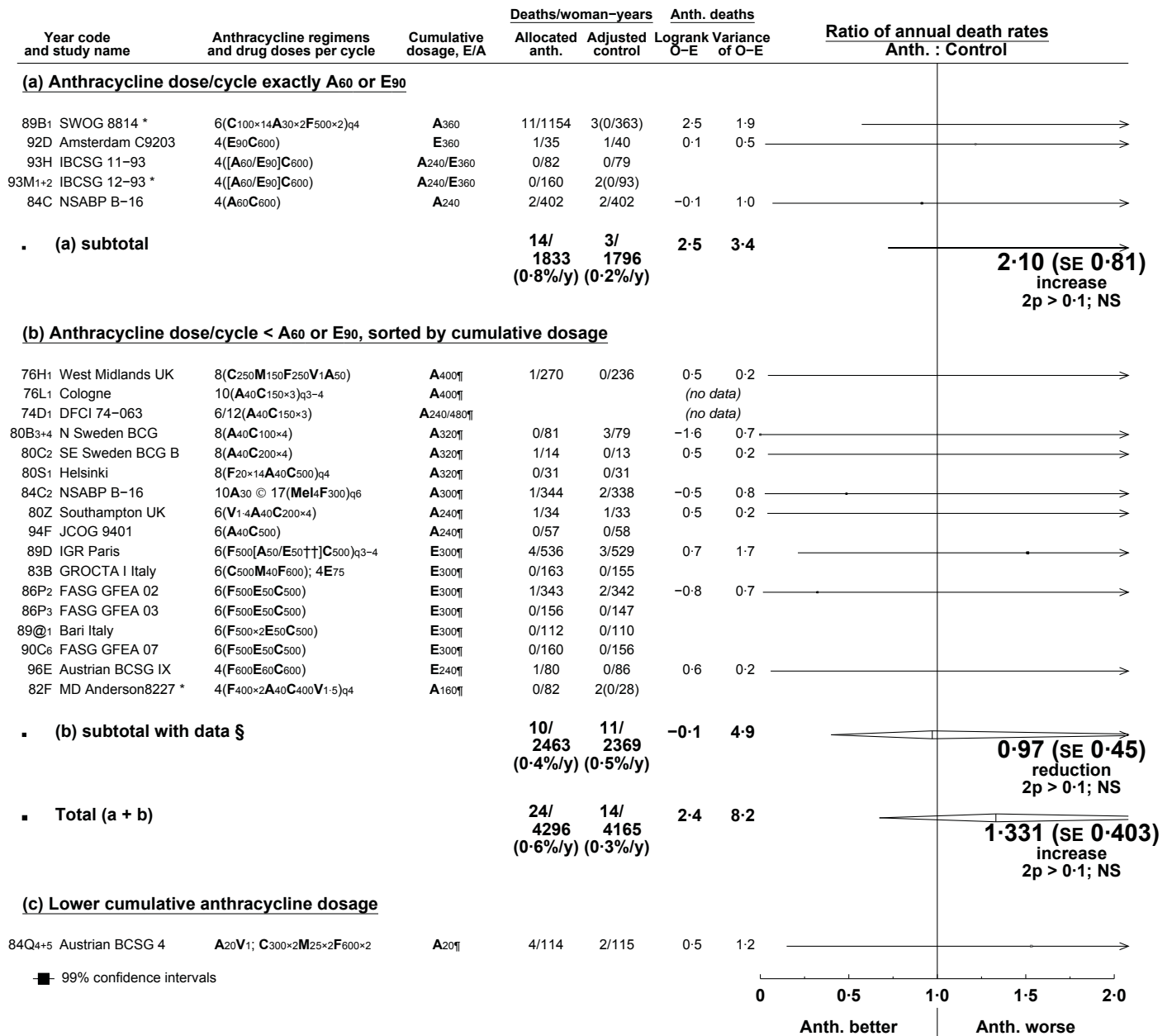
All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

P 36: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of any anthracycline-based regimen vs. No chemotherapy



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

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

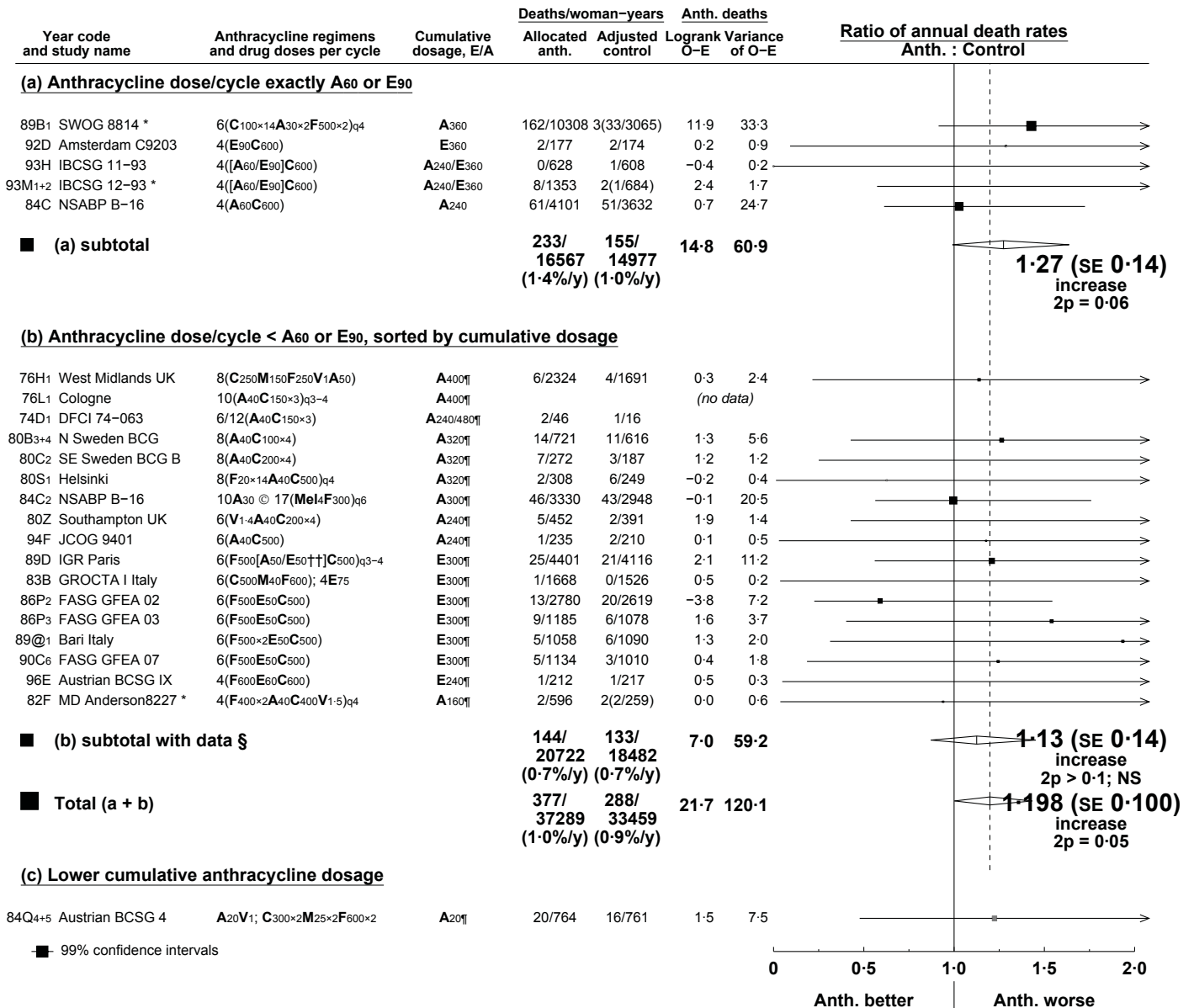
All regimens q3week (unless specified as q4). Semicolon [;] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

P 37: MORTALITY WITHOUT RECURRENCE in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

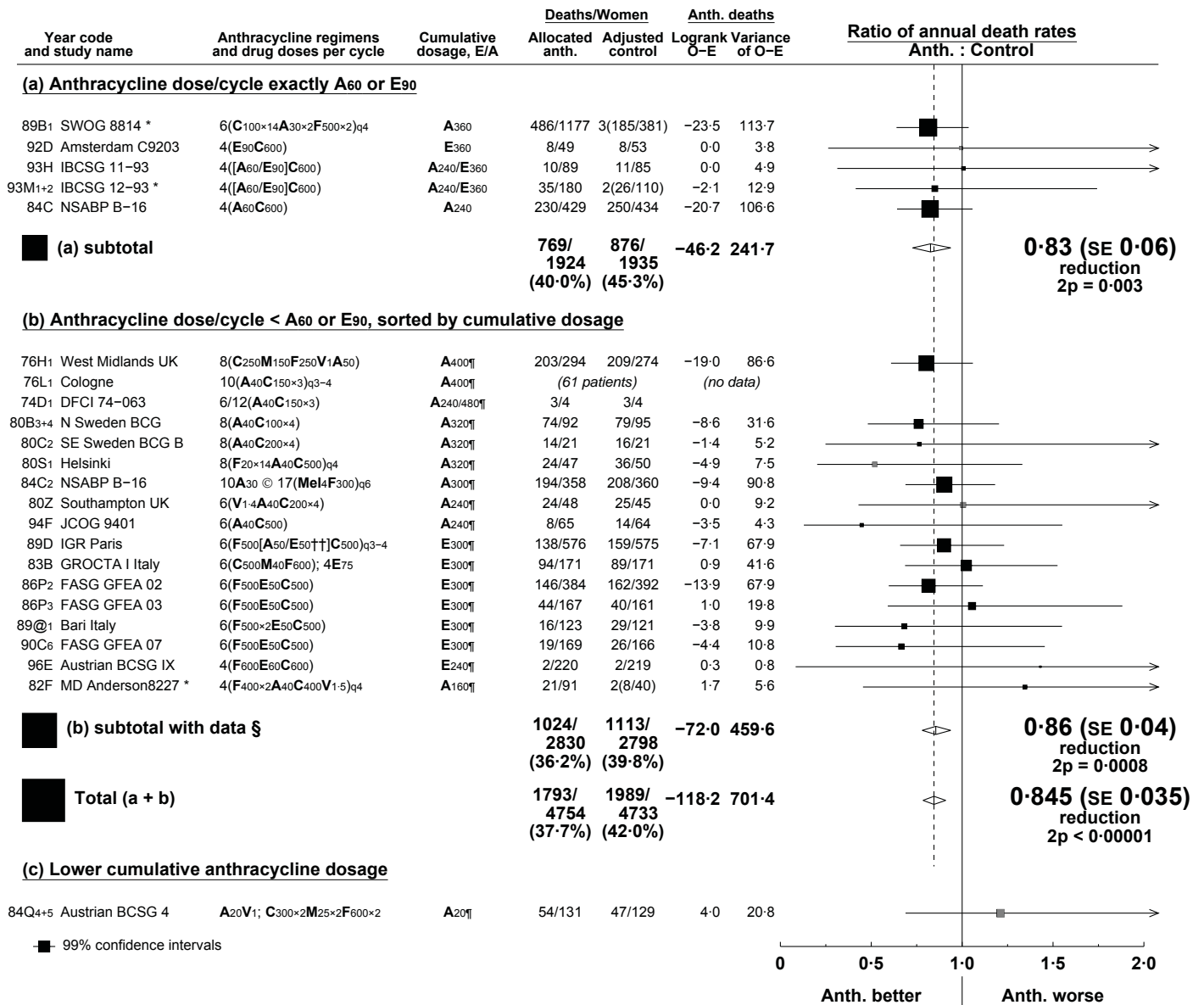
All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence, © indicates concurrent regimens

x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

P 38: OVERALL MORTALITY in trials of any anthracycline-based regimen vs. No chemotherapy



§ 1 trial with no data does not contribute to subtotals or to the overall total.

* For balance, subtotals and totals count control patients 2 or 3 times in trials with 2 or 3 times as many allocated chemotherapy; logrank statistics are unaffected.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

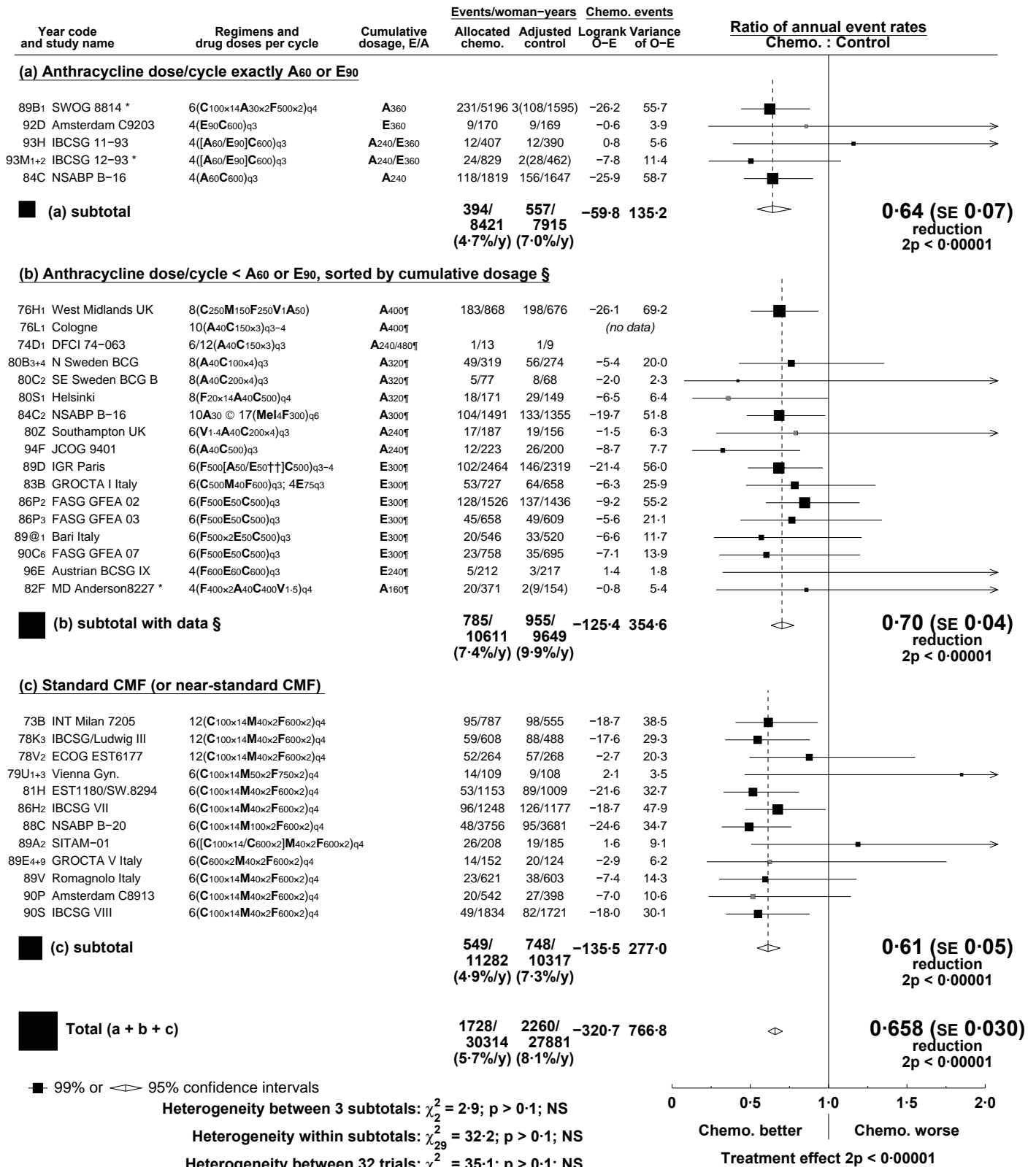
All regimens q3week (unless specified as q4). Semicolon [:] indicates treatment sequence, © indicates concurrent regimens

×2 means d1,8 iv; ×4 means d3-6 iv

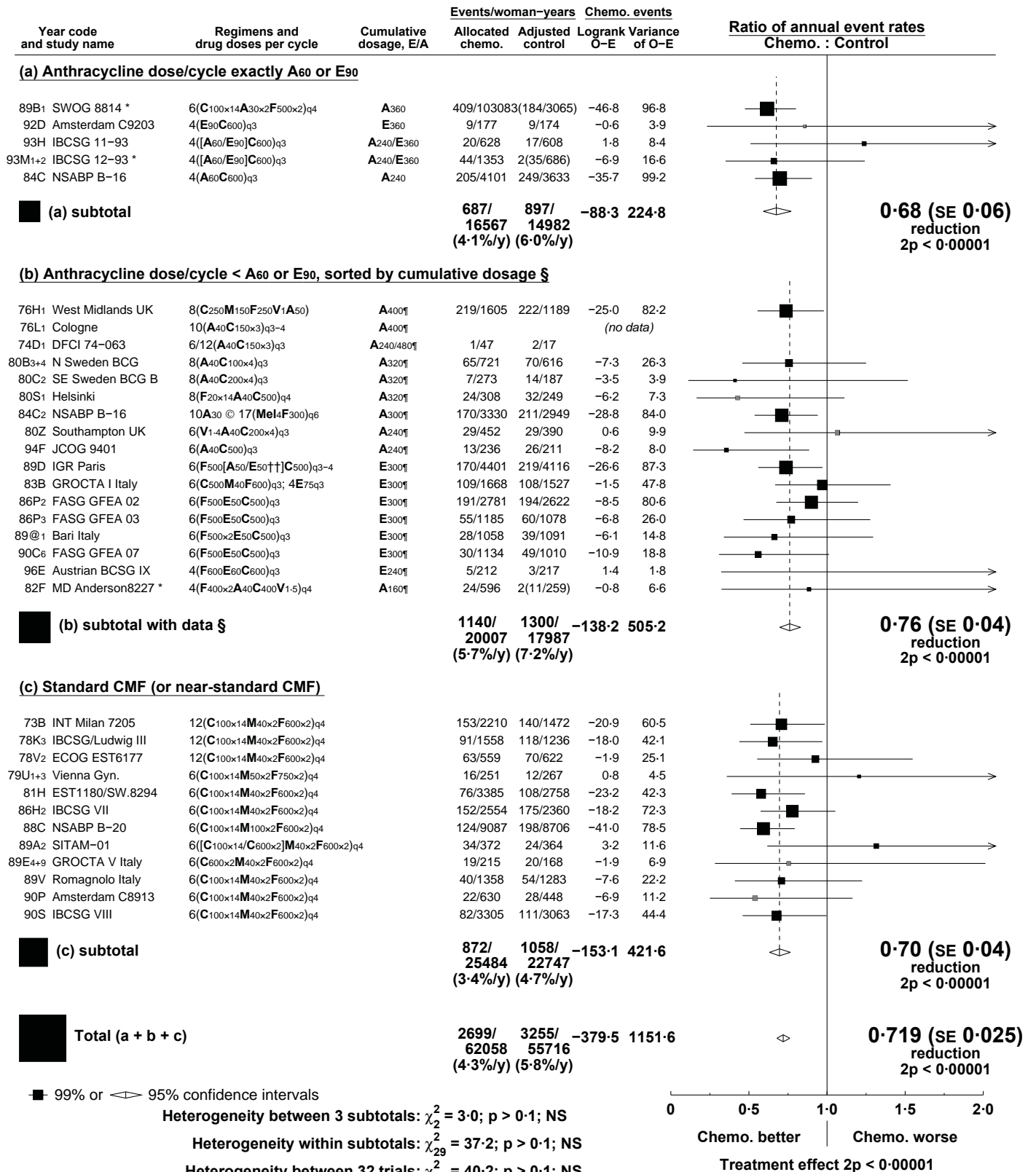
¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

P 39: EARLY RECURRENCE (first 5 years) in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy



P 40: RECURRENCE in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 3.0$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{29} = 37.2$; $p > 0.1$; NS

Heterogeneity between 32 trials: $\chi^2_{31} = 40.2$; $p > 0.1$; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

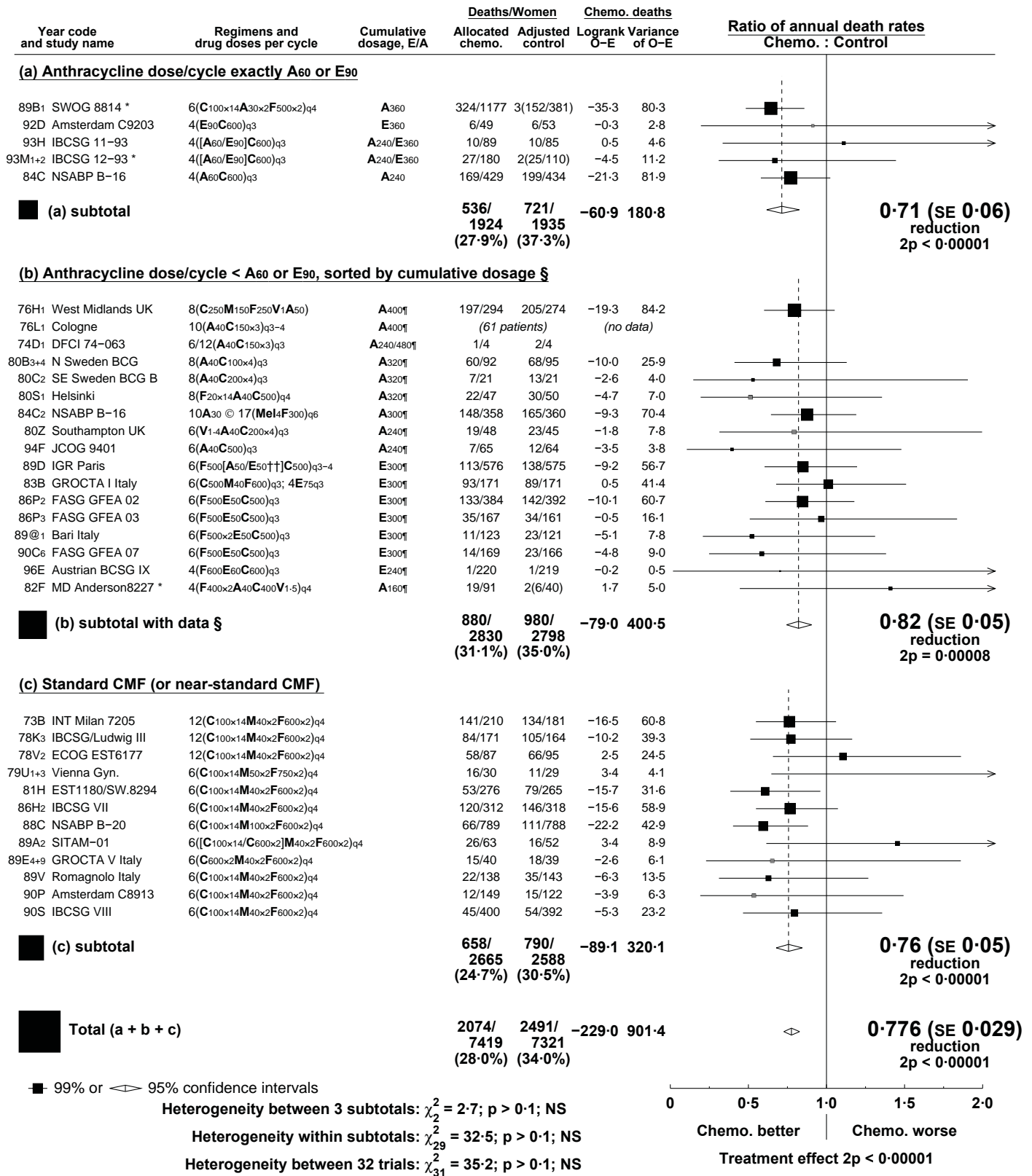
×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

0 0.5 1.0 1.5 2.0
Chemo. better | Chemo. worse
Treatment effect 2p < 0.00001

P 41: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 2.7$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{29} = 32.5$; $p > 0.1$; NS

Heterogeneity between 32 trials: $\chi^2_{31} = 35.2$; $p > 0.1$; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

P 42: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy

Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Deaths/woman-years		Chemo. deaths		Ratio of annual death rates Chemo. : Control	
			Allocated chemo.	Adjusted control	Logrank O-E	Variance of O-E		
(a) Anthracycline dose/cycle exactly A60 or E90								
89B1 SWOG 8814 *	6(C100x14A30x2F500x2)q4	A360	11/1154	3(0/363)	2.5	1.9		
92D Amsterdam C9203	4(E90C600)q3	E360	1/35	1/40	0.1	0.5		
93H IBCSG 11-93	4((A60/E90)C600)q3	A240/E360	0/82	0/79				
93M1+2 IBCSG 12-93 *	4((A60/E90)C600)q3	A240/E360	0/160	2(0/93)				
84C NSABP B-16	4(A60C600)q3	A240	2/402	2/402	-0.1	1.0		
(a) subtotal			14/ 1833 (0.8%/y)	3/ 1796 (0.2%/y)	2.5	3.4	2.10 (SE 0.81) increase 2p > 0.1; NS	
(b) Anthracycline dose/cycle < A60 or E90, sorted by cumulative dosage §								
76H1 West Midlands UK	8(C250M150F250V1A50)	A400¶	1/270	0/236	0.5	0.2		
76L1 Cologne	10(A40C150x3)q3-4	A400¶			(no data)			
74D1 DFCl 74-063	6/12(A40C150x3)q3	A240/480¶			(no data)			
80B3+4 N Sweden BCG	8(A40C100x4)q3	A320¶	0/81	3/79	-1.6	0.7		
80C2 SE Sweden BCG B	8(A40C200x4)q3	A320¶	1/14	0/13	0.5	0.2		
80S1 Helsinki	8(F20x14A40C500)q4	A320¶	0/31	0/31				
84C2 NSABP B-16	10A30 © 17(Mel4F300)q6	A300¶	1/344	2/338	-0.5	0.8		
80Z Southampton UK	6(V1-4A40C200x4)q3	A240¶	1/34	1/33	0.5	0.2		
94F JCOG 9401	6(A40C500)q3	A240¶	0/57	0/58				
89D IGR Paris	6(F500[A50/E50†]C500)q3-4	E300¶	4/536	3/529	0.7	1.7		
83B GROCTA I Italy	6(C500M40F600)q3; 4E75q3	E300¶	0/163	0/155				
86P2 FASG GFEA 02	6(F500E50C500)q3	E300¶	1/343	2/342	-0.8	0.7		
86P3 FASG GFEA 03	6(F500E50C500)q3	E300¶	0/156	0/147				
89@1 Bari Italy	6(F500x2E50C500)q3	E300¶	0/112	0/110				
90C6 FASG GFEA 07	6(F500E50C500)q3	E300¶	0/160	0/156				
96E Austrian BCSG IX	4(F600E60C600)q3	E240¶	1/80	0/86	0.6	0.2		
82F MD Anderson8227 *	4(F400x2A40C400V1.5)q4	A160¶	0/82	2(0/28)				
(b) subtotal with data §			10/ 2463 (0.4%/y)	11/ 2369 (0.5%/y)	-0.1	4.9	0.97 (SE 0.45) reduction 2p > 0.1; NS	
(c) Standard CMF (or near-standard CMF)								
73B INT Milan 7205	12(C100x14M40x2F600x2)q4		1/198	1/160	-0.1	0.5		
78K3 IBCSG/Ludwig III	12(C100x14M40x2F600x2)q4		6/148	1/138	2.5	1.7		
78V2 ECOG EST6177	12(C100x14M40x2F600x2)q4		1/78	0/77	0.5	0.2		
79U1+3 Vienna Gyn.	6(C100x14M50x2F750x2)q4		0/18	0/19				
81H EST1180/SW.8294	6(C100x14M40x2F600x2)q4		3/258	1/248	0.9	1.0		
86H2 IBCSG VII	6(C100x14M40x2F600x2)q4		3/292	2/289	0.7	1.2		
88C NSABP B-20	6(C100x14M100x2F600x2)q4		1/774	0/777	0.5	0.2		
89A2 SITAM-01	6((C100x14/C600x2)M40x2F600x2)q4		0/45	0/39				
89E+9 GROCTA V Italy	6(C600x2M40x2F600x2)q4		0/32	0/28				
89V Romagnolo Italy	6(C100x14M40x2F600x2)q4		1/132	0/137	0.5	0.2		
90P Amsterdam C8913	6(C100x14M40x2F600x2)q4		0/141	0/112				
90S IBCSG VIII	6(C100x14M40x2F600x2)q4		0/377	0/371				
(c) subtotal			16/ 2493 (0.6%/y)	5/ 2395 (0.2%/y)	5.5	5.2	2.88 (SE 0.78) increase 2p = 0.02	
Total (a + b + c)			40/ 6789 (0.6%/y)	19/ 6560 (0.3%/y)	7.8	13.4	1.792 (SE 0.371) increase 2p = 0.03	

■ 99% or ◁ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 3.1$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{15} = 12.9$; $p > 0.1$; NS

Heterogeneity between 18 trials: $\chi^2_{17} = 16.0$; $p > 0.1$; NS

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

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

0 0.5 1.0 1.5 2.0
Chemo. better | Chemo. worse
Treatment effect 2p = 0.03, adverse

P 43: MORTALITY WITHOUT RECURRENCE in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy

Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Deaths/woman-years		Chemo. deaths		Ratio of annual death rates Chemo. : Control	
			Allocated chemo.	Adjusted control	Logrank O-E	Variance of O-E		
(a) Anthracycline dose/cycle exactly A60 or E90								
89B1 SWOG 8814 *	6(C100x14A30x2F500x2)q4	A360	162/10308	3(33/3065)	11.9	33.3		
92D Amsterdam C9203	4(E90C600)q3	E360	2/177	2/174	0.2	0.9		
93H IBCSG 11-93	4((A60/E90)C600)q3	A240/E360	0/628	1/608	-0.4	0.2		
93M1+2 IBCSG 12-93 *	4((A60/E90)C600)q3	A240/E360	8/1353	2(1/684)	2.4	1.7		
84C NSABP B-16	4(A60C600)q3	A240	61/4101	51/3632	0.7	24.7		
■ (a) subtotal			233/ 16567	155/ 14977	14.8	60.9	1.27 (SE 0.14) increase 2p = 0.06	
(b) Anthracycline dose/cycle < A60 or E90, sorted by cumulative dosage §								
76H1 West Midlands UK	8(C250M150F250V1A50)	A400¶	6/2324	4/1691	0.3	2.4		
76L1 Cologne	10(A40C150x3)q3-4	A400¶				(no data)		
74D1 DFCI 74-063	6/12(A40C150x3)q3	A240/480¶	2/46	1/16				
80B3+4 N Sweden BCG	8(A40C100x4)q3	A320¶	14/721	11/616	1.3	5.6		
80C2 SE Sweden BCG B	8(A40C200x4)q3	A320¶	7/272	3/187	1.2	1.2		
80S1 Helsinki	8(F20x14A40C500)q4	A320¶	2/308	6/249	-0.2	0.4		
84C2 NSABP B-16	10A30 @ 17(Mel4F300)q6	A300¶	46/3330	43/2948	-0.1	20.5		
80Z Southampton UK	6(V1.4A40C200x4)q3	A240¶	5/452	2/391	1.9	1.4		
94F JCOG 9401	6(A40C500)q3	A240¶	1/235	2/210	0.1	0.5		
89D IGR Paris	6(F500[A50/E50††]C500)q3-4	E300¶	25/4401	21/4116	2.1	11.2		
83B GROCTA I Italy	6(C500M40F600)q3; 4E75q3	E300¶	1/1668	0/1526	0.5	0.2		
86P2 FASG GFEA 02	6(F500E50C500)q3	E300¶	13/2780	20/2619	-3.8	7.2		
86P3 FASG GFEA 03	6(F500E50C500)q3	E300¶	9/1185	6/1078	1.6	3.7		
89@1 Bari Italy	6(F500x2E50C500)q3	E300¶	5/1058	6/1090	1.3	2.0		
90C6 FASG GFEA 07	6(F500E50C500)q3	E300¶	5/1134	3/1010	0.4	1.8		
96E Austrian BCSG IX	4(F600E60C600)q3	E240¶	1/212	1/217	0.5	0.3		
82F MD Anderson8227 *	4(F400x2A40C400V1.5)q4	A160¶	2/596	2(2/259)	0.0	0.6		
■ (b) subtotal with data §			144/ 20722	133/ 18482	7.0	59.2		1.13 (SE 0.14) increase 2p > 0.1; NS
(c) Standard CMF (or near-standard CMF)								
73B INT Milan 7205	12(C100x14M40x2F600x2)q4		24/2210	19/1472	0.7	8.2		
78K3 IBCSG/Ludwig III	12(C100x14M40x2F600x2)q4		37/1558	20/1235	4.0	11.6		
78V2 ECOG EST6177	12(C100x14M40x2F600x2)q4		8/559	7/622	1.8	3.0		
79U1+3 Vienna Gyn.	6(C100x14M50x2F750x2)q4		4/250	10/266	0.7	1.0		
81H EST1180/SW.8294	6(C100x14M40x2F600x2)q4		31/3385	25/2758	0.7	12.5		
86H2 IBCSG VII	6(C100x14M40x2F600x2)q4		40/2554	28/2359	5.9	16.0		
88C NSABP B-20	6(C100x14M100x2F600x2)q4		54/9087	51/8706	2.1	25.9		
89A2 SITAM-01	6((C100x14/C600x2)M40x2F600x2)q4		5/370	3/364	-0.2	1.3		
89E4+9 GROCTA V Italy	6(C600x2M40x2F600x2)q4		0/215	1/167	-0.6	0.2		
89V Romagnolo Italy	6(C100x14M40x2F600x2)q4		8/1358	4/1283	1.8	2.9		
90P Amsterdam C8913	6(C100x14M40x2F600x2)q4		0/630	0/448				
90S IBCSG VIII	6(C100x14M40x2F600x2)q4		4/3305	2/3063	1.4	1.4		
■ (c) subtotal			215/ 25481	170/ 22743	18.1	84.0	1.24 (SE 0.12) increase 2p = 0.05	
■ Total (a + b + c)			592/ 62770	458/ 56202	39.9	204.1	1.216 (SE 0.077) increase 2p = 0.005	

■ 99% or ◁ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 0.5$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{28} = 19.1$; $p > 0.1$; NS

Heterogeneity between 31 trials: $\chi^2_{30} = 19.7$; $p > 0.1$; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than A60 or E90 per cycle

††91% given E, 9% given A

0 0.5 1.0 1.5 2.0
Chemo. better | Chemo. worse
Treatment effect 2p = 0.005, adverse

P 44: OVERALL MORTALITY in trials of anthracycline-based regimen (eg, standard 4AC) or standard CMF (or near-standard CMF) vs. No chemotherapy

Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Deaths/Women		Chemo. deaths		Ratio of annual death rates Chemo. : Control	
			Allocated chemo.	Adjusted control	Logrank O-E	Variance of O-E		
(a) Anthracycline dose/cycle exactly A60 or E90								
89B1 SWOG 8814 *	6(C100x14A30x2F500x2)q4	A360	486/1177	3(185/381)	-23.5	113.7		
92D Amsterdam C9203	4(E90C600)q3	E360	8/49	8/53	0.0	3.8		
93H IBCSG 11-93	4((A60/E90)C600)q3	A240/E360	10/89	11/85	0.0	4.9		
93M1+2 IBCSG 12-93 *	4((A60/E90)C600)q3	A240/E360	35/180	2(26/110)	-2.1	12.9		
84C NSABP B-16	4(A60C600)q3	A240	230/429	250/434	-20.7	106.6		
(a) subtotal			769/ 1924 (40.0%)	876/ 1935 (45.3%)	-46.2	241.7	0.83 (SE 0.06) reduction 2p = 0.003	
(b) Anthracycline dose/cycle < A60 or E90, sorted by cumulative dosage §								
76H1 West Midlands UK	8(C250M150F250V1A50)	A400†	203/294	209/274	-19.0	86.6		
76L1 Cologne	10(A40C150x3)q3-4	A400†	(61 patients)		(no data)			
74D1 DFCl 74-063	6/12(A40C150x3)q3	A240/480†	3/4	3/4				
80B3+4 N Sweden BCG	8(A40C100x4)q3	A320†	74/92	79/95	-8.6	31.6		
80C2 SE Sweden BCG B	8(A40C200x4)q3	A320†	14/21	16/21	-1.4	5.2		
80S1 Helsinki	8(F20x14A40C500)q4	A320†	24/47	36/50	-4.9	7.5		
84C2 NSABP B-16	10(A30 @ 17(Mel4F300)q6	A300†	194/358	208/360	-9.4	90.8		
80Z Southampton UK	6(V1.4A40C200x4)q3	A240†	24/48	25/45	0.0	9.2		
94F JCOG 9401	6(A40C500)q3	A240†	8/65	14/64	-3.5	4.3		
89D IGR Paris	6(F500[A50/E50††]C500)q3-4	E300†	138/576	159/575	-7.1	67.9		
83B GROCTA I Italy	6(C500M40F600)q3; 4E75q3	E300†	94/171	89/171	0.9	41.6		
86P2 FASG GFEA 02	6(F500E50C500)q3	E300†	146/384	162/392	-13.9	67.9		
86P3 FASG GFEA 03	6(F500E50C500)q3	E300†	44/167	40/161	1.0	19.8		
89@1 Bari Italy	6(F500x2E50C500)q3	E300†	16/123	29/121	-3.8	9.9		
90C6 FASG GFEA 07	6(F500E50C500)q3	E300†	19/169	26/166	-4.4	10.8		
96E Austrian BCSG IX	4(F600E60C600)q3	E240†	2/220	2/219	0.3	0.8		
82F MD Anderson8227 *	4(F400x2A40C400V1.5)q4	A160†	21/91	2(8/40)	1.7	5.6		
(b) subtotal with data §			1024/ 2830 (36.2%)	1113/ 2798 (39.8%)	-72.0	459.6		0.86 (SE 0.04) reduction 2p = 0.0008
(c) Standard CMF (or near-standard CMF)								
73B INT Milan 7205	12(C100x14M40x2F600x2)q4		165/210	153/181	-15.8	69.0		
78K3 IBCSG/Ludwig III	12(C100x14M40x2F600x2)q4		121/171	125/164	-6.1	50.9		
78V2 ECOG EST6177	12(C100x14M40x2F600x2)q4		66/87	73/95	4.3	27.5		
79U1+3 Vienna Gyn.	6(C100x14M50x2F750x2)q4		20/30	21/29	4.1	5.1		
81H EST1180/SW.8294	6(C100x14M40x2F600x2)q4		84/276	104/265	-15.0	44.1		
86H2 IBCSG VII	6(C100x14M40x2F600x2)q4		160/312	174/318	-9.7	74.9		
88C NSABP B-20	6(C100x14M100x2F600x2)q4		120/789	162/788	-20.2	68.7		
89A2 SITAM-01	6((C100x14/C600x2)M40x2F600x2)q4		31/63	19/52	3.1	10.3		
89E4+9 GROCTA V Italy	6(C600x2M40x2F600x2)q4		15/40	19/39	-3.2	6.3		
89V Romagnolo Italy	6(C100x14M40x2F600x2)q4		30/138	39/143	-4.5	16.4		
90P Amsterdam C8913	6(C100x14M40x2F600x2)q4		12/149	15/122	-3.9	6.3		
90S IBCSG VIII	6(C100x14M40x2F600x2)q4		49/400	56/392	-4.0	24.6		
(c) subtotal			873/ 2665 (32.8%)	960/ 2588 (37.1%)	-70.9	404.1	0.84 (SE 0.05) reduction 2p = 0.0004	
Total (a + b + c)			2666/ 7419 (35.9%)	2949/ 7321 (40.3%)	-189.1	1105.5	0.843 (SE 0.028) reduction 2p < 0.00001	

■ 99% or ◊ 95% confidence intervals

Heterogeneity between 3 subtotals: $\chi^2_2 = 0.2$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{29} = 25.5$; $p > 0.1$; NS

Heterogeneity between 32 trials: $\chi^2_{31} = 25.7$; $p > 0.1$; NS

§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **Mel** = Melphalan; **V** = vincristine

(Not shown: antibiotic, hormonal, local or steroid therapies)

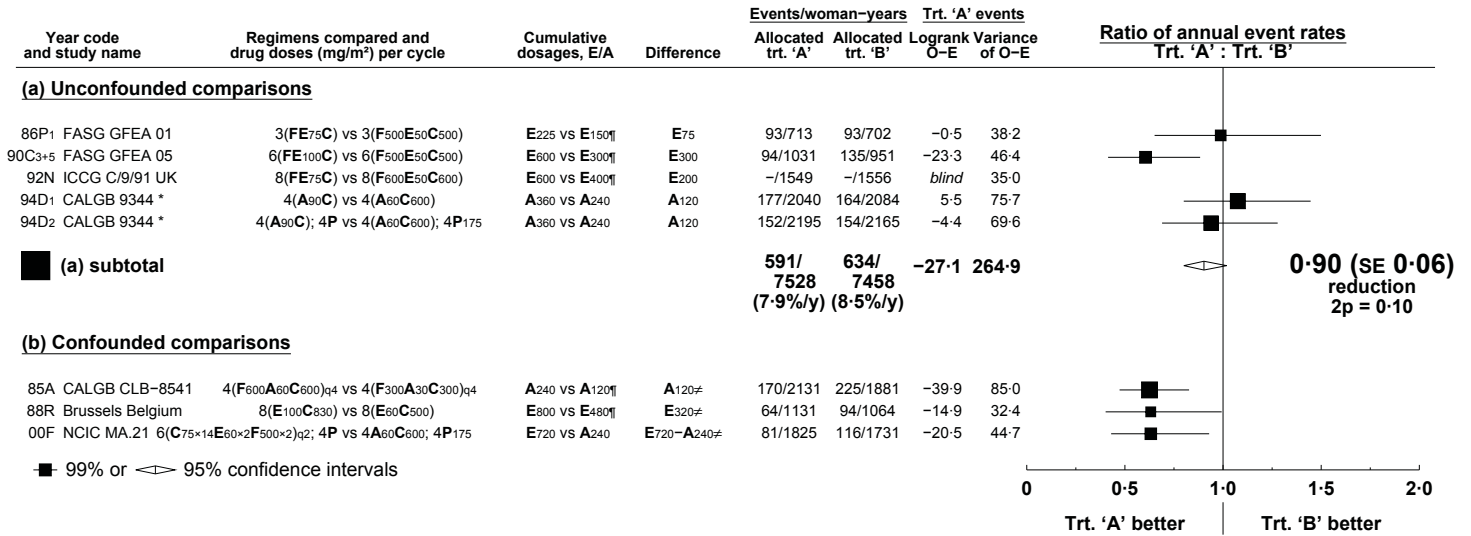
x2 means d1,8 iv; x4 means d3-6 iv

† Dose less than A60 or E90 per cycle

†† 91% given E, 9% given A

0 0.5 1.0 1.5 2.0
Chemo. better | Chemo. worse
Treatment effect 2p < 0.00001

P 45: EARLY RECURRENCE (first 5 years) in trials of anthracycline dosage



■ 99% or ◊ 95% confidence intervals

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [:] indicates treatment sequence

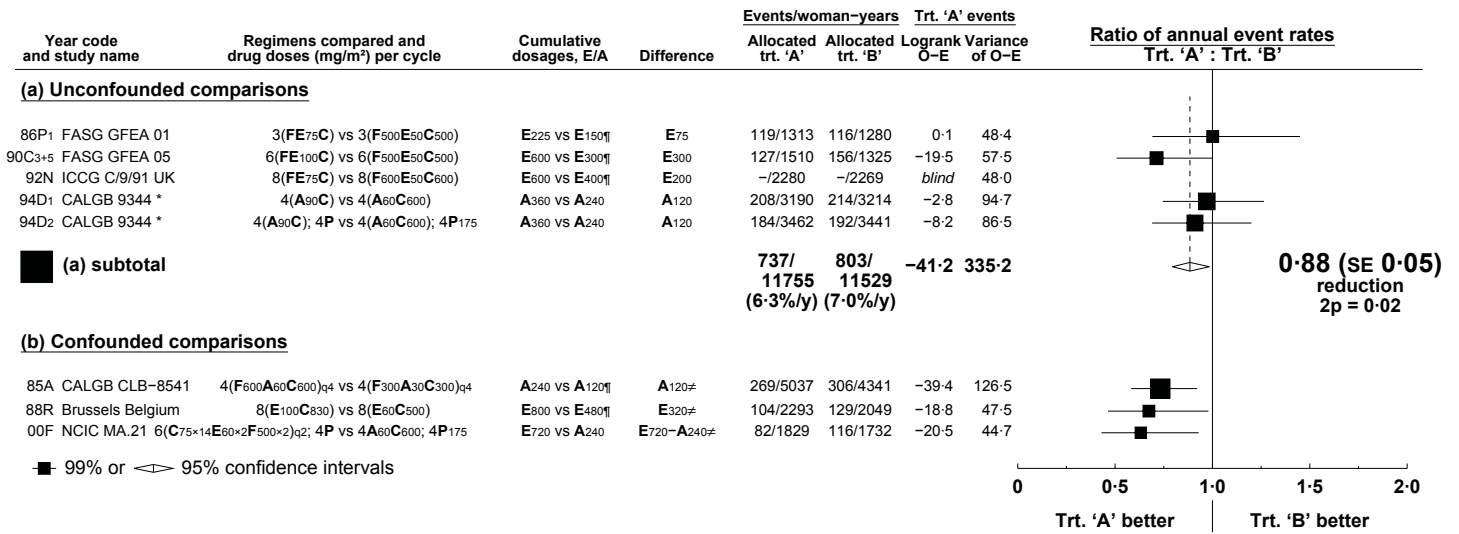
x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than E90 or A60 per q3w (E120 or A75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 46: RECURRENCE in trials of anthracycline dosage



■ 99% or ◁▷ 95% confidence intervals

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [;] indicates treatment sequence

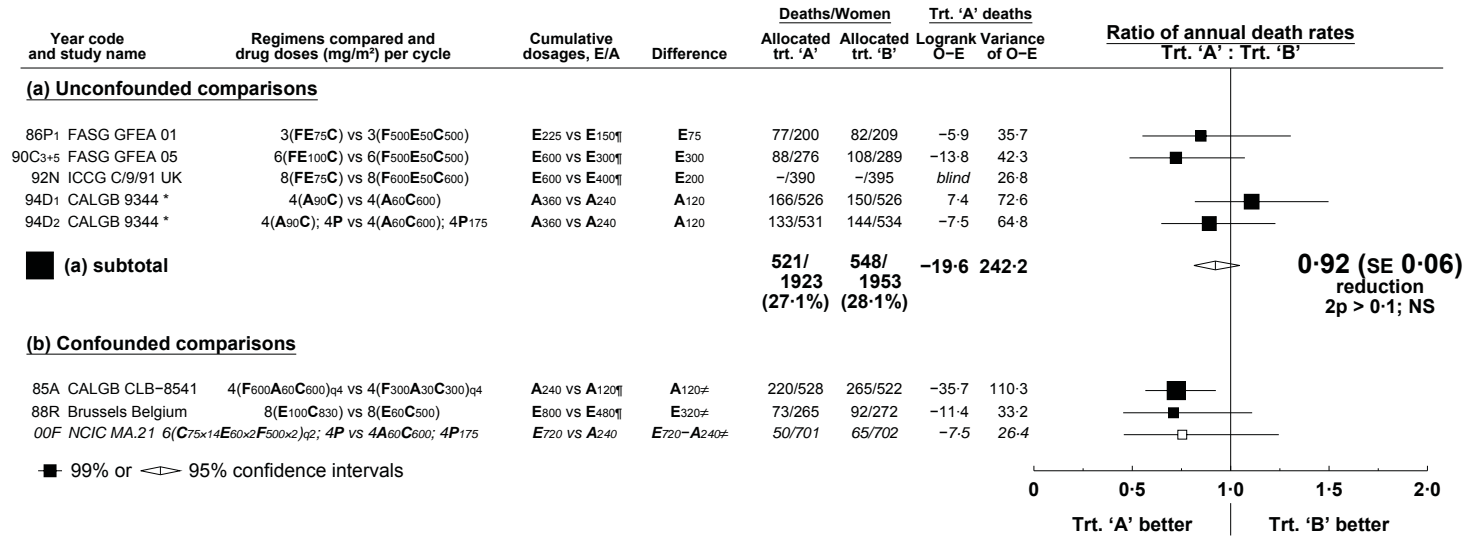
x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than E90 or A60 per q3w (E120 or A75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 47: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of anthracycline dosage



Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [:] indicates treatment sequence

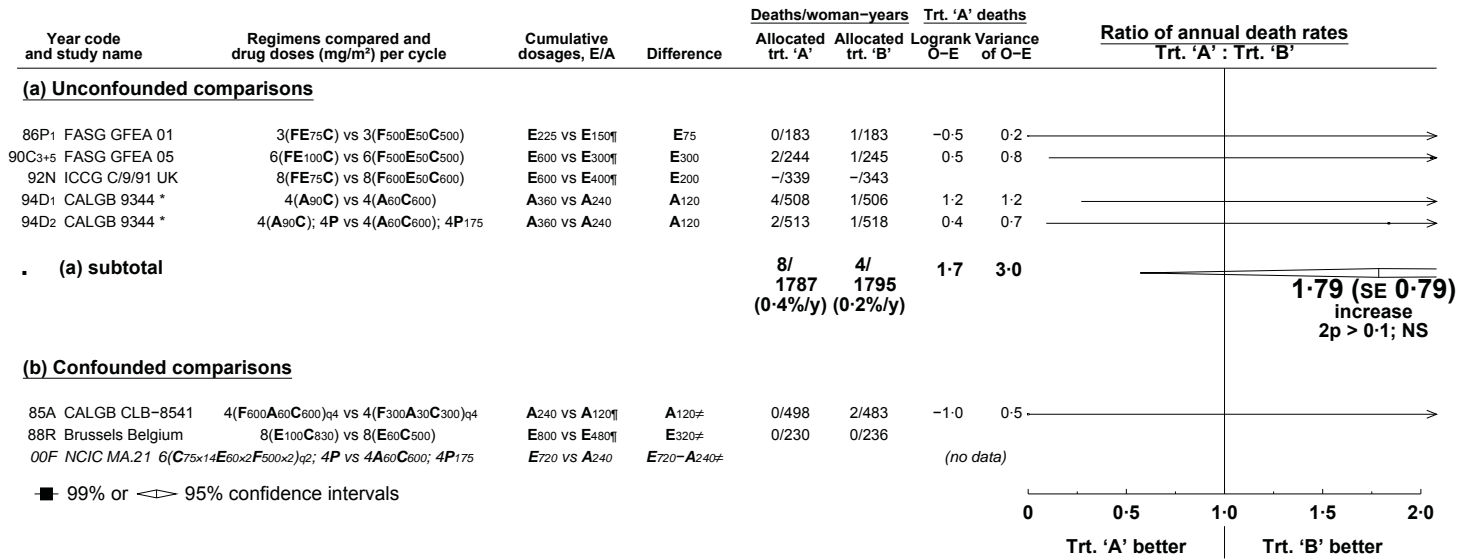
x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than E90 or A60 per q3w (E120 or A75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 48: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of anthracycline dosage



§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [:] indicates treatment sequence

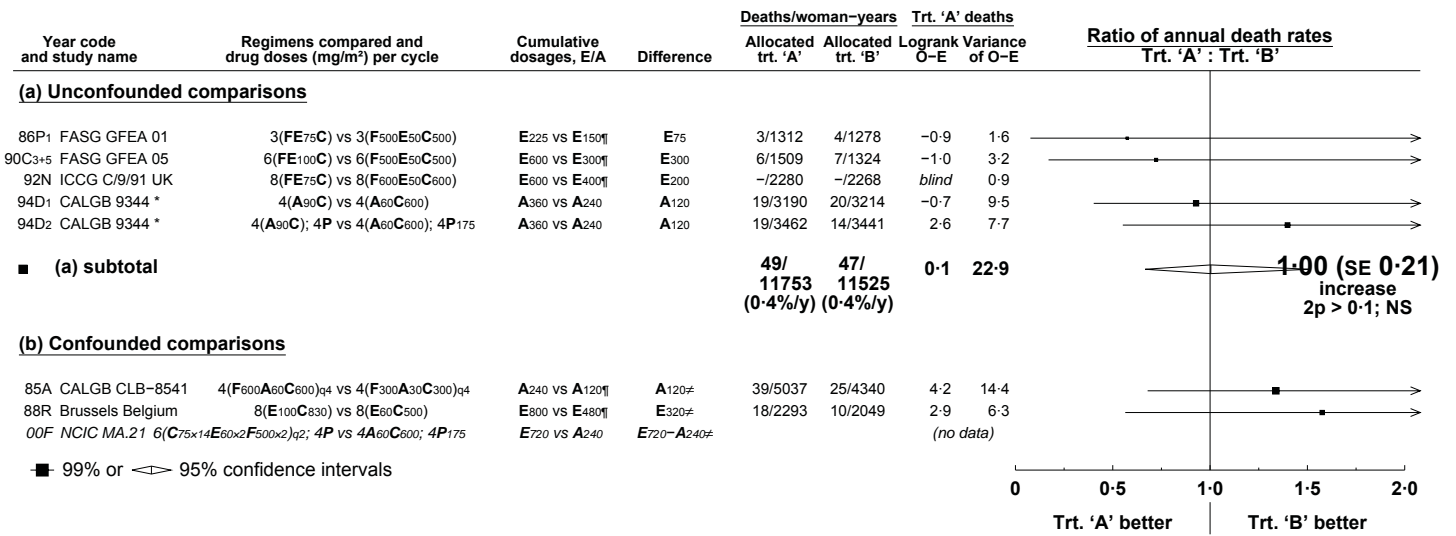
×2 means d1,8 iv; ×4 means d3-6 iv

¶ Dose less than E90 or A60 per q3w (E120 or A75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 49: MORTALITY WITHOUT RECURRENCE in trials of anthracycline dosage



§ 1 trial with no data does not contribute to subtotals or to the overall total.

Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [:] indicates treatment sequence

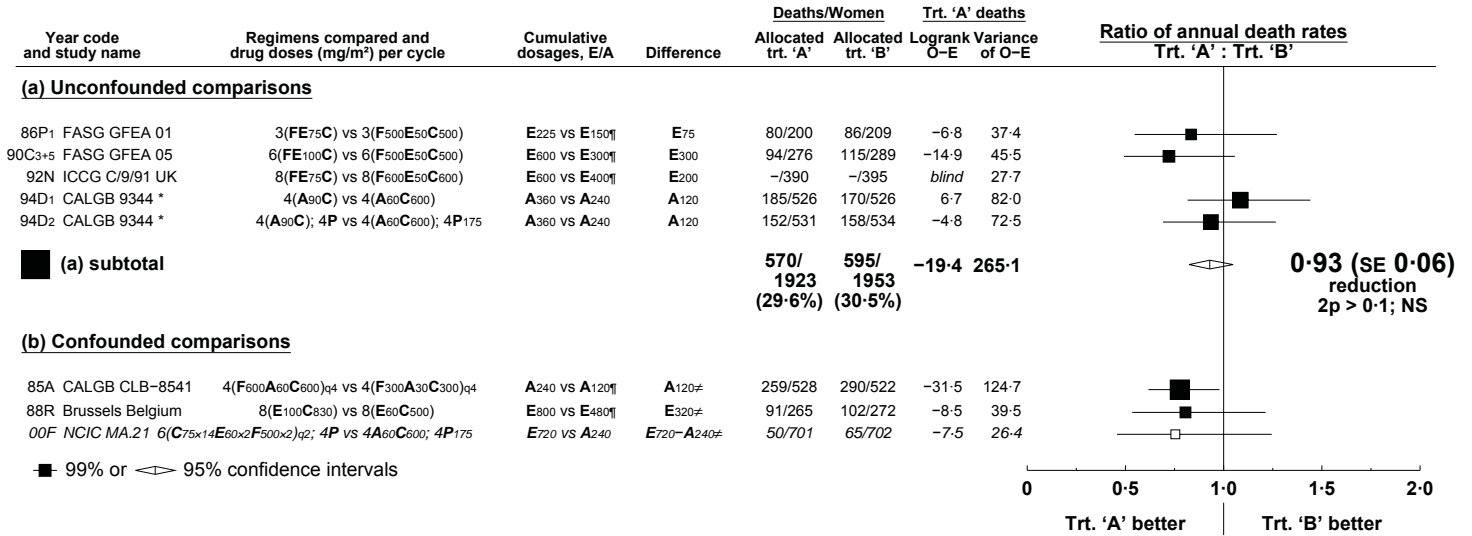
x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than E90 or A60 per q3w (E120 or A75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 50: OVERALL MORTALITY in trials of anthracycline dosage



Anthracyclines: **A** = doxorubicin (Adriamycin); **E** = Epirubicin

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **P** = paclitaxel

(Not shown: antibiotic, hormonal, local or steroid therapies)

All regimens q3w (unless specified as q4). Semicolon [:] indicates treatment sequence

x2 means d1,8 iv; x4 means d3-6 iv

¶ Dose less than E90 or A60 per q3w (E120 or A75 per q4w) cycle

≠ Taxane and control regimens differ in ways other than cumulative anthracycline dose

* These analyses compare the highest and lowest of the 3 anthracycline doses studied in 94D CALGB 9344, ignoring the middle dose

P 51: EARLY RECURRENCE (first 5 years) in trials of CMF regimen vs. No chemotherapy

Year code and study name	CMF regimens and doses per cycle	Events/woman-years		CMF events		Ratio of annual event rates CMF : Control		
		Allocated CMF	Adjusted control	Logrank O-E	Variance of O-E			
(a) Standard CMF (or near-standard CMF) regimens								
73B INT Milan 7205	12(C100×14M40×2F600×2)q4	95/787	98/555	-18.7	38.5			
78K3 IBCSG/Ludwig III	12(C100×14M40×2F600×2)q4	59/608	88/488	-17.6	29.3			
78V2 ECOG EST6177	12(C100×14M40×2F600×2)q4	52/264	57/268	-2.7	20.3			
79U1+3 Vienna Gyn.	6(C100×14M50×2F750×2)q4	14/109	9/108	2.1	3.5			
81H EST1180/SW.8294	6(C100×14M40×2F600×2)q4	53/1153	89/1009	-21.6	32.7			
86H2 IBCSG VII	6(C100×14M40×2F600×2)q4	96/1248	126/1177	-18.7	47.9			
88C NSABP B-20	6(C100×14M100×2F600×2)q4	48/3756	95/3681	-24.6	34.7			
89A2 SITAM-01	6((C100×14/C600×2)M40×2F600×2)q4	26/208	19/185	1.6	9.1			
89E4+9 GROCTA V Italy	6(C600×2M40×2F600×2)q4	14/152	20/124	-2.9	6.2			
89V Romagnolo Italy	6(C100×14M40×2F600×2)q4	23/621	38/603	-7.4	14.3			
90P Amsterdam C8913	6(C100×14M40×2F600×2)q4	20/542	27/398	-7.0	10.6			
90S IBCSG VIII	6(C100×14M40×2F600×2)q4	49/1834	82/1721	-18.0	30.1			
(a) subtotal		549/11282	748/10317	-135.5	277.0		0.61 (SE 0.05) reduction 2p < 0.00001	
(b) Other CMF regimens								
75E2 Manchester I	12(C80×14M32×2F480×2)q4	23/195	24/173	-1.5	8.3			
76C Glasgow	12(C300×2M40×2F600×2)q4	53/384	62/279	-12.9	19.4			
76E EORTC 09771	24(C50×14M15×2F350×2)q4	92/869	109/765	-14.4	43.0			
77B1+2 Danish BCG 77b	12(C80×14M30×2F500×2)q4	76/754	100/649	-17.8	31.7			
78E UK/Asia Collab.	8(C50M25F600)q3; 16(C100×4M25F600)q4	88/674	108/602	-9.4	33.9			
79E Guy's/Manch. II	6(C80×14M32×2F480×2)q4	77/672	125/577	-25.5	33.4			
79H Paris	6(C400×2M40×2F400×2)q4	35/716	46/659	-7.8	18.1			
80F FM Italy 8004	12(C600M40F600)q3	9/218	23/155	-8.7	6.9			
82C DBCG 82c postmenop.	9(C600M40×2F400×2)q4	350/2476	392/2414	-31.0	145.2			
84D NCIC MA.4	8(C600M40F600)q3	125/1427	143/1359	-12.2	58.8			
86H2 IBCSG VII *	3(C100×14M40×2F600×2)q4	224/2471	2(126/1177)	-16.7	65.2			
87D3 GABG 3 Germany	6(C500×2M40×2F600×2)q4	45/943	51/821	-5.8	21.6			
88D IBCSG IX	3(C100×14M40×2F600×2)q4	90/3903	125/3799	-18.9	51.7			
89J1 CRCRAMS Moscow	6(C550×2M25×2F500×2)q3-4	2/37	4/24	-1.1	1.4			
90X1 Tokyo CIH	6(C500M30F500)q3	16/545	14/552	1.2	6.9			
90E Sweden-Finland	9(C600M40F600)q3			(no data)				
93S Hamburg, Germany	6(C500×2M40×2F600×2)q4	15/377	21/406	-2.4	8.0			
93X INC Brazil	6(C600M40F600)q3			(no data)				
94P Charles U Prague	6(C500×2M40×2F600×2)q4			(no data)				
(b) subtotal with data §		1320/16661	1599/15588	-185.0	553.4	0.72 (SE 0.04) reduction 2p < 0.00001		
Total (a + b)		1869/27943	2347/25905	-320.5	830.3	0.680 (SE 0.029) reduction 2p < 0.00001		

■ 99% or ◊ 95% confidence intervals

Difference between treatment effects in 2 subtotals: $\chi^2_1 = 4.4$; $2p = 0.04$

Heterogeneity within subtotals: $\chi^2_{26} = 36.9$; $p = 0.08$

Heterogeneity between 28 trials: $\chi^2_{27} = 41.3$; $p = 0.04$

§ 3 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/woman-years.

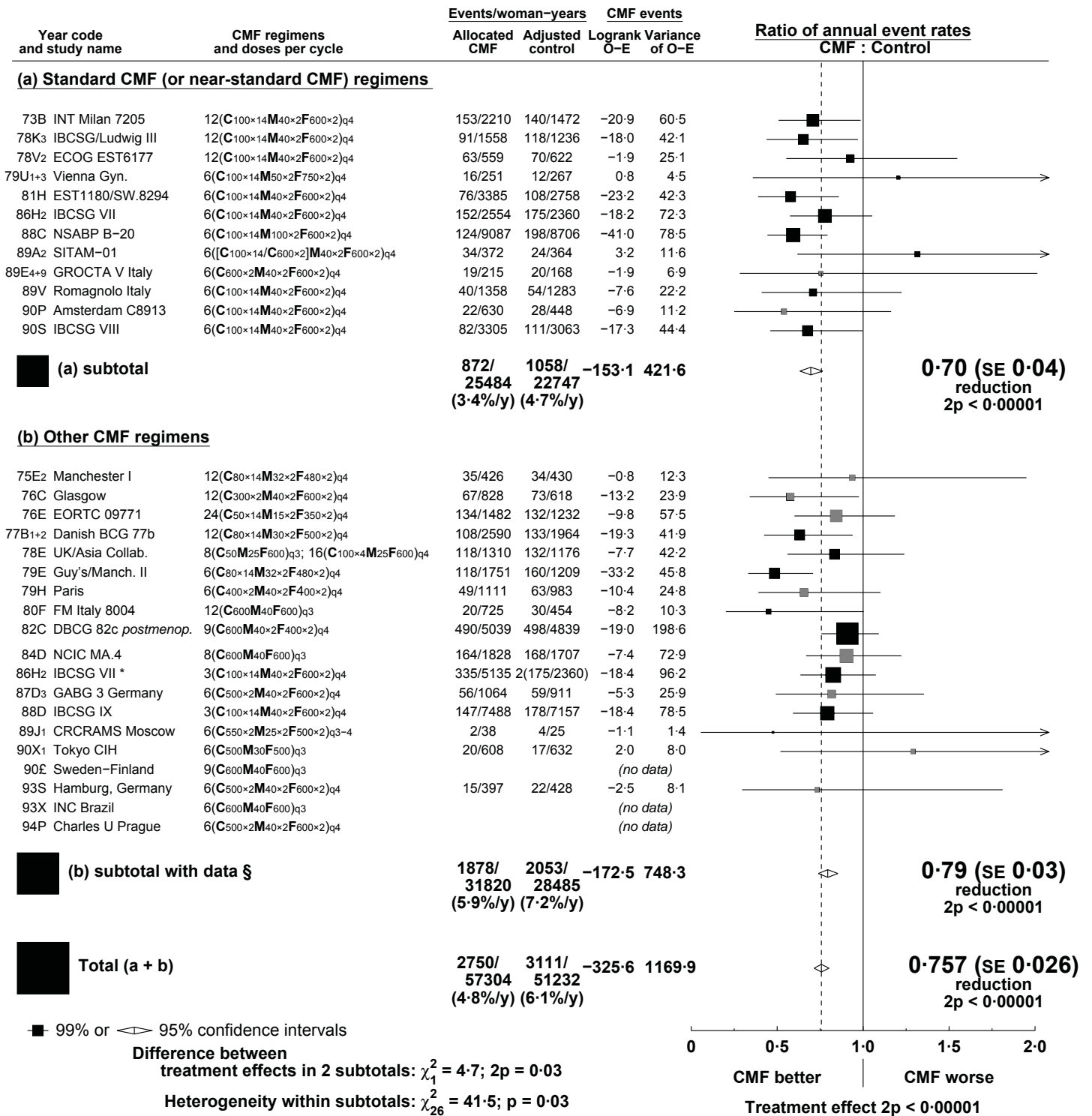
Agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate

(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [:] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3-6 iv

0 0.5 1.0 1.5 2.0
CMF better | CMF worse
Treatment effect $2p < 0.00001$

P 52: RECURRENCE in trials of CMF regimen vs. No chemotherapy



■ 99% or ◊ 95% confidence intervals

Difference between treatment effects in 2 subtotals: $\chi^2_1 = 4.7$; 2p = 0.03

Heterogeneity within subtotals: $\chi^2_{26} = 41.5$; p = 0.03

Heterogeneity between 28 trials: $\chi^2_{27} = 46.3$; p = 0.01

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

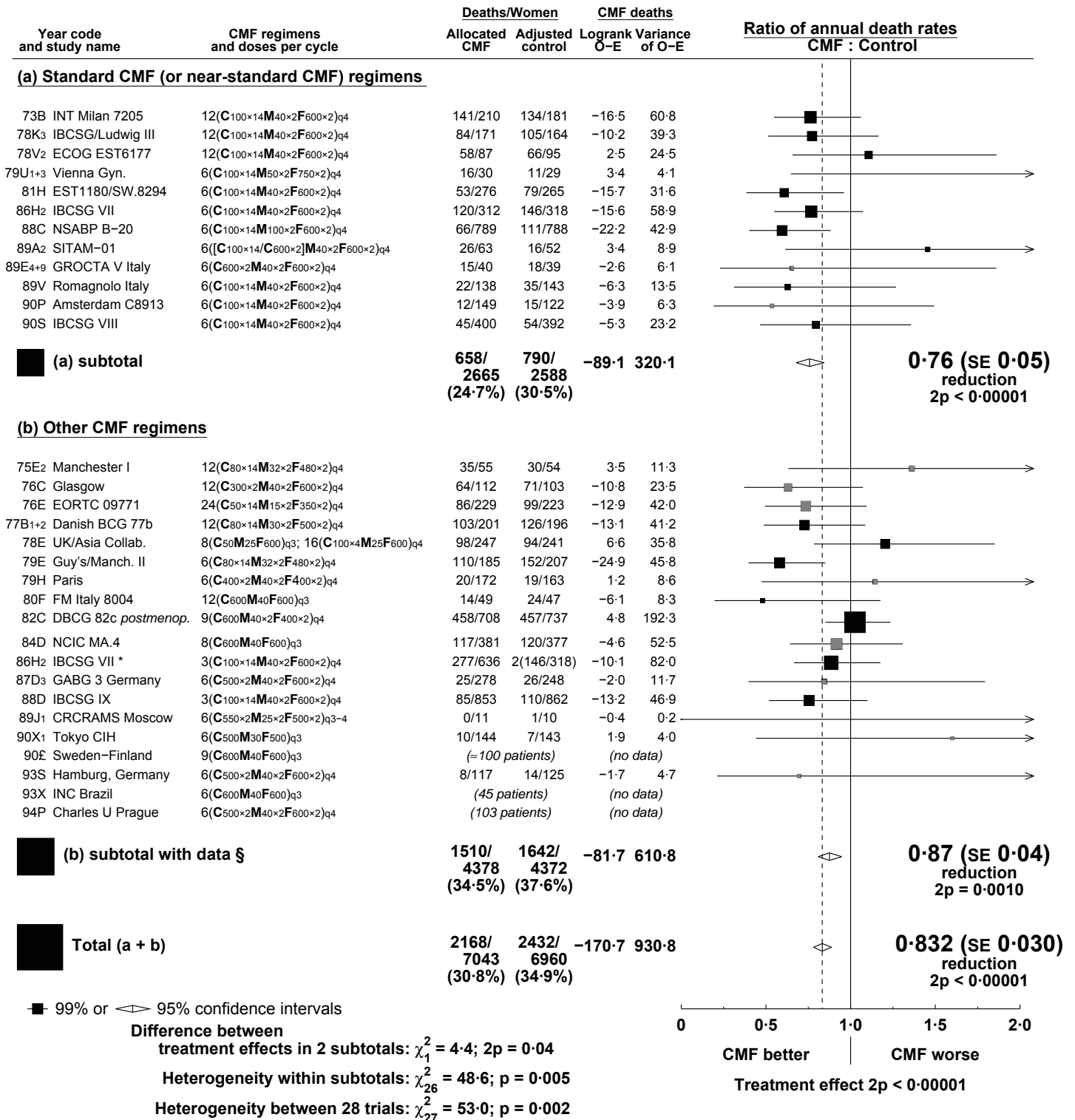
* For balance, control patients in 3-way trials or trial strata count half or twice in subtotal(s) and in final total of events/woman-years.

Agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate

(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [:] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3-6 iv

P 53: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of CMF regimen vs. No chemotherapy



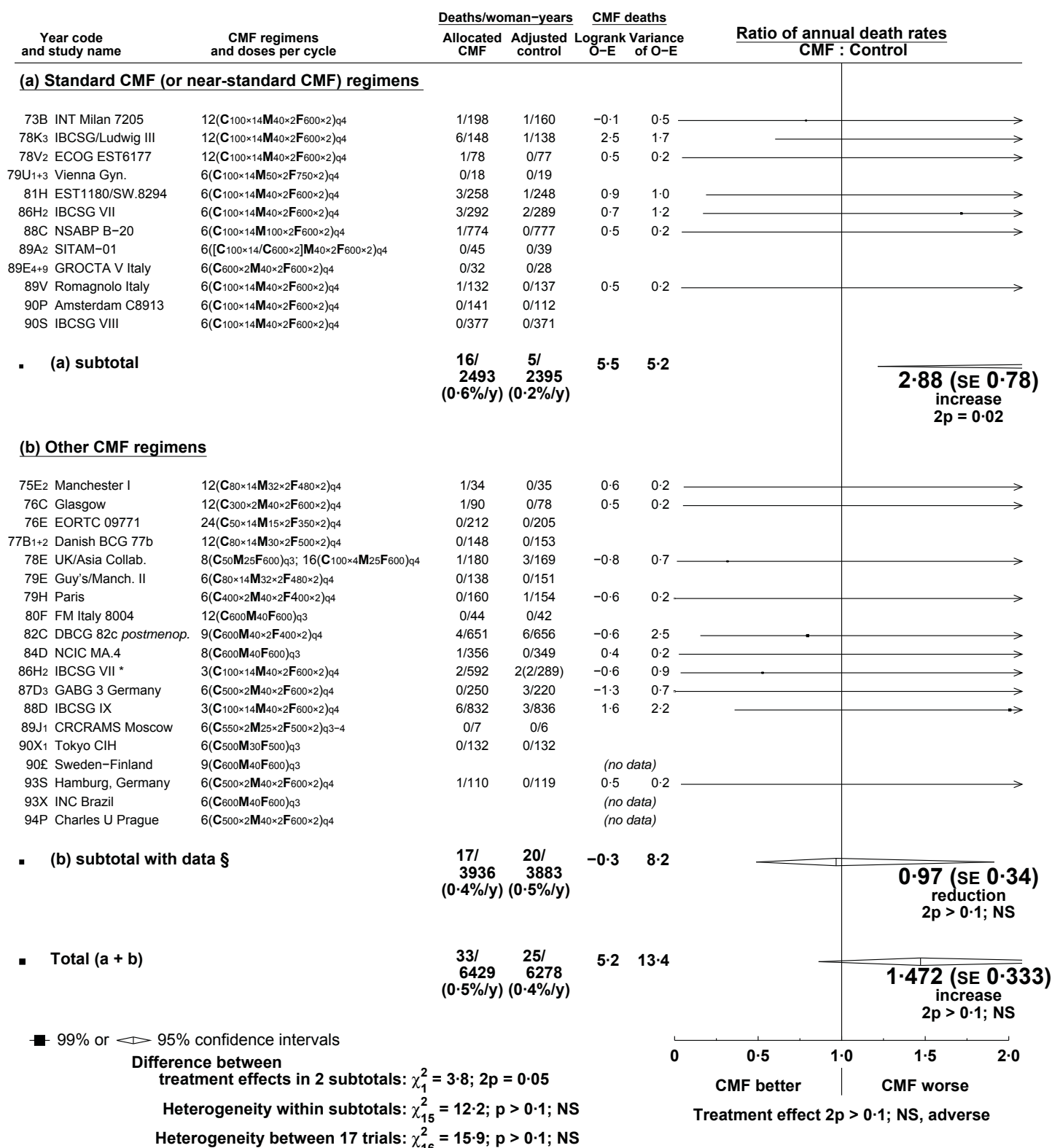
§ 3 trials with no data do not contribute to subtotals or to the overall total.

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

Agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3-6 iv

P 54: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of CMF regimen vs. No chemotherapy



■ 99% or ◁▷ 95% confidence intervals

Difference between treatment effects in 2 subtotals: $\chi^2_1 = 3.8$; 2p = 0.05

Heterogeneity within subtotals: $\chi^2_{15} = 12.2$; p > 0.1; NS

Heterogeneity between 17 trials: $\chi^2_{16} = 15.9$; p > 0.1; NS

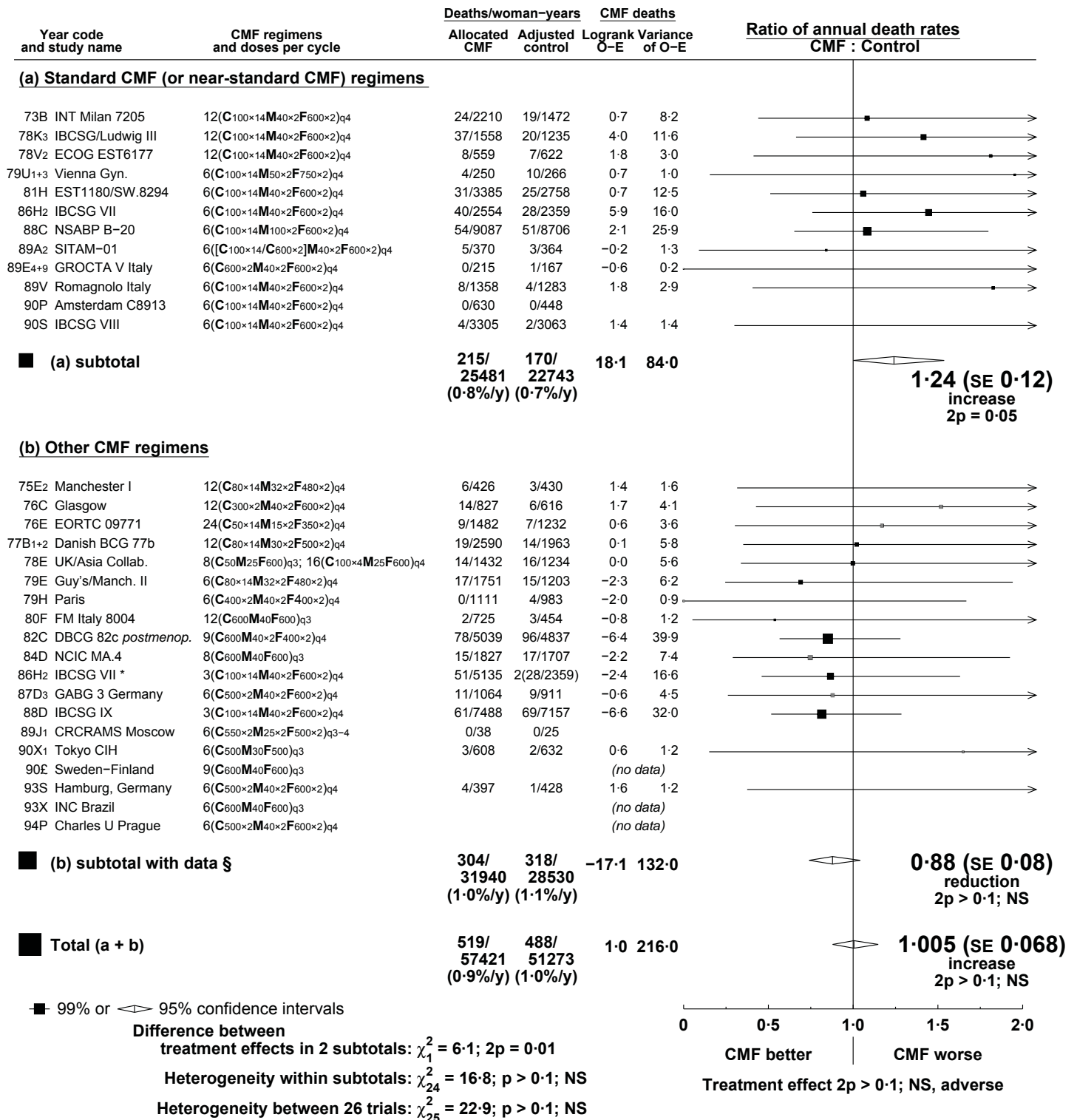
§ 3 trials with no data do not contribute to subtotals or to the overall total.

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

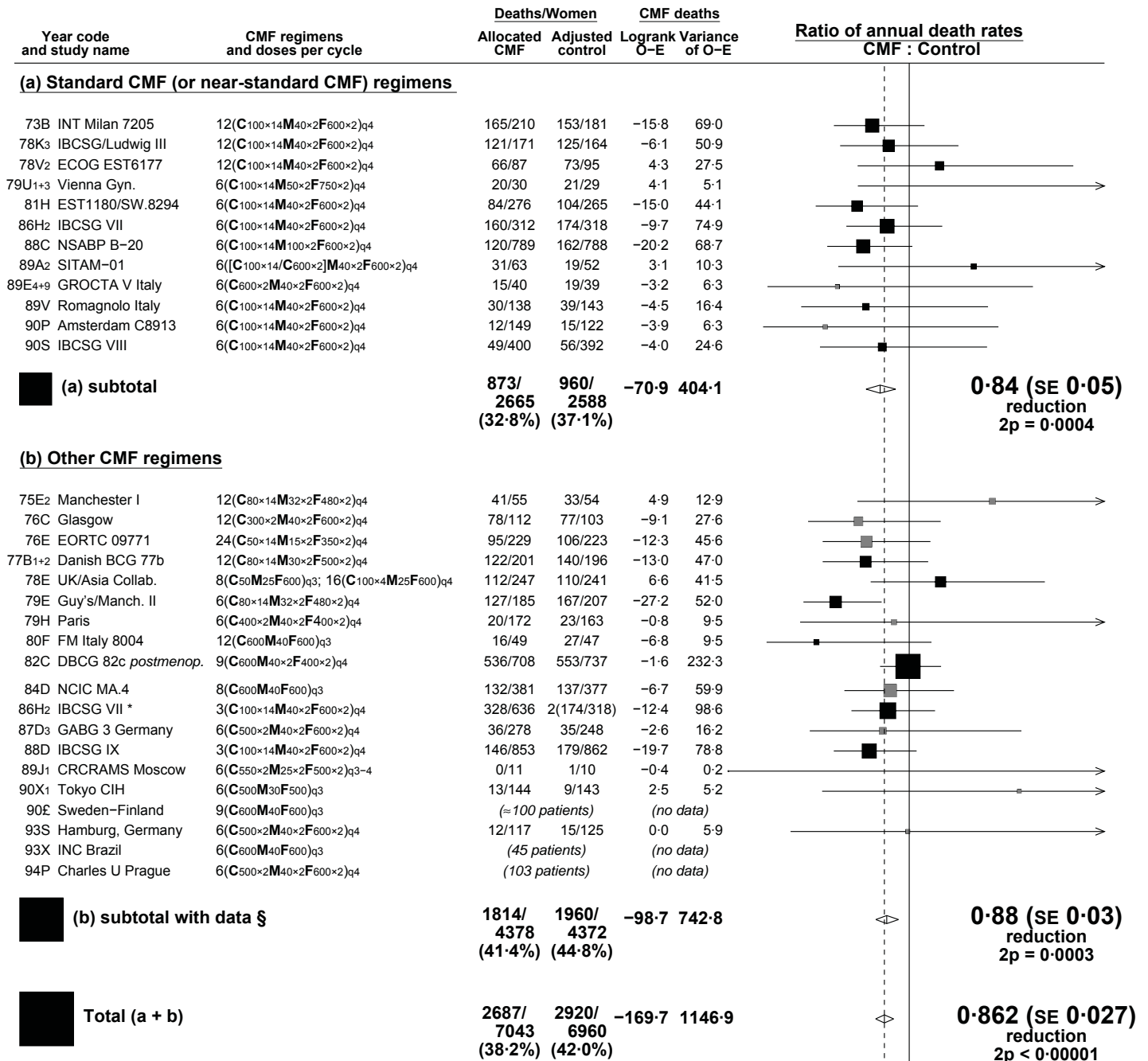
Agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

Semicolon [;] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3-6 iv

P 55: MORTALITY WITHOUT RECURRENCE in trials of CMF regimen vs. No chemotherapy



P 56: OVERALL MORTALITY in trials of CMF regimen vs. No chemotherapy



■ 99% or ◊ 95% confidence intervals

Difference between treatment effects in 2 subtotals: $\chi^2_1 = 0.5$; $2p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{26} = 43.6$; $p = 0.02$

Heterogeneity between 28 trials: $\chi^2_{27} = 44.1$; $p = 0.02$

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

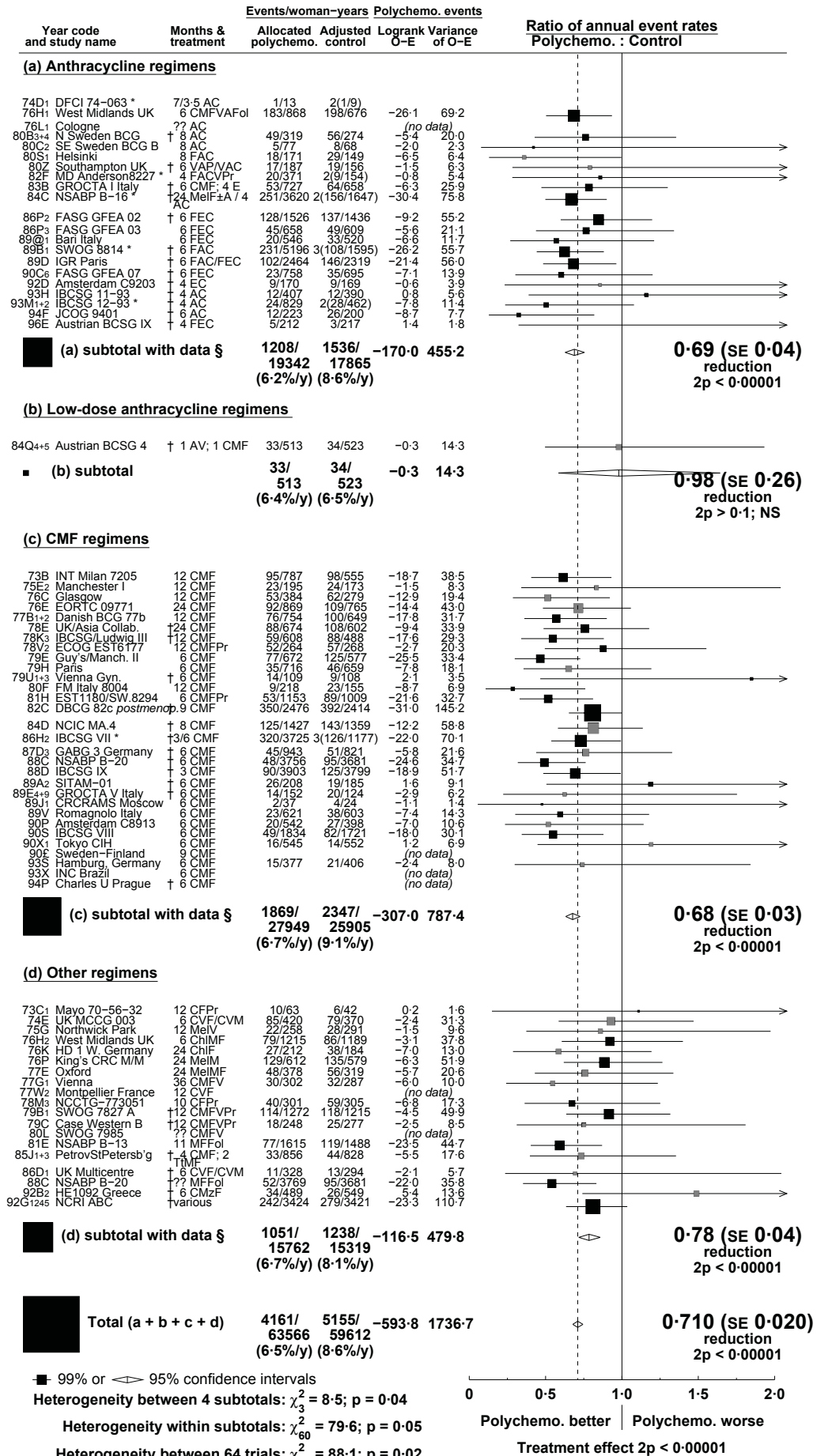
* For balance, control patients in 3-way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/women.

Agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate
(Not shown: antibiotic, hormonal, local or steroid therapies)

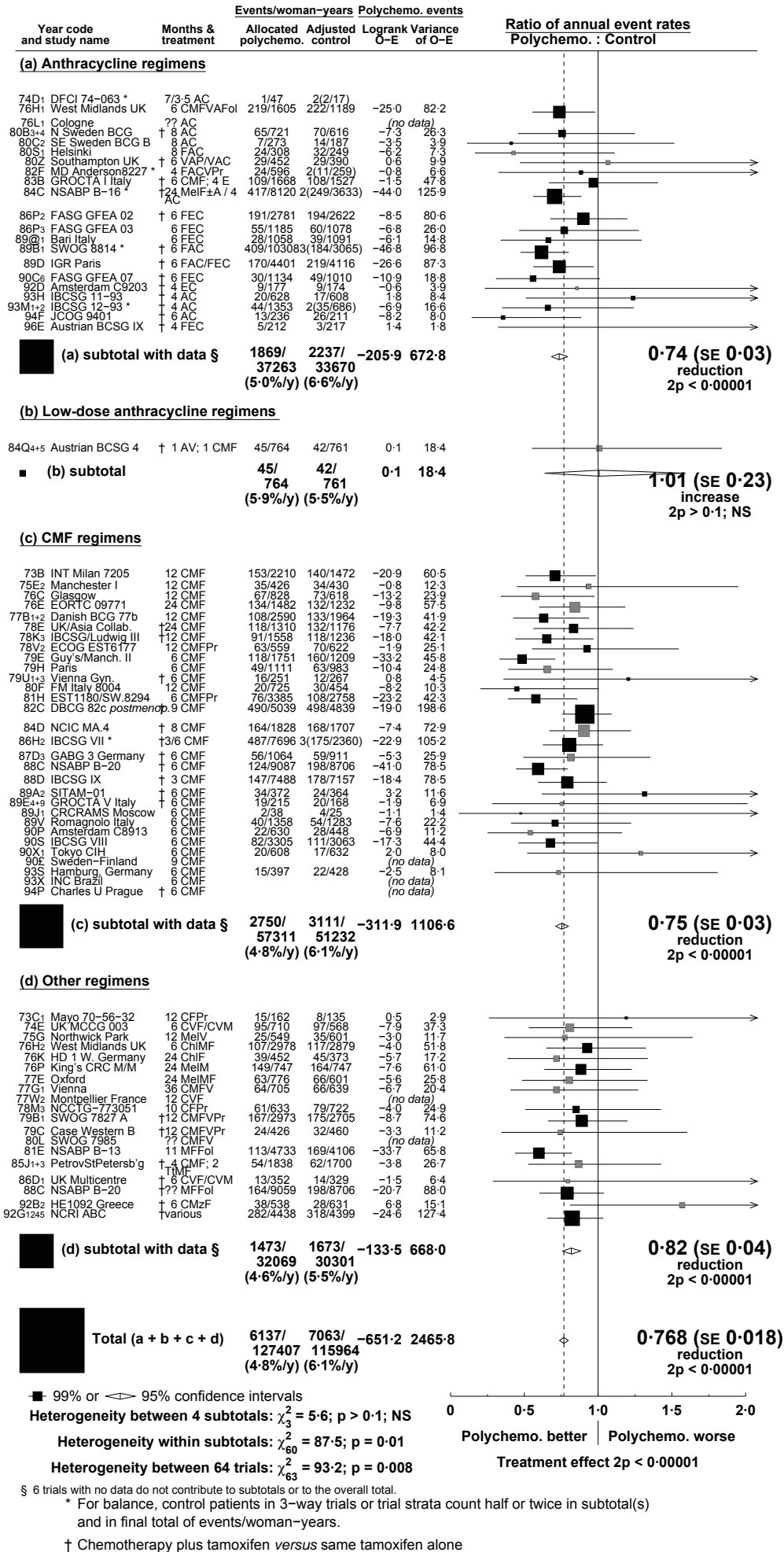
Semicolon [:] indicates treatment sequence; ×2 means d1,8 iv; ×4 means d3-6 iv

0 0.5 1.0 1.5 2.0
CMF better | CMF worse
Treatment effect $2p < 0.00001$

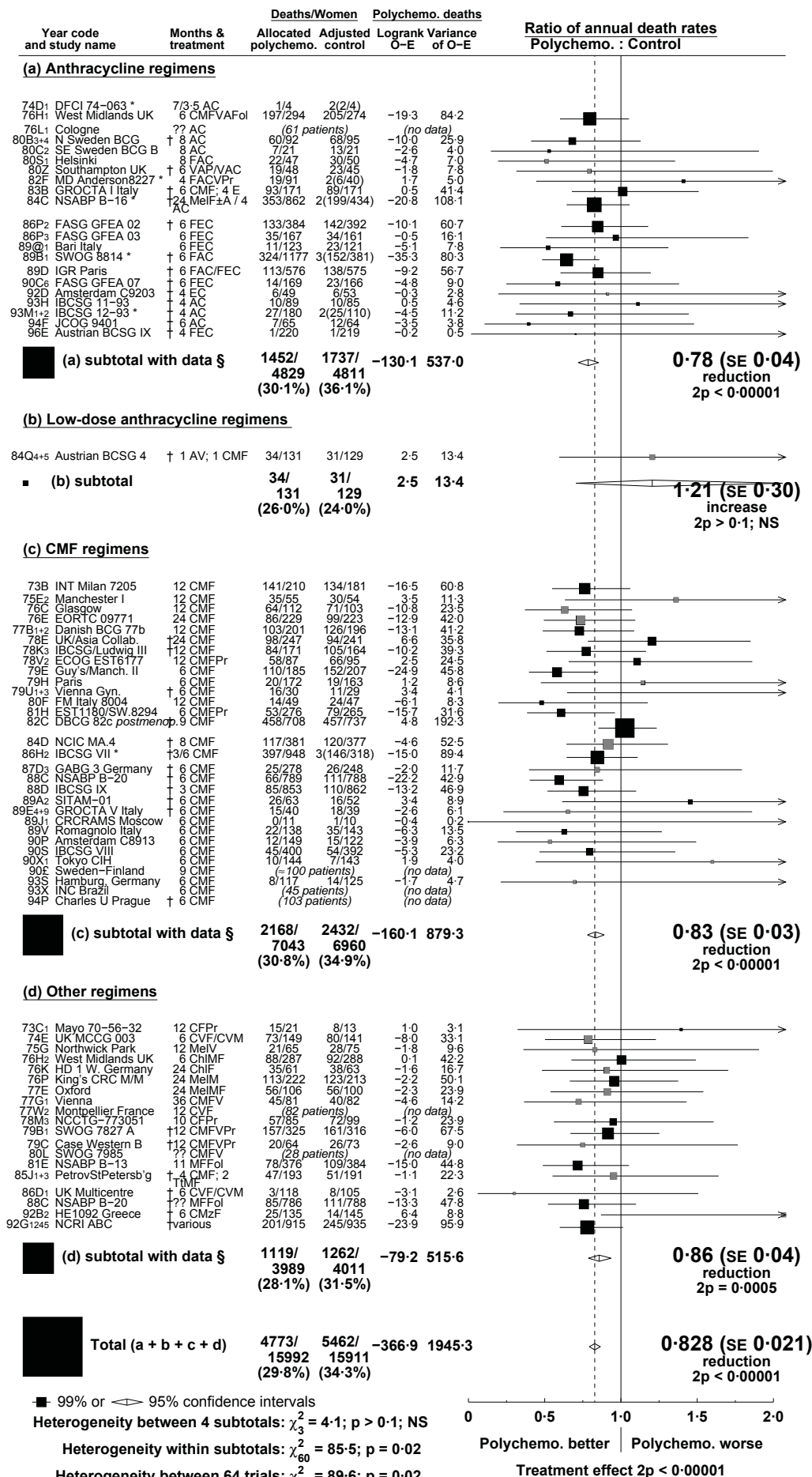
P 57: EARLY RECURRENCE (first 5 years) in trials of polychemotherapy vs. No chemotherapy



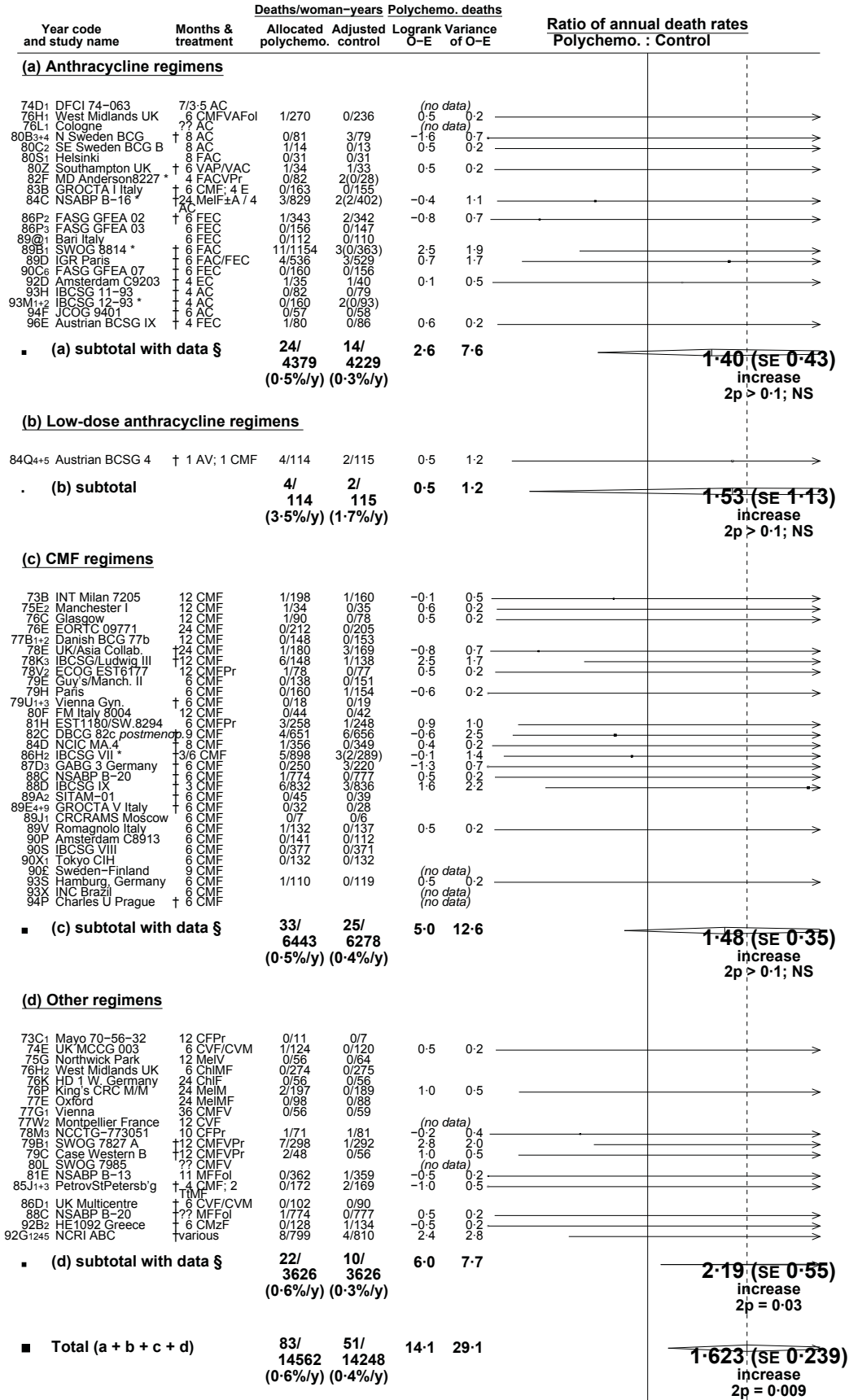
P 58: RECURRENCE in trials of polychemotherapy vs. No chemotherapy



P 59: BREAST CANCER MORTALITY (MORTALITY WITH RECURRENCE) in trials of polychemotherapy vs. No Chemotherapy



P 60: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR in trials of polychemotherapy vs. No chemotherapy



■ 99% or ◁▷ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 1.0; p > 0.1; NS$

Heterogeneity within subtotals: $\chi^2_{33} = 38.2; p > 0.1; NS$

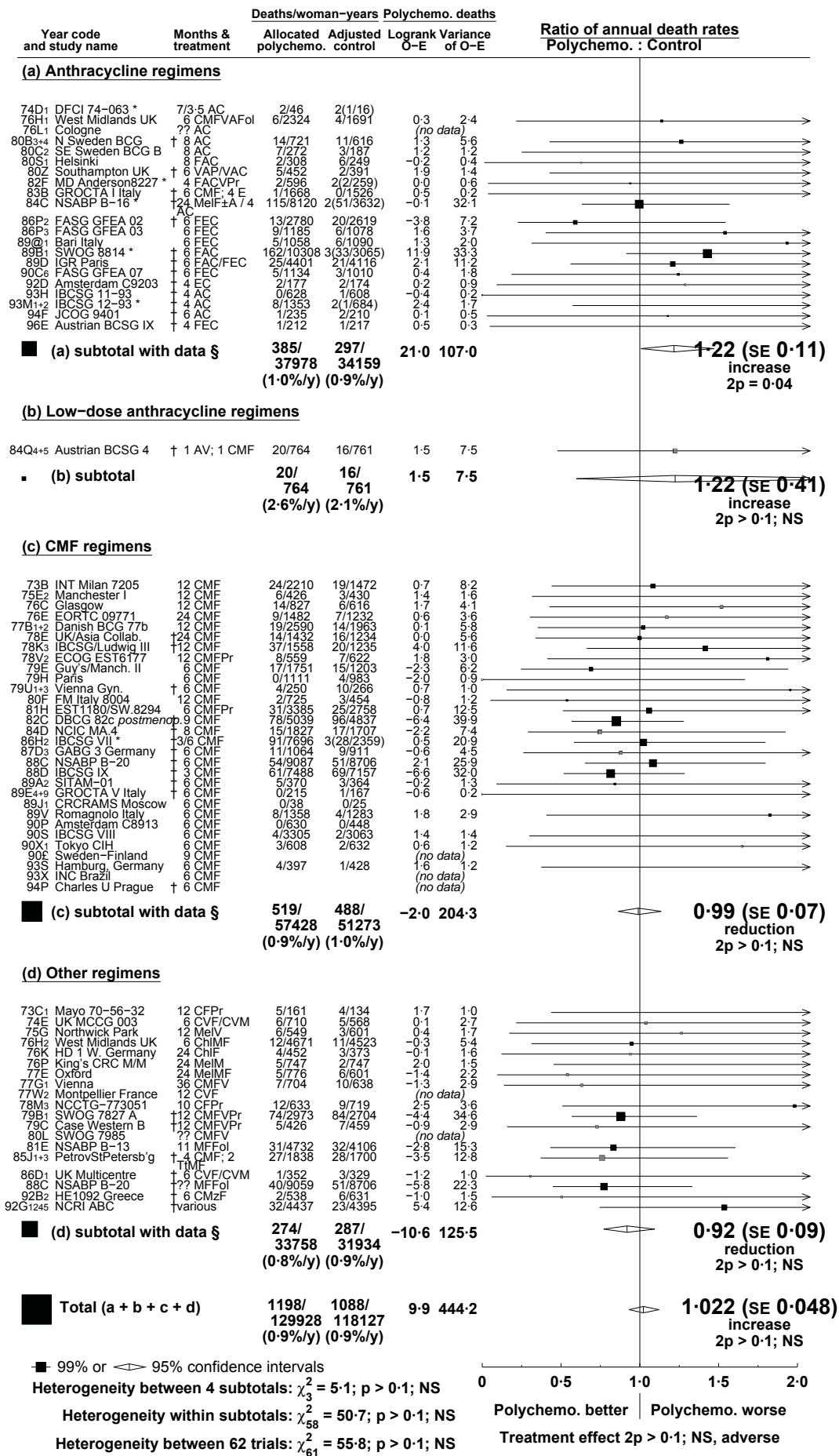
Heterogeneity between 37 trials: $\chi^2_{36} = 39.1; p > 0.1; NS$

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

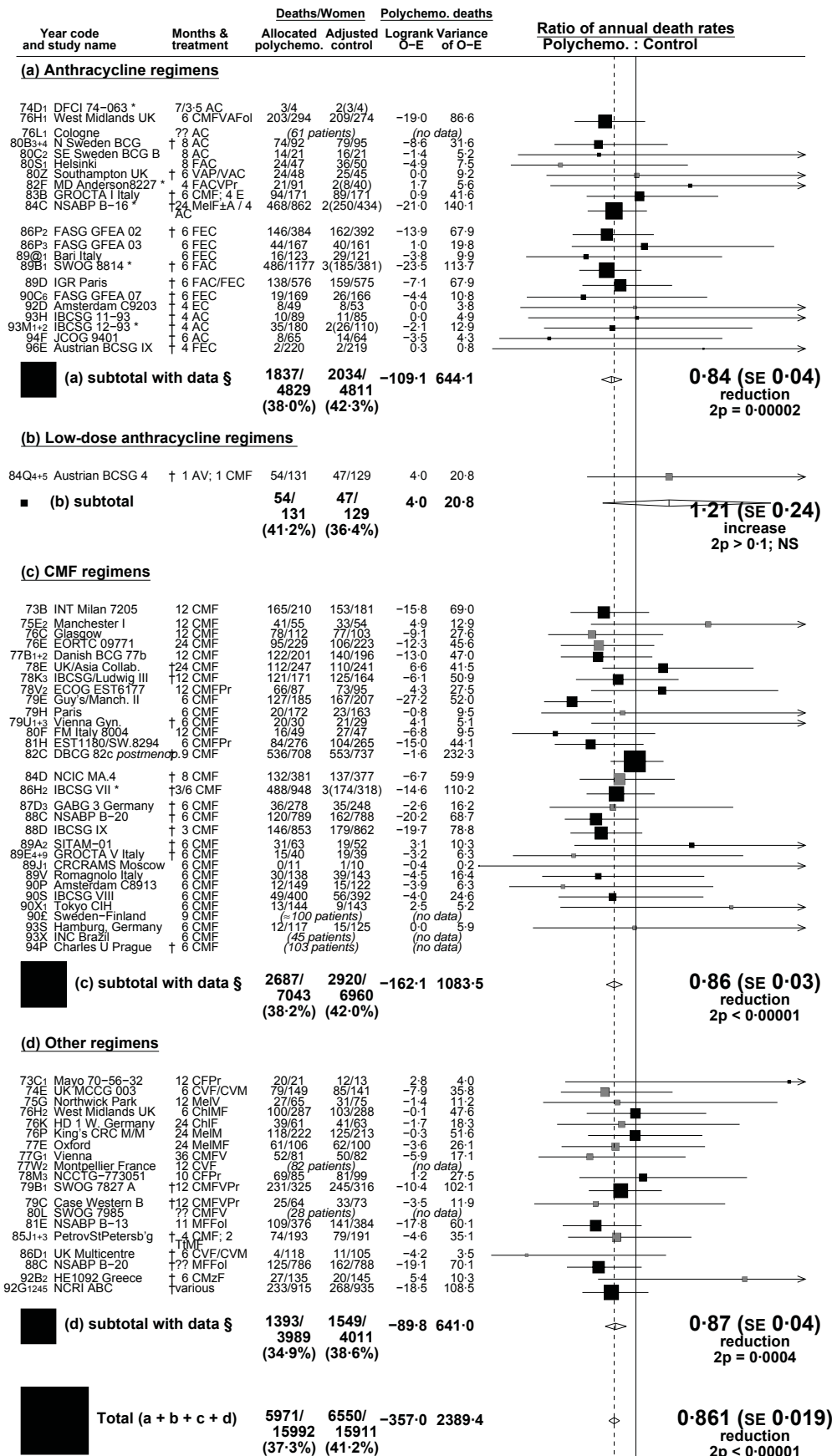
* For balance, control patients in 3-way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/woman-years.

† Chemotherapy plus tamoxifen versus same tamoxifen alone

P 61: MORTALITY WITHOUT RECURRENCE in trials of polychemotherapy vs. No chemotherapy



P 62: OVERALL MORTALITY in trials of polychemotherapy vs. No chemotherapy



■ 99% or ◊ 95% confidence intervals

Heterogeneity between 4 subtotals: $\chi^2_3 = 2.7$; $p > 0.1$; NS

Heterogeneity within subtotals: $\chi^2_{60} = 72.5$; $p > 0.1$; NS

Heterogeneity between 64 trials: $\chi^2_{63} = 75.2$; $p > 0.1$; NS

§ 6 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/women.

† Chemotherapy plus tamoxifen versus same tamoxifen alone

0 0.5 1.0 1.5 2.0
Polychemo. better | Polychemo. worse
Treatment effect 2p < 0.00001

P63: Table of non-breast-cancer mortality without recurrence during the first year after randomisation, by age for various chemotherapy comparisons

Treatments compared (Active vs Control)	Entry age (years)*	Deaths/woman-years	
		Active	Control**
1. Taxane-plus-anthracycline-based regimen vs same or more non-taxane chemotherapy	<55	28/13174 (0.2%)	21/13117 (0.2%)
	55-69	31/6303 (0.5%)	19/6269 (0.3%)
	70+	7/244 (2.9%)	6/264 (2.3%)
	All	66/19721 (0.3%)	46/19650 (0.2%)
2. Any anthracycline-based regimen* vs standard CMF	<55	12/6416 (0.2%)	13/6405 (0.2%)
	55-69	11/1821 (0.6%)	13/1780 (0.7%)
	70+	0/78 (0.0%)	1/80 (1.3%)
	All	23/8358 (0.3%)	27/8321 (0.3%)
3. Any anthracycline-based regimen vs no chemotherapy	<55	3/1356 (0.2%)	4/1324 (0.3%)
	55-69	17/2766 (0.6%)	10/2677 (0.4%)
	70+	4/168 (2.4%)	0/162 (0.0%)
	All	24/4296 (0.6%)	14/4165 (0.3%)
4. Any CMF regimen vs no chemotherapy†	<55	3/2748 (0.1%)	5/2613 (0.2%)
	55-69	27/3452 (0.8%)	15/3435 (0.4%)
	70+	3/228 (1.3%)	5/231 (2.2%)
	All	33/6429 (0.5%)	25/6279 (0.4%)

* The few women of unknown age are excluded from the age-specific subgroups but included in the totals; none of them died in year 0 without recurrence.

** For balance, control patients count twice in the few trials with allocation ratio 2:1.

† 8/468 (2.1%) vs 2/540 (0.4%) in 3 small, old (began 1973-78) trials of 12 cycles of standard CMF, 8/2194 (0.4%) vs 3/2047 (0.15%) in trials of 6 cycles of standard CMF, and 14/4374 (0.4%) vs 20/4370 (0.5%) in trials of other CMF regimens.

P 64: One or more references for each trial in the forest plots on pp 21-50 of breast cancer mortality (in the same order as in those forest plots)

Trials of TAXANES (see webappendix page 23):

(a) Taxane-plus-anthracycline-based regimen (with taxane courses NOT overlapping with any other chemo. courses) vs the SAME non-taxane cytotoxic regimen, but without the taxane courses

Year Code	Trial name	Publication(s)
98B	Taxit216 Italy	Cognetti F, De Laurentiis M, De Matteis A, et al. Sequential epirubicin-docetaxel-CMF as adjuvant therapy for node-positive early stage breast cancer: updated results of the Taxit216 randomized trial. <i>Ann Oncol</i> 2008; 19 : viii77, A1820 (abstract). Bianco AR, De Laurentiis M, De Placido S, et al. Sequential epirubicin-docetaxel-CMF as adjuvant therapy for node-positive early-stage breast cancer: Subgroup analysis of the Taxit216 randomized trial. Breast Cancer Symposium 5-7 Sep 2008, A187 (abstract); Washington DC, USA.
99T	GOIM 9902 Italy	Lopez M, Brandi M, Foggi P, et al. Toxicity of epirubicin and cyclophosphamide (EC) vs. docetaxel (D) followed by EC in the adjuvant (adj) treatment of node positive breast cancer. A multicenter randomized phase III study (GOIM9902). <i>J Clin Oncol</i> 2006; 24 : A10526 (abstract).
95J1-2	NSABP B-27	Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. <i>J Clin Oncol</i> 2006; 24 : 2019-27.
95K	NSABP B-28	Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. <i>J Clin Oncol</i> 2005; 23 : 3686-96.
94D1-3	CALGB 9344	Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. <i>J Clin Oncol</i> 2003; 21 : 976-83. Berry DA, Thor A, Jewell SD, et al. Benefits of adding paclitaxel to adjuvant doxorubicin/cyclophosphamide depending on HER2 & ER status: analysis of tumor tissue microarrays and immunohistochemistry in CALGB 9344 (Intergroup 0148). <i>Cancer Res</i> 2009; 69 : A606 (abstract).

(b) Taxane-plus-anthracycline-based regimen (with taxane courses NOT overlapping with any other chemo. courses) vs MORE (but < doubled) non-taxane cytotoxic chemotherapy

Year Code	Trial name	Publication(s)
00S	WSG/AGO AM-02	Nitz U, Huober J, Lisboa B, et al. Superiority of sequential docetaxel over standard FE100C in patients with intermediate risk breast cancer: survival results of the randomized intergroup phase III trial EC-Doc. <i>Cancer Res</i> 2009; 69 : A78 (abstract).
95T	HORG Greece	Polyzos A, Malamos N, Boukovinas I, et al. FEC versus sequential docetaxel followed by epirubicin/cyclophosphamide as adjuvant chemotherapy in women with axillary node-positive early breast cancer: a randomized study of the Hellenic Oncology Research Group (HORG). <i>Breast Cancer Res Treat</i> 2010; 119 : 95-104.
00E	FinHer/FBCG 00-01	Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. <i>J Clin Oncol</i> 2009; 27 : 5685-92.
98D1	BIG 02-98	Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. <i>J Natl Cancer Inst</i> 2008; 100 : 121-33. Di Leo A, Francis P, Crown JP, et al. Overall survival benefit for sequential doxorubicin-docetaxel compared to concomitant doxorubicin and docetaxel in node-positive breast cancer. 8-year results of the Breast International Group (BIG) 2-98 phase III adjuvant trial. <i>Cancer Res</i> 2009; 69 : A601 (abstract).
99K	GEICAM 9906 Spain	Rodriguez-Lescure A, Martin M, Ruiz A, et al. Subgroup analysis of GEICAM 9906 trial comparing six cycles of FE90C (FEC) to four cycles of FE90C followed by 8 weekly paclitaxel administrations (FECp): Relevance of HER2 and hormonal status (HR). <i>J Clin Oncol</i> 2007; 25 : A10598 (abstract).
97R	HE1097 Greece	Fountzilas G, Skarlos D, Dafni U, et al. Postoperative dose-dense sequential chemotherapy with epirubicin, followed by CMF with or without paclitaxel, in patients with high-risk operable breast cancer: a randomized phase III study conducted by the Hellenic Cooperative Oncology Group. <i>Ann Oncol</i> 2005; 16 : 1762-71.
00F1	NCIC MA.21	Burnell M, Levine MN, Chapman JAW, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. <i>J Clin Oncol</i> 2010; 28 : 77-82.
00U	AERO B-2000 France	Delbaldo C, Serin D, Mousseau M, et al. A phase III adjuvant randomized trial of 6 cycles of 5-fluorouracil - epirubicin-cyclophosphamide (FEC100) versus 4 FEC 100 followed by 4 taxol (FEC-T) in node positive breast cancer patients (trial B2000). <i>Cancer Res</i> 2010; 70 : P5-10-05 (abstract).
03R	GIM 1 Italy	http://www.slidefinder.net/c/clinical_trials_breast_cancer_italy/8472086

(c) Taxane-plus-anthracycline-based regimen (with taxane given CONCURRENTLY with other cytotoxic drugs) vs MORE (but < doubled) non-taxane cytotoxic chemotherapy

Year Code	Trial name	Publication(s)
01E1+3	PACS 04 France	Roché H, Allouache D, Romieu G, et al. Five-year analysis of the FNCLCC-PACS04 trial: FEC100 vs ED75 for the adjuvant treatment of node positive breast cancer. <i>Cancer Res</i> 2009; 69 : A602 (abstract).
97L	BCIRG 001	Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. <i>N Engl J Med</i> 2005; 352 : 2302-13. Hugh J, Hanson J, Cheang MCU, et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: Use of an immunohistochemical definition in the BCIRG 001 trial. <i>J Clin Oncol</i> 2009; 27 : 1168-76.
99%	GEICAM 9805 Spain	Martin M, Seguí MA, Antón A, et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. <i>N Engl J Med</i> 2010; 363 : 2200-10.

98D2	BIG 02-98	Francis P, Crown J, Di Leo A, et al. Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial. <i>J Natl Cancer Inst</i> 2008; 100 : 121-33. Di Leo A, Francis P, Crown JP, et al. Overall survival benefit for sequential doxorubicin-docetaxel compared to concomitant doxorubicin and docetaxel in node-positive breast cancer. 8-yr. Results of the Breast International Group (BIG) 2-98 phase III adjuvant trial. <i>Cancer Res</i> 2009; 69 : A601 (abstract).
99N	RAPP-01 France	Brain EGC, Bachelot T, Serin D, et al. Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer. <i>JAMA</i> 2005; 293 : 2367-71. Brain EG, Debled M, Eymard J, et al. Final results of the RAPP-01 phase III trial comparing doxorubicin and docetaxel with doxorubicin and cyclophosphamide in the adjuvant treatment of high-risk node negative and limited node positive (<=3) breast cancer patients. <i>Cancer Res</i> 2009; 69 : A4101.
98T	ECOG EST2197	Goldstein LJ, O'Neill A, Sparano JA, et al. Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup trial E 2197. <i>J Clin Oncol</i> 2008; 26 : 4092-99. Badve SS, Baehner FL, Gray RP, et al. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory. <i>J Clin Oncol</i> 2008; 26 : 2473-81.
96W1-2	ECTO Italy	Gianni L, Baselga J, Eiermann W, et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. <i>J Clin Oncol</i> 2009; 27 : 2474-81.
96%	Multicentre Germany	Kümmel S, Krockner J, Kohls A, et al. Randomised trial: survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer. <i>Br J Cancer</i> 2006; 94 : 1237-44.
96X	GONO Italy MIG 5	Del Mastro L, Costantini M, Durando A, et al. Cyclophosphamide, epirubicin, and 5-fluorouracil versus epirubicin plus paclitaxel in node-positive early breast cancer patients: A randomized, phase III study of Gruppo Oncologico Nord Ovest-Mammella Intergroup. <i>J Clin Oncol</i> 2008; 26 : 10s, A516 (abstract).

(d) Taxane-plus-anthracycline-based regimen (with taxane courses NOT overlapping with any other chemo. courses) vs DOUBLED (or ≈ doubled) non-taxane cytotoxic chemotherapy

Year Code	Trial name	Publication(s)
01F	TACT UK (Control A)	Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. <i>Lancet</i> 2009; 373 : 1681-92. Tutt A, Gillett C, Pinder S, et al. Microtubule associated protein tau expression as a predictive and prognostic marker in a trial assessing sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT). <i>Cancer Res</i> 2009; 69 : A607 (abstract).
01G	TACT UK (Control B)	Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. <i>Lancet</i> 2009; 373 : 1681-92. Tutt A, Gillett C, Pinder S, et al. Microtubule associated protein tau expression as a predictive and prognostic marker in a trial assessing sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT). <i>Cancer Res</i> 2009; 69 : A607 (abstract).
01T	LMU Munich ADEBAR	Sommer HL, Jueckstock JK, Genes E, et al. Influence of sequencing of chemotherapy and radiotherapy regarding adverse effects of cytostatic treatment: Results of the ADEBAR trial. <i>J Clin Oncol</i> 2007; 25 : 17s, A559 (abstract). Janni WJ, Harbeck N, Sommer H, et al. Sequential treatment with epirubicin/cyclophosphamide followed by docetaxel is equi-effective, but less toxic, than FEC120 in the adjuvant treatment of breast cancer patients with extensive lymph node involvement: The German ADEBAR phase III study. <i>Cancer Res</i> 2009; 69 : A604 (abstract).
96F	Aberdeen Scotland	Walker LG, Walker MB, Anderson J, et al. Quality of life during primary chemotherapy for breast cancer with continuing cyclophosphamide, vincristine, adriamycin and prednisolone versus sequential docetaxel: a randomised trial. <i>Breast Cancer Res Treat</i> 2002; 76 : S52, A160 (abstract).
97J	PACS 01 France	Coudert B, Campone M, Spielmann M, et al. Benefit of the sequential administration of docetaxel after standard FEC regimen for node-positive breast cancer: long-term follow-up results of the FNCLCC-PACS 01 trial. <i>Cancer Res</i> 2009; 69 : A603 (abstract).
97A	DEVA UK	Coombes RC, Bliss JM, Espie M, et al. DEVA: Randomized trial of sequential epirubicin and docetaxel versus epirubicin alone in node-positive postmenopausal early breast cancer (EBC) patients. <i>J Clin Oncol</i> 2010; 28 : 76S, A536 (abstract).
94B	MD Anderson	Buzdar AU, Singletary SE, Valero V, et al. Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomized trial. <i>Clin Cancer Res</i> 2002; 8 : 1073-79.
00F2	NCIC MA.21	Burnell M, Levine MN, Chapman JAW, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. <i>J Clin Oncol</i> 2010; 28 : 77-82.
02D	GBG 42 / NNBC 3-Eur.	Thomssen C, Kantelhardt EJ, Plueckhahn K, et al. Report of toxicities from the multicenter, randomized NNBC 3-Europe trial: 6xFEC versus 3xFEC-3xDoc for high-risk node-negative breast cancer patients. <i>J Clin Oncol</i> 2010; 28 : 80S, A554 (abstract). Kantelhardt EJ, Thomssen C, Vetter M, et al. Molecular types and prognostic markers uPA/PAI-1 for 2,497 early breast cancer patients in the multicenter, randomized NNBC 3-Europe trial. <i>J Clin Oncol</i> 2010; 28 : A10539.

(e) Taxane trial with no anthracycline in one allocation

Year Code	Trial name	Publication(s)
00S	WSG/AGO AM-02	Nitz U, Huober J, Lisboa B, et al. Superiority of sequential docetaxel over standard FE100C in patients with intermediate risk breast cancer: survival results of the randomized intergroup phase III trial EC-Doc. <i>Cancer Res</i> 2009; 69 : A78 (abstract).
97N	USO 97-35	Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. <i>J Clin Oncol</i> 2009; 27 : 1177-83.

Trials of any anthracycline-based regimen vs. standard CMF (or near-standard CMF) (see webappendix page 29):

(a) Anthracycline dose/cycle \geq A60 or E90

i. Cumulative anthracycline dose A360 or E720-800

Year Code	Trial name	Publication(s)
88R	Brussels Belgium	Bernard Marty C, Mano M, Paesmans M, et al. Second malignancies following adjuvant chemotherapy: 6-year results from a Belgian randomized study comparing cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with an anthracycline-based regimen in adjuvant treatment of node-positive breast cancer patients. <i>Ann Oncol</i> 2003; 14 : 693-98.
89R	NCIC MA.5	Pritchard KI, Shepherd LE, O'Malley FP, et al. <i>HER2</i> and responsiveness of breast cancer to adjuvant chemotherapy. <i>N Engl J Med</i> 2006; 354 : 2103-11.
89B2	SWOG 8897	Hutchins LF, Green SJ, Ravdin PM, et al. Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup protocol INT-0102. <i>J Clin Oncol</i> 2005; 23 : 8313-21.

ii. Cumulative anthracycline dose A300 or E400-480

Year Code	Trial name	Publication(s)
86S	GOCCNE Italy	Galligioni E, Cetto G, Nascimben O, et al. High dose epirubicin and cyclophosphamide (EC) vs cyclophosphamide, methotrexate, fluorouracil (CMF) as adjuvant chemotherapy in high risk premenopausal breast cancer patients (PTS). A prospective randomized trial. <i>Eur J Cancer</i> 1998; 34 (suppl 1): 84 (abstract).
97G	FM Italy GMB1	<i>Personal communication</i>
90Z	GOIRC SANG2 Italy	Colozza M, Bisagni G, Mosconi AM, et al. Epirubicin versus CMF as adjuvant therapy for stage I and II breast cancer: a prospective randomised study. <i>Eur J Cancer</i> 2002; 38 : 2279-88.
84K1	GUN-3 Naples	De Placido S, Perrone F, Carlomagno C, et al. CMF vs alternating CMF/EV in the adjuvant treatment of operable breast cancer. A single centre randomised clinical trial (Naples GUN-3 study). <i>Br J Cancer</i> 1995; 71 : 1283-87.
96N	GOCSI MAM2 Italy	De Matteis A, De Laurentiis M, Nuzzo F, et al. Preliminary results from the IMPACT-B01/MAM2 GOCSI randomized trial of adjuvant therapy for breast cancer. <i>Ann Oncol</i> 2002; 13 : 16, A53 (abstract).
96A	NEAT, UK	Earl HM, Hiller L, Dunn JA, et al. NEAT: National Epirubicin Adjuvant Trial-toxicity, delivered dose intensity and quality of life. <i>Br J Cancer</i> 2008; 99 : 1226-31.
97U1+2	IBIS 03 Italy	Cyclophosphamide, Methotrexate, and Fluorouracil, With or Without Epirubicin Hydrochloride, in Treating Women Who Have Undergone Surgery for Breast Cancer [Internet] 2009 [updated 2009 Dec 13; cited 2011 Jun 16]. Available from: http://clinicaltrials.gov/ct2/show/study/NCT01031030?term=ibis+03&rank=1 Amadori D, Silvestrini R, De Lena M, et al. Randomized phase III trial of adjuvant epirubicin followed by cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) versus CMF followed by epirubicin in patients with node-negative or 1-3 node-positive rapidly proliferating breast cancer. <i>Breast Cancer Res Treat</i> 2011; 125 : 775-84.
91Q	GOCSI MAM1 Italy	De Placido S, De Laurentiis M, De Lena M, et al. A randomised factorial trial of sequential doxorubicin and CMF vs CMF and chemotherapy alone vs chemotherapy followed by goserelin plus tamoxifen as adjuvant treatment of node-positive breast cancer. <i>Br J Cancer</i> 2005; 92 : 467-74.

iii. Cumulative anthracycline dose A240

Year Code	Trial name	Publication(s)
84B1	NSABP B-15	Wickerham D, Fisher B, Brown A, et al. Two months of adriamycin + cyclophosphamide (AC) with and without interval reinduction therapy vs 6 months of conventional CMF in positive node breast cancer patients (pts) nonresponsive to tamoxifen: results of NSABP B-15. <i>Proc Annu Meet Am Soc Clin Oncol</i> 1990; 9 : A73 (abstract).
84B2	NSABP B-15	Wickerham D, Fisher B, Brown A, et al. Two months of adriamycin + cyclophosphamide (AC) with and without interval reinduction therapy vs 6 months of conventional CMF in positive node breast cancer patients (pts) nonresponsive to tamoxifen: results of NSABP B-15. <i>Proc Annu Meet Am Soc Clin Oncol</i> 1990; 9 : A73 (abstract).
91H	NSABP B-23	Fisher B, Anderson S, Tan Chiu E, et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. <i>J Clin Oncol</i> 2001; 19 : 931-42.

(b) Anthracycline dose/cycle < A60 or E90

Year Code	Trial name	Publication(s)
78L2	ONCOFRANCE	Misset JL, di Palma M, Delgado M, et al. Adjuvant treatment of node-positive breast cancer with cyclophosphamide, doxorubicin, fluorouracil, and vincristine versus cyclophosphamide, methotrexate, and fluorouracil: final report after a 16-year median follow-up duration. <i>J Clin Oncol</i> 1996; 14 : 1136-45.
88R	Brussels Belgium	Bernard Marty C, Mano M, Paesmans M, et al. Second malignancies following adjuvant chemotherapy: 6-year results from a Belgian randomized study comparing cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with an anthracycline-based regimen in adjuvant treatment of node-positive breast cancer patients. <i>Ann Oncol</i> 2003; 14 : 693-98.
94J1+2+3	GOIRC SANG 2B R1	<i>Personal communication</i>
84L	ICCG C/2/84 UK	Coombes RC, Bliss JM, Wils J, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. The International Collaborative Cancer Group. <i>J Clin Oncol</i> 1996; 14 : 35-45.
80C1	SE Sweden BCG A	Hrafinkelsson J, Nilsson K, Soderberg M. Tolerance of radiotherapy combined with adjuvant chemotherapy in breast cancer. <i>Acta Oncol</i> 1987; 26 : 269-72.
84N	ICCG C/6/89 UK	Marty M, Hall E, Wils J, et al. Evaluation of tolerability of CMF versus FEC in a randomised trial in node negative poor risk primary breast cancer patients. <i>Proc Annu Meet Am Soc Clin Oncol</i> 2002; 21 : 69a, A273 (abstract).

[End of anthracycline vs CMF; anthracycline vs nil follows]

Trials of Anthracycline-based regimen vs. No chemotherapy (see webappendix page 35):

(a) Anthracycline dose/cycle exactly A60 or E90

Year Code	Trial Name	Publication(s)
89B1	SWOG 8814	Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. <i>Lancet</i> 2009; 374 : 2055-63.
92D	Amsterdam C9203	Nortier JWR; Slee PHT; Veenhof CHN, et al. Adjuvant Tamoxifen plus combination chemotherapy with epirubicin and cyclophosphamide versus tamoxifen alone in postmenopausal node-positive breast cancer patients. Amsterdam Integraal Kankercentrum, The Netherlands, Sep 1993. (Protocol 12706, supplied by trialists)
93H	IBCSG 11-93	Thürlimann B, Price KN, Gelber RD, et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. <i>Breast Cancer Res Treat</i> 2009; 113 : 137-44.
93M1+2	IBCSG 12-93	International Breast Cancer Study Group. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. <i>Ann Oncol</i> 2004; 15 :1749-1759
84C	NSABP B-16	Fisher B, Redmond C, Legault Poisson S, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: Results from the National Surgical Adjuvant Breast and Bowel Project B-16. <i>J Clin Oncol</i> 1990; 8 : 1005-18.

(b) Anthracycline dose/cycle < A60 or E90, sorted by cumulative dose

Year Code	Trial Name	Publication(s)
76H1	West Midlands UK	Morrison JM, Howell A, Kelly KA, et al. West Midlands Oncology Association trials of adjuvant chemotherapy in operable breast cancer: Results after a median follow up of 7 years. I Patients with involved axillary lymph nodes. <i>Br J Cancer</i> 1989; 60 : 911-18.
76L1	Cologne	<i>Personal communication</i>
74D1	DFCI 74-063	Henderson IC, Gelman R, Parker LM, et al. 15 vs. 30 weeks (wks) of adjuvant chemotherapy for breast cancer patients (pts) with a high risk of recurrence: A randomized trial. <i>Proc Ann Meet Am Soc Clin Oncol</i> 1982: C-290 (abstract).
80B3+4	N Sweden BCG	<i>Personal communication</i>
80C2	SE Sweden BCG B	Hrafinkelsson J, Nilsson K, Soderberg M. Tolerance of radiotherapy combined with adjuvant chemotherapy in breast cancer. <i>Acta Oncol</i> 1987; 26 : 269-72.
80S1	Helsinki	Blomqvist C, Tiusanen K, Elomaa I, et al. The combination of radiotherapy, adjuvant chemotherapy (cyclophosphamide doxorubicin fluorouracil) and tamoxifen in stage II breast cancer. Long term follow up results of a randomised trial. <i>Br J Cancer</i> 1992; 66 : 1171-76.
84C2	NSABP B-16	Fisher B, Redmond C, Legault Poisson S, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: Results from the National Surgical Adjuvant Breast and Bowel Project B-16. <i>J Clin Oncol</i> 1990; 8 : 1005-18.
80Z	Southampton UK	Williams CJ, Buchanan RB, Hall V, Taylor I. Adjuvant chemotherapy for T1-2, N0, M0 estrogen receptor (ER) negative breast cancer: preliminary results of a randomized trial. Fifth International Conference on the Adjuvant Therapy of Cancer. March 11-14 1987, Tucson, Arizona. page 46 (abstract).
94F	JCOG 9401	<i>Personal communication</i>
89D	IGR Paris	Arriagada R, Spielmann M, Koscielny S, et al. Patterns of failure in a randomized trial of adjuvant chemotherapy in postmenopausal patients with early breast cancer treated with tamoxifen. <i>Ann Oncol</i> 2002; 13 : 1378-1386 Arriagada R, Spielmann M, Koscielny S et al. Results of two randomized trials evaluating adjuvant anthracycline-based chemotherapy in 1146 patients with early breast cancer. <i>Acta Oncol</i> 2005; 44 : 458-466 Andre F, Khalil A, Slimane K, et al. Mitotic index and benefit of adjuvant anthracycline-based chemotherapy in patients with early breast cancer. <i>J Clin Oncol</i> 2005; 23 : 2996-3000.
83B	GROCTA I Italy	Boccardo F, Rubagotti A, Amoroso D, et al. Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group Trials. GROCTA Trials. <i>Recent Results Cancer Res</i> 1998; 152 : 453-70.
86P2	FASG GFEA 02	Namer M, Fargeot P, Roche H, et al. Improved disease-free survival with epirubicin-based chemoendocrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. <i>Ann Oncol</i> 2006; 17 : 65-73.
86P3	FASG GFEA 03	Hery M, Bonnetterre J, Roche H, et al. Epirubicin-based chemotherapy as adjuvant treatment for poor prognosis, node-negative breast cancer: 10-year follow-up results of the French Adjuvant Study Group 03 trial. <i>Bull Cancer</i> 2006; 93 : E109-14.
89@1	Bari Italy	Paradiso A, Schittulli F, Cellamare G, et al. Randomized clinical trial of adjuvant fluorouracil, epirubicin, and cyclophosphamide chemotherapy for patients with fast-proliferating, node-negative breast cancer. <i>J Clin Oncol</i> 2001; 19 : 3929-37.
90C6	FASG GFEA 07	Namer M, Fargeot P, Roche H, et al. Improved disease-free survival with epirubicin-based chemoendocrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. <i>Ann Oncol</i> 2006; 17 : 65-73.
96E	Austrian BCSG IX	Taucher S, Salat A, Gnant M, et al. Impact of pretreatment thrombocytosis on survival in primary breast cancer. <i>Thromb Haemost</i> 2003; 89 : 1098-1106.
82F	MD Anderson 8227	<i>Personal communication</i>

(c) Lower cumulative anthracycline dose

Year Code	Trial Name	Publication
84Q4+5	Austrian BCSG 4	Jakesz R, Hausmaninger H, et al. Randomized trial of low-dose chemotherapy added to tamoxifen in patients with receptor-positive and lymph node-positive breast cancer. <i>J Clin Oncol</i> 1999; 17 : 1701-09.

Trials of Standard CMF vs. No chemotherapy (see webappendix page 41):

Year Code	Trial name	Publication(s)
73B	INT Milan 7205	Bonadonna G, Zambetti M, Moliterni A, et al. Clinical relevance of different sequencing of doxorubicin and cyclophosphamide, methotrexate, and fluorouracil in operable breast cancer. <i>J Clin Oncol</i> 2004; 22 :1614-20. Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. <i>BMJ</i> 2005; 330 : 217-23.
78K3	IBCSG/Ludwig III	Pagani O, Price KN, Gelber RD, et al. Patterns of recurrence of early breast cancer according to estrogen receptor status: A therapeutic target for a quarter of a century. <i>Breast Cancer Res Treat</i> 2009; 117 : 319-324.
78V2	ECOG EST6177	Taylor SG, Knuiiman MW, Sleeper LA, et al. Six-year results of the Eastern Cooperative Oncology Group trial of observation versus CMFP versus CMFPT in postmenopausal patients with node-positive breast cancer. <i>J Clin Oncol</i> 1989; 7 : 879-89.
79U1+3	Vienna Gyn.	Kubista E, Salzer H, Fischl F, et al. [Treatment of breast cancer at the 1st Gynecology Clinic at the University of Vienna]. <i>Wien Med Wochenschr</i> 1984; 134 : 251-5.
81H	EST1180/SW.8294	Mansour EG, Gray R, Shatila AH, et al. Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. An Intergroup study. <i>N Engl J Med</i> 1989; 320 : 485-90.
86H2	IBCSG VII	The International Breast Cancer Study Group. Effectiveness of adjuvant chemotherapy in combination with tamoxifen for node-positive postmenopausal breast cancer patients. <i>J Clin Oncol</i> 1997; 15 : 1385-93.
88C	NSABP B-20	Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. <i>J Clin Oncol</i> 2010; 28 : 1677-83.
89A2	SITAM-01	Belfiglio M, Mari E, Nicolucci A, et al. Sitam-01 adjuvant breast trial for patients > 50 years. <i>Eur J Cancer</i> 1996; 32 (suppl 1): 21 (abstract).
89E4+9	GROCTA V Italy	Boccardo F, Rubagotti A, Amoroso D, et al. Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group Trials. GROCTA Trials. <i>Recent Results Cancer Res</i> 1998; 152 : 453-70.
89V	Romagnolo Italy	Amadori D, Nanni O, Volpi A, et al. Phase III randomized multicenter study on the effects of adjuvant CMF in patients with node-negative, rapidly proliferating breast cancer: twelve-year results and retrospective subgroup analysis. <i>Breast Cancer Res Treat</i> 2008; 108 : 259-64.
90P	Amsterdam C8913	<i>Personal communication</i>
90S	IBCSG VIII	Karlsson P, Sun Z, Braun D, et al. Long term results of International Breast Cancer Study Group Trial VIII: adjuvant chemotherapy plus goserelin compared with either therapy alone for premenopausal patients with node-negative breast cancer. <i>Ann Oncol</i> 2011; 22 : 2216-26.

Trials of Anthracycline Dosage (see webappendix page 47):

(a) Unconfounded comparisons

Year Code	Trial name	Publication(s)
86P1	FASG GFEA 01	Benchalal M, Le Prise E, De Lafontan B, et al. Influence of the time between surgery and radiotherapy on local recurrence in patients with lymph node-positive, early-stage, invasive breast carcinoma undergoing breast-conserving surgery: Results of the French Adjuvant Study Group. <i>Cancer</i> 2005; 104 : 240-250. Fumoleau P, Devaux Y, Vo-Van ML, et al. Premenopausal patients with node positive resectable breast cancer: a randomized trial comparing three adjuvant regimens: FEC50 x 6 cycles vs FEC50 x 3 cycles vs FEC75 x 3 cycles, preliminary results. <i>Ann Oncol</i> 1992; 3 : 203 (abstract).
90C3+5	FASG GFEA 05	Bonnetterre J, Roche H, Kerbrat P, et al. French Adjuvant Study Group 05 trial (FEC 50 vs FEC 100): 10-year update of benefit/risk ratio after adjuvant chemotherapy (CT) in node-positive (N+), early breast cancer (EBC) patients (pts). <i>Proc Annu Meet Am Soc Clin Oncol</i> 2003; 22 : 24, A93 (abstract). Bonnetterre JM, French Adjuvant Study Group. Long-term efficacy and toxicity of the FEC100 regimen. <i>Oncology (Williston Park)</i> 2004; 18 (14), suppl 14: 56-58.
92N	ICCG C/9/91 UK	Bliss JM, Wils J, Marty M, et al. Evaluation of the tolerability of FE50C versus FE75C in a prospective randomised trial in adjuvant breast cancer patients. <i>Proc Annu Meet Am Soc Clin Oncol</i> 2002; 21 : 51b, A2017 (abstract).
94D1&2	CALGB 9344	Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. <i>J Clin Oncol</i> 2003; 21 : 976-83. Berry DA, Thor A, Jewell SD, et al. Benefits of adding paclitaxel to adjuvant doxorubicin/cyclophosphamide depending on HER2 & ER status: analysis of tumor tissue microarrays and immunohistochemistry in CALGB 9344 (Intergroup 0148). <i>Cancer Res</i> 2009; 69 : A606 (abstract).

(b) Confounded comparisons

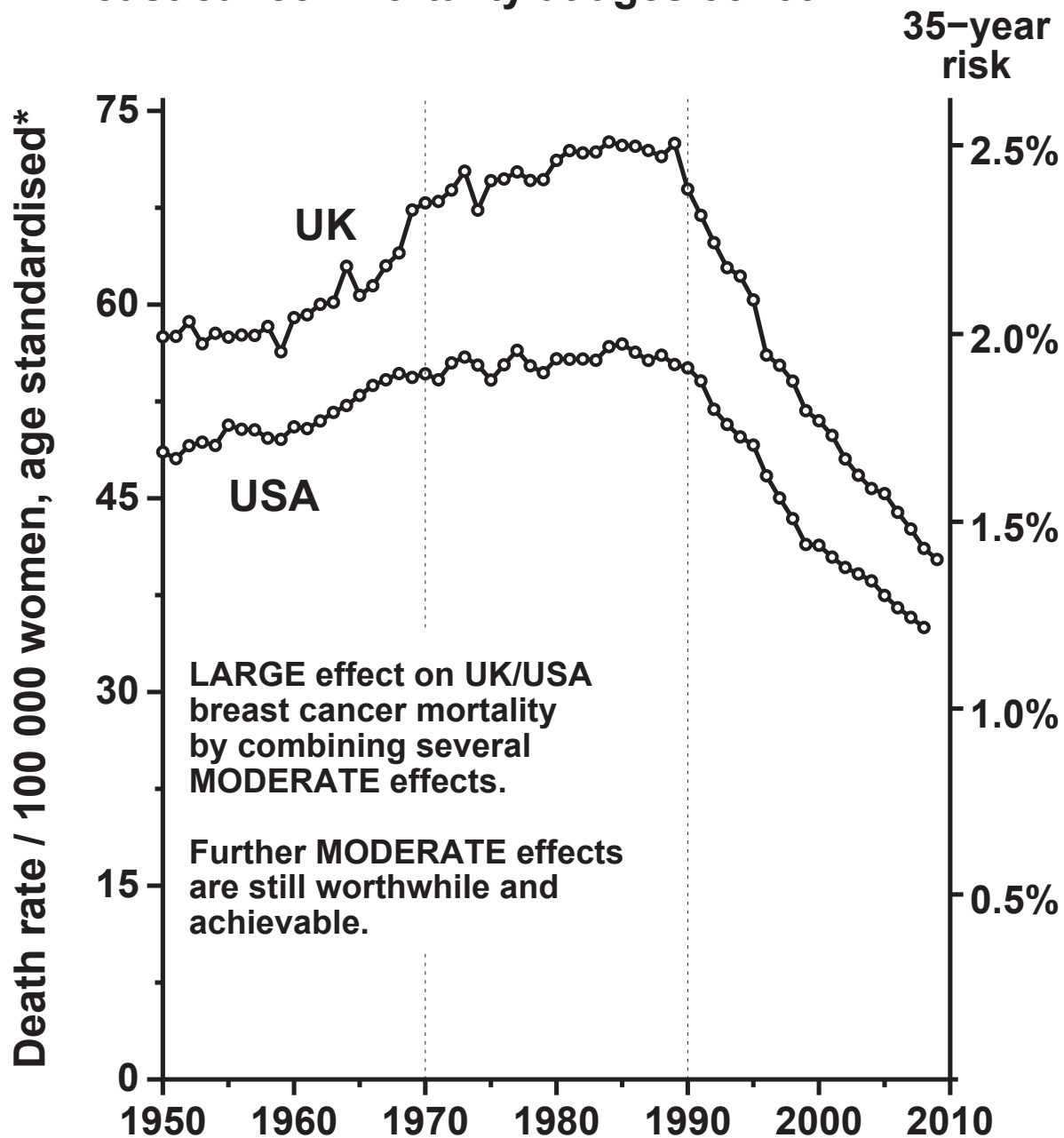
Year Code	Trial name	Publication(s)
85A	CALGB CLB-8541	Muss HB, Berry DA, Cirincione C, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B experience. <i>J Clin Oncol</i> 2007; 25 : 3699-3704. Wood WC, Budman DR, Korzun AH, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node positive breast carcinoma. <i>N Engl J Med</i> 1994; 330 : 1253-59.
88R	Brussels Belgium	Bernard Marty C, Mano M, Paesmans M, et al. Second malignancies following adjuvant chemotherapy: 6-year results from a Belgian randomized study comparing cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with an anthracycline-based regimen in adjuvant treatment of node-positive breast cancer patients. <i>Ann Oncol</i> 2003; 14 : 693-98.
00F	NCIC MA21	Burnell M, Levine MN, Chapman JAW, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. <i>J Clin Oncol</i> 2010; 28 : 77-82.

[End of webappendix]

**Local and systemic therapies:
several MODERATE survival gains**

**MODERATE improvements in early detection,
in local control, in endocrine therapy and
in chemotherapy have, in aggregate,
SUBSTANTIALLY reduced national mortality rates**

**UK 1950–2009 and USA (to 2008):
Breast cancer mortality at ages 35–69**



*Mean of annual rates in the seven component 5-year age groups

WHO (& 2008 US NCHS) mortality and UN population estimates

Reliable assessment of MODERATE differences in LONG-TERM survival by the 5-yearly worldwide overview (with tens of thousands randomised)

Need all the main randomised trial results, both to get big enough numbers and to avoid undue emphasis on particular studies

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

**So as not to miss any MODERATE
differences in long-term survival,
the world's trialists have shared
their data every 5 years since 1985**

1985, 1990, 1995, 2000, 2005, 2010

620 names of EBCTCG collaborators in local and systemic therapy trials, listed alphabetically by institution, then name. Lancet 2011; 378: 771-84.

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Bourcier, C Hill, S Koscielny, A Laplanche, M G Le, M Spielmann. *Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU, NCR), UK* R A' Hern, J Bliss, P Ellis, L Kilburn, J R Yarnold. *Integraal Kankercentrum, Amsterdam, Netherlands* J Benraadt, M Kooi, A O van de Velde, J A van Dongen, J B Vermorken. *International Breast Cancer Study Group (IBCSG), Bern, Switzerland* M Castiglione, A Coates, M Colleoni, J Collins, J Forbes, R D Gelber, A Goldhirsch, J Lindtner, K N Price, M M Regan, C M Rudenstam, H J Senn, B Thuerlimann. *International Collaborative Cancer Group, Charing Cross Hospital, London, UK* J M Bliss, C E D Chivers, R C Coombes, E Hall, M Marty. *International Drug Development Institute, Louvain-la-Neuve, Belgium* M Buyse. *International TABLE Study Group, Berlin, Germany* K Possinger, P Schmid, M Untch, D Wallwiener. *ISD Cancer Clinical Trials Team (incorporating the former Scottish Cancer Therapy Network), Edinburgh, UK* L Foster, W D George, H J Stewart, P Stroner. *Israel NSABC, Tel Aviv, Israel* R Borovik, H Hayat, M J Inbar, E Robinson. *Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy* P Bruzzi, L Del Mastro, P Pronzato, M R Sertoli, M Venturini. *Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy* T Camerini, G De Palo, M G Di Mauro, F Formelli, P Valagussa. *Istituto Oncologico Romagnolo, Forli, Italy* D Amadori. *Italian Cooperative Chemo-Radio-Surgical Group, Bologna, Italy* A Martoni, F Annuti. *Italian Oncology Group for Clinical Research (GOIRC), Parma, Italy* R Camisa, G Cocconi, A Colozza, R Passalacqua. *Japan Clinical Oncology Group- Breast Cancer Study Group, Matsuyama, Japan* K Aogi, S Takashima. *Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan* O Abe, T Ikeda, K Inokuchi, K Kikuchi, K Sawa. *Kawasaki Medical School, Japan* H Sonoo. *Krakow Oncology, Poland* S Korzeniowski, J Skolyszewski. *Kumamoto University Group, Japan* M Ogawa, J Yamashita. *Leiden University Medical Center, Netherlands* E Bastiaansen, C J H van de Velde, W van de Water, J G H van Nes. *Leuven Akademisch Ziekenhuis, Gasthuisberg, Belgium* R Christiaens, P Neven, R Paridaens, W Van den Bogaert. *Ludwig-Maximilians University, Munich, Germany* S Braun, W Janni. *Marseille Laboratoire de Cancérologie Biologique APM, France* P Martin, S Romain. *Medical University Vienna - General Hospital - Department of Obstetrics and Gynaecology and Department of Medicine I, Vienna, Austria* M Janauer, M Seifert, P Sevelda, C C Zielinski. *Memorial Sloan-Kettering Cancer Center, New York, NY, USA* T Hakes, C A Hudis, L Norton, R Wittes. *Metaxas Memorial Cancer Hospital, Athens, Greece* G Giokas, D Kondylis, B Lissaios. *Mexican National Medical Center, Mexico City, Mexico* R de la Huerta, M G Sainz. *National Cancer Institute, Bethesda, MD, USA* R Altemus, K Camphausen, K Cowan, D Danforth, A Lichter, M Lippman, J O' Shaughnessy, L J Pierce, S Steinberg, D Venzon, J A Zujewski. *National Cancer Institute of Bari, Italy* C-D' Amico, M Lioce, A Paradiso. *NCIC Clinical Trials Group, Kingston, Ontario, Canada* J A-W Chapman, K Gelmon, P E Goss, M N Levine, R Meyer, W Parulekar, J L Pater, K I Pritchard, L E Shepherd, D Tu, T Whelan. *National Kyushu Cancer Center, Japan* Y Nomura, S Ohno. *National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, PA, USA*

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EBCTCG, Lancet 2011

**Comparisons between different polychemo-
therapy regimens for early breast cancer:
meta-analyses of long-term outcome among
100,000 women in 123 randomised trials**

**Early Breast Cancer Trialists' Collaborative Group
(EBCTCG)**

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Direct and indirect comparisons between different polychemotherapy regimens, based on ~100,000 randomised women

45,000 taxane vs no taxane*

(44,000 with anthracycline in both arms)

22,000 anthracycline vs CMF

(18,000 vs “standard” CMF)

5,000 more vs less anthracycline

(2000 comparing currently relevant doses)

31,000 polychemotherapy vs no adjuvant chemo

(13,000 CMF vs Nil; 10,000 anthr.-based regimen vs Nil)

* Excludes trials of one taxane regimen vs another

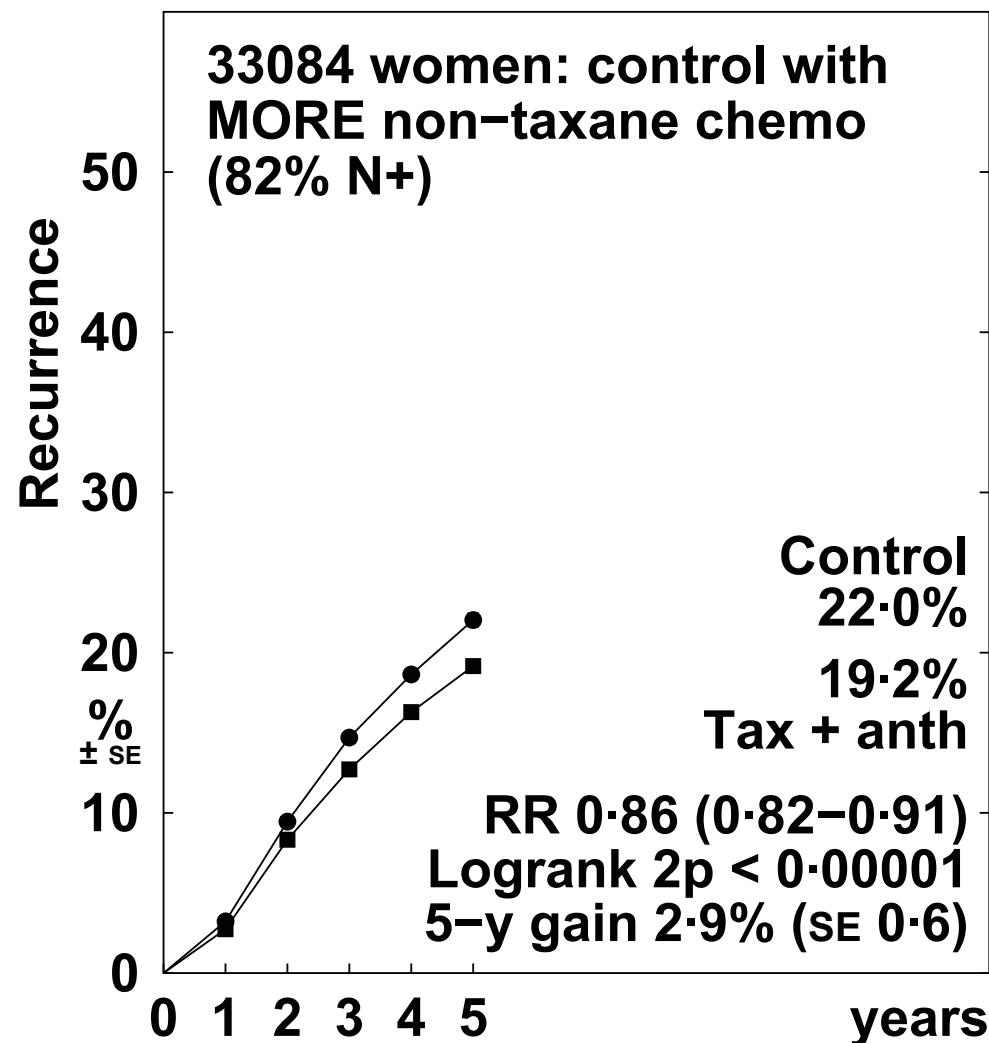
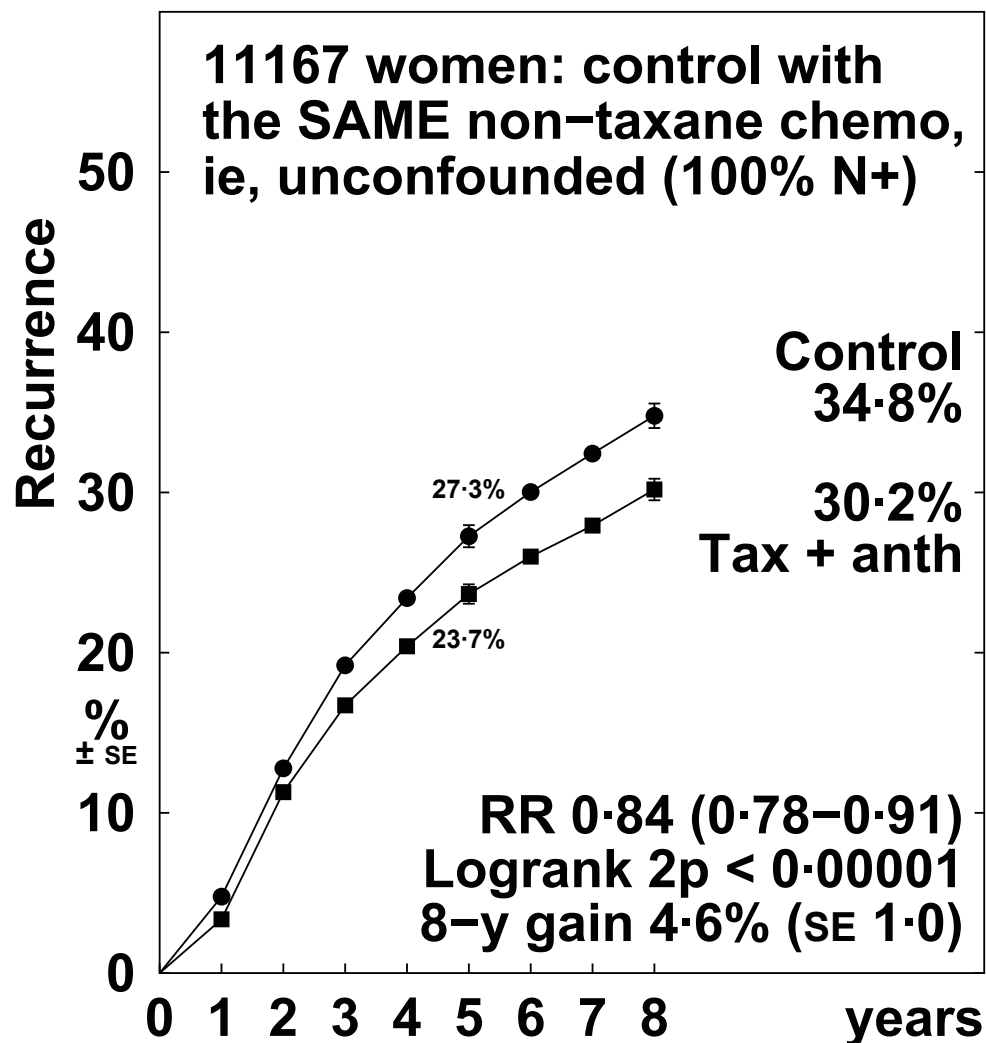
Taxane trials

Data on 44,000 women in randomised trials of a taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemotherapy

11,000 in trials where the non-taxane regimen was the SAME, and **33,000** in trials where it was MORE

[15% node-negative; mean follow-up only 5 years;
mean recurrence rate about 5% per year]

Taxane-plus-anthracycline-based regimens vs (L) the SAME, or (R) MORE, non-taxane chemo.

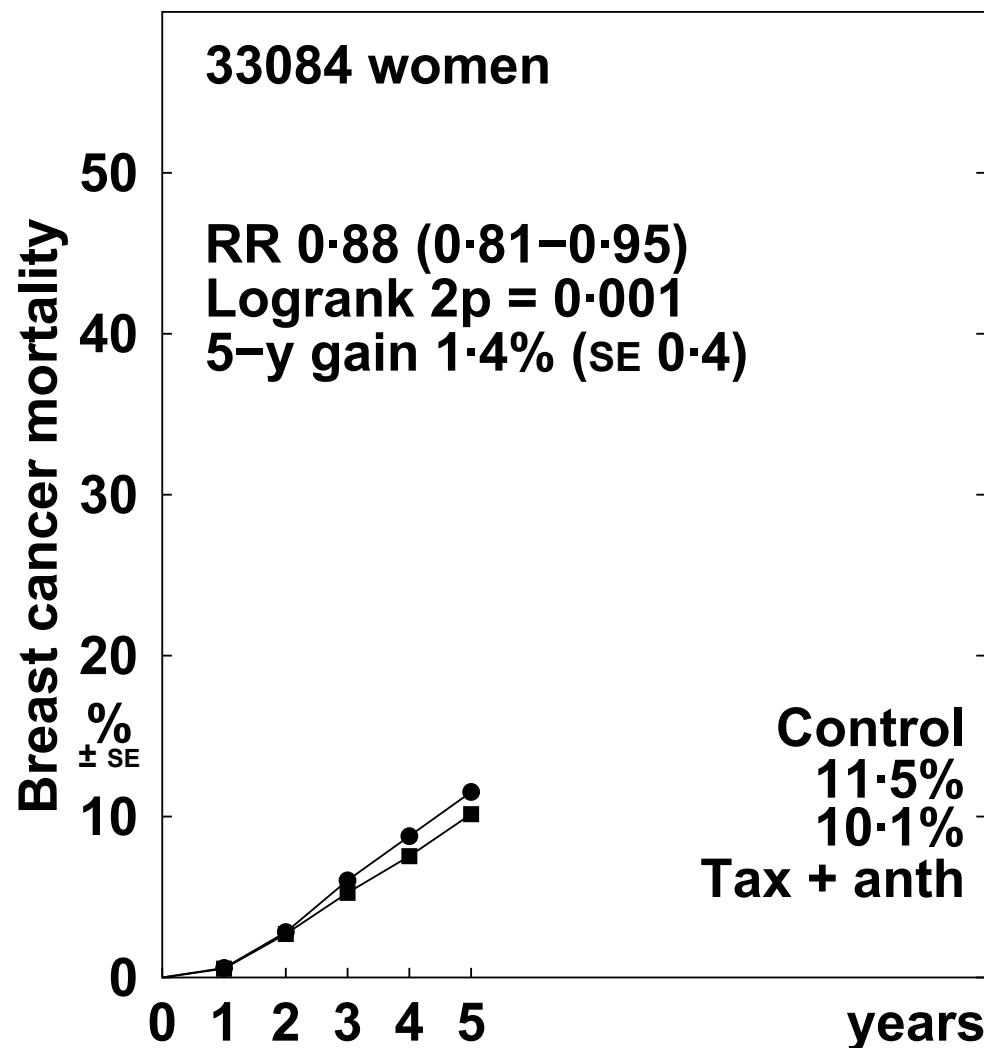
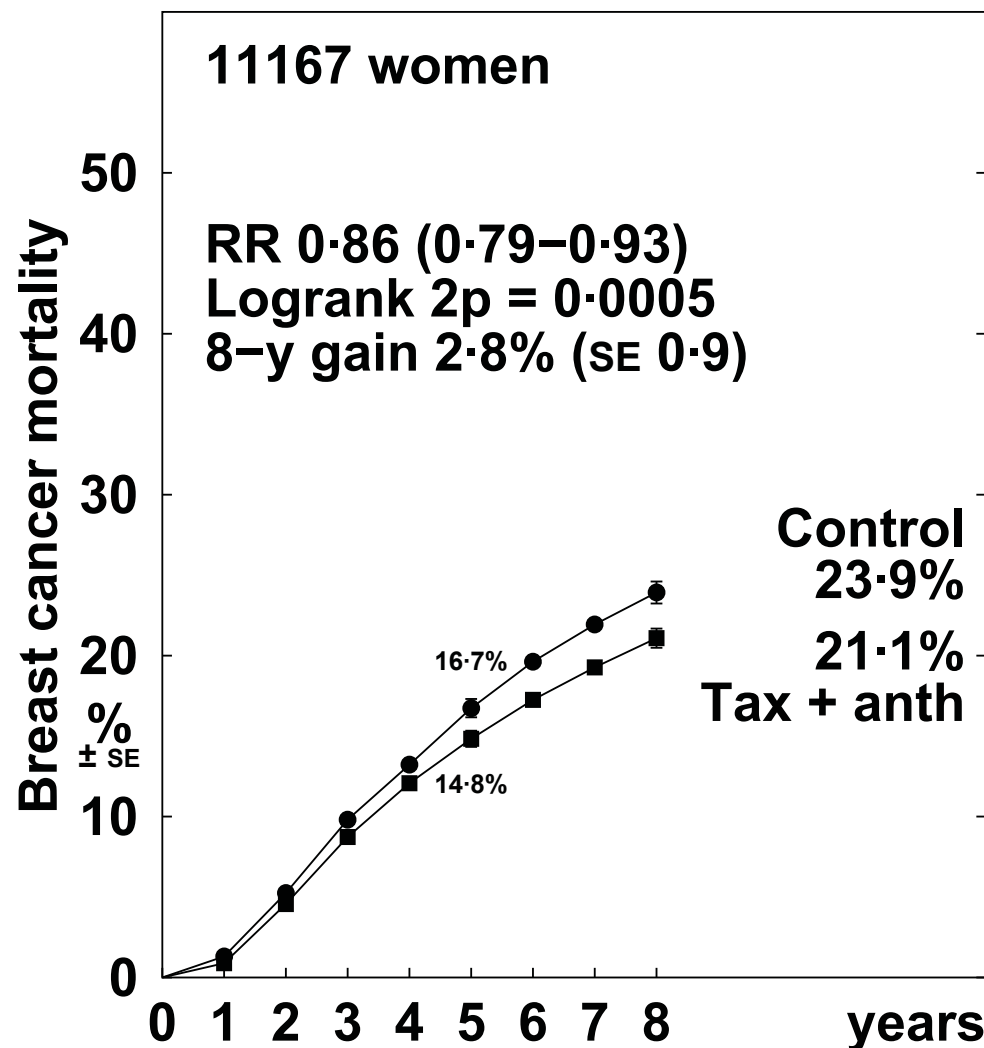


Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 - 4	Year 5+
Tax + anth	5.51 (1280 / 23249)	3.10 (413 / 13343)
Control	6.43 (1239 / 19259)	3.62 (381 / 10534)
Rate ratio	0.84 SE 0.04	0.85 SE 0.07
(O-E) / V	-95.5 / 557.3	-30.5 / 182.8

Years 0 - 4	Year 5+
4.37 (2607 / 59665)	3.01 (153 / 5082)
5.02 (2586 / 51508)	2.69 (127 / 4727)
0.85 SE 0.03	1.03 SE 0.13
-181.4 / 1153.8	1.9 / 63.6

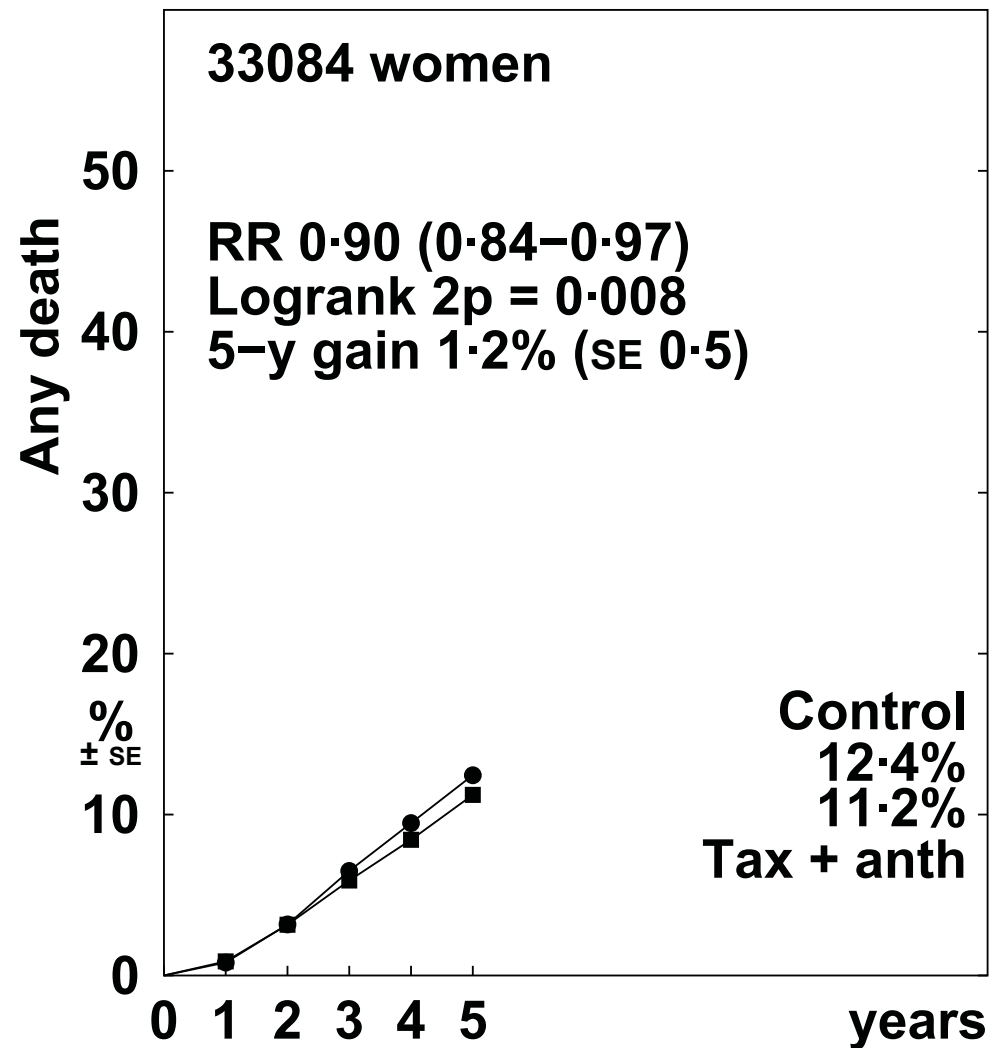
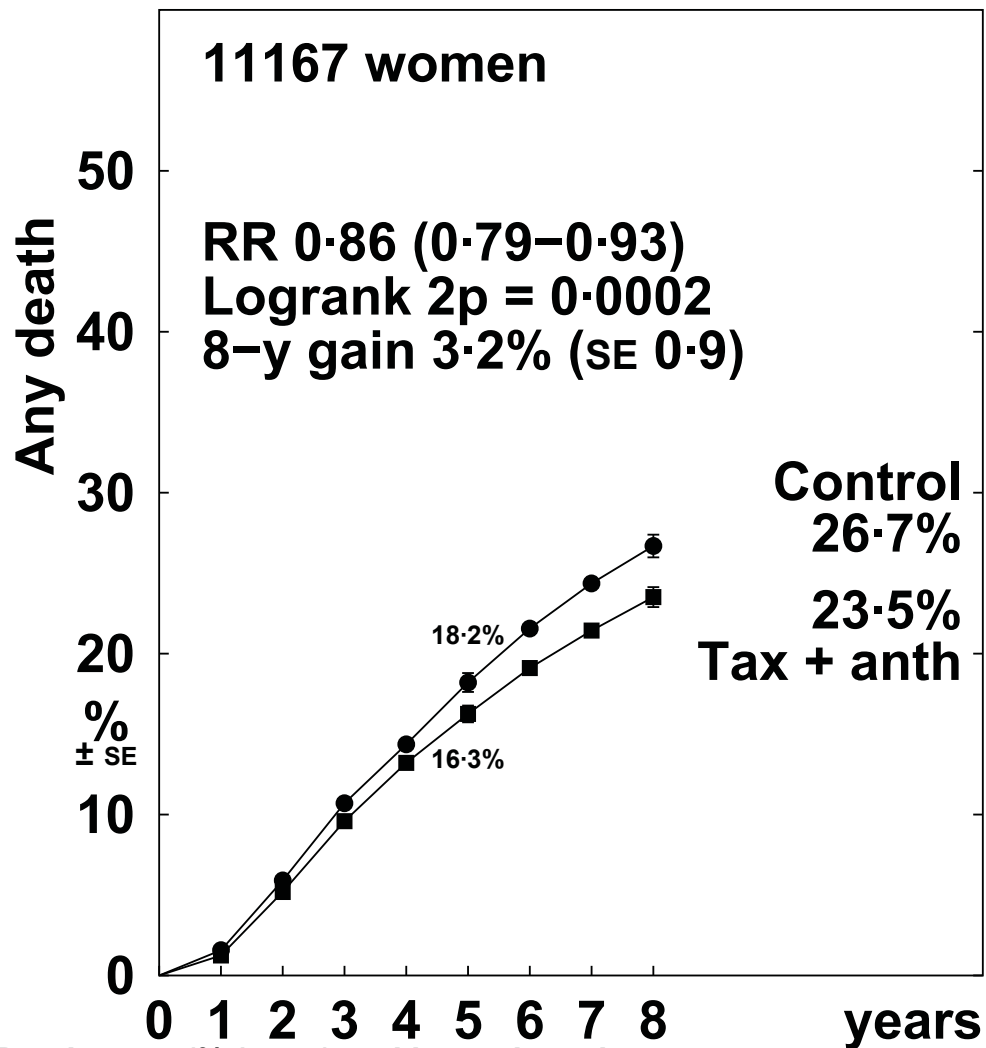
Taxane-plus-anthracycline-based regimens vs (L) the SAME, or (R) MORE, non-taxane chemo.



Death rates (% / year: total rate – rate in women without recurrence)	Years 0 – 4	Year 5+
Allocation	Years 0 – 4	Year 5+
Tax + anth	3.21 SE 0.11	2.48 SE 0.13
Control	3.58 SE 0.13	3.06 SE 0.16
Rate ratio	0.88 SE 0.05	0.82 SE 0.07
(O-E) / V	-46.4 / 348.5	-33.3 / 172.3

Death rates (% / year: total rate – rate in women without recurrence)	Years 0 – 4	Year 5+
Allocation	Years 0 – 4	Year 5+
Tax + anth	2.01 SE 0.06	2.37 SE 0.20
Control	2.30 SE 0.07	2.26 SE 0.21
Rate ratio	0.87 SE 0.04	0.97 SE 0.13
(O-E) / V	-77.0 / 549.5	-1.7 / 57.4

Taxane-plus-anthracycline-based regimens vs (L) the SAME, or (R) MORE, non-taxane chemo.



Death rates (% / year) and logrank analyses

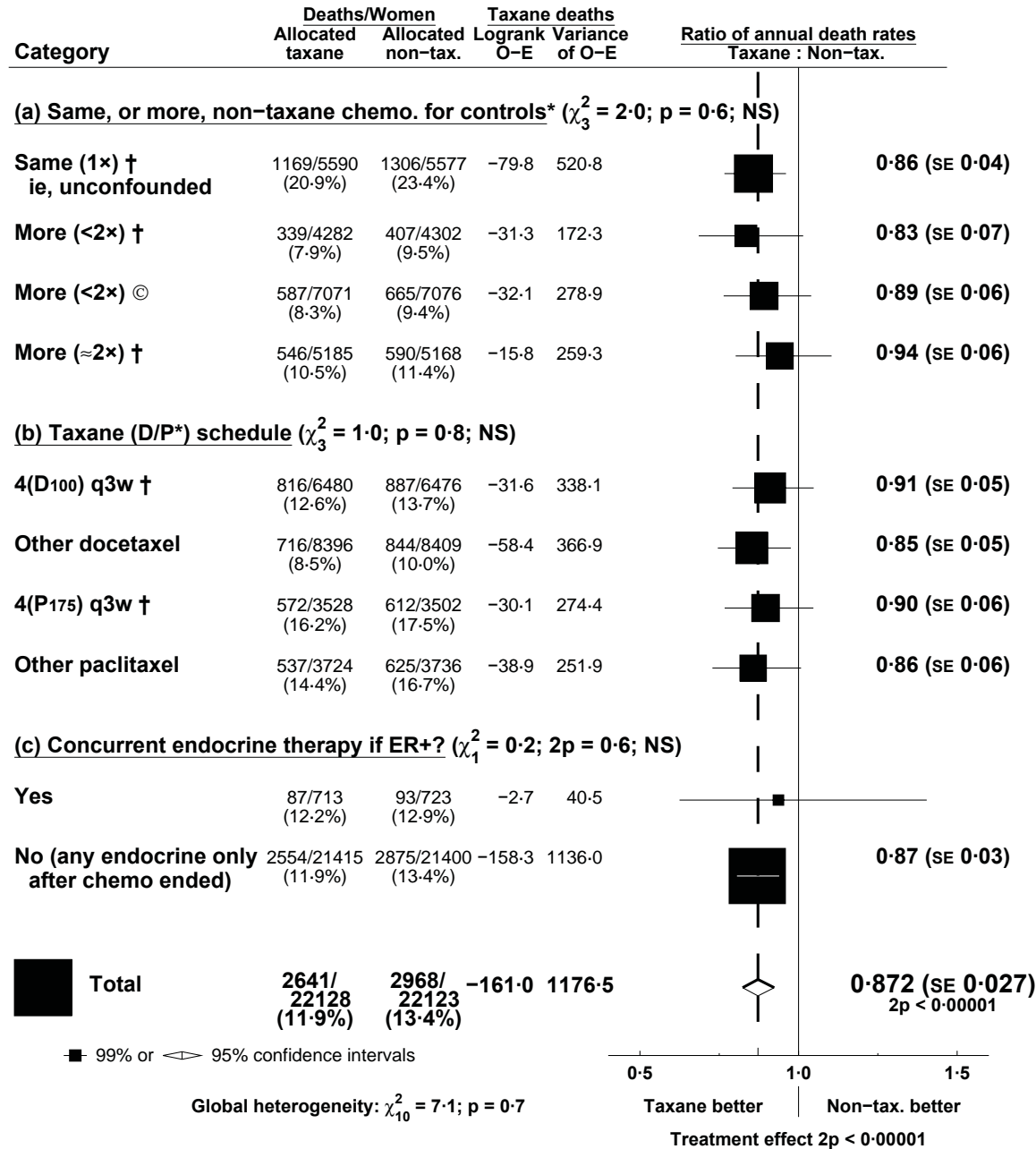
Allocation	Years 0 – 4	Year 5+
Tax + anth	3.55 (881 / 24821)	3.09 (465 / 15061)
Control	3.93 (819 / 20850)	3.76 (458 / 12178)
Rate ratio	0.88 SE 0.05	0.82 SE 0.06
(O-E) / V	-48.6 / 386.0	-41.3 / 213.4

Allocation	Years 0 – 4	Year 5+
Tax + anth	2.24 (1326 / 59104)	2.85 (161 / 5658)
Control	2.51 (1326 / 52888)	2.84 (152 / 5358)
Rate ratio	0.90 SE 0.04	0.96 SE 0.12
(O-E) / V	-66.3 / 608.4	-3.1 / 70.9

Taxane comparisons, subdivided according to:

- (a) how the non-taxane treatments compare (active = control, active = $\frac{1}{2}$ control, or an intermediate ratio), and**
- (b) whether the cycles of taxane are given concurrently (©) with the anthracycline, or whether taxanes are given alone (†).**

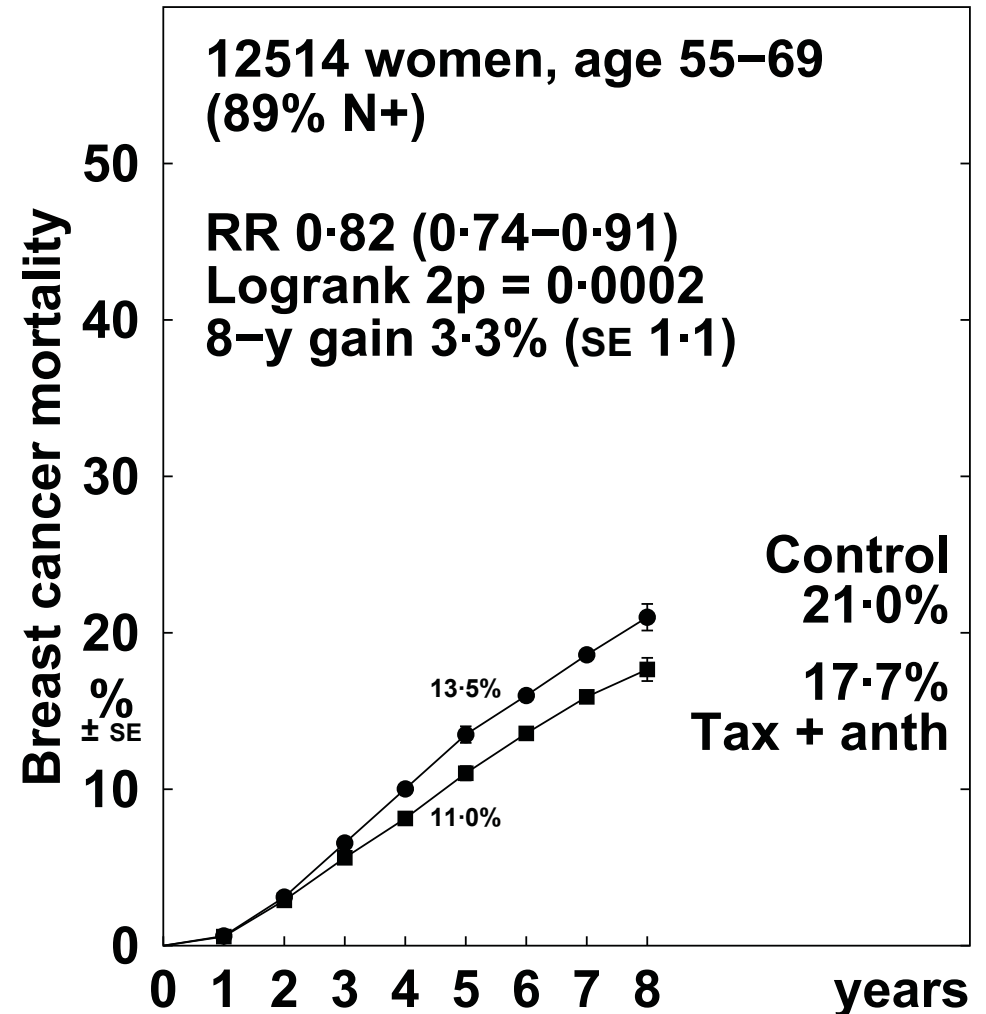
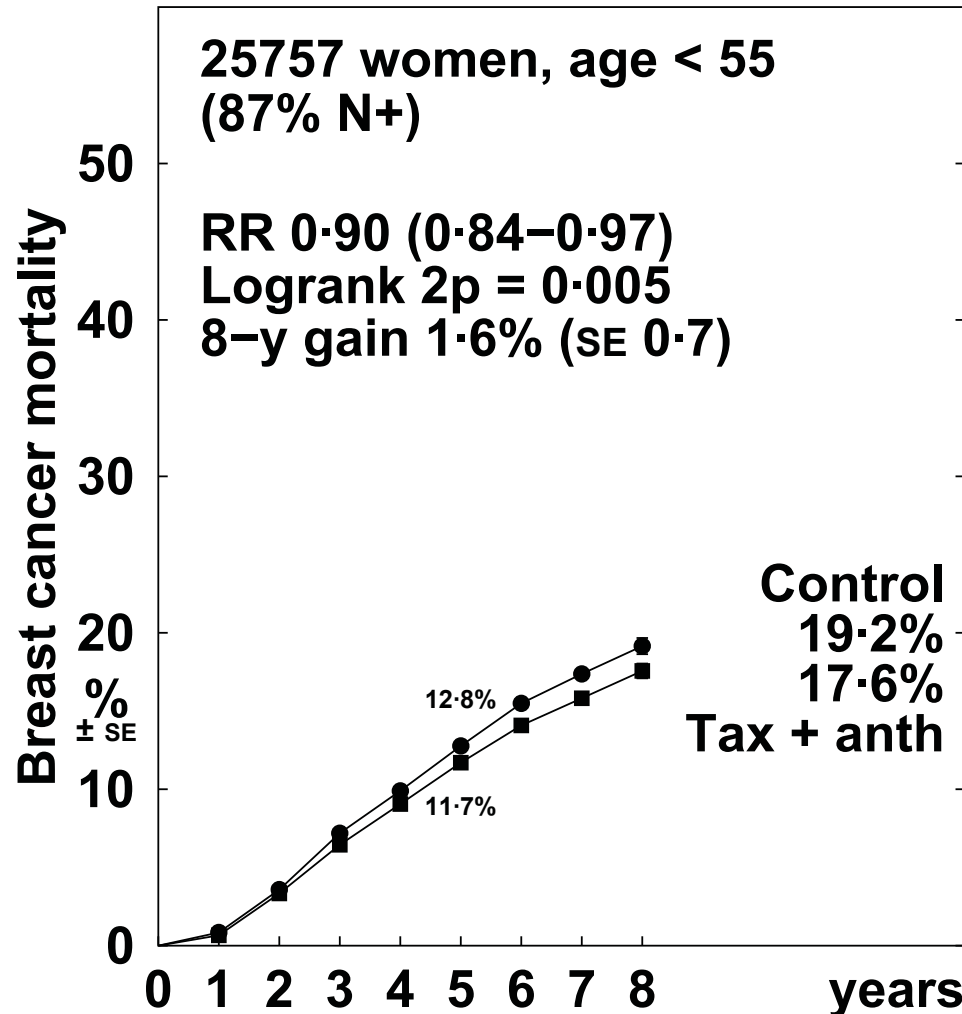
Breast cancer mortality ratio in taxane trials, by TYPE of treatment comparison



**Taxane trials: subgroup analyses
by age, stage and ER status**

**Taxane-plus-anthracycline-based regimen
vs
an anthracycline-based control regimen
with the SAME, or MORE, of each
non-taxane cytotoxic drug**

Taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemo, by ENTRY AGE

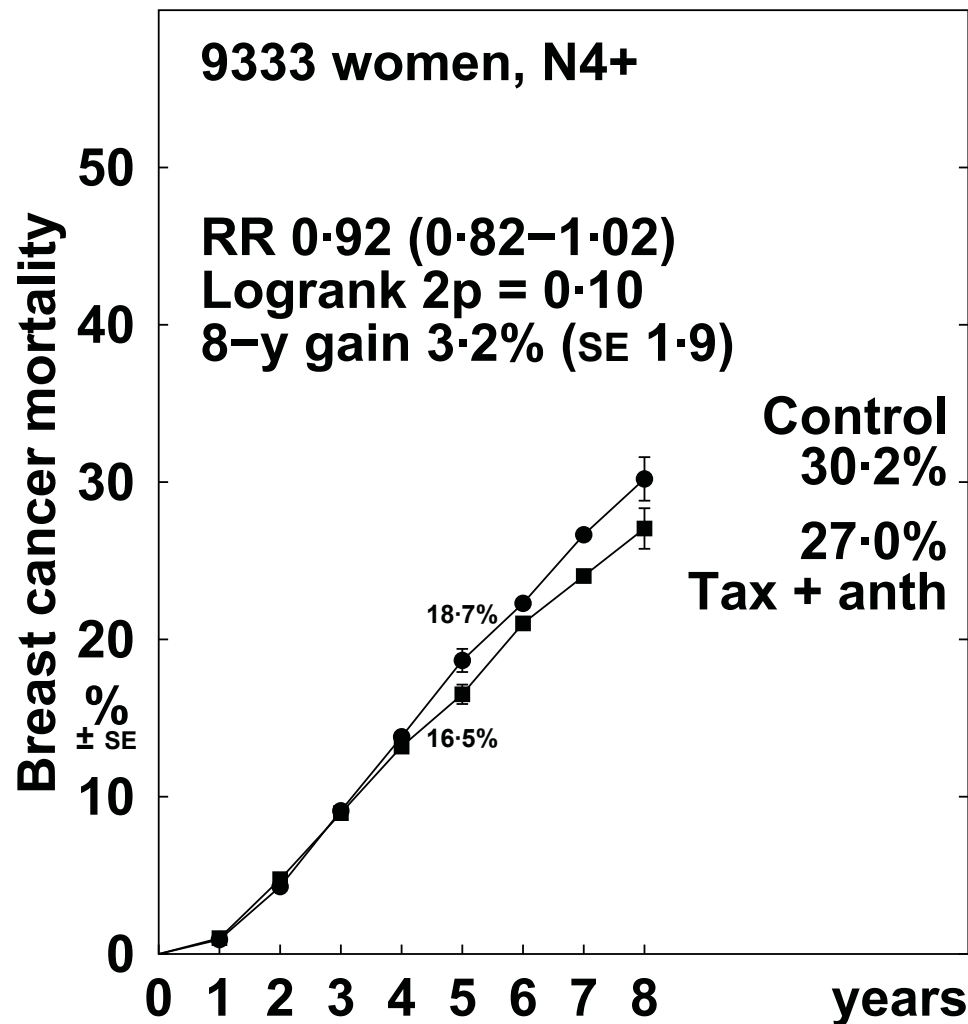
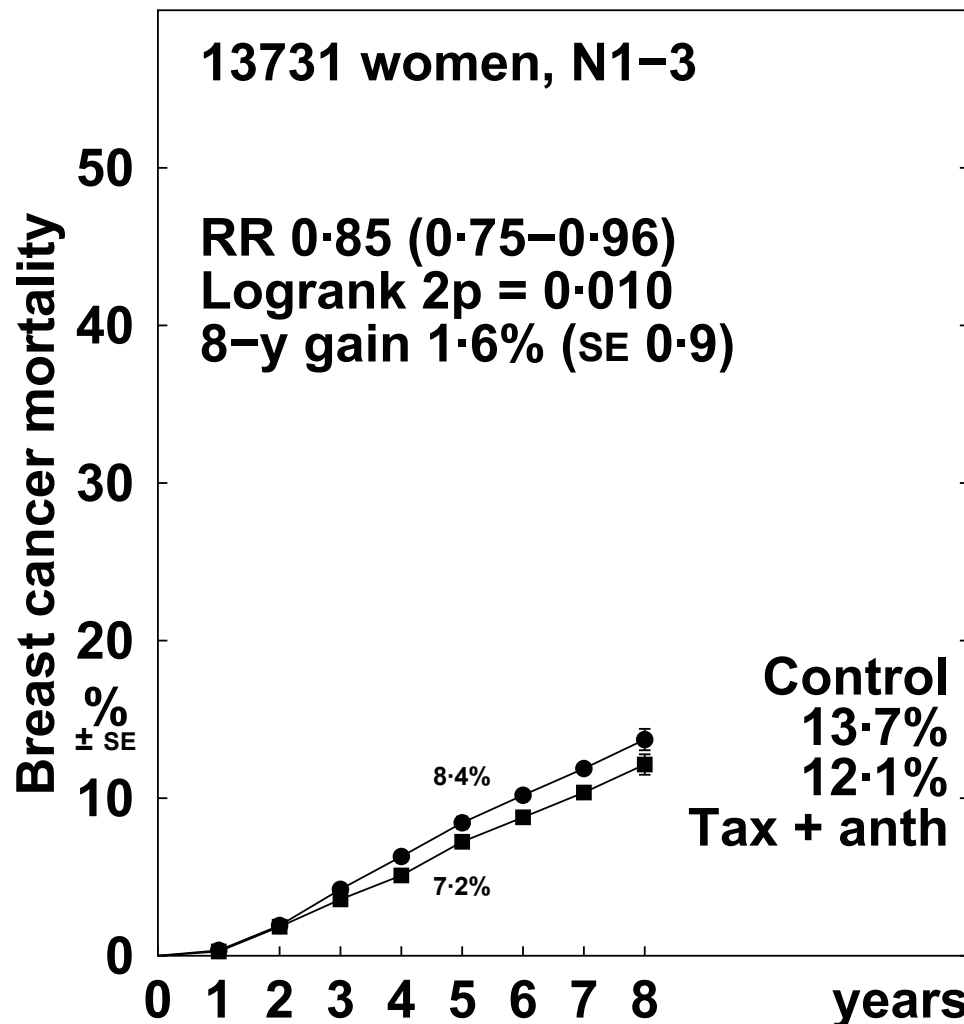


Death rates (% / year: total rate – rate in women without recurrence)

Allocation	Years 0 – 4	Year 5+
Tax + anth	2.42 SE 0.07	2.36 SE 0.13
Control	2.62 SE 0.07	2.63 SE 0.15
Rate ratio	0.91 SE 0.04	0.88 SE 0.08
(O–E) / V	–58.4 / 604.0	–19.6 / 152.8

Allocation	Years 0 – 4	Year 5+
Tax + anth	2.21 SE 0.09	2.64 SE 0.21
Control	2.69 SE 0.11	3.14 SE 0.25
Rate ratio	0.81 SE 0.05	0.85 SE 0.11
(O–E) / V	–57.7 / 275.4	–11.4 / 71.0

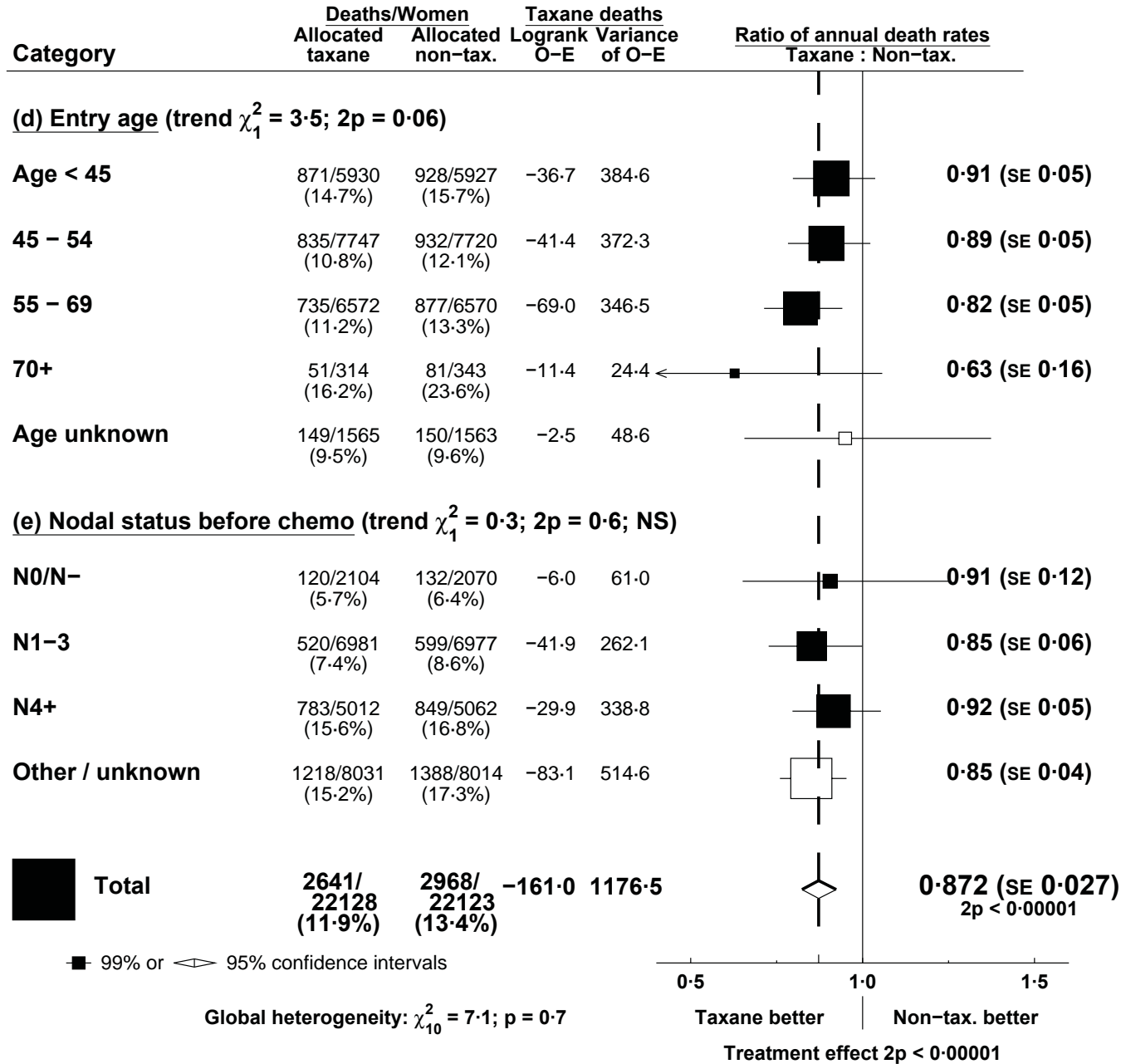
Taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemo, by NODAL STATUS before chemotherapy



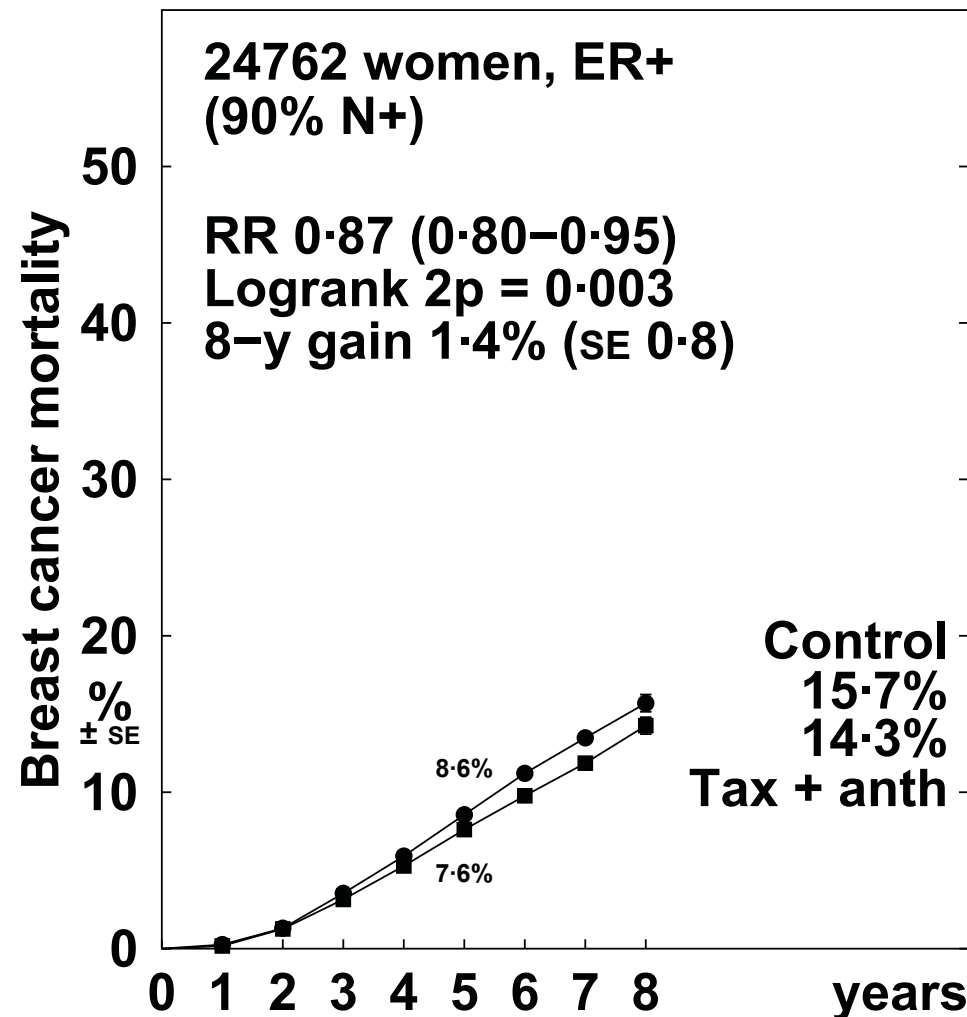
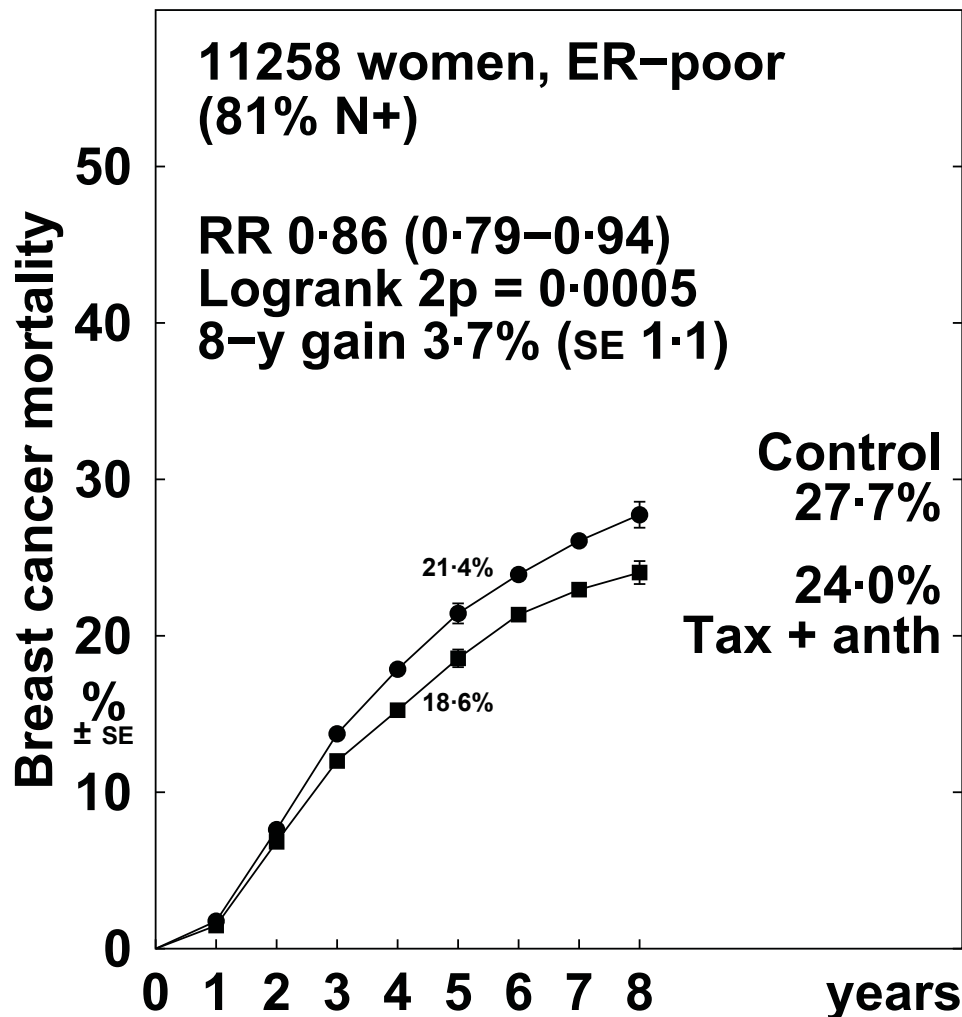
Allocation	Death rates (% / year: total rate - rate in women without recurrence)	
	Years 0 - 4	Year 5+
Tax + anth	1.39 SE 0.07	1.76 SE 0.17
Control	1.68 SE 0.08	1.96 SE 0.18
Rate ratio	0.84 SE 0.06	0.89 SE 0.13
(O-E) / V	-35.7 / 206.9	-6.3 / 55.1

Allocation	Death rates (% / year: total rate - rate in women without recurrence)	
	Years 0 - 4	Year 5+
Tax + anth	3.41 SE 0.13	4.58 SE 0.41
Control	3.82 SE 0.15	4.72 SE 0.45
Rate ratio	0.91 SE 0.06	0.96 SE 0.14
(O-E) / V	-27.9 / 286.1	-2.0 / 52.6

Breast cancer mortality ratio in taxane trials, by AGE and STAGE



Taxane-plus-anthracycline-based regimen vs the SAME, or MORE, non-taxane chemo, by ER STATUS

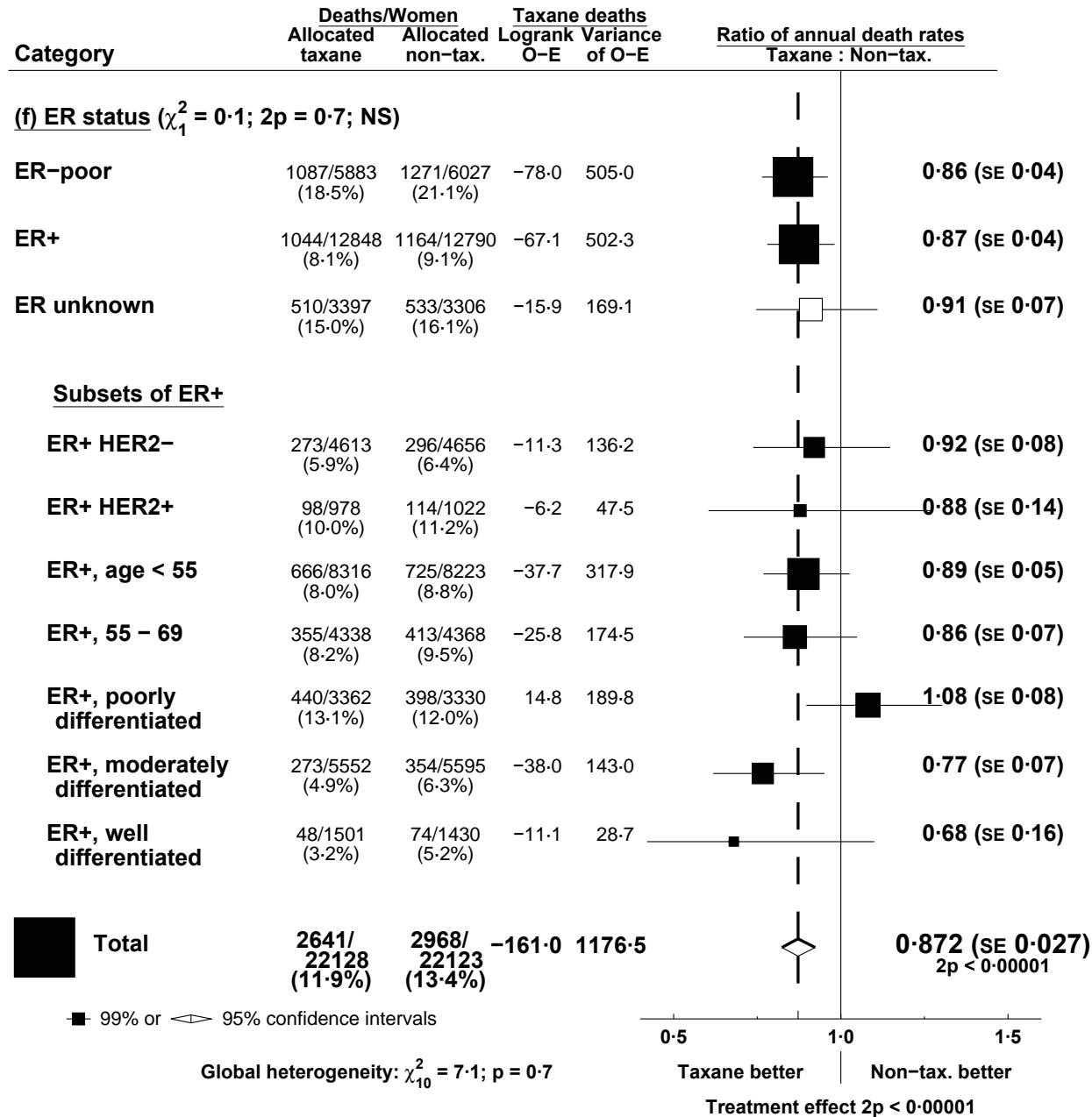


Death rates (% / year: total rate - rate in women without recurrence)

Allocation	Years 0 - 4	Year 5+
Tax + anth	4.00 SE 0.13	2.44 SE 0.20
Control	4.86 SE 0.15	2.67 SE 0.23
Rate ratio	0.85 SE 0.04	0.91 SE 0.12
(O-E) / V	-71.7 / 438.8	-6.2 / 66.1

Allocation	Years 0 - 4	Year 5+
Tax + anth	1.45 SE 0.05	2.51 SE 0.15
Control	1.62 SE 0.06	2.87 SE 0.16
Rate ratio	0.89 SE 0.05	0.85 SE 0.08
(O-E) / V	-44.3 / 365.5	-22.8 / 136.8

Breast cancer mortality ratio in taxane trials, by ER STATUS and subsets of ER+



Trials of any anthracycline-based regimen* vs standard CMF

***Standard 4AC, standard 4EC,
or higher-cumulative-dosage
regimens (eg, CAF or CEF)**

Definitions of “standard” CMF and 4AC

(mg/m² x frequency/cycle)

Standard CMF:

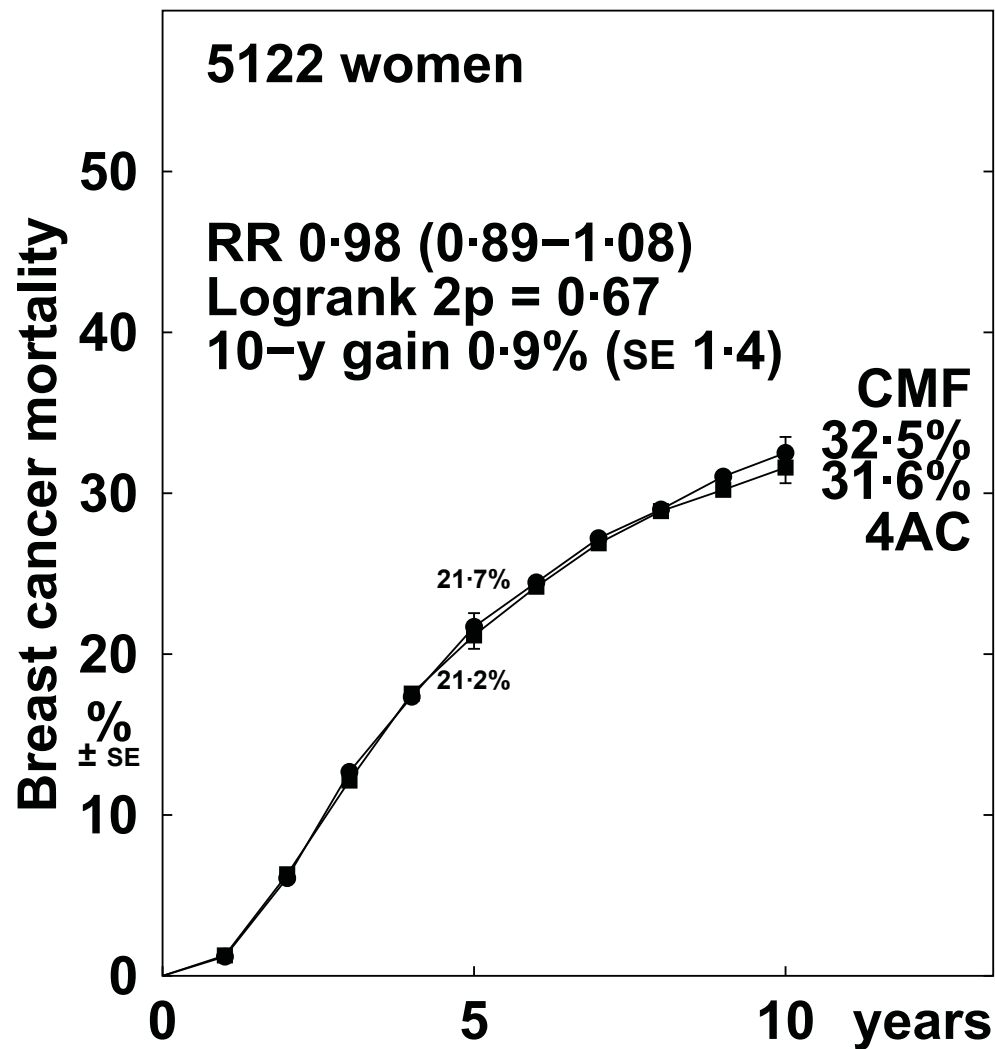
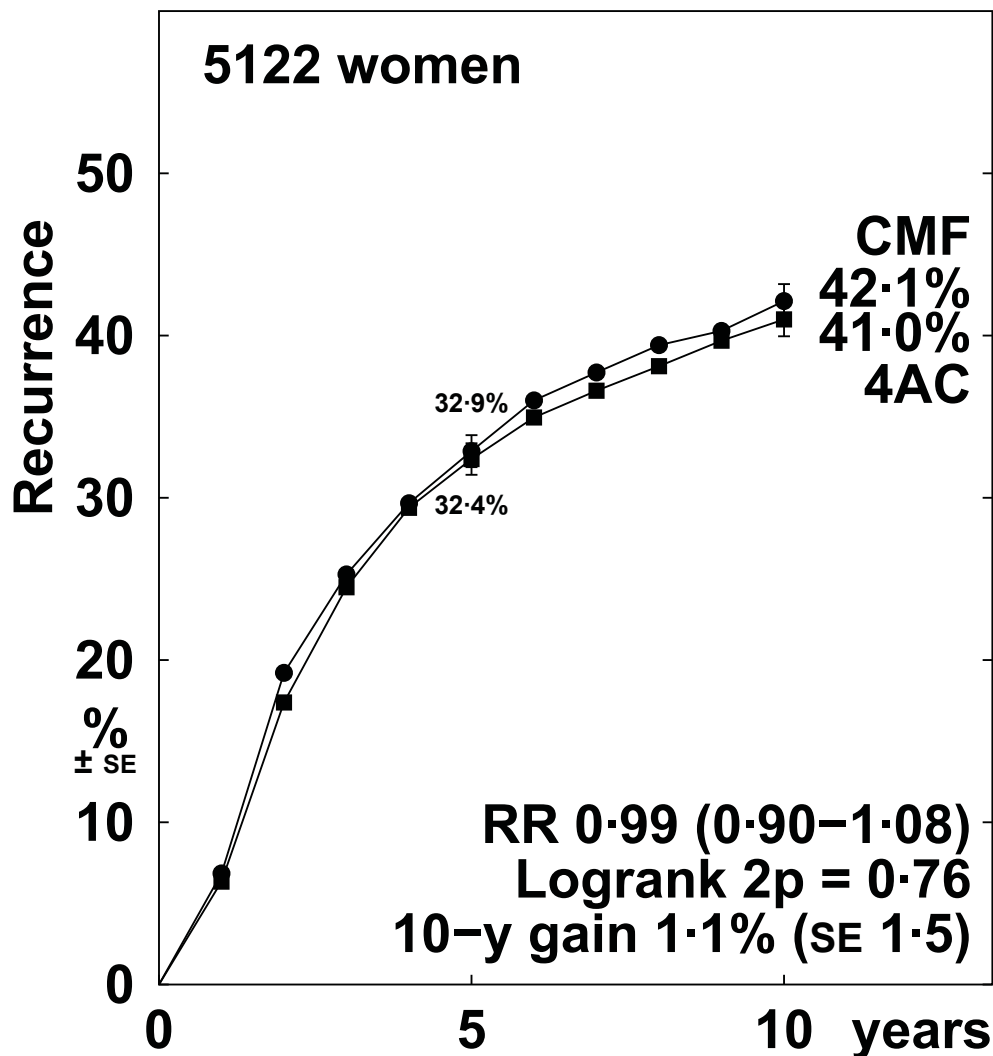
Six 4-weekly cycles of **C**100x14 oral **M**40x2 iv **F**600x2 iv

Standard 4AC:

Four 3-weekly cycles of **A**60 iv **C**600 iv

Approximate equivalence:
in the trials of standard AC vs standard CMF,
both appeared to be of comparable efficacy

Standard 4AC vs standard CMF: approximate equivalence



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
4AC	7.97 (820 / 10292)	2.86 (194 / 6795)	2.36 (100 / 4237)
CMF	8.21 (830 / 10108)	2.99 (199 / 6658)	1.87 (76 / 4054)
Rate ratio	0.98 SE 0.05	0.91 SE 0.10	1.28 SE 0.17
(O-E) / V	-8.7 / 355.5	-8.5 / 92.1	10.4 / 42.3

Years 0 – 4	Years 5 – 9	Year 10+
4.65 SE 0.20	2.94 SE 0.19	2.06 SE 0.20
4.81 SE 0.21	3.04 SE 0.20	1.96 SE 0.20
0.97 SE 0.06	0.97 SE 0.09	1.03 SE 0.15
-6.3 / 245.2	-3.7 / 111.6	1.5 / 48.9

Examples of higher-cumulative-dosage* anthracycline-based regimens

(mg/m² x frequency/cycle)

CAF:

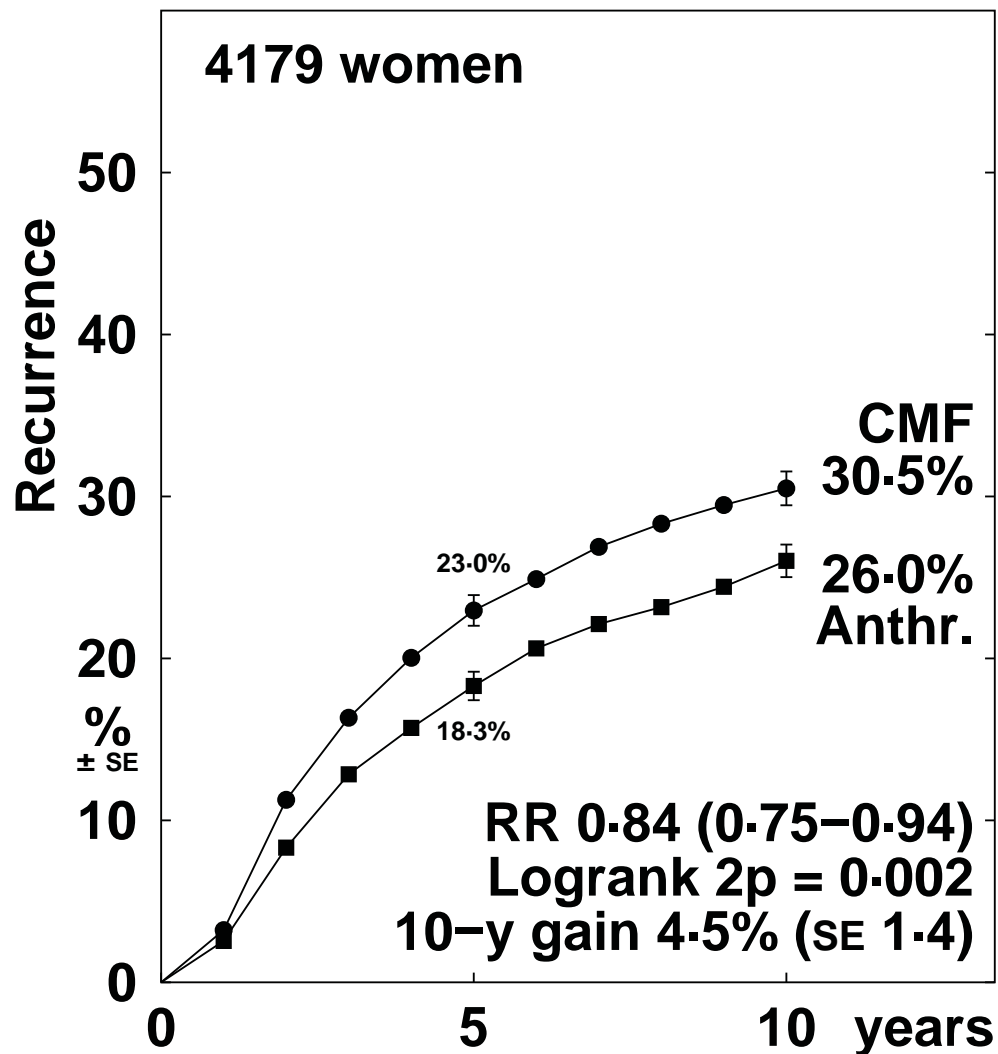
Six 4-weekly cycles of **C**100x14 oral **A**40x2 iv **F**500x2 iv

CEF:

Six 4-weekly cycles of **C**75x14 oral **E**60x2 iv **F**500x2 iv

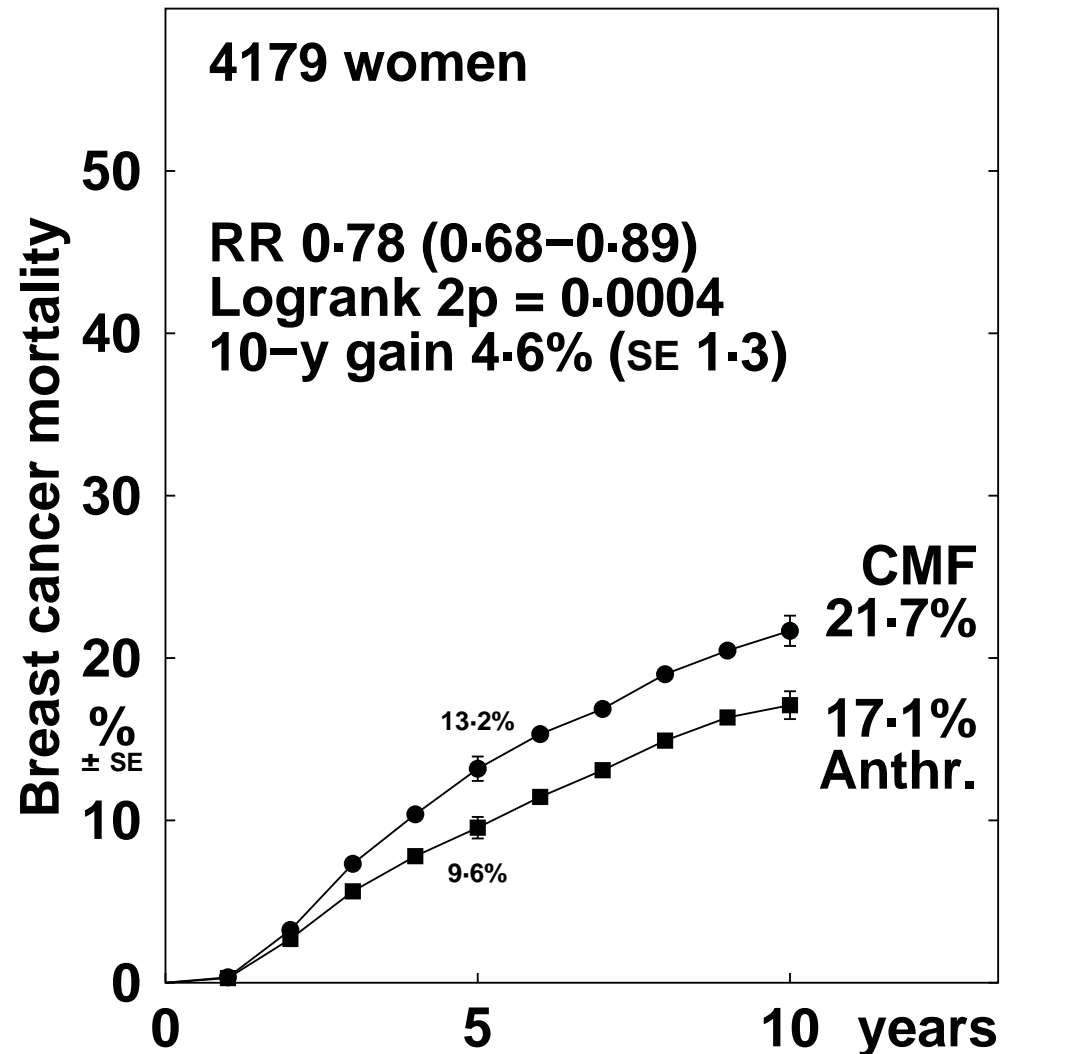
* Higher dosage than standard 4AC not only of anthracycline but also of other cytotoxic drugs; scheduled dosages could be reduced for toxicity

Anthracycline-based regimens with higher cumulative dosage (eg CAF/CEF) vs standard CMF



Recurrence rates (% / year) and logrank analyses

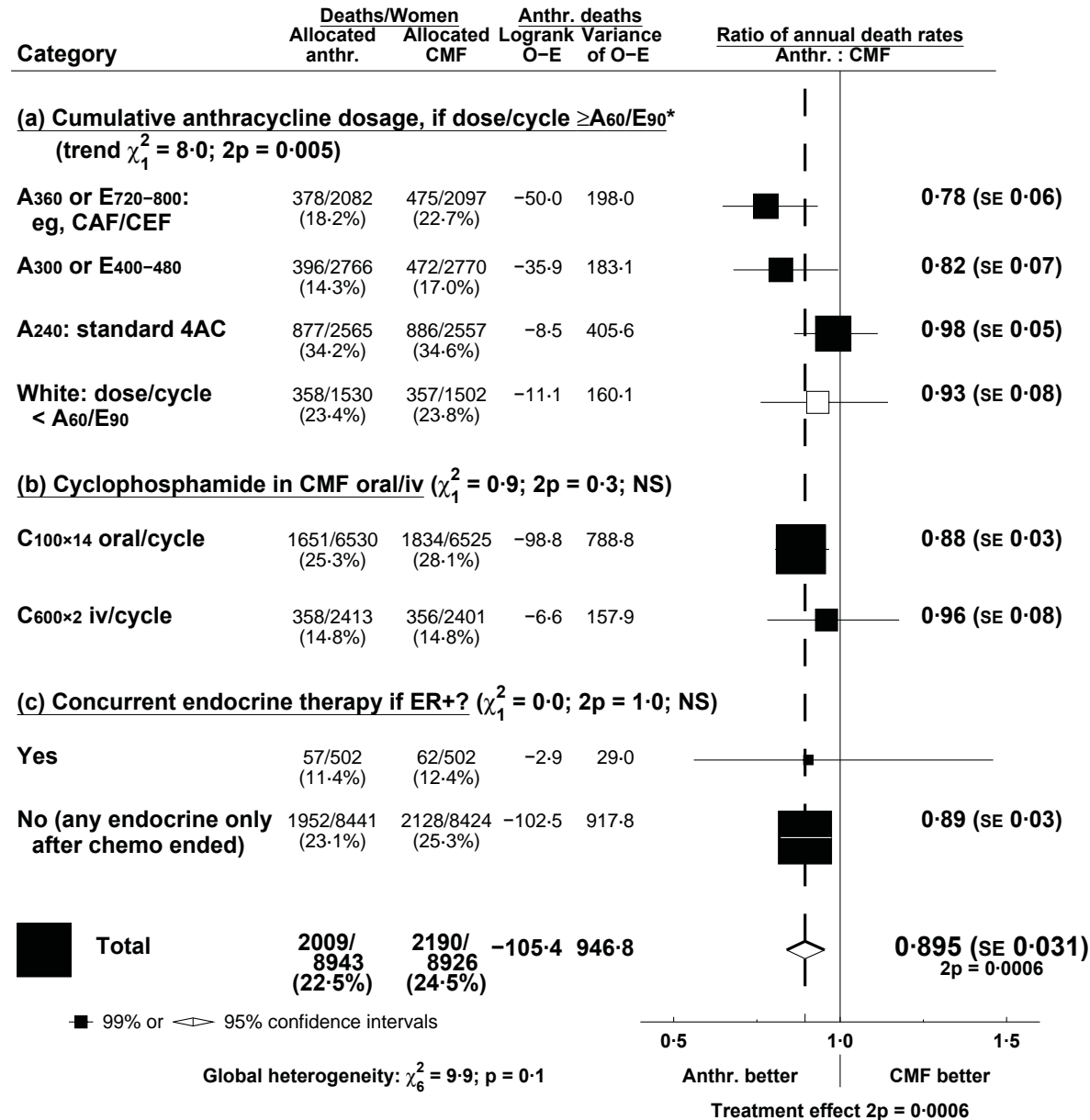
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthr.	4.11 (381 / 9268)	2.00 (146 / 7312)	1.60 (58 / 3623)
CMF	5.21 (473 / 9082)	2.10 (147 / 7012)	1.37 (50 / 3644)
Rate ratio	0.77 SE 0.06	0.96 SE 0.12	1.11 SE 0.21
(O-E) / V	-50.9 / 194.3	-3.2 / 69.6	2.6 / 24.2



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

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anthr.	2.03 SE 0.14	1.75 SE 0.15	0.88 SE 0.15
CMF	2.76 SE 0.17	2.11 SE 0.16	0.93 SE 0.15
Rate ratio	0.71 SE 0.08	0.85 SE 0.11	0.94 SE 0.24
(O-E) / V	-37.0 / 109.0	-11.8 / 72.2	-1.1 / 16.7

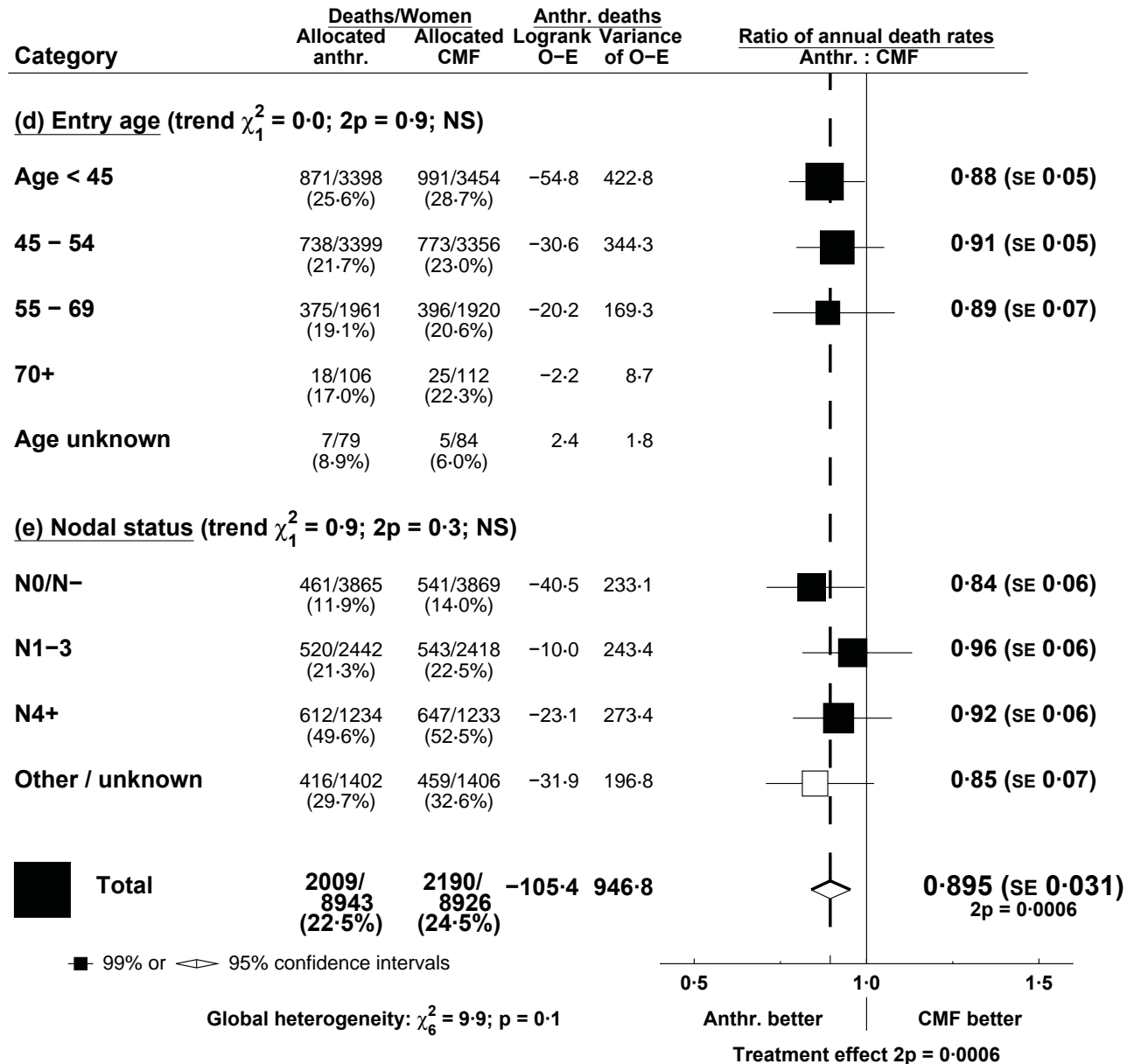
Breast cancer mortality ratio: anthracycline-based regimen vs standard CMF, by TYPE of treatment comparison



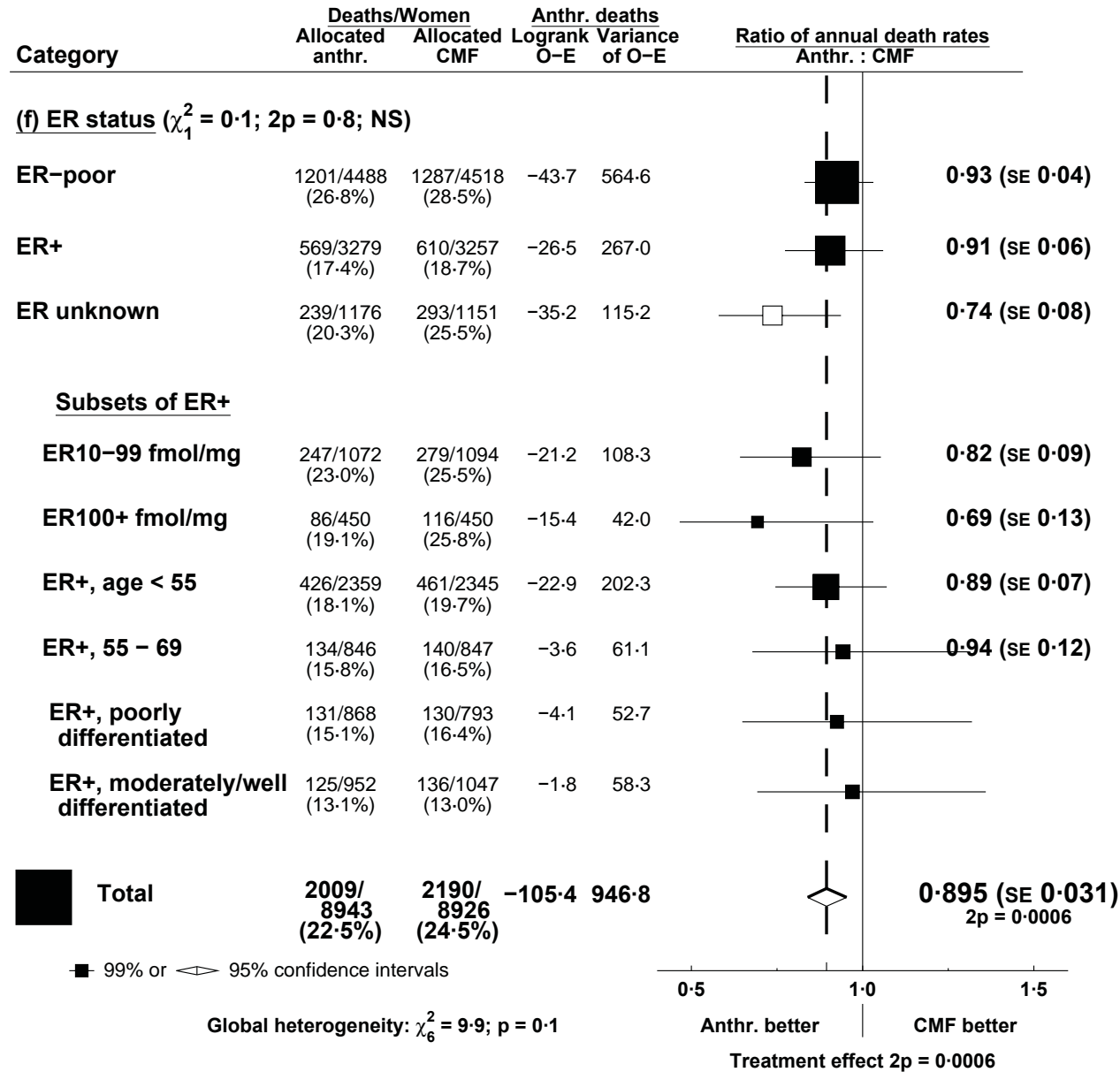
**Trials of any anthracycline-based
regimen vs standard CMF:**

**subgroup analyses
by age, stage and ER status**

Breast cancer mortality ratio: anthracycline-based regimen vs standard CMF, by AGE and STAGE



Breast cancer mortality ratio: anthracycline-based regimen vs standard CMF, by ER STATUS and subsets of ER+

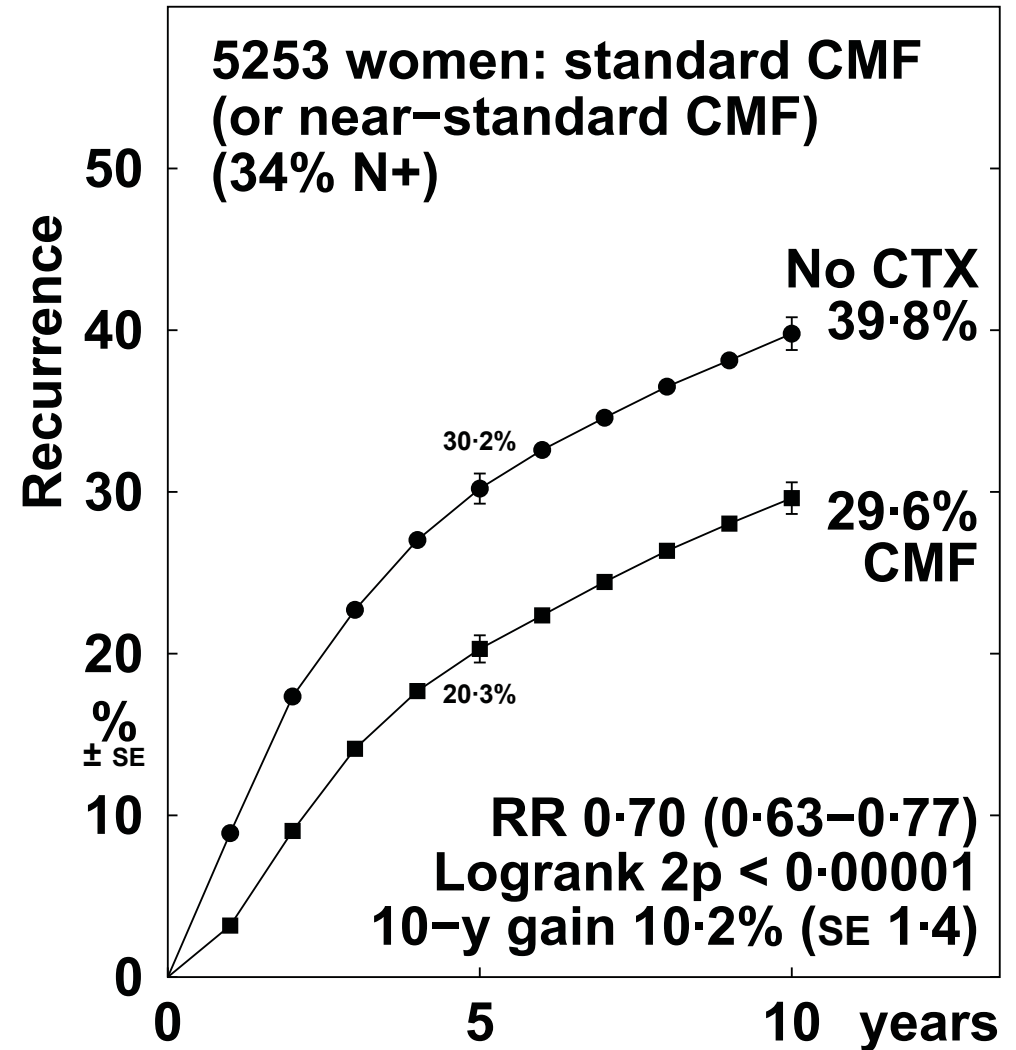
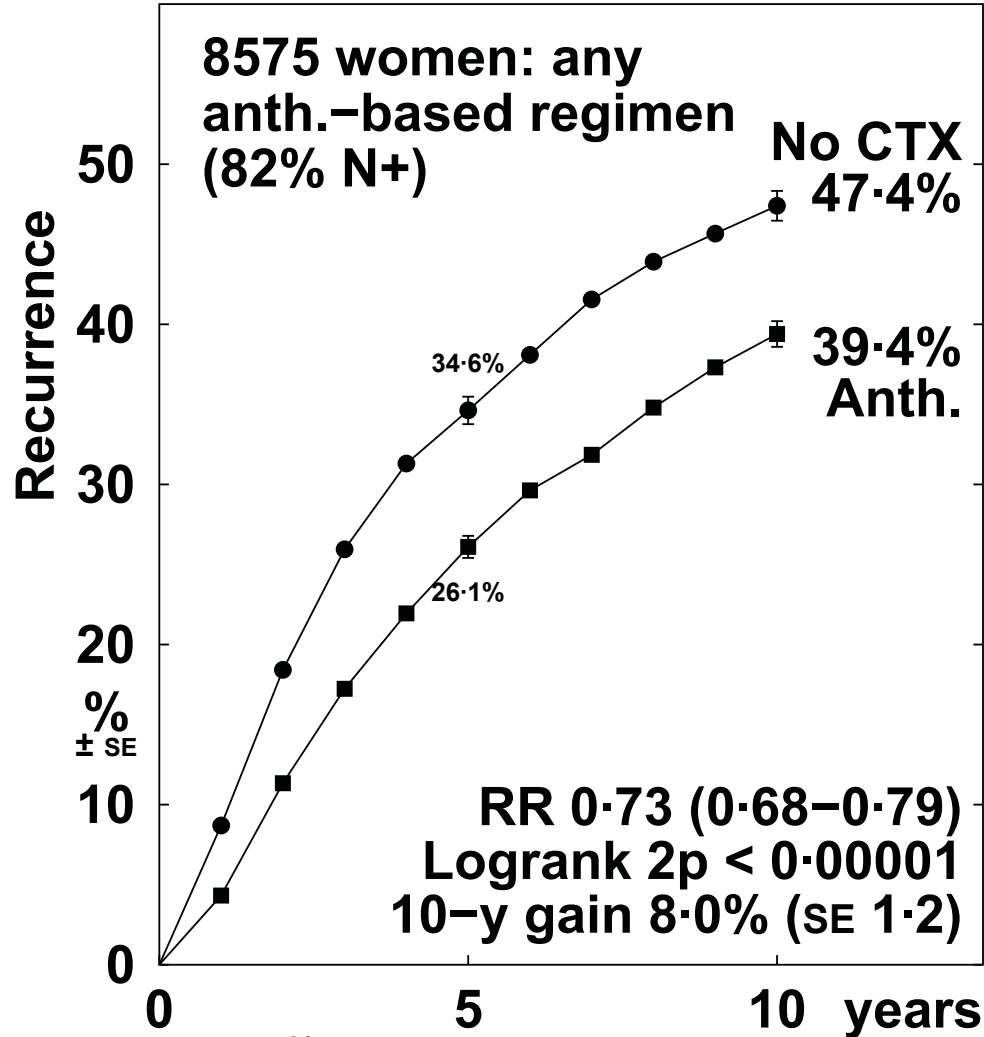


Trials of chemotherapy vs no adjuvant chemotherapy

- Any anthracycline-based regimen
(eg, standard 4AC) vs nil**
- Standard CMF vs nil**

Chemotherapy vs no adjuvant chemotherapy

L: anthracycline-based regimen (eg, standard 4AC), R: standard CMF



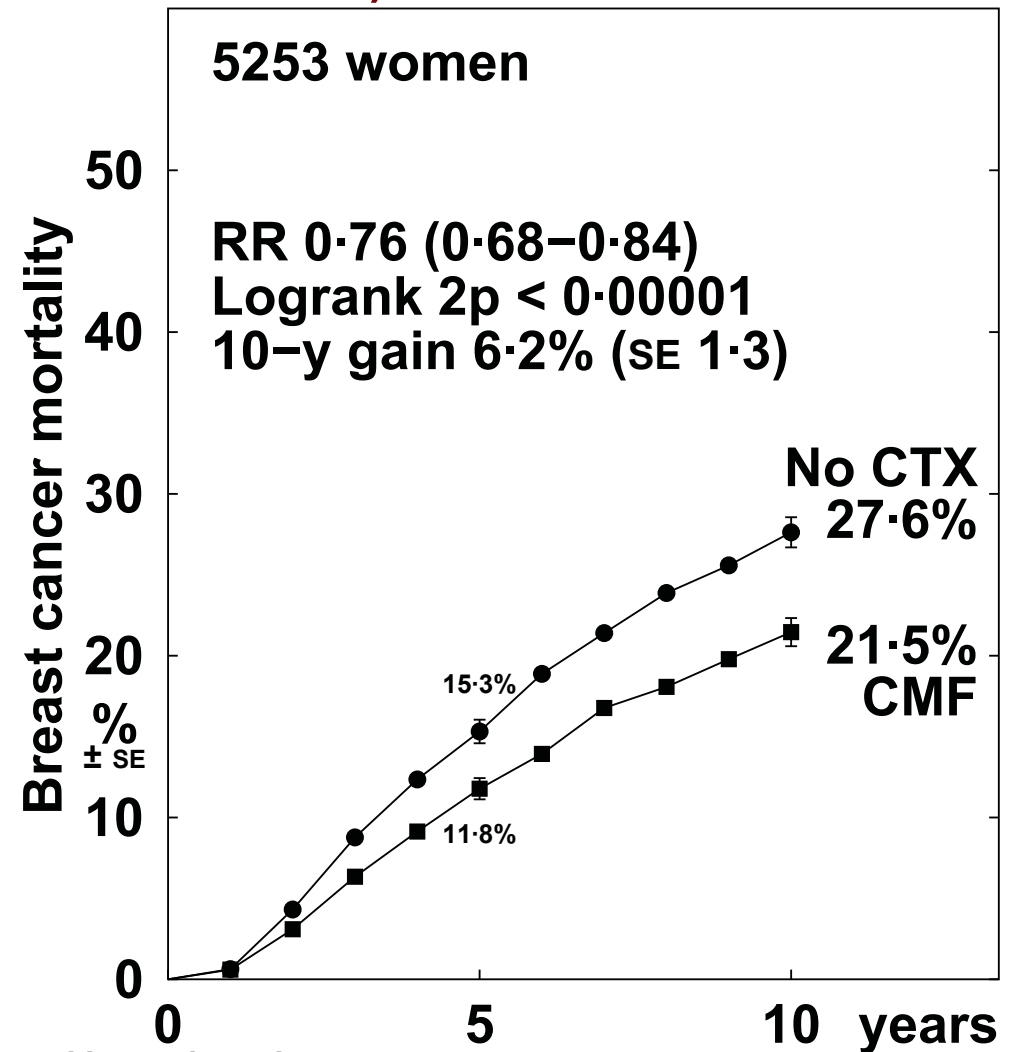
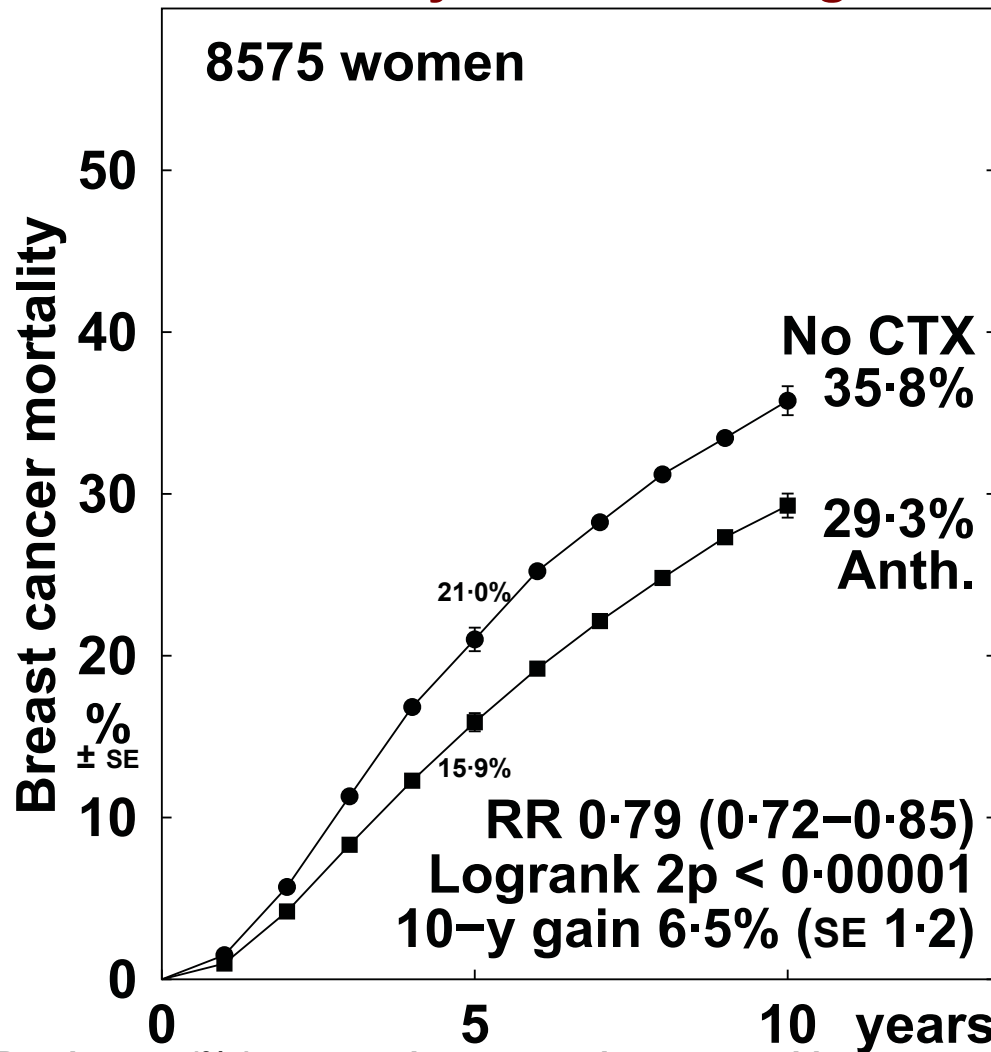
Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	6.14 (1179 / 19190)	4.06 (487 / 11981)	2.91 (161 / 5530)
No CTX	9.06 (1259 / 13899)	4.56 (365 / 8011)	3.87 (159 / 4104)
Rate ratio	0.69 SE 0.04	0.89 SE 0.07	0.72 SE 0.11
(O-E) / V	-185.2 / 489.8	-20.0 / 174.7	-21.2 / 65.5

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
CMF	4.83 (549 / 11357)	2.58 (207 / 8038)	1.88 (116 / 6155)
No CTX	7.20 (748 / 10385)	2.93 (210 / 7158)	1.90 (100 / 5260)
Rate ratio	0.61 SE 0.05	0.84 SE 0.09	0.99 SE 0.14
(O-E) / V	-135.5 / 277.0	-16.9 / 95.9	-0.7 / 48.7

Chemotherapy vs no adjuvant chemotherapy

L: anthracycline-based regimen (eg, standard 4AC), R: standard CMF



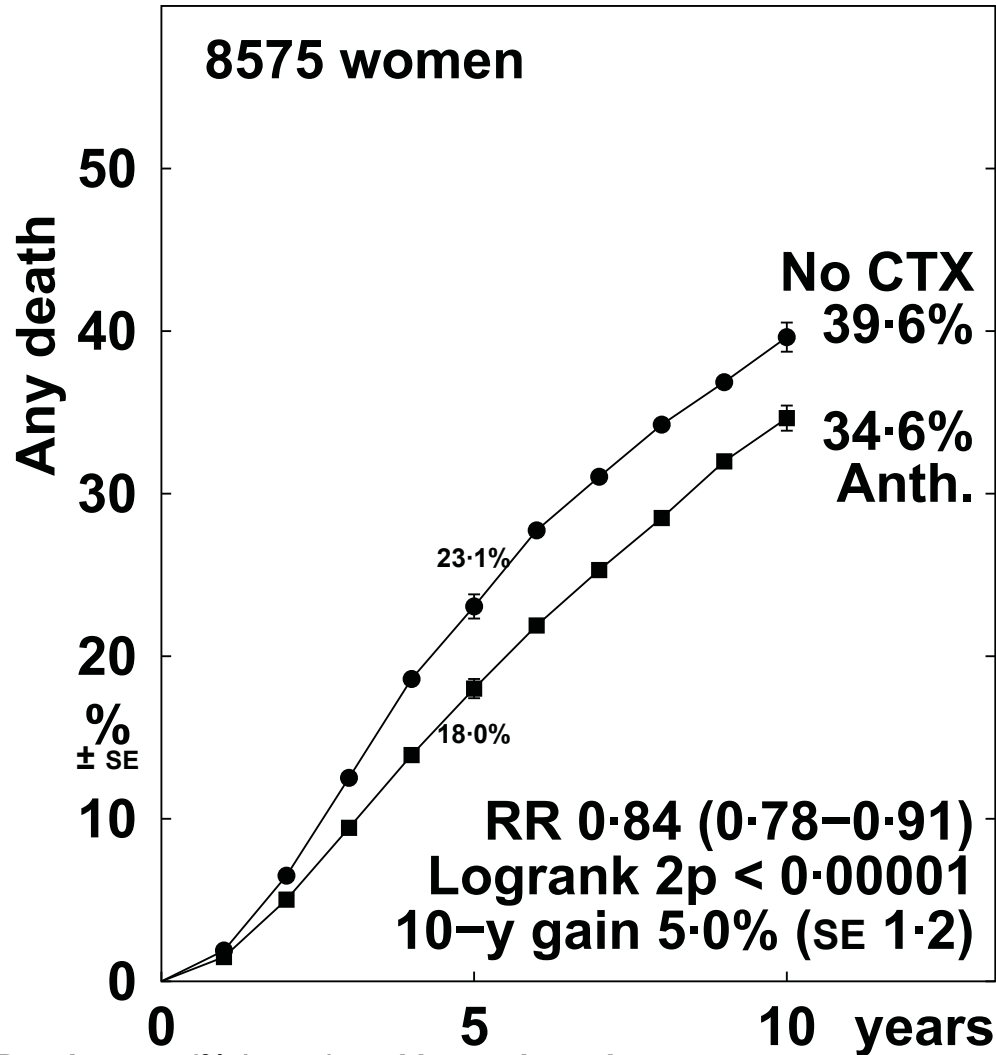
Death rates (% / year: total rate – rate in women without recurrence) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	3.38 SE 0.13	3.57 SE 0.16	2.83 SE 0.19
No CTX	4.77 SE 0.17	4.31 SE 0.21	2.98 SE 0.22
Rate ratio	0.73 SE 0.05	0.83 SE 0.07	0.92 SE 0.11
(O-E) / V	-97.5 / 307.0	-35.9 / 193.2	-6.7 / 81.0

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
CMF	2.51 SE 0.14	2.42 SE 0.16	1.80 SE 0.16
No CTX	3.23 SE 0.17	3.14 SE 0.19	2.10 SE 0.18
Rate ratio	0.75 SE 0.07	0.74 SE 0.08	0.82 SE 0.12
(O-E) / V	-43.5 / 151.3	-33.7 / 109.6	-11.9 / 59.1

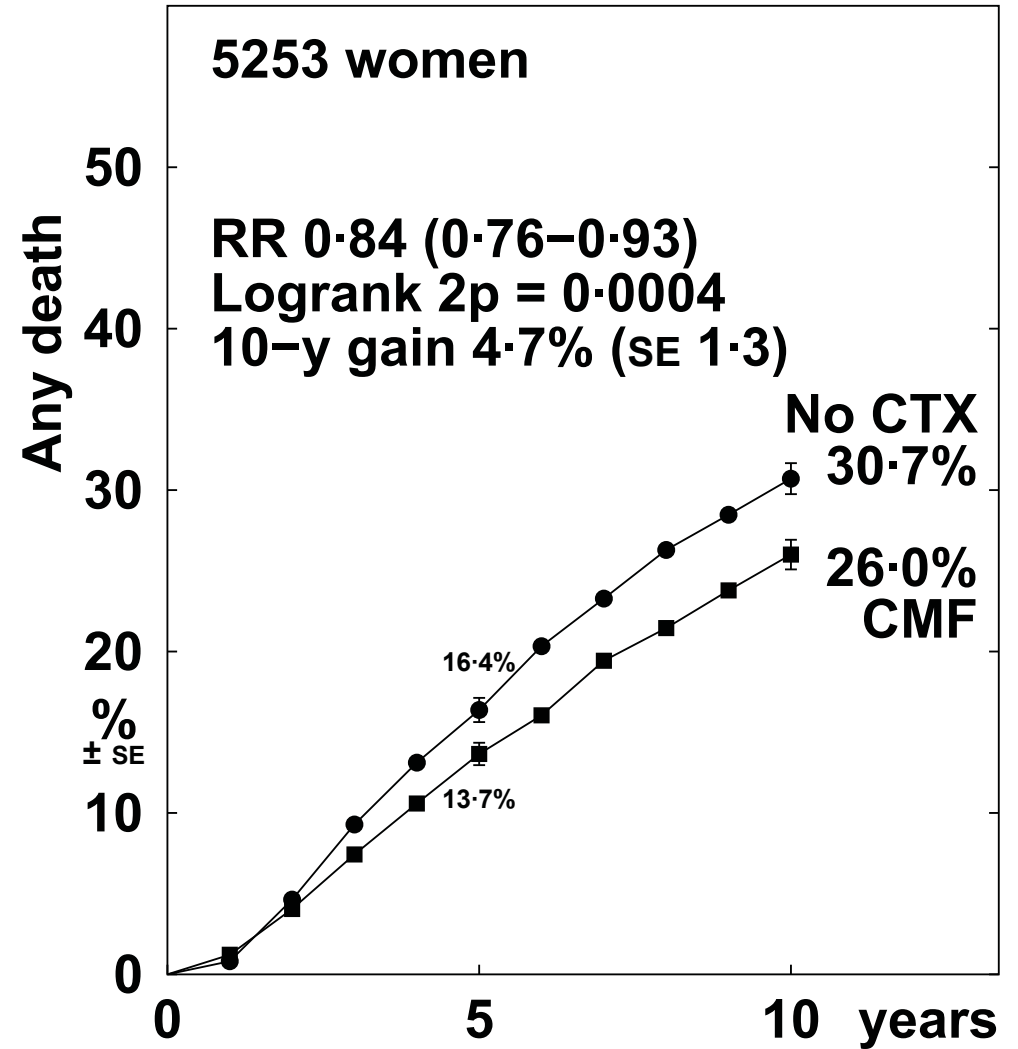
Chemotherapy vs no adjuvant chemotherapy

L: anthracycline-based regimen (eg, standard 4AC), R: standard CMF



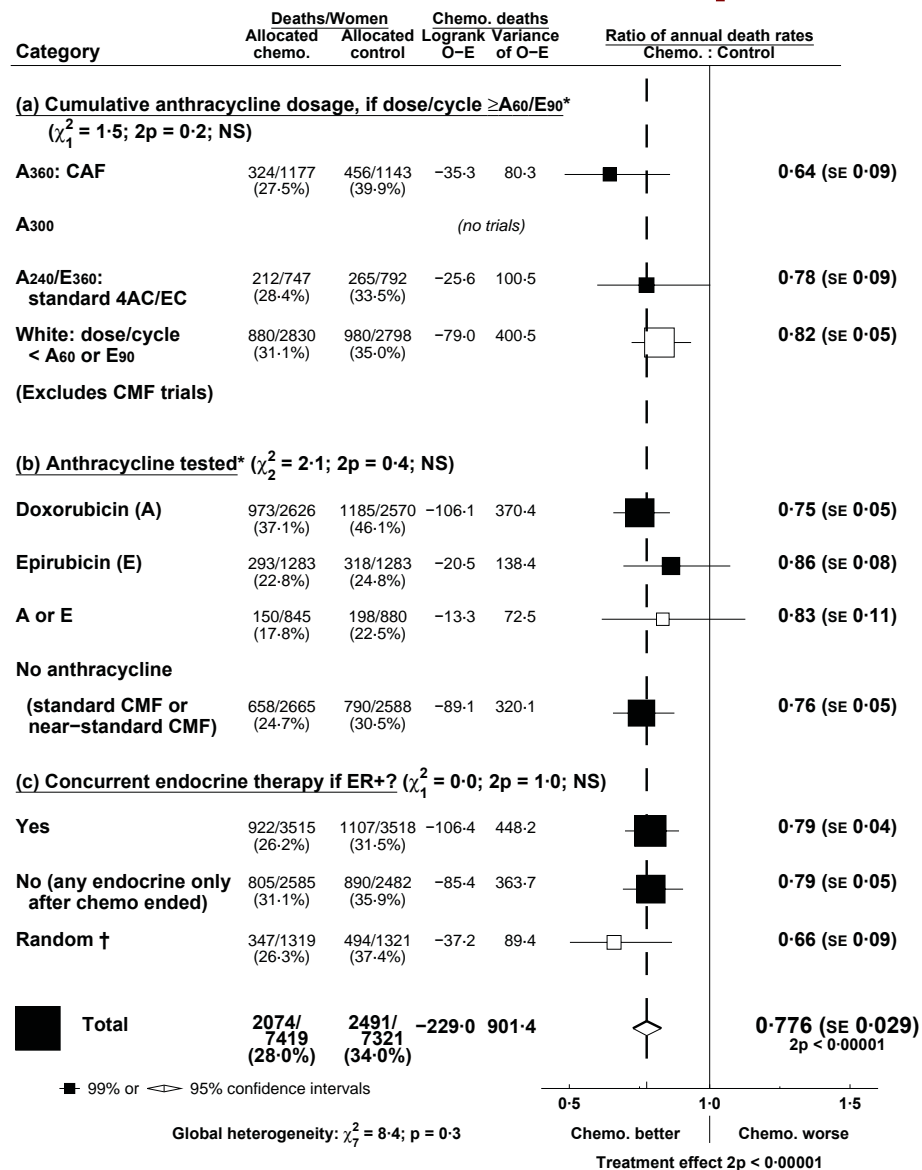
Death rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	3.91 (811 / 20718)	4.62 (645 / 13969)	4.39 (337 / 7680)
No CTX	5.25 (834 / 15889)	4.93 (492 / 9975)	4.34 (259 / 5969)
Rate ratio	0.75 SE 0.05	0.92 SE 0.06	1.00 SE 0.09
(O-E) / V	-99.0 / 346.4	-19.1 / 234.6	-0.1 / 120.2

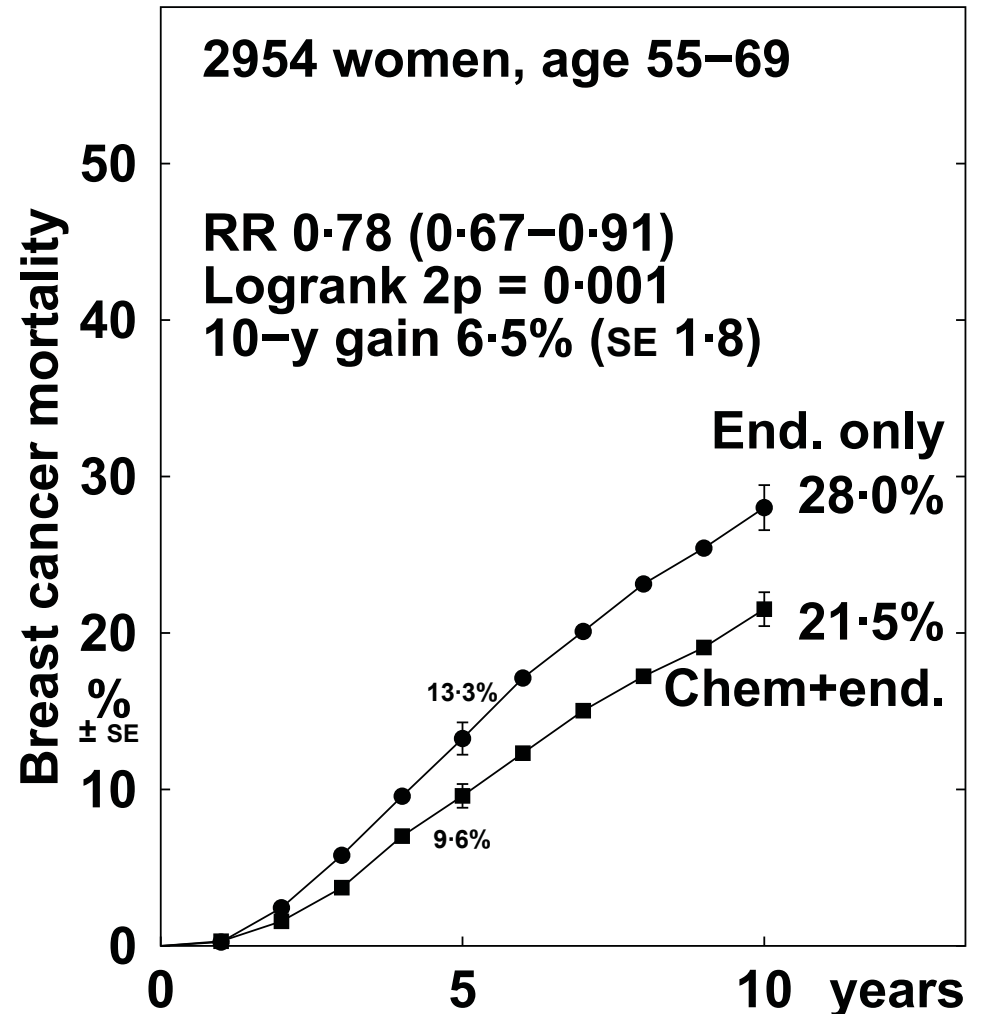
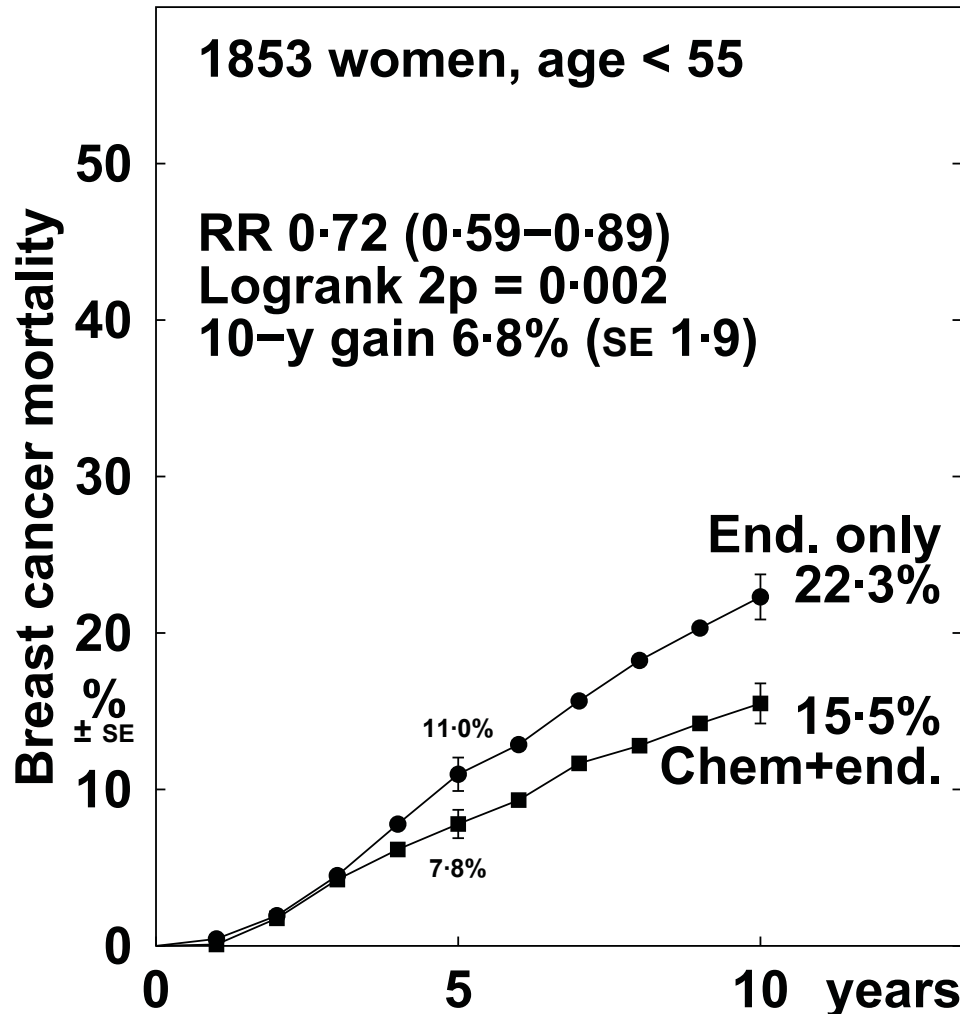


Allocation	Years 0 – 4	Years 5 – 9	Year 10+
CMF	2.93 (357 / 12167)	3.15 (286 / 9091)	3.14 (230 / 7318)
No CTX	3.49 (410 / 11756)	3.78 (326 / 8617)	3.39 (224 / 6612)
Rate ratio	0.82 SE 0.07	0.81 SE 0.08	0.91 SE 0.10
(O-E) / V	-33.6 / 170.7	-28.5 / 137.2	-8.8 / 96.2

Breast cancer mortality ratio: anthracycline-based regimen (eg, standard 4AC) or standard CMF vs no chemotherapy, by TYPE of treatment comparison



Chemotherapy (anthracycline-based regimen or standard CMF) + 5 year endocrine therapy vs 5 year endocrine therapy only, ER+ disease only: by ENTRY AGE



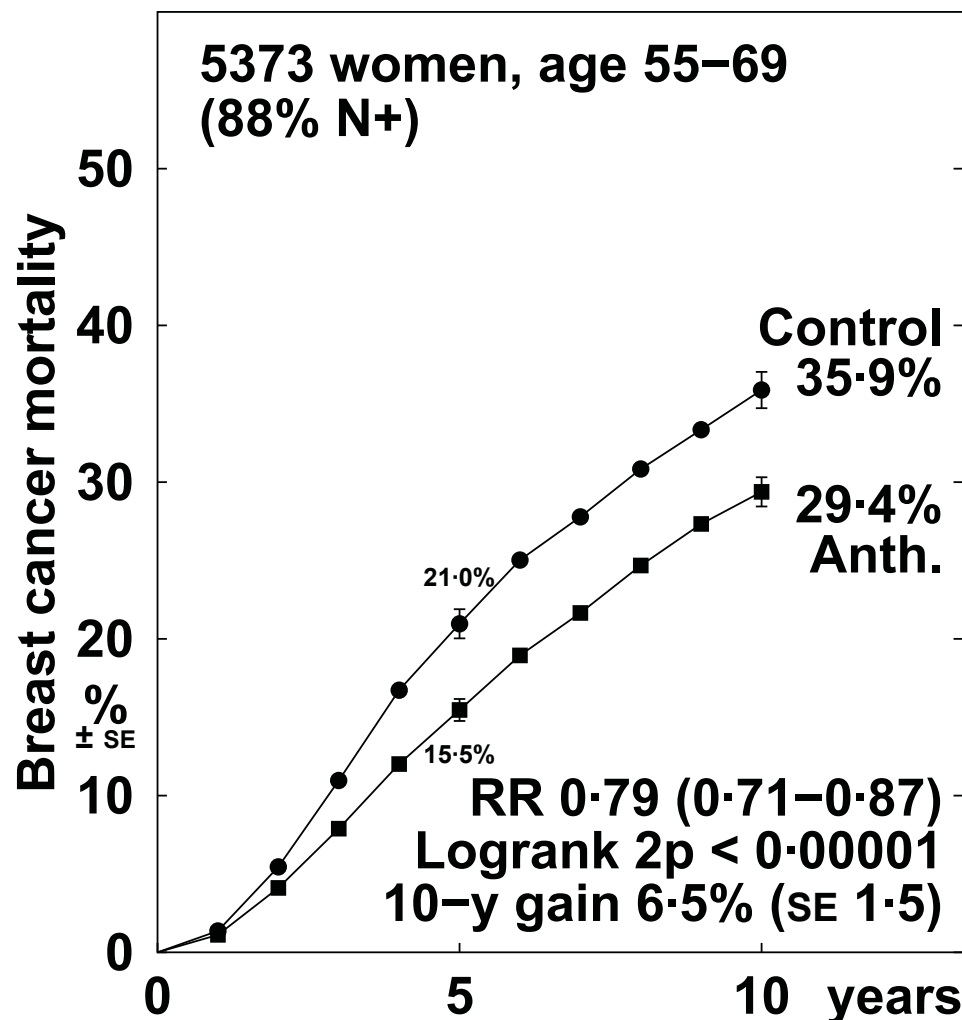
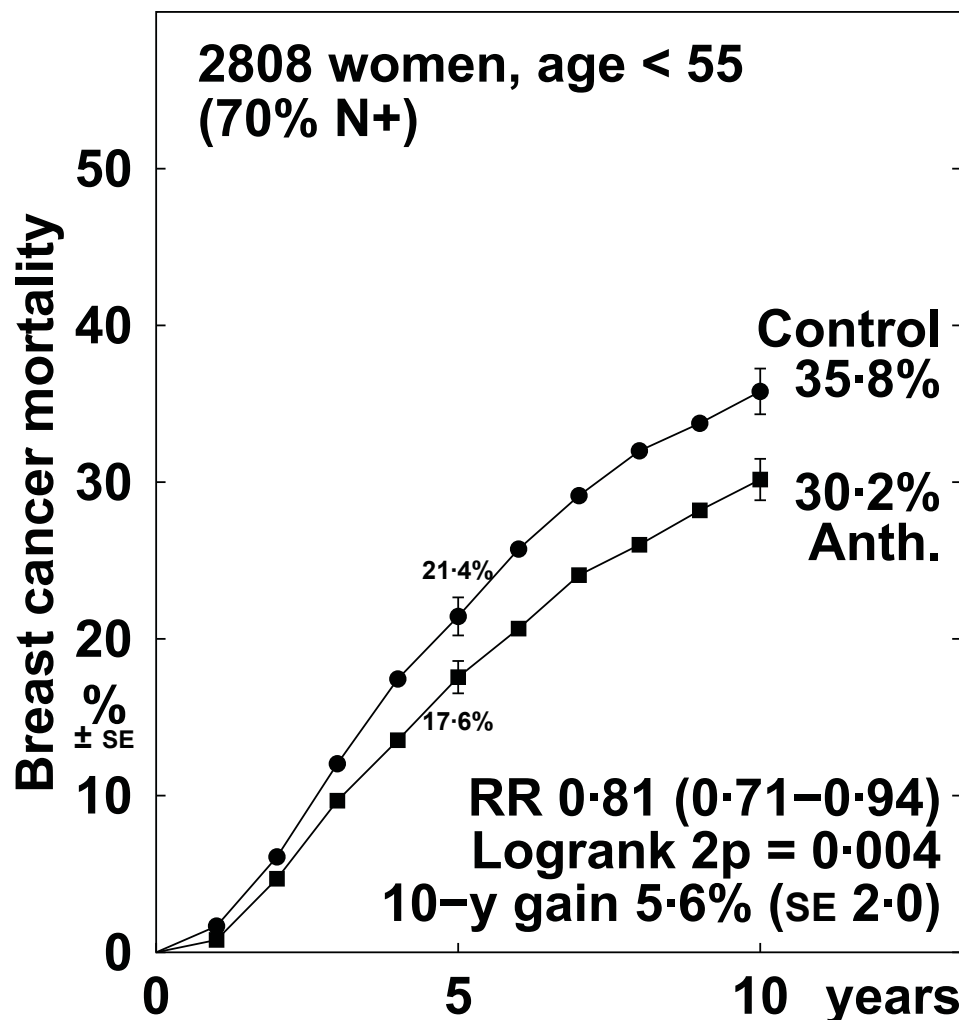
Death rates (% / year: total rate – rate in women without recurrence) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+	Years 0 – 4	Years 5 – 9	Year 10+
Chem+end.	1.72 SE 0.19	1.99 SE 0.23	1.77 SE 0.28	2.09 SE 0.16	2.88 SE 0.22	3.03 SE 0.31
End. only	2.20 SE 0.23	2.53 SE 0.28	1.69 SE 0.29	2.75 SE 0.23	3.96 SE 0.32	2.88 SE 0.35
Rate ratio	0.71 SE 0.14	0.65 SE 0.14	0.96 SE 0.24	0.70 SE 0.10	0.75 SE 0.10	1.03 SE 0.17
(O–E) / V	–13.0 / 37.8	–14.7 / 33.8	–0.6 / 16.2	–23.1 / 66.0	–19.7 / 69.4	1.0 / 34.5

Trials of any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy:

Subgroup analyses by age, stage and ER status, and by subsets of ER+ disease

Any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ENTRY AGE

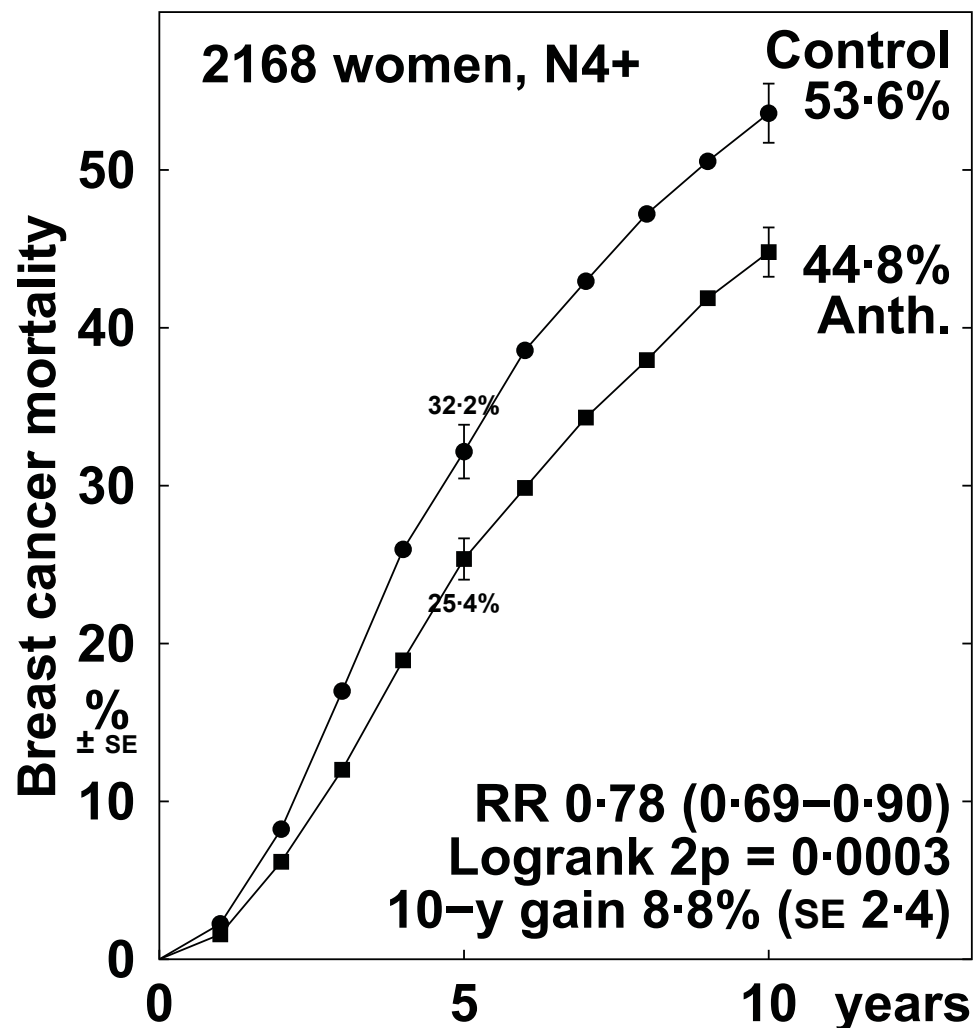
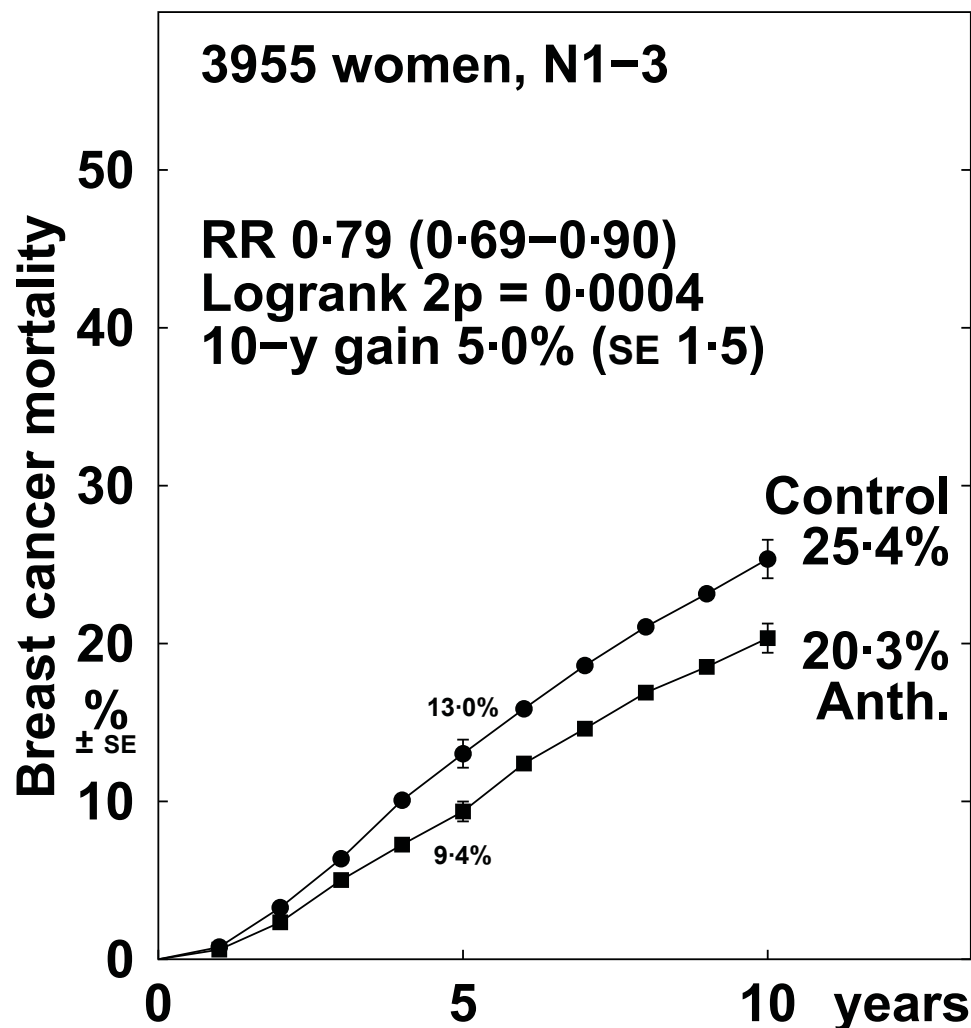


Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	3.81 SE 0.24	3.53 SE 0.28	1.85 SE 0.25
Control	4.77 SE 0.29	4.11 SE 0.34	2.01 SE 0.28
Rate ratio	0.79 SE 0.09	0.81 SE 0.11	0.96 SE 0.21
(O-E) / V	-25.5 / 108.4	-13.5 / 63.4	-0.9 / 21.0

Allocation	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	3.26 SE 0.16	3.63 SE 0.20	3.43 SE 0.28
Control	4.79 SE 0.22	4.40 SE 0.27	3.65 SE 0.33
Rate ratio	0.71 SE 0.06	0.86 SE 0.08	0.94 SE 0.13
(O-E) / V	-65.9 / 193.2	-19.2 / 125.4	-3.5 / 58.3

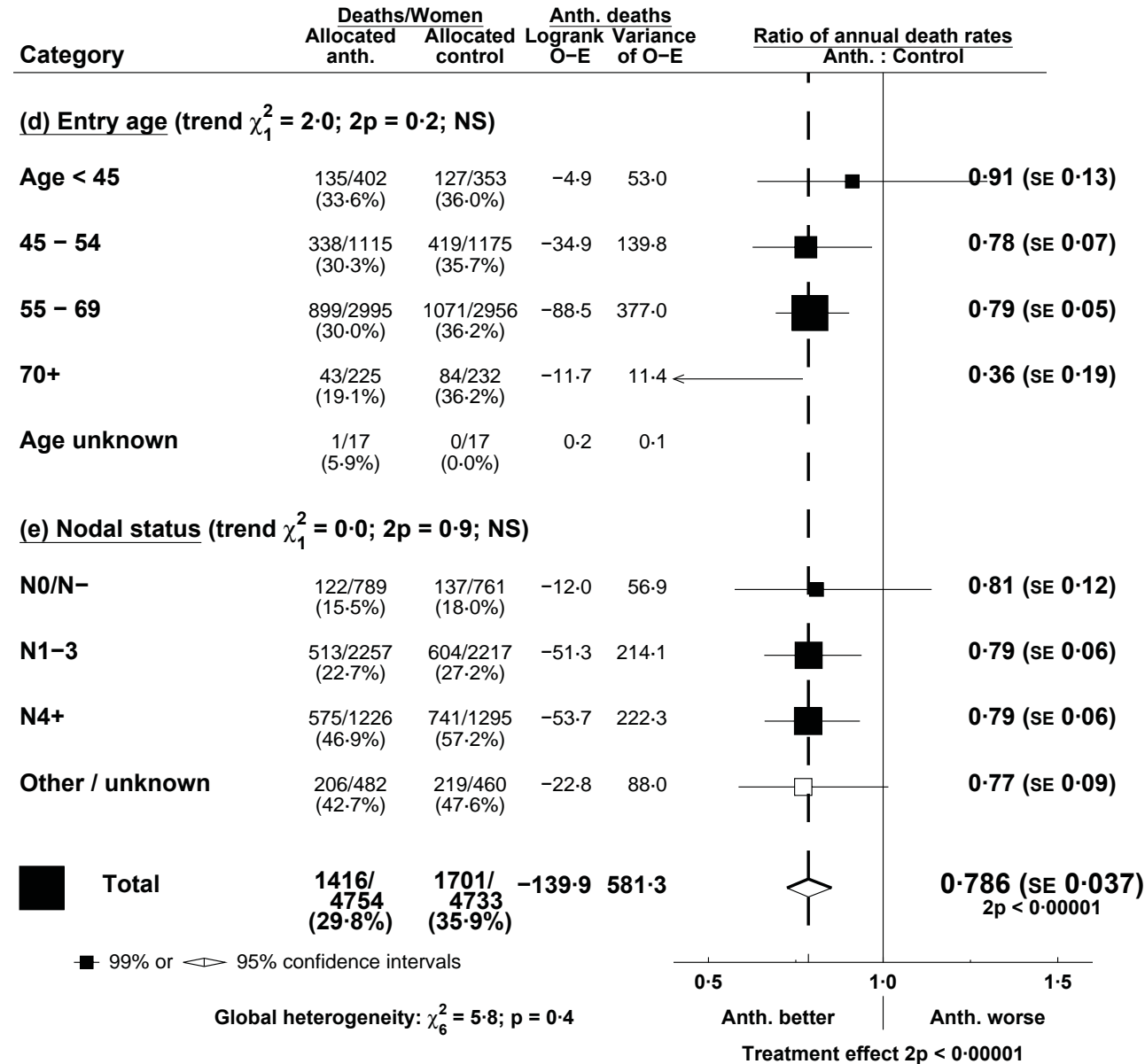
Any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by NODAL STATUS



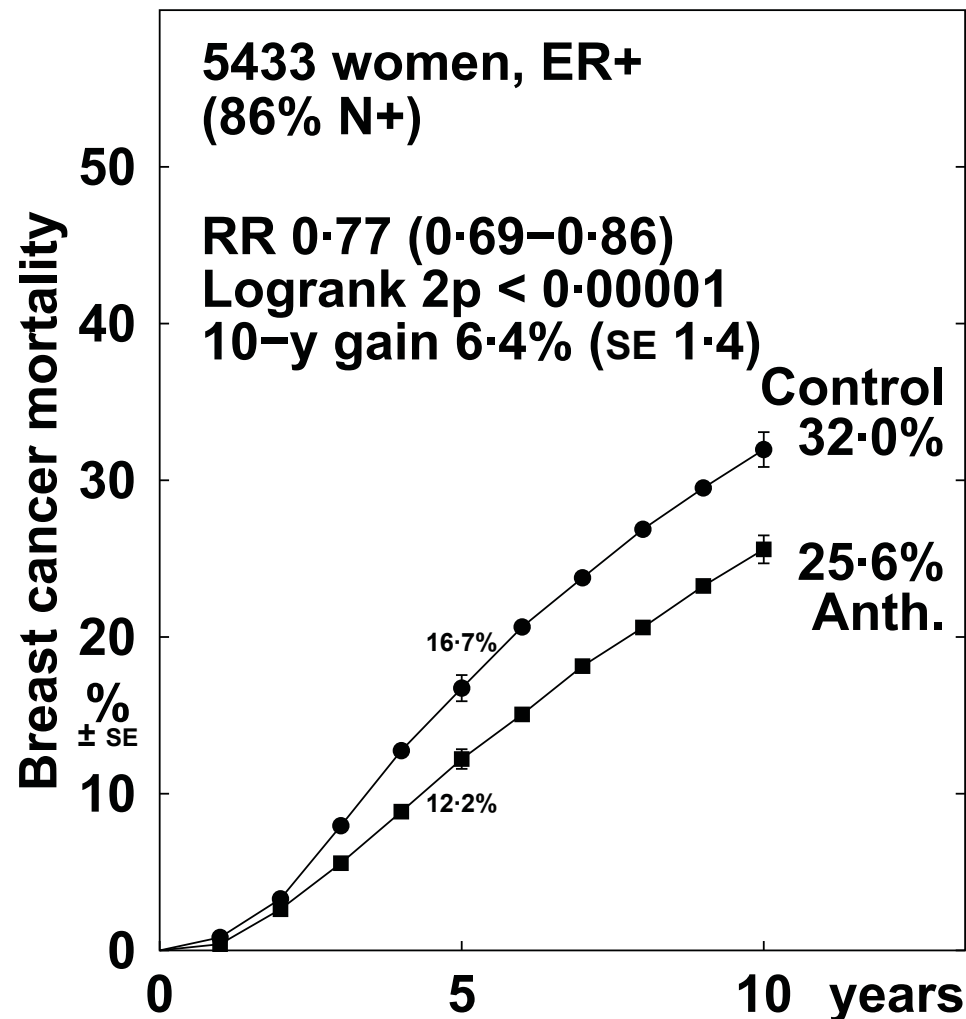
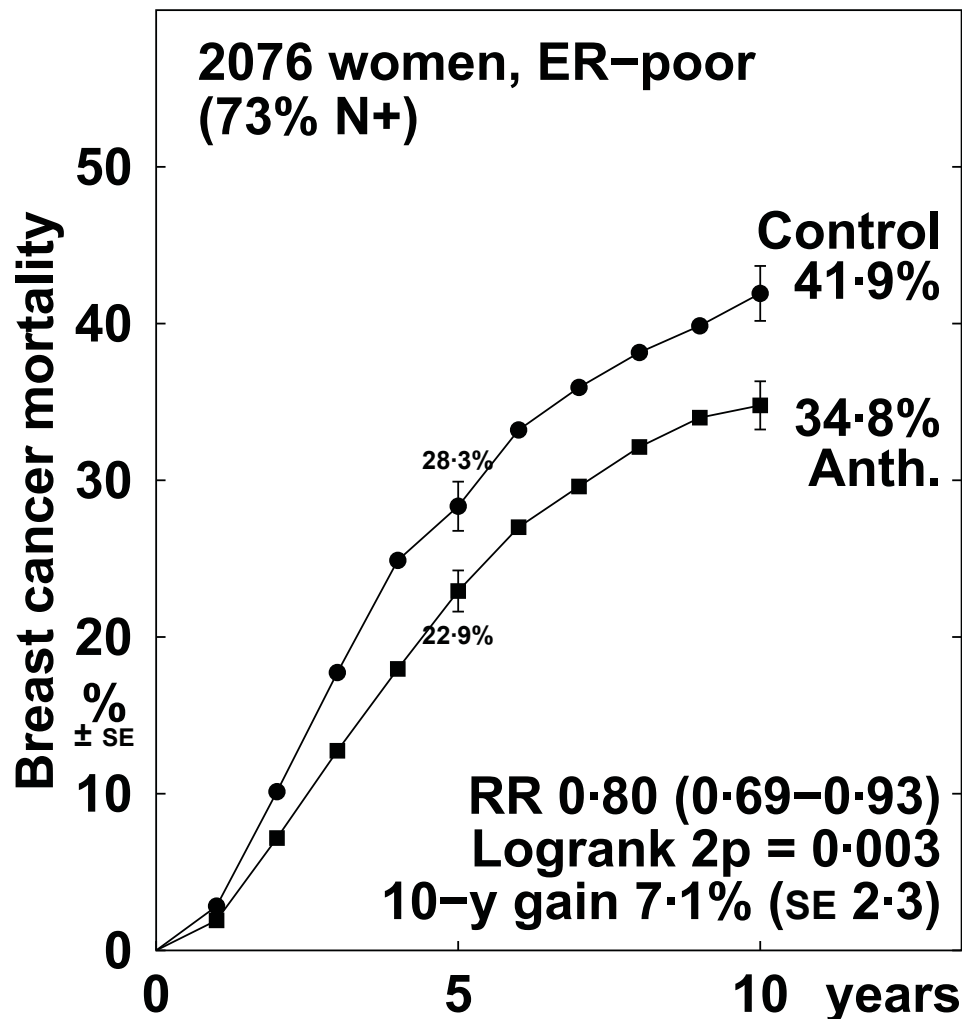
Death rates (% / year: total rate - rate in women without recurrence) and logrank analyses

Allocation	Years 0 - 4	Years 5 - 9	Year 10+	Years 0 - 4	Years 5 - 9	Year 10+
Anth.	1.91 SE 0.14	2.62 SE 0.19	2.91 SE 0.27	5.53 SE 0.32	6.15 SE 0.43	4.61 SE 0.53
Control	2.92 SE 0.20	3.22 SE 0.25	3.16 SE 0.33	7.87 SE 0.45	8.11 SE 0.61	4.72 SE 0.61
Rate ratio	0.71 SE 0.09	0.85 SE 0.10	0.86 SE 0.14	0.74 SE 0.08	0.78 SE 0.10	1.07 SE 0.20
(O-E) / V	-32.3 / 92.9	-12.4 / 78.4	-6.6 / 42.7	-36.7 / 120.7	-19.0 / 75.5	1.9 / 26.0

Breast cancer mortality ratio: any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by AGE and STAGE



Any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ER STATUS

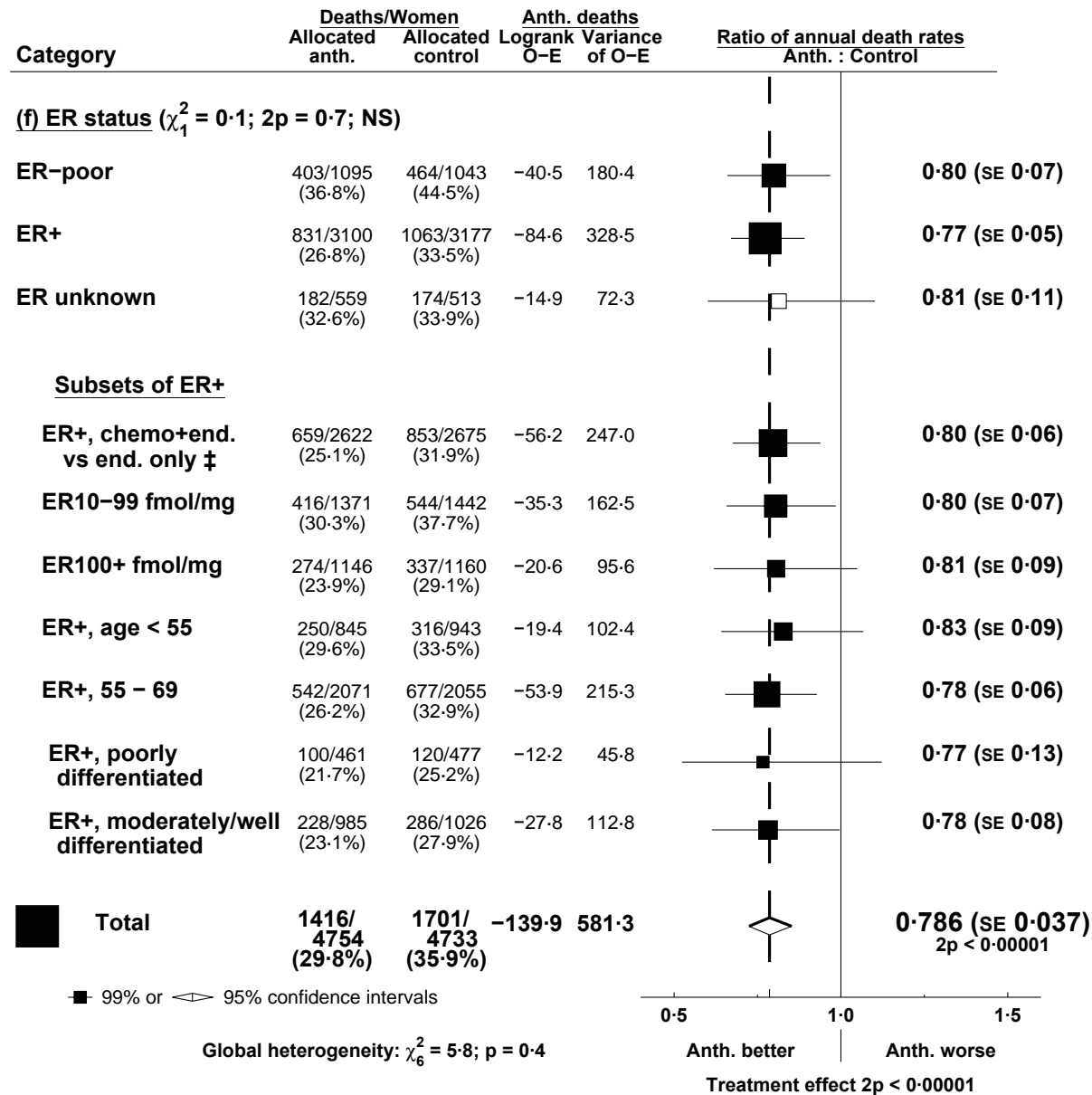


Death rates (% / year: total rate – rate in women without recurrence) and logrank analyses

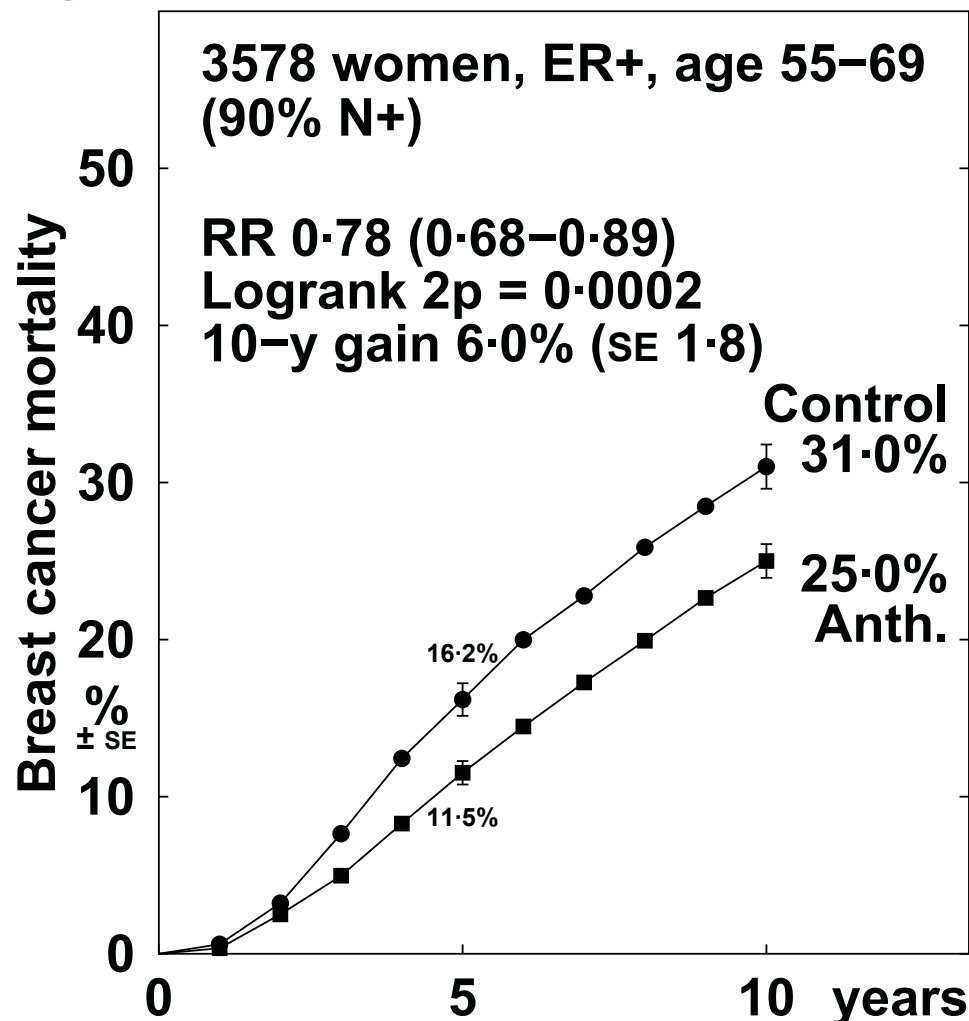
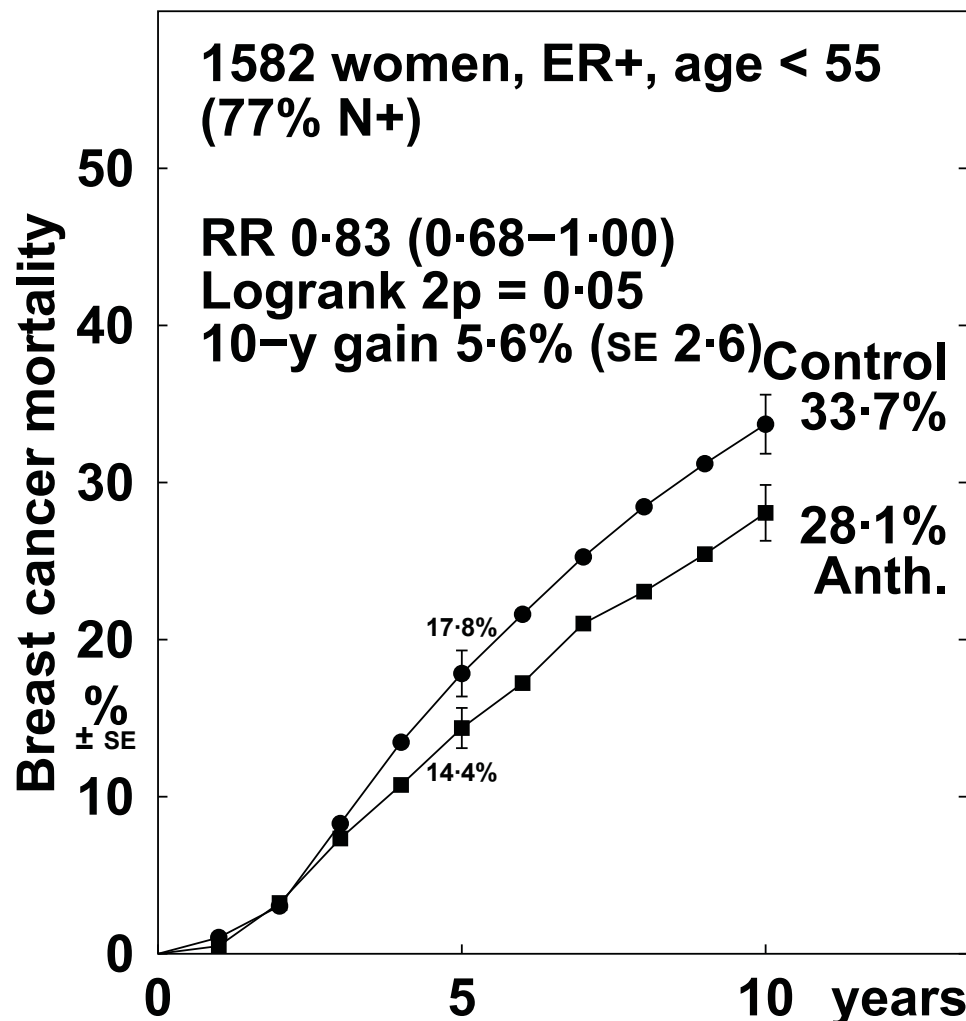
Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	4.96 SE 0.32	3.50 SE 0.33	2.64 SE 0.36
Control	6.84 SE 0.41	4.47 SE 0.42	2.92 SE 0.41
Rate ratio	0.76 SE 0.08	0.80 SE 0.13	0.98 SE 0.20
(O-E) / V	-29.2 / 107.7	-10.8 / 48.7	-0.5 / 24.1

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	2.60 SE 0.14	3.40 SE 0.19	3.09 SE 0.26
Control	3.63 SE 0.19	4.17 SE 0.25	3.14 SE 0.30
Rate ratio	0.71 SE 0.07	0.81 SE 0.08	0.92 SE 0.14
(O-E) / V	-54.3 / 156.2	-26.4 / 123.3	-4.0 / 48.9

Breast cancer mortality ratio: any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ER STATUS and subsets of ER+



**Any anthracycline-based regimen (eg, standard 4AC)
vs no adjuvant chemotherapy,
ER+ disease only: by ENTRY AGE**



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

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	3.12 SE 0.28	3.76 SE 0.38	2.19 SE 0.39
Control	3.76 SE 0.34	4.14 SE 0.44	1.93 SE 0.39
Rate ratio	0.79 SE 0.12	0.80 SE 0.14	1.14 SE 0.33
(O–E) / V	–12.4 / 52.9	–8.5 / 38.8	1.4 / 10.8

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Anth.	2.44 SE 0.16	3.31 SE 0.23	3.42 SE 0.34
Control	3.54 SE 0.23	4.12 SE 0.32	3.76 SE 0.43
Rate ratio	0.69 SE 0.08	0.84 SE 0.10	0.92 SE 0.16
(O–E) / V	–36.8 / 98.4	–14.0 / 80.4	–3.1 / 36.4

Halving big risks and halving small risks by chemotherapy

- Proportional risk reduction does not depend much on age, ER status or nodal status (or on tumour grade or tumour diameter)
- Absolute risk reduction, however, depends on the prognosis – and, for ER+ disease, this is the prognosis with endocrine therapy
- Information lacking on tumour gene expression and on quantitative immunohistochemistry