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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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±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*.

Category	Deaths/ Allocated taxane	Women Allocated non-tax.	<u>Taxan</u> Logranl O−E	e deaths k Variance of O-E	Ratio of annual d Taxane : No	eath rates on-tax.
(a) Same, or more, non	-taxane che	emo. for co	ontrols	$x^{*}(\chi^{2} = 2$	·0; p = 0·6; NS)	
Same (1×) † ie, unconfounded	1169/5590 (20·9%)	1306/5577 (23·4%)	-79.8	520-8	-	0.86 (se 0.04)
More (<2×) †	339/4282	407/4302	-31.3	172-3		0.83 (SE 0.07)
More (<2×) ©	587/7071	(3·370) 665/7076	-32-1	278-9	_ # _+	0.89 (se 0.06)
More (≈2×) †	(8-3%) 546/5185 (10-5%)	(9·4%) 590/5168 (11.4%)	-15-8	259-3		0.94 (se 0.06)
(b) Taxane (D/P*) sched	dule $(\chi_{2}^{2} = 1)$	•0; p = 0•8;	NS)			
4(D100) q3w †	816/6480	887/6476	-31.6	338-1		0·91 (se 0·05)
Other docetaxel	(12-070) 716/8396 (8-5%)	(13-77,0) 844/8409 (10-0%)	-58-4	366-9		0.85 (se 0.05)
4(P175) q3w †	572/3528	612/3502 (17.5%)	-30-1	274-4	_ # +	0·90 (se 0·06)
Other paclitaxel	(10-278) 537/3724 (14-4%)	625/3736 (16-7%)	-38-9	251.9	_₩	0.86 (se 0.06)
(c) Concurrent endocri	ne therapy	if ER+? (γ	² = 0·2:	; 2p = 0·6	; NS)	
Yes	87/713	93/723	-2.7	40.5	, , , , , , , , , , , , , , , , , , ,	
No (any endocrine only	(12·2%) 2554/21415 (11.0%)	(12·9%) 2875/21400	-158-3	1136-0		0-87 (se 0-03)
after chemo ended)	(11.976)	(13-470)				
(d) Entry age (trend χ_1^2	= 3·5; 2p = (0-06)				
Age < 45	871/5930 (14-7%)	928/5927 (15·7%)	-36.7	384-6		0·91 (se 0·05)
45 - 54	835/7747 (10-8%)	932/7720 (12·1%)	-41-4	372-3	-#	0.89 (SE 0.05)
55 - 69	735/6572 (11·2%)	877/6570 (13·3%)	-69-0	346.5		0.82 (SE 0.05)
70+	51/314 (16·2%)	81/343 (23.6%)	-11-4	24∙4 ←	_	0.63 (se 0.16)
Age unknown	149/1565 (9·5%)	150/1563 (9·6%)	-2.5	48.6		
(e) Nodal status before	chemo (tre	and $\chi_1^2 = 0.3$	3; 2p =	0.6; NS)		
N0/N-	120/2104	132/2070 (6.4%)	-6-0	61.0		0·91 (se 0·12)
N1-3	520/6981 (7-4%)	(8 4 %) 599/6977 (8 6%)	-41.9	262-1		0.85 (se 0.06)
N4+	783/5012 (15-6%)	849/5062 (16-8%)	-29-9	338-8		0-92 (SE 0-05)
Other / unknown	1218/8031 (15-2%)	1388/8014 (17-3%)	-83-1	514-6		0-85 (se 0-04)
(f) ER status ($\gamma^2 = 0.1$;	2p = 0·7; NS	5)				
ER-poor	1087/5883 (18-5%)	, 1271/6027 (21.1%)	-78-0	505.0		0.86 (se 0.04)
ER+	1044/12848	1164/12790	-67-1	502.3	-	0·87 (se 0·04)
ER unknown	(8-1%)	(9.1%) 533/3306	-15-9	169-1		- 0·91 (se 0·07)
	(15-0%)	(16·1%)				
Subsets of ER+					I	
ER+ HER2-	273/4613 (5-9%)	296/4656 (6·4%)	-11.3	136-2		0.92 (se 0.08)
ER+ HER2+	98/978 (10-0%)	114/1022 (11·2%)	-6-2	47.5	_	0.88 (se 0.14)
ER+, age < 55	666/8316 (8-0%)	725/8223 (8-8%)	-37.7	317-9	-₩	0·89 (SE 0·05)
ER+, 55 - 69	355/4338 (8·2%)	413/4368 (9·5%)	-25.8	174-5		0-86 (se 0-07)
ER+, poorly differentiated	440/3362 (13-1%)	398/3330 (12·0%)	14-8	189-8	╷─┼∎	<u>1-</u> 08 (se 0-08)
ER+, moderately differentiated	273/5552 (4-9%)	354/5595 (6·3%)	-38-0	143-0		0.77 (se 0.07)
ER+, well differentiated	48/1501 (3·2%)	74/1430 (5·2%)	-11.1	28.7		0.68 (SE 0.16)
Total	2641/ 22128 (11·9%)	2968/ - 22123 (13·4%)	-161-0	1176-5	÷	0-872 (SE 0-027) 2p < 0-00001
- ■ - 99% or <-> 95%	confidence int	ervals		_	0-5 1-0	1.5
Global	heterogeneity	$\chi^2 = 7.1; \mu$	o = 0·7		Taxane better	Non-tax. better p < 0.00001

* Forest plots (webappendix pp 21-26) give details of each trial's cytotoxic regimens

D = docetaxel; **P** = paclitaxel; $4(D_{100}) q_{3W}$ 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*.

Category	Deaths/ Allocated anthr.	Women Allocated CMF	Anthr Lograni O-E	<u>. deaths</u> k Variance of O−E	e Ratio of annual de Anthr. : CM	eath rates F
(a) Cumulative anthracy (trend $\gamma^2 = 8.0$; 2p = 0	cline dosa 0-005)	ge, if dose	e/cycle	e ≥A60/E9	<u>°</u> *	
A360 or E720-800:	378/2082 (18·2%)	475/2097 (22·7%)	-50.0	198-0	_ _	0-78 (se 0-06)
A300 or E400-480	396/2766	472/2770	-35.9	183-1		0-82 (se 0-07)
A240: standard 4AC	877/2565 (34·2%)	886/2557 (34·6%)	-8.5	405.6	4	0.98 (SE 0.05)
White: dose/cycle < A60/E90	358/1530 (23·4%)	357/1502 (23·8%)	-11.1	160-1	_ <u>_</u> b	_ 0·93 (se 0·08)
(b) Cyclophosphamide i	n CMF ora	<u>l/iv</u> ($\chi_1^2 = 0$	•9; 2p	= 0·3; NS	s)	
C100×14 oral/cycle	1651/6530 (25·3%)	1834/6525 (28·1%)	-98.8	788.8		0.88 (SE 0.03)
C600×2 iv/cycle	358/2413 (14·8%)	356/2401 (14·8%)	-6.6	157.9		— 0·96 (se 0·08)
(c) Concurrent endocrin	e therapy	if ER+? (χ	² ₁ = 0-0	; 2p = 1·0); NS)	
Yes	57/502 (11·4%)	62/502 (12·4%)	-2.9	29.0	P	
No (any endocrine only after chemo ended)	1952/8441 (23·1%)	2128/8424 (25·3%)	-102.5	917-8		0·89 (se 0·03)
(d) Entry age (trend χ_4^2 =	0-0; 2p = 0)∙9; NS)			I	
Age < 45	871/3398	991/3454 (28.7%)	-54.8	422.8		0.88 (SE 0.05)
45 - 54	(28 678) 738/3399 (21.7%)	(23 7 %) 773/3356 (23.0%)	-30.6	344-3		0·91 (se 0·05)
55 - 69	375/1961	(20.6%)	-20.2	169.3	_	0.89 (se 0.07)
70+	(19:17%) 18/106 (17:0%)	(20·078) 25/112 (22·3%)	-2.2	8.7		
Age unknown	7/79 (8·9%)	5/84 (6·0%)	2.4	1.8		
<u>(e) Nodal status</u> (trend χ	² = 0-9; 2p	= 0·3; NS))			
N0/N-	461/3865 (11·9%)	541/3869 (14·0%)	-40.5	233-1	=	0-84 (se 0-06)
N1-3	520/2442 (21·3%)	543/2418 (22·5%)	-10.0	243.4		0.96 (SE 0.06)
N4+	612/1234 (49·6%)	647/1233 (52·5%)	-23-1	273-4		0-92 (SE 0-06)
Other / unknown	416/1402 (29·7%)	459/1406 (32·6%)	-31.9	196-8		0.85 (SE 0.07)
(f) ER status ($\chi_1^2 = 0.1; 2$)	o = 0·8; NS	5)				
ER-poor	1201/4488 (26·8%)	1287/4518 (28·5%)	-43.7	564.6	-	0-93 (se 0-04)
ER+	569/3279 (17·4%)	610/3257 (18·7%)	-26.5	267.0		0·91 (se 0·06)
ER unknown	239/1176 (20·3%)	293/1151 (25·5%)	-35-2	115-2		0.74 (se 0.08)
Subsets of ER+						
ER10-99 fmol/mg	247/1072 (23·0%)	279/1094 (25·5%)	-21.2	108-3		0.82 (SE 0.09)
ER100+ fmol/mg	86/450 (19·1%)	(116/450 (25·8%)	-15-4	42.0		0.69 (se 0.13)
ER+, age < 55	426/2359 (18·1%)	461/2345 (19·7%)	-22.9	202.3		0.89 (se 0.07)
ER+, 55 - 69	134/846 (15·8%)	140/847 (16·5%)	-3.6	61.1		0-94 (se 0-12)
ER+, poorly differentiated	131/868 (15·1%)	130/793 (16·4%)	-4-1	52.7		
ER+, moderately/well differentiated	125/952 (13·1%)	136/1047 (13⋅0%)	-1.8	58.3	_	
Total	2009/ 8943 (22·5%)	2190/ - 8926 (24·5%)	-105-4	946-8	$\left \right $	0-895 (SE 0-031) 2p = 0-0006
- ■ 99% or <>> 95% c	onfidence inte	ervals		_	0.5 1.0	1.5
Global h	eterogeneity	ν: χ ₆ ² = 9-9; p	= 0-1		Anthr. better Treatment effect 2	CMF better p = 0-0006

* Forest plots (webappendix pp 27-32) give details of each trial's cytotoxic regimens

Anthracyclines: $\mathbf{A} = doxorubicin (Adriamycin), \mathbf{E} = epirubicin. Other cytotoxics: <math>\mathbf{C} = cyclophosphamide, \mathbf{M} = methotrexate, \mathbf{F} = fluorouracil Dose/cycle (and cumulative dosage) is given after the drug name in mg/m², <math>\mathbf{A}_{e0}/\mathbf{E}_{90}$ 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*.

Category	Deaths/ Allocated anth.	Women Allocated control	Anth Lograni O-E	deaths Variance of O-E	Ratio of annu Anth.	al death rates Control
(a) Cumulative anthracy	cline dosa	ige, if dos	e/cycle	≥ A60/E90	*	
(χ ₁ ² = 1·5; 2p = 0·2; NS	5)				1	
A360: CAF	324/1177 (27-5%)	456/1143 (39-9%)	-35.3	80-3		0·64 (se 0·09)
A300			(no	trials)		
A240/E360: standard 4AC/EC	212/747 (28·4%)	265/792 (33-5%)	-25.6	100.5		0·78 (se 0·09)
White: dose/cycle < A60/E90	880/2830 (31·1%)	980/2798 (35·0%)	-79.0	400.5		0·82 (se 0·05)
(b) Anthracycline tested	* (χ ² = 1·9	; 2p = 0·2;	NS)		1	
Doxorubicin (A)	973/2626 (37·1%)	1185/2570 (46-1%)	-106-1	370-4		0·75 (se 0·05)
Epirubicin (E)	293/1283 (22·8%)	318/1283 (24-8%)	-20.5	138-4	╶╌┤╋┻╌╴	— 0·86 (se 0·08)
A or E	150/845 (17·8%)	198/880 (22-5%)	-13-3	72.5		0·83 (se 0·11)
(c) Concurrent endocrin	e therapy	if ER+? (χ	² = 0·3	; 2p = 0⋅6;	NS)	
Yes	607/2004 (30-3%)	693/2014 (34-4%)	-54-4	288-0	_ #	0·83 (se 0·05)
No (any endocrine only	462/1431	514/1398	-48-2	203-8	#	0·79 (se 0·06)
after chemo ended) Random †	(32-3%)	(30-8%) 494/1321	-37.2	89-4		0.66 (se 0.09)
(d) Entry age (trend x^2 –	(∠o·3%) 2.0· 2n – i	(37.4%) 0.2: NG)			I I	
Age < 45	135/402	127/353	-4.9	53.0	 	0-91 (se 0-13)
45 - 54	(33.6%)	(36·0%) 419/1175	-34.9	139.8		0.78 (SE 0.07)
55 - 69	(30·3%) 899/2995	(35·7%) 1071/2956	-88.5	377.0	_ ■	0·79 (se 0·05)
70.	(30.0%)	(36-2%)	44 7			0.26 (0= 0.10)
70+ A ma umlum auum	43/225 (19·1%)	84/232 (36·2%)	-11.7	11.4 ←	I	0.36 (SE 0.19)
Age unknown	(5.9%)	0/17 (0·0%)	0.2	0.1	I	
(e) Nodal status (trend χ	² = 0·0; 2p	o = 0∙9; NS)		I	
N0/N-	122/789 (15-5%)	137/761 (18·0%)	-12.0	56-9	P	0.81 (se 0.12)
N1-3	513/2257 (22·7%)	604/2217 (27-2%)	-51.3	214-1	_ #	0.79 (se 0.06)
N4+	575/1226 (46·9%)	741/1295	-53.7	222.3	_ #	0·79 (se 0·06)
Other / unknown	206/482 (42·7%)	219/460 (47·6%)	-22.8	88.0		0.77 (se 0.09)
(f) ER status ($\chi_1^2 = 0.1$; 2p	o = 0∙7; NS	5)			1	
ER-poor	403/1095	464/1043	-40.5	180-4	_ #	0·80 (se 0·07)
ER+	(30 070) 831/3100 (26-8%)	1063/3177 (33·5%)	-84.6	328-5		0.77 (se 0.05)
ER unknown	182/559 (32·6%)	174/513 (33-9%)	-14-9	72-3		0.81 (se 0.11)
Subsets of ER+					1	
ER+, chemo+end.	659/2622 (25.1%)	853/2675 (31.9%)	-56-2	247.0	#_	0·80 (se 0·06)
ER10-99 fmol/mg	416/1371	(31-370) 544/1442 (27.7%)	-35-3	162-5	#	0·80 (se 0·07)
ER100+ fmol/mg	(30-3%) 274/1146 (23-9%)	(377770) 337/1160 (29.1%)	-20.6	95-6		0.81 (se 0.09)
ER+, age < 55	250/845	316/943	-19.4	102-4		— 0·83 (se 0·09)
ER+, 55 - 69	(29·6%) 542/2071	(33-5%) 677/2055	-53.9	215.3	_ #	0·78 (se 0·06)
ER+, poorly	(26-2%) 100/461	(32·9%) 120/477	-12-2	45-8	∓	0·77 (se 0·13)
differentiated ER+, moderately/well	(∠1·7%) 228/985	(∠5·2%) 286/1026	-27.8	112.8	 ₽	0-78 (se 0-08)
differentiated	(23-1%)	(27-9%)			т ,	
Total	1416/ 4754 (29·8%)	1701/ - 4733 (35•9%)	-139-9	581.3	\Rightarrow	0·786 (SE 0·037) 2p < 0·00001
- ₽ 99% or <⇒ 95% co	onfidence int	ervals		0	 •5 1	-0 1-5
Global h	eterogeneity	y: χ ₆ ² = 5·8; p	= 0-4	Ū	Anth. better	Anth. worse
					Treatment effe	ct 2p < 0.00001

* Forest plots (webappendix pp 33-38) give details of each trial's cytotoxic regimens

Anthracyclines: $\mathbf{A} = doxorubicin (Adriamycin), \mathbf{E} = epirubicin. Other cytotoxics: <math>\mathbf{C} = cyclophosphamide, \mathbf{M} = methotrexate, \mathbf{F} = fluorouracil Dose/cycle (and cumulative dosage) is given after the drug name in mg/m²; <math>\mathbf{A}_{60}/\mathbf{E}_{90}$ 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

Category	Deaths/ Allocated CMF	Women Allocated control	CMF Logran O-E	deaths k Varianc of O-E	e <u>Ratio of annual</u> CMF : C	death rates control
(a) Standard CMF (or nea	ar-standa	rd CMF)?	* $(\chi_{4}^{2} =$	4·4; 2p :	= 0.04)	
Yes (shown below)	658/2665 (24·7%)	790/2588 (30·5%)	-89·1	320.1		0·76 (se 0·05)
No (excluded)	1512/4378 (34·5%)	1643/4372 (37·6%)	-81.4	611.1	I	0·88 (se 0·04)
(b) Cyclophosphamide c	oral/iv (χ_1^2 :	= 0·1; 2p =	• 0·7; N	S)	I	
C100×14 oral/cycle	617/2562 (24·1%)	756/2497 (30·3%)	-89.9	305-1		0·74 (se 0·05)
C600×2 iv/cycle	15/40 (37·5%)	18/39 (46·2%)	-2.6	6-1	I	
Optional (oral/iv)	26/63 (41·3%)	16/52 (30⋅8%)	3.3	8-9	I	
(c) Concurrent endocrin	e therapy	<u>if ER+?</u> (χ	$r_{1}^{2} = 0.3$; 2p = 0·	6; NS)	
Yes	301/1342 (22·4%)	391/1338 (29·2%)	-47.2	151.2		0·73 (se 0·07)
No (any endocrine only after chemo ended)	357/1323 (27·0%)	399/1250 (31·9%)	-41.9	168.9		0·78 (se 0·07)
(d) Entry age (trend χ_1^2 =	10·0; 2p =	= 0·002)			I	
Age < 45	115/739 (15·6%)	150/635 (23·6%)	-33-0	62-2	_ _	0·59 (se 0·10)
45 - 54	165/803 (20·5%)	230/853 (27·0%)	-35.5	86-1		0.66 (SE 0.09)
55 - 69	356/1043 (34·1%)	385/994 (38•7%)	-21.8	163-0		0·87 (se 0·07)
70+	22/77 (28·6%)	25/105 (23·8%)	1.2	8.8	1	
Age unknown	0/3 (0·0%)	0/1 (0·0%)			I	
(e) Nodal status (trend χ	² = 6·5; 2p	o = 0·01)			I	
N0/N-	197/1754 (11·2%)	294/1711 (17·2%)	-54.0	117-2	_∎_+	0·63 (se 0·07)
N1-3	218/513 (42·5%)	257/499 (51.5%)	-27.8	105.7	P	0·77 (se 0·09)
N4+	231/365	230/351 (65,5%)	-10.4	93.5	╷╼┼	0·90 (se 0·10)
Other / unknown	12/33 (36·4%)	9/27 (33·3%)	3.1	3.6	1	
(f) ER status ($\chi_1^2 = 0.3$; 2p	o = 0·6; NS	5)			1	
ER–poor	167/629	209/617	-17.6	79-2		0·80 (se 0·10)
ER+	(20070) 295/1646 (17.9%)	387/1635 (23.7%)	-47.2	155.7		0·74 (se 0·07)
ER unknown	196/390 (50·3%)	194/336 (57·7%)	-24.3	85-2		0·75 (se 0·09)
Subsets of ER+					I	
ER+, chem+end. vs end. onlv ±	225/1379 (16·3%)	285/1358 (21.0%)	-34.3	117.6		0·75 (se 0·08)
Ditto, age < 55	85/778 (10·9%)	129/754 (17·1%)	-28.2	50∙3 ≼		0·57 (se 0·11)
Ditto, 55 – 69	129/550 (23·5%)	146/540 (27·0%)	-6.3	62.6	-! = +	0·90 (se 0·12)
ER10-99 fmol/mg	130/884 (14·7%)	207/888 (23·3%)	-39.9	73.8		0·58 (se 0·09)
ER100+ fmol/mg	100/493 (20·3%)	120/494 (24·3%)	-6.2	48-2		0·88 (se 0·14)
ER+, age < 55	107/922 (11·6%)	184/918 (20·0%)	-40.7	67∙1 ≼	<u>-</u> ∎	0·55 (se 0·09)
ER+, 55 - 69	176/664 (26·5%)	192/646 (29·7%)	-6.6	83.5		0·92 (se 0·11)
ER+, poorly differentiated	75/311 (24·1%)	114/361 (31.6%)	-14.5	43.8		0·72 (se 0·13)
ER+, moderately/well differentiated	89/879 (10·1%)	136/850 (16·0%)	-23-2	53.4		0·65 (se 0·11)
Total	658/ 2665 (24·7%)	790/ 2588 (30·5%)	- 89·1	320·1	$\left \right\rangle$	0·757 (se 0·049) ₂p < 0·00001
- ■ 99% or <>> 95% co	onfidence int	ervals		_	0.5 1.0	1.5
Global h	eterogeneity	y: χ ₆ ² = 21⋅6;	p = 0·00	1	CMF better	CMF worse 2p < 0.00001

* 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

	Deaths/ Allocated	Women Allocated	Chem Logran	o. deaths k Variance	e Ratio of annual	death rates
Category	chemo.	control	Ŏ-E	of O-E	Chemo. : C	ontrol
(a) Cumulative anthracy ($\gamma^2 = 1.5$: 2p = 0.2: NS	cline dosa S)	ige, if dos	e/cycle	≥ A 60/E9	<u>90</u> *	
A360: CAF	324/1177	456/1143	-35-3	80.3	_ _	0.64 (SE 0.09)
A300	(21.070)	(33-378)	(no	trials)		
A240/E360:	212/747	265/792	-25.6	100.5		0·78 (se 0·09)
standard 4AC/EC White: dose/cycle	(28·4%) 880/2830	(33.5%) 980/2798	-79.0	400.5		0·82 (se 0·05)
< A60 or E90	(31.1%)	(35.0%)				
(Excludes CMF trials)					I	
(b) Anthracycline tested	* (χ ₂ ² = 2·1;	; 2p = 0·4;	NS)		I	
Doxorubicin (A)	973/2626 (37·1%)	1185/2570 (46·1%)	-106-1	370.4		0·75 (SE 0·05)
Epirubicin (E)	293/1283	318/1283	-20.5	138-4	-+	0.86 (SE 0.08)
A or E	(22.87%)	(24·8 %) 198/880	-13.3	72.5	-+0	0·83 (se 0·11)
No anthracycline	(17.0%)	(22.5%)			1	
(standard CMF or near-standard CMF)	658/2665 (24·7%)	790/2588 (30·5%)	-89-1	320.1		0·76 (se 0·05)
(c) Concurrent endocrin	e therany	if FR+? ($v^2 = 0.0^{-1}$	2n = 1.	0'NS) I	
Yes	922/3515	1107/3518	~1 −106-4	448.2		0·79 (se 0·04)
No (any ondegring only	(26·2%)	(31.5%)	_05 4	262 7		0.79 (ar 0.05)
after chemo ended)	805/2585 (31·1%)	890/2482 (35·9%)	-85-4	363-7		0.79 (SE 0.05)
Random †	347/1319 (26·3%)	494/1321 (37·4%)	-37-2	89.4		0.66 (SE 0.09)
(d) Entry age (trend χ_4^2 =	1·2; 2p =	0·3; NS)			I	
Age < 45	250/1141	277/988	-37-9	115-2		0·72 (SE 0·08)
45 - 54	(21.976) 503/1918	(20.076) 649/2028	-70-4	225.8		0·73 (se 0·06)
55 - 69	(26·2%) 1255/4038	(32·0%) 1456/3950	-110-4	540.0	-	0·82 (se 0·04)
70+	(31.1%)	(36.9%)	40.5	00.0		0.50 (05.0.17)
/ U+	(21.5%)	(32.3%)	-10.5	20•2 ≪		0.59 (SE 0.17)
Age unknown	1/20 (5·0%)	0/18 (0·0%)	0-2	0.1		
<u>(e) Nodal status</u> (trend χ	² = 3·2; 2p	o = 0·07)				
N0/N-	319/2543 (12·5%)	431/2472 (17·4%)	-66-0	174-1		0.68 (SE 0.06)
N1-3	731/2770 (26·4%)	861/2716 (31·7%)	-79-1	319.8		0·78 (se 0·05)
N4+	806/1591 (50·7%)	971/1646 (59·0%)	-64.0	315-8		0·82 (se 0·05)
Other / unknown	218/515	228/487	-19.7	91.7	b	0·81 (se 0·09)
(f) EP status $(\sqrt{2} = 0.4: 2)$	(42·3%)	(40.0%)			I	
$\frac{(1) \text{ ER status}}{\text{ER-poor}} (\chi_1 = 0.4, 2)$	570/1724	673/1660	-58.0	259.6	_	0·80 (se 0·06)
FR+	(33·1%)	(40.5%)	-131.8	181.2		0·76 (s= 0·04)
EIV.	(23.7%)	(30.1%)	101.0	404-2		0 70 (32 0 04)
ER unknown	378/949 (39·8%)	368/849 (43·3%)	-39-2	157.5		0·78 (se 0·07)
Subsets of ER+						
ER+, chem+5yr end.	686/2964	926/3026	-80.0	271.6		0·74 (se 0·05)
vs 5yr end. only ‡	(23·1%)	(30.6%)	-28 /	87.7		0.72 (s= 0.00)
Ditto, age < 55	(19.9%)	(26.4%)	-20.4	07-7		0-72 (SE 0-03)
EB10-00 fm-1/	(25·3%)	(32.8%)	-41.8	170-0		0-70 (SE 0.07)
	546/2255 (24-2%)	(32·2%)	-/5.2	236-3		U-73 (SE U-U6)
ER100+ tmol/mg	374/1639 (22·8%)	457/1654 (27.6%)	-26.8	143.8		U·83 (SE 0·08)
ER+, poorly differentiated	175/772 (22·7%)	234/838 (27·9%)	-26.6	89.6		0·74 (se 0·09)
ER+, moderately/well differentiated	317/1864 (17·0%)	422/1876 (22·5%)	-51.0	166-2	_∎_	0·74 (se 0·07)
Total	2074/ 7419 (28-0%)	2491/ 7321	-229.0	901·4		0·776 (SE 0·029) 2p < 0·00001
- ■ 99% or <>> 95% c	onfidence int	ervals		_		
Global h	eterogeneitv	γ: χ ² = 8·4: ι	o = 0·3		0·5 1·0 Chemo. better	1·5 Chemo. worse
0.00011		~7,1			Treatment effect	2p < 0·00001

* 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; Aeo/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, toremifine)

P 7: Subgroup analyses of RECURRENCE, 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*.

Early recurrence (first 5 years)

	taxane	Allocated I non-tax.	Logrank O-E	Variance of O-E	Ratio of annu Taxane :	al event rates Non-tax.
(a) Same, or more, non	I-taxane che	emo. for co	ontrols	$(\chi_3^2 = 1)$	l·2; p = 0·01)	
Same (1×) † ie, unconfounded	1280/23191 (5-5%/y)	1449/22515 (6-4%/y)	-95-6	557-3		0-84 (se 0-04
More (<2×) †	582/14214 (4-1%/v)	762/13901 (5-5%/v)	-89-6	304-5	∎ ÷	0-75 (SE 0-05
More (<2×) ©	1093/27383 (4-0%/v)	1251/27092 (4-6%/y)	-74-2	513-8	-	0-87 (SE 0-04
More (≂2×) †	932/17824	979/17520	-19-6	428-4		0-96 (SE 0-05
(b) Tayane (D/P*) sche	(5·2%/y)	(5-6%/y) 7: n = 0.05	.			
4(D100) q3w †	1148/22573	1264/22003	-61.7	483-8		0-88 (se 0-04
Other docetaxel	(5-1%/y)	(5-7%/y)	=137.0	668.8		0.81 (se 0.03
	(3-9%/y)	(4-8%/y)	107-0	000-0		001 (02 000
4(P175) q3w †	764/12139 (6-3%/y)	787/11916 (6-6%/y)	-14-8	350-9	L	0-96 (SE 0-05
Other paclitaxel	656/14241 (4-6%/y)	799/13966 (5-7%/y)	-64-6	300-4		0-81 (SE 0-05
(c) Concurrent endocri	ine therapy	if ER+? (χ	² = 0-4;	2p = 0-5	NS)	
Yes No (any endocrine only after chemo ended)	117/2491 (4-7%/y) 3770/80121 (4-7%/y)	145/2393 (6-1%/y) 4296/78635 (5-5%/y)	-14-2 -262-8	58-3 1652-8		
(d) Entry age (trend χ ₁ Age < 45	= 1.4; 2p = (1545/23392	-87-3	595-5	1	0-86 (SF 0-04
	(5-8%/y)	(6-6%/y)				
45 - 54	(4-2%/y)	(4-8%/y)	-79-6	581-7		0-87 (SE 0-04
55 - 69	1104/25592 (4-3%/y)	1296/24985 (5-2%/y)	-97-4	506-4	-	0-83 (SE 0-04
70+	59/1168 (5-1%/v)	94/1218 (7-7%/y)	-12-8	27-5 🗲		- 0.63 (se 0.15
Age unknown	0/5 (0-0%/y)	0/0 [°] /			1	
(e) Nodal status before	244/10084	nd χ ₁ = 0-0	J; 2p =	0-8; NS)	L	0.97 (e= 0.09
N1-3	(2-4%/y) 866/28034	(2·7%/y) 1000/27588	-67-4	429-4		0-85 (SE 0-04
N4+	(3-1%/y) 1216/17834	(3-6%/y) 1393/17572	-83-2	519-2		0-85 (SE 0-04
	(6-8%/y)	(7-9%/y)	00.2	010-2	- 1	0.00 (02.0.04
Other / unknown	1561/26680 (5-9%/y)	1781/25939 (6-9%/y)	-110.7	644-9		0-84 (SE 0-04
(<u>f) ER status</u> (χ ₁ ² = 0-0;	2p = 0-8; NS	5)			-	
ER-poor	1600/22984 (7-0%/v)	1856/22731 (8-2%/v)	-108-3	695-8		0-86 (se 0-04
ER+	1863/52444	2123/51609	-144.7	874-6		0-85 (se 0-03
	(3-6%/y)	(4-1%/y)				
ER unknown	424/7184 (5-9%/y)	462/6688 (6-9%/y)	-24-0	140-7	¢	_ 0-84 (se 0-08
Subsets of ER+						
ER+ PR-poor	374/8277 (4-5%/v)	454/8063 (5-6%/y)	-46-1	178-9	_ 	0-77 (SE 0-07
ER+ PR+	1279/39301 (3-3%/y)	1458/38676 (3-8%/y)	-96-5	605-0	- -	0-85 (se 0-04
ER+ N0/N-	94/5441	105/5619	-4-8	47-6		
ER+ N1-3	(1.7%/y) 472/20845 (2.3%/y)	(1-9%/y) 566/20543 (2-8%/y)	-47-9	245-7		0-82 (SE 0-06
ER+ N4+	681/12769 (5-3%/y)	772/12383 (6-2%/y)	-51-8	302-5	-#	0-84 (se 0-05
ER10-99 fmol/mg	69/1758 (3-9%/y)	73/1600 (4-6%/y)	-4-9	30-0	+-	
ER100+ fmol/mg ER+, unknown	5/133 (3-8%/v) 1789/50541	8/117 (6-8%/y) 2042/49898	-1.5 -135.1	1-8 846-9		0-85 (SE 0-03
level (eg, by IHC)	(3-5%/y)	(4-1%/y)				
ER+ HER2-	540/40700					
	(3-0%/y)	579/16890 (3-4%/y)	-33-9	257-8		0-88 (SE 0-06
ER+ HER2+	(3-0%/y) 183/3579 (5-1%/y)	579/16890 (3-4%/y) 227/3589 (6-3%/y)	-33-9 -22-1	257-8 90-4		_ 0-88 (SE 0-06
ER+ HER2+ ER+ HER2 unk.	(3-0%/y) 183/3579 (5-1%/y) 1170/32045 (3-7%/y)	579/16890 (3-4%/y) 227/3589 (6-3%/y) 1317/31093 (4-2%/y)	-33-9 -22-1 -86-2	257-8 90-4 524-4		_ 0.88 (SE 0.06 _ 0.78 (SE 0.09 0.85 (SE 0.04
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat	(3.0%)/(3.0%)/(3.0%)/(3.0%)/(3.0%)/(3.1%)/	579/16890 (3-4%/y) 227/3589 (6-3%/y) 1317/31093 (4-2%/y) 7; 2p = 0-10	-33-9 -22-1 -86-2); NS)	257-8 90-4 524-4	- ₽ -₽ - - -	0-88 (se 0-06 0-78 (se 0-09 0-85 (se 0-04
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff.	$\frac{10^{10780}}{(3.0\%/y)}$ $\frac{183(3579)}{(5.1\%/y)}$ $\frac{1170(32045)}{(3.7\%/y)}$ $\frac{100}{(\chi_1^2 = 2.7)}$ $\frac{1429(22556)}{(6.3\%/y)}$	579/16890 (3-4%/y) 227/3589 (6-3%/y) 1317/31093 (4-2%/y) 7; 2p = 0-10 1568/22202 (7-1%/y)	-33-9 -22-1 -86-2 (); NS) -70-9	257-8 90-4 524-4 648-3	-∎- -∔- - -	_ 0-88 (se 0-06 _ 0-78 (se 0-09 0-85 (se 0-04 0-90 (se 0-04
ER+ HER2+ ER+ HER2 unk. (g) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff.	$\frac{(3.0\%)}{(3.0\%)}$ $\frac{(3.0\%)}{183/3579}$ $\frac{(5.1\%)}{(5.1\%)}$ $\frac{(5.1\%)}{(170/32045)}$ $\frac{(3.7\%)}{(3.7\%)}$ $\frac{(21)}{(3.2\%)}$ $\frac{(21)}{(3.2\%)}$ $\frac{(21)}{(3.2\%)}$	57916890 (3-4%/y) 227/3589 (6-3%/y) 1317/31093 (4-2%/y) 7; 2p = 0-10 1568/22202 (7-1%/y) 1042/25819 (4-0%/y)	-33-9 -22-1 -86-2); NS) -70-9	257-8 90-4 524-4 648-3 415-0	 	_ 0-88 (se 0-06 - 0-78 (se 0-09 0-85 (se 0-04 0-90 (se 0-04 0-78 (se 0-04
ER+ HER2+ ER+ HER2 unk. (g) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Well-diff.	$\frac{(3.0\%/s)}{(3.0\%/s)}$ $\frac{(3.0\%/s)}{183/3579}$ $\frac{(5.1\%/y)}{(5.1\%/y)}$ $\frac{1170/32045}{(3.7\%/y)}$ $\frac{1429/22556}{(6.3\%/y)}$ $\frac{827/28164}{(3.2\%/y)}$	57916890 (3-4%/y) 227/3589 (6-3%/y) 1317/31093 (4-2%/y) 7; 2p = 0-10 1568/22202 (7-1%/y) 1042/25819 (4-0%/y) 231/8205	-33-9 -22-1 -86-2 (); NS) -70-9 (-103-9 -6-3	257-8 90-4 524-4 648-3 415-0 103-0	╪ ╪	- 0-88 (se 0-06 - 0-78 (se 0-09 0-85 (se 0-04 0-90 (se 0-04 0-78 (se 0-04 0-94 (se 0-10
ER+ HER2+ ER+ HER2 unk. (g) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Well-diff. Grade unknown	S10/16740 (3-0%/y) 183/3579 (5-1%/y) 1170/32045 (3-7%/y) sion (χ_1^2 = 2-7 1429/22556 (6-3%/y) 827/26164 (3-2%/y) 1416/25523 (5-5%/y)	57916890 (3-4%/y) 227/3589 (6-3%/y) 1317/31093 (4-2%/y) 7; 2p = 0-10 1568/22202 (7-1%/y) 1042/25819 (4-0%/y) 1600/24961 (6-4%/y)	-33.9 -22.1 -86.2 D; NS) -70.9 →103.9 -6.3 -97.0	257-8 90-4 524-4 648-3 415-0 103-0 579-3	╕╅ ╪ ╼╸╴╴╡┿	- 0-88 (se 0-06 - 0-78 (se 0-09 0-85 (se 0-04 0-90 (se 0-04 0-78 (se 0-04 0-94 (se 0-10 0-85 (se 0-04
ER+ HER2+ ER+ HER2 unk. (g) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Well-diff. Grade unknown (h) Tumour diameter (t	$\frac{(3-0\%/4)}{(3-0\%/4)}$ $\frac{(3-0\%/4)}{183/3579}$ $\frac{(5-1\%/4)}{(5-7\%/4)}$ $\frac{(5-1\%/4)}{(3-7\%/4)}$ $\frac{(5-1\%/4)}{(3-7\%/4)}$ $\frac{(5-7\%/4)}{(2-5\%/4)}$ $\frac{215/8517}{(2-5\%/4)}$ $\frac{(2-5\%/4)}{(2-5\%/4)}$ rend $\chi^2_{-} = 0$	579(1884)0 (3-4%)) (227(358) (6-3%)) 1317(3103) 1317(3103) 1317(3103) (4-2%)) (1568/22202 (7-1%)) 1042(25819) 1042(25819) (4-0%)) 1042(25819) (2-3%)) 1042(25819) (4-0%)) 231/8205 (2-8%)) 1040(25819) (4-0%)) 231/8205 (2-8%)) 1040(25819) (4-0%)) 231/8205 (2-8%)) 1040(25819) (4-0%)) 231/8205 (2-8%)) 1040(25819) (4-9%)) 231/8205 (2-8%)) 232 (2-8%)) 23	-33-9 -22-1 -86-2 0; NS) -70-9 - 103-9 -6-3 -97-0 : NS)	257-8 90-4 524-4 648-3 415-0 103-0 579-3	- ⋵⋕≢ ᇔ - ⋵┤ ө	- 0-88 (se 0-06 - 0-78 (se 0-09 0-85 (se 0-04 0-90 (se 0-04 0-78 (se 0-04 0-85 (se 0-04
ER+ HER2+ ER+ HER2 unk. (g) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Grade unknown (h) <u>Tumour diameter</u> (t 1 - 20 mm (T1)	$\begin{array}{c} & (3-0\%)\\ (3-0\%)\\ (3-0\%)\\ 183/3579\\ (5-1\%)\\ 1170/32045\\ (3-7\%)\\ 1170/32045\\ (3-7\%)\\ 11429/22556\\ (6-3\%)\\ (3-2\%)\\ 11429/22556\\ (6-3\%)\\ (3-2\%)\\ 125/8517\\ (2-5\%)\\ 1416/22552\\ (5-5\%)\\ 1416/2552\\ (5-5\%)\\ (5-5\%)\\ (5-5\%)\\ (3-2\%)\\ (5-5\%)\\ (3-2\%)\\ (5-5\%)\\ (3-2\%)\\ (5-5\%)\\ (3-2\%)\\ (5-5\%)\\ (3-2\%)\\ $	579/16890 (3.45%)/ 227/3589 (6.3%/)/ 137/31093 (4.2%/)/ 7; 2p = 0.10 1568/22202 (7.1%/) 1042/25819 (4.0%/) 231/8205 (2.8%/) 1600/24961 (6.4%/) 0; 2p = 1.0 1041/27942	-33.9 -22.1 -86.2 0; NS) -70.9 - 103.9 -6.3 -97.0 ; NS) -61.1	257-8 90-4 524-4 648-3 415-0 103-0 579-3 431-2	● - 白 ┿ ♥ ● - 白 ┿ ●	 0-88 (sc 0.06 0-78 (sc 0.05 0-85 (sc 0.04 0-90 (sc 0.04 0-78 (sc 0.04 0-78 (sc 0.04 0-94 (sc 0.10 0-85 (sc 0.04 0-85 (sc 0.04
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Weil-diff. Grade unknown (h) Tumour diameter (t 1 – 20 mm (T1)	$\begin{aligned} & \sum_{i=1}^{i} (3,0\%)^{i} \\ & \sum_{i=1}^{i} (3,0\%)^{i} \\ & \sum_{i=1}^{i} (3,7\%)^{i} \\ & \sum_{i=1}^{i} (3,$	579/16890 (3.43%)/ 227/3589 (6.3%)/ 1317/31093 (4.2%)/ 7; 2p = 0.10 1568/22202 (7.1%)/ 1042/25819 (4.0%)/ 1600/24881 (6.4%)/ 1600/24881 (6.4%)/ 00; 2p = 1.0 1041/27942 (3.7%)/	-33.9 -22.1 -86.2); NS) -70.9 →103.9 -6.3 -97.0 ; NS) -61.1 -132.4	257-8 90-4 524-4 648-3 415-0 103-0 579-3 431-2 762-9	₽₩ -⊖╀╋ ₩- ᠪ┽╇	 0-88 (st 0.06 0-78 (st 0.05 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.16 0-85 (st 0.04 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.04
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Welt-diff. Grade unknown (b) Tumour diameter (t 1 - 20 mm (T1) 21 - 50 mm (T2)	$\begin{aligned} & \begin{array}{l} & \end{array}{} & \begin{array}{l} & \begin{array}{l} & \end{array}{} & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \begin{array}{l} & \end{array}{} & \begin{array}{l} & \end{array}{} & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \begin{array}{l} & \end{array}{} & \end{array}{} \\ & \begin{array}{l} & \begin{array}{l} & \end{array}{} & \begin{array}{l} & \end{array}{} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ & \end{array}{} \\ \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ \end{array}{} \\ \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ \end{array}{} \\ \begin{array}{l} & \end{array}{} \\ & \end{array}{} \\ \end{array}{} \\ \begin{array}{l} & \end{array}{} \\ \end{array}{} \\ \end{array}{} \\ \begin{array}{l} & \end{array}{} \\ \end{array}{} \\ \end{array}{} \\ \begin{array}{l} & \end{array}{} \\ \end{array}{} \\ \end{array}{} \\ \end{array}{} \\ \begin{array}{l} & \end{array}{} \end{array}{} \\ \end{array}{} \\ \end{array}{} \end{array}{} \\ \end{array}{} \\ \end{array}{} \end{array}{} \end{array}{} \\ \begin{array}{l} & \end{array}{} \end{array}{} \\ \end{array}{} \end{array}{} \\ \end{array}{} \\ \end{array}{} \end{array}{} \end{array}{} \end{array}{} \end{array}{} \end{array}{} \end{array}{} \end{array}{} \end{array}{} \end{array}{}$	57916880 (3.43%)) 22773589 (6.33%)) 1317731093 (4.23%)) 7; 2p = 0.10 (568/22202 (2.8%)) 1600/24961 (6.4%)) 0; 2p = 1.0 1041/27942 (3.7%)) 1923/29716 (6.5%))	-33.9 -22.1 -86.2 D; NS) -70.9 -6.3 -97.0 ; NS) -61.1 -132.4	257-8 90-4 524-4 648-3 415-0 103-0 579-3 431-2 762-9	·● + ← → + ● - ← + ●	 0-88 (st 0.06 0-78 (st 0.05 0-85 (st 0.04 0-90 (st 0.04 0-78 (st 0.04 0-78 (st 0.04 0-84 (st 0.10 0-87 (st 0.04 0-84 (st 0.03
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Mell-diff. Grade unknown (b) Tumour diameter (t (t) Tumour diameter (t 21 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T3/T4)	$ \begin{array}{l} \begin{array}{c} \text{Solution} \\ \text{(3.0%)} \\ \text{(3.0%)} \\ \text{(3.0%)} \\ \text{(3.0%)} \\ \text{(3.7\%)} \\ \text{(3.2\%)} \\ ($	57916880 (3.43%)) 227/3589 (6.33%)) 1317/31093 (4.23%)) 7; 2p = 0-10 1568/22202 (2.43%)) 1004225818 (6.47%)) 231/8205 (2.83%)) 10022458 1 (6.47%)) 0; 2p = 1-0 1041/27942 (3.73%)) 1223/29716 (6.57%))	-33.9 -22.1 -86.2); NS) -70.9 -70.9 -6.3 -97.0 ; NS) -61.1 -132.4 -28.6	257-8 90-4 524-4 648-3 415-0 103-0 579-3 431-2 762-9 229-8	┍┿ ╼ ┿╺═┿	 0-88 (st 0.06 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.10 0-94 (st 0.10 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.02 0-88 (st 0.05
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Moderately-diff. Grade unknown (h) Tumour diameter (t 1 - 20 mm (T4) 21 - 50 mm (T2) > 50 mm (T3/T4) Other / unknown	$\begin{array}{c} \text{Substrate} \\ \text{(3.90%)} \\ \text{(3.90%)} \\ \text{(3.90%)} \\ \text{(3.90%)} \\ \text{(3.90%)} \\ \text{(3.70\%)} \\ (3.70\%)$	579/16890 (3.43%)/ (3.43%)/ (3.43%)/ 127/3589 (6.33%)/ 1317/31093 (1317/31093) (1317/310) (1317/31093) (1317/310) (131	-33.9 -22.1 -86.2); NS) -70.9 -6.3 -97.0 ; NS) -61.1 -132.4 -28.6 -64.3	257-8 90-4 524-4 648-3 415-0 103-0 579-3 431-2 762-9 229-8 289-9	┿╆╬╶╇╪╬╴╪╡╸	 0-88 (st 0.06 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.16 0-85 (st 0.04 0-87 (st 0.04 0-87 (st 0.04 0-84 (st 0.02 0-88 (st 0.02 0-88 (st 0.06 0-80 (st 0.05
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Well-diff. Grade unknown (h) Tumour diameter (t 1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T3T4) Other / unknown (j) Tumour differentiati	$\begin{array}{c} \lim_{t \to \infty} \max_{x \in [0, 1]} \sum_{i \in [0, 1]} \max_{x \in [0, 1]} \sum_{i \in [0, 1]} \max_{x \in [0, 1]} \max_{x$	$\begin{array}{c} 5791680\\ (3.4\%)\\ (3.4\%)\\ (3.4\%)\\ 227(3589\\ (6.3\%)\\ (13)7(31093\\ (4.2\%)\\ (7,1\%)\\ (7,1\%)\\ (7,1\%)\\ (7,1\%)\\ (7,1\%)\\ (1042)2581\\ (4.4\%)\\ (1042)2581\\ (4.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.4\%)\\ (1042)2581\\ (6.5\%)\\ (1042)2581\\ (6.5\%)\\ (1042)2581\\ (1042)2$	-33.9 -22.1 -86.2); NS) -70.9 +103.9 -6.3 -97.0 ; NS) -61.1 -132.4 -28.6 -64.3 p = 0.0	257-8 90-4 524-4 648-3 4115-0 103-0 579-3 431-2 762-9 229-8 289-9 1)	┿╋ ╩ ┿╘╛┼╪	- 0-88 (st 0.06 - 0-78 (st 0.05 0-85 (st 0.04 0-90 (st 0.04 0-78 (st 0.04 0-78 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 - 0-88 (st 0.05 0-80 (st 0.05
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Moderately-diff. (h) Tumour diameter (f (h) Tumour diameter (f 1 - 20 mm (T-1) 21 - 50 mm (T-2) 50 mm (T-3/T4) Other / unknown (i) Tumour differentiati Poorly, ER-poor	$\begin{array}{l} \begin{array}{l} \begin{array}{l} \begin{array}{l} \begin{array}{l} \begin{array}{l} \begin{array}{l} \begin{array}{l} $	$\begin{array}{l} 57916890\\ (3.4\%)\\ (3.4\%)\\ 22773589\\ (6.3\%)\\ (4.2\%)\\ (7,2p=0.10\\ (7.1\%)\\ (7.1\%)\\ (7.1\%)\\ (7.1\%)\\ (1042/25818\\ (4.4\%)\\ (4.4\%)\\ (4$	-33.9 -22.1 -86.2); NS) -70.9 +103.9 -6.3 -97.0 -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 1) 322.4	┿╶┽┿ ╩ ┿╶╘╛╬ _╋ ╇╴╴╘┙ <mark>┥</mark> ┿	- 0-88 (st 0.06 - 0-78 (st 0.09 0-85 (st 0.04 0-90 (st 0.04 0-78 (st 0.04 - 0-78 (st 0.04 - 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 0-80 (st 0.05
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Moderately-diff. (b) Tumour diameter (t 1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T3)T4) Other / unknown (i) Tumour differentiati Poorly, ER-poor Poorly, ER+	130 (1964) 133 (137) 133 (137) 133 (137) 117 (0320) 117 (0320) 117 (0320) 117 (0320) 117 (0320) 117 (0320) 117 (0320) 117 (0320) 117 (0320) 117 (0320) 117 (1320) 117 (1320) 118 (1325) 118 ($\begin{array}{c} 57918890\\ (3.4\%)\\ (3.4\%)\\ 22773589\\ (6.3\%)\\ 111\\ (5.3\%)\\ 12773589\\ (7.3\%)\\ (5.3\%)\\ 121\\ (5.3\%)\\ 111\\ (5.3\%)\\ (5$	-33.9 -22.1 -86.2 -70.9 +103.9 -6.3 -97.0 (NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 1) 322.4 303.0	┿╆⋳╴ ╪ ╪⋳╴╪ ═ ┿ _┿ ╴┿ [┿]	- 0-88 (sc 0.06 - 0-78 (sc 0.04 0-85 (sc 0.04 0-90 (sc 0.04 - 0-78 (sc 0.04 - 0-85 (sc 0.04 - 0-85 (sc 0.04 0-85 (sc 0.04 - 0-86 (sc 0.05 - 0-88 (sc 0.05 - 0-88 (sc 0.05 - 0-86 (sc 0.05)
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Well-diff. Grade unknown (b) Tumour diameter (t 1 – 20 mm (T2) > 50 mm (T3) > 50 mm (T3) > 50 mm (T3) > 50 mm (T3) > 50 mm (T3) Dother / unknown (1) Tumour differentiati Poorly, ER+ Poorly, ER+ Mod /Well ER-poor	$\begin{array}{c} 1.30 \text{MeV}_{1} \\ 1.33 \text{MeV}_{2} \\ 1.33 $	$\begin{array}{c} 57918890\\ (3.4\%)\\ (3.4\%)\\ 22773589\\ (6.3\%)\\ 111\\ (5.3\%)\\ 12773589\\ (7.3\%)\\ 12773589\\ (7.3\%)\\ 111\\ (5.3\%)\\ 1111\\ (5.3\%)\\ 1111\\ (5.3\%)\\ 111\\ (5.3\%)\\ 1111\\ (5.3\%)\\ 111\\ (5.3\%)\\ 111\\ (5.3\%)\\ 111\\ ($	-33.9 -22.1 -86.2 -70.9 -103.9 -6.3 -97.0 (NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -54.8 -13.0 -54.8	2578 904 5244 648-3 415-0 103-0 579-3 431-2 229-8 289-9 1) 322-4 303-0 150-7	┿┝┿╼ ┿ ╋╺╘╴╡ _╇ ╋╺╴╘╷	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 - 0-78 (st 0.04 0-78 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 - 0-88 (st 0.05 0-80 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-96 (st 0.06 0-96 (st 0.06
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Well-diff. Grade unknown (b) Tumour diameter (t 1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T2) Poorly, ER- Poorly, ER- Mod /Well ER+ Dorly (ER-Poor	$\begin{array}{c} 10090\%)\\ 01090\%)\\ 130367\%\\ 130367\%\\ 11032036\%\\ 117032046\%$	57818880 (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.4%)/ (3.1%)/ (3.1%)/ (4.2%	-33.9 -22.1 -86.2); NS) -70.9 -103.9 -6.3 -97.0 ; NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2	257.8 90.4 524.4 415.0 103.0 579.3 431.2 762.9 229.8 289.9 1) 322.4 303.0 150.7 349.2	╪╄┺┿╶ ╽ ┿ ╩ ┿╶╘┤╀ _╇ ┺╸╘┤ <mark>┥</mark>	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 - 0-78 (st 0.04 - 0-78 (st 0.04 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.05 - 0-88 (st 0.05 0-80 (st 0.05 - 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 - 0.96 (st 0.06) - 0.96 (st 0.06)
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (t (1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T3/T4) Other / unknown (i) Tumour differentiati Poorly, ER-poor Poorly, ER+ Mod/Well ER-poor Mod/Well ER+ Any unknown	$\begin{array}{c} 1.3 \\ 0.3 \\ 0.5 \\$	$\begin{array}{c} 5^{+}_{77}(8800)\\ (4480)\\ (4480)\\ (4280$	-33.9 -22.1 -86.2); NS) -70.9 -103.9 -6.3 -97.0 ; NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -97.2 -0.9	257.8 90.4 524.4 415.0 103.0 579.3 431.2 762.9 229.8 289.9 1) 322.4 303.0 150.7 349.2 558.0	┿╪⋳╴ ᄤ ᇾ╄⋵╴╈ œ ┿┽╴┿┸╄	- 0-88 (st 0.06 - 0-78 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-78 (st 0.04 0-78 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 0-88 (st 0.05 0-84 (st 0.05 0-96 (st 0.06 0-76 (st 0.05 0-84 (st 0.05 0-85 (st 0.04 0-85 (st 0.05 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.05 0-85 (st 0.04 0-85 (st 0.04)))))))))))))))))))))))))))))))))))
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (h) Tumour diameter (t (h) Tumour diameter (t) 21 – 50 mm (T2) > 50 mm (T3/T4) Other / unknown (i) Tumour differentiati Poorly, ER-poor Poorly, ER- Mod./Well ER+ Any unknown (i) Entry age and ER st	$\begin{array}{c} 1.3 \ 0.5 \$	$\begin{array}{c} 5^{+}_{7} (1+68) \\ (4+3), \\ (4+3$	-33.9 -22.1 -86.2); NS) -70.9 -103.9 -61.3 -97.0 ; NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -103.9 NS)	2578 904 5244 6483 4150 1030 5793 431-2 2298 2899 1) 3224 3030 1507 3492 5580	┿╆⋳╴ ᄤ _╇ ╄⋳╴┿ ═ ┿ᇅ╴┿ [┑] ╃ _╇ ╒┅	_ 0-88 (st 0.06 _ 0-78 (st 0.04 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.16 0-85 (st 0.04 0-87 (st 0.04 0-87 (st 0.05 0-88 (st 0.05 0-84 (st 0.05 0-96 (st 0.06 0-76 (st 0.05 0-84 (st 0.04
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (fr. (T) Tumour diameter (fr. (a) Tumour diameter (fr. (a) Tumour diameter (fr. (b) Tumour diameter (fr. (c) Tumour diameter (fr. (c) Tumour diameter (fr. (c) Tumour differentiati Poorly, ER-poor Poorly, ER-poor Poorly, ER, Poor Mod/Well ER+ Any unknown (j) Entry age and ER. str. Age < 45, ER-poor	$\begin{array}{c} 1.30057\\ 0.30049\\ 1.330579\\ (513049)\\ 1.330579\\ (513049)\\ 1.330579\\ (513049)\\ 1.33057\\ (513049)\\ 1.33057\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ 1.429022556\\ (532049)\\ (532049)\\ (532049)\\ 1.4290226\\ (532049)\\ 1.4290226\\ (532049)\\ 1.4290$	$\begin{array}{c} 5^{+}_{77}(1680)\\ (4450)\\ (2450)\\ (2450)\\ (2450)\\ (2550$	-33.9 -22.1 -86.2 -70.9 -70.9 -6.3 -97.0 -6.3 -97.0 -6.1.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -103.9 NS) -25.1	2578 904 5244 6483 4150 1030 5793 4312 2298 2899 1) 3224 3030 1507 3492 5580	┿┟╛╴╇ _╋ ╋┍╛╴┿ ╦┿ ┶╴╤┿ _╋ ╘╴╴┿	 0-88 (st 0.06 0-78 (st 0.05 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-85 (st 0.05 0-84 (st 0.05 0-88 (st 0.05 0-84 (st 0.05 0-96 (st 0.05 0-96 (st 0.05 0-84 (st 0.04 0-84 (st 0.04
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (t 1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T3)T4) Dther/ unknown (i) Tumour differentiati Poorly, ER+ Mod/Well ER-poor Mod/Well ER+ Any unknown (j) Entry age and EE st Age < 45, ER+ poor	$\begin{array}{c} 1.30 {\rm corr}_{(1)} \\ 3.30 {\rm corr}_$	$ \begin{array}{l} 5^{-1} \\ 5^{-1} \\ (4^{-1} \\ (4^{-1} \\ 3^{-1} \\ (4^{-1} \\ 3^{-1} \\ 3^{-1} \\ (4^{-1} \\ 3^{-1} \\ $	-33.9 -22.1 -86.2 -70.9 -70.9 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -103.9 NS) -25.1 -61.4	257.8 90.4 524.4 (103.0 579.3 431.2 762.9 229.8 289.9 322.4 303.0 150.7 349.2 598.0 150.7 349.2 598.0 259.8	┿╁Ġ╶ᄤ _╋ ╪⋵╴┿ ᇔ ┿ _┶ ╴┽╪	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 - 0-78 (st 0.04 0-78 (st 0.04 0-84 (st 0.05 0-84 (st 0.05 0-88 (st 0.05 0-84 (st 0.05)))))))))))))))))))))))))))))))))))
ER+ HER2+ ER+ HER2 unk. (a) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Well-diff. Grade unknown (b) <u>Tumour diameter</u> (t 1 – 20 mm (T1) 21 – 50 mm (T2) > 50 mm (T3) > 50 mm (T3)	$\begin{array}{c} 1.3 \ 0.5 \$	$\begin{array}{c} 5^{+}_{12}(1+630)\\ (4-2)^{+}_{12}(1+1$	-33.9 -22.1 -86.2); NS) -70.9 -103.9 -61.3 -97.0 ; NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -103.9 NS) -25.1 -61.4 -6.4	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 782.9 229.8 289.9 1) 322.4 303.0 150.7 349.2 598.0 259.8 259.9 259.8 259.9 229.8 269.9 229.8 269.9 229.8 269.9 229.8 269.9 229.8 269.9 229.8 269.9 229.8 269.9 200.7 200.	┿╆┾╶⋳╕ [╈] ╆ _┢ ┍┾╋╋╋╺╒╡╅ [╋] ╈╸╒┤	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 - 0-78 (st 0.04 0-90 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 0-88 (st 0.06 0-80 (st 0.06 0-96 (st 0.06 0-94 (st 0.05 0-84 (st 0.05) 0-84 (st 0.05 0-84 (st 0.05) 0-84 (st 0.05) 0
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Moderately-diff. Grade unknown (b) Tumour diameter (t 1 – 20 mm (T1) 21 – 50 mm (T2) > 50 mm (T2	$\begin{array}{c} 1.3 \ 0.5 \$	$\begin{array}{c} 5^{+}_{7} (1+680)\\ (4-25)\\ (4-2$	-33.9 -22.1 -86.2); NS) -70.9 -103.9 -61.3 -97.0 ; NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -103.9 NS) -25.1 -61.4 -43.6 -22.1	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 229.8 289.9 1) 322.4 303.0 150.7 349.2 558.0 247.6 222.1 241.9 221.5	╡┿╈┾╶─╛ _╇ ╄┍┾╶┿╋╋┿╶╴╛ [╋] ╋ [╋] ╸╴╴╛	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 - 0-78 (st 0.04 - 0-78 (st 0.04 - 0-94 (st 0.05 - 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.05 - 0-88 (st 0.05 - 0-86 (st 0.05 - 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-84 (st 0.05 0-84 (st 0.05) 0-84 (st 0.05 0-84 (st 0.05) 0-84 (st 0.05) 0
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Moderately-diff. Grade unknown (b) Tumour diameter (t 1 - 20 mm (T3) 21 - 50 mm (T2) > 50 mm (T3/T4) Other / unknown (c) Tumour differentiati Poorly, ER- Mod./Well ER-poor Poorly, ER, ER-poor Any Unknown (j) Entry age and ER st Age < 45, ER, Poor	$\begin{array}{c} 1.3 \\ 0.3 \\$	$\begin{array}{c} 5^{+}_{77}(1680)\\ (4^{-}_{77})_{47}(16^{-$	-33.9 -22.1 -86.2); NS) -70.9 -6.3 -97.0 -6.3 -97.0 (NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -103.9 NS) -25.1 -61.4 -43.6 -43.6 -6.3 -6.3 -6.3 -6.3 -6.3 -6.3 -6.4 -7.4 -6.4 -7.4	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 229.8 289.9 1) 322.4 303.0 150.7 349.2 588.0 247.6 282.1 241.9 291.5	┥╡┿┿┿╶╘╛ ┇ ┡┺┿╌╶┾╇ ╝ ╡╸╘╛┦ _╋ ╺╞╴╘┤	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 0-86 (st 0.05 0-86 (st 0.05 0-84 (st 0.05 0-83 (st 0.06 0-83 (st 0.06) 0-83 (st
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (fr. (b) Tumour diameter (fr. (c) Tumour differentiati (c) Tum	$\begin{array}{c} 1.3 \\ 0.3 \\ 0.3 \\ 0.3 \\ 0.3 \\ 0.4 \\$	$\begin{array}{c} 5^{+}_{77}(1680)\\ (4^{+}_{2}3)\\ (4^{+$	-33.9 -22.1 -86.2); NS) -70.9 -6.3 -97.0 -6.3 -97.0 (NS) -61.1 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -6.9 -97.2 -103.9 NS) -25.1 -6.1 -6.3 -6.3 NS) -25.1 -6.3 -6.3 -6.3 -6.3 -6.3 -6.4 -7.4 -6.4 -6.4 -7.4 -6.4 -7.4 -6.4 -7.4 -6.4 -7	257.8 904 5244 1524 1030 5793 431.2 7629 2298 2399 1) 3224 3030 150.7 3492 5880 247.6 2921 241.9 291.5 195.1	╪╪╪┿┾┾╶╘╛ ┇ ╄┶┿╶╌┾┿ ═ ╞╴╶┝┿═┿╴╡	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 - 0-78 (st 0.04 0-90 (st 0.04 0-94 (st 0.05 - 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.05 - 0-88 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-83 (st 0.06 0-83 (st 0.06 0-84 (st 0.07 0-83 (st 0.06 0-84 (st 0.07 0-84 (st 0.07) 0-84
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Grade unknown (b) Tumour diameter (f Carde unknown (c) Tumour diameter (f 21 – 50 nm (T3)T4) 21 – 50 nm	$\begin{array}{c} \begin{array}{c} 1.0 \ 0.00 $	57916800 (4250)	-33.9 -22.1 -86.2); NS) -70.9 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -132.4 -28.6 -64.3 p = 0.0 -64.8 -13.0 -6.48 -13.0 -6.7 -6.48 NS) -6.48 -13.0 -6.48 -6.49 -6.48 -13.0 -6.48 -6.48 -1.48 -6.49 -6.48 -1.48 -6.49 -6.48 -6.49 -7.22 -1.03.9 -6.14 -6.48 -7.25.1 -6.14 -7.25.1 -6.14 -7.25.1 -6.14 -7.25.1 -6.14 -7.25.1 	227.8 904 5244 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 150.7 303.0 150.7 309.2 598.0 247.6 282.1 241.9 241.9 150.7 309.2 150.7 150.7 150.7 10.7	╎ ┤┿┿ _╈ ┿┿ _┢ ╶╔╛ [╈] _{┢┢} ╘┿╶└┾┿═╈╸╴╒╛╁ [╪] ╺╈╸╴╒┤┿	- 0-88 (st 0.06 - 0.78 (st 0.09 0-85 (st 0.04 - 0.78 (st 0.04 - 0.78 (st 0.04 - 0.78 (st 0.04 - 0.94 (st 0.10 - 0.85 (st 0.04 - 0.84 (st 0.05 - 0.88 (st 0.06 - 0.96 (st 0.06 - 0.96 (st 0.06 - 0.96 (st 0.06 - 0.96 (st 0.06 - 0.94 (st 0.05 - 0.93 (st 0.06 - 0.94 (st 0.97 - 0.93 (st 0.06 - 0.94 (st 0.97) - 0.95 (st 0.95) - 0.95 (
ER+ HER2+ ER+ HER2 unk. (g) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Grade unknown (b) <u>Tumour diameter</u> (t 1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T3) 21 - 50 mm (T2) > 50 mm (T2) > 50 mm (T3) 21 - 50 mm (T2) 21 - 50 mm (T2) 21 - 50 mm (T2) 21 - 50 mm (T3) 21 - 50 mm (T3	$\begin{array}{c} 1.3 \\ 0.3 \\ 0.5 \\$	57916800 (343) 2263%) 2263%) 12753163 (4250) 121731163 157731163 15773163 1577731 1577731 1577771 157771 157771 157771 1577771 1577771 15777771 15777771	-33.9 -22.1 -86.2); NS) -70.9 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -13.2 -28.6 -64.3 p = 0.0 -64.8 -13.0 -6.48 -6.48 -1.48 -6.49 -7.25 -6.48 -7.25 -6.48 -7.25 -6.48 -7.25 -6.48 -7.25 -6.48 -7.25 -7.55 -7.5	227.8 904 52244 6483 4150 1030 5793 4312 7629 2298 2298 2298 10 3224 3030 150.7 3092 5980 2221 2419 2921 2419 2921 2419 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 309.2 5980 150.7 5980 150.7 599.2 5980 150.7 599.2 5980 150.7 599.2 599.2 599.2 599.2 150.7 599.2 599.2 150.7 599.2 150.7 599.2 150.7 150.7 150.7 150.7 150.7 150.7 190.2 195.1 1	╞╎┤┿┿ _╈ ╪┿┿ _┷ ╶╔╛ [╈] ┢╔┿╶╬┿╋╪╺╒╎╅ [╋] ╈╶╒╎┤┿	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 - 0-78 (st 0.04 0-90 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 0-84 (st 0.05) 0-84 (st 0.05 0-84 (st 0.05) 0-84 (st 0.05)
ER+ HER2+ ER+ HER2 unk. (a) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Moderately-diff. (b) <u>Tumour diameter</u> (t 1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm	$\begin{array}{c} 1.3 \ 0.0 \$	$\begin{array}{c} 5^{-1} {\rm TriesGa}\\ (z^{-1} {\rm Sym}_{1}, z^{-1} {\rm Sym}_{1}, z^{-1} {\rm Sym}_{2}, z^{-1} {\rm Sym}_{2}$	-33.9 -22.1 -86.2); NS) -70.9 -61.3 -97.0 -61.3 -97.0 -61.4 -132.4 -28.6 -64.3 p = 0.0 -54.8 -13.0 -97.2 -103.9 NS) -25.1 -61.4 -61.3 -63.9 -97.2 -103.9 NS) -25.1 -61.4 -64.3 -64.4 -64.3 -64.5 -64.3 -64.5 -64.5 -64.3 -64.5	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 10 322.4 303.0 150.7 349.2 598.0 247.6 2421.0 247.6 2421.0 247.6 242.1 241.9 247.6 247	╴╞╎┤┿┿ _╈ ┿┿╆╶╒╛ [╈] ╆ _┢ ╼╴╴ [┿] ╆┲┿╶╒┤┿	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.16 0-85 (st 0.04 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.05 0-84 (st 0.05 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-90 (st 0.06 0-93 (st 0.06) (st 0.0
ER+ HER2+ ER+ HER2 unk. (a) <u>Tumour differentiat</u> Poorly-diff. Moderately-diff. Moderately-diff. (b) <u>Tumour diameter</u> (t 1 – 20 mm (T1) 21 – 50 mm (T2) > 50 mm (T3)) 21 – 50 mm (T2) > 50 mm (T3)) Other / unknown (1) <u>Tumour differentiati</u> Poorly, ER+ Mod./Well ER-poor Mod./Well ER-poor Mod./Well ER-poor Mod./Well ER- Agge < 45, ER- 45 – 54, ER-poor 55 – 69, ER-poor 55 – 69, ER-poor 70, ER-poor 70, ER-poor 70, ER-poor 70, ER-poor 70, ER-poor	$\begin{array}{c} 1.3 \ 0.5 \$	$ \begin{array}{c} 5^{+}_{12} (1+630) \\ (4-25) \\ ($	-33.0 (33.0)	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 299.9 1) 322.4 330.0 150.7 349.2 538.0 247.6 292.1 241.9 291.5 105.1 277.9 291.5 105.1 277.9 291.5 105.1 277.9 292.4 294.4 294.4 294.4 294.4 294.4 294.4 294.4 294.4 294.4 294.4 294.4 294.4 295.4	┝╶┝╎┤┿┿ _╈ ┿┿╴╌╕ [╈] _{┢┢} ╈╸╌┾┿ ╦ ┿╶╒╕╁ [╪] _╈ ╸╴╒┤┿	- 0-88 (st 0.06 - 0.78 (st 0.09 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-87 (st 0.04 0-87 (st 0.04 0-87 (st 0.04 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-83 (st 0.06 0-90 (st 0.06 0-93 (st 0.06 0-94 (st 0.05 0-84 (st 0.08 0-84 (st 0.08) 0-84 (st 0.08) 0
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (r (c) Tumour differentiati (c) Tumour differen	$\begin{array}{c} 1.3 \\ 0.3 \\ 0.5 \\$	$\begin{split} & \text{5-transmission} \\ & 5-transmission$	-33.0 (1997) -22.1 (1997) -22.1 (1997) -30.2 (1997) -3	227.8 90.4 522.4 648.3 415.0 103.0 579.3 431.2 762.9 229.6 229.6 229.9 1) 322.4 303.0 150.7 349.2 538.0 247.6 291.5 195.1 197.5 112.2 41.9 211.2 41.9 2	┝┿╶┝╎┤┿┿ _╈ ┿┿ _┿ ╶╔╛ [╈] ╆ _{┢┢} ┿╸╌ [┝] ┿╋╋╈╶╒╛╁ [╋] ╈╸╴╒┤┿	- 0-88 (st 0.06 - 0.78 (st 0.09 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-94 (st 0.05 0-80 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-83 (st 0.06 0-90 (st 0.06 0-93 (st 0.06 0-
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Grade unknown (h) Tumour diameter (f Grade unknown (h) Tumour diameter (f 1 - 20 mm (T 1) 21 - 50 mm (T 3) 21 - 50	$\begin{array}{l} \begin{array}{c} 1.0 \ 0.00 $	$\begin{split} & \text{Frameson} \\ & Frames$	-33.0 (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	227.8 904 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 1) 322.4 303.0 247.6 289.0 247.6 289.1 105.7 349.2 598.0 247.6 295.1 105.7	窗┾┿╶┟╎┾┿ _╈ ┿┿ _┿ ╶╔ ╵ ╘╌┿┲╸╌╌┿┺╸╴╴╛╁ [╈] ╺╻╴╴╴	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-80 (st 0.04 0-85 (st 0.04 0-94 (st 0.16 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 - 0-88 (st 0.05 0-80 (st 0.06 0-76 (st 0.06 0-76 (st 0.06 0-81 (st 0.05 0-83 (st 0.06 0-83 (st 0.06 0-84 (st 0.07 0-82 (st 0.05 0-84 (st 0.07 0-82 (st 0.07 0-84 (st 0.07) 0-84 (st 0.07 0-84 (st 0.07) 0-84 (st 0.07 0-84 (st 0.07) 0-84 (st 0.07) 0-8
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Grade unknown (b) Tumour diameter (fr Grade unknown (b) Tumour diameter (fr 1 - 20 mm (T2) > 50 mm ($\begin{array}{c} 1.000\% \\ 0.100$	$\begin{array}{c} 5^{-1}_{771}(680)\\ (4^{-2}_{771})\\ (4^{$	-33.0 (12) -22.1 (12) -22.1 (12) -22.1 (12) -22.1 (12) -22.1 (12) -33.0 (12) -43.0 (12) -43.0 (12) -44.0 (12) -45.0	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 11 229.8 289.9 11 229.8 289.9 11 229.8 289.9 11 20.7 29.4 289.0 247.6 289.1 29.5 155.1 277.9 11.2 41.0 29.5 155.1 27.7 29.4 29.5 155.1 27.7 29.4 29.5 155.1 27.7 29.5 20.5 2	·ᡂ┥┿╶╞╎┤┿┿╪┿┿╈╶╔╛ [╈] ╆┶┷╶╴╧╡	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.05 0-84 (st 0.05 0-87 (st 0.05)))))))))))))))))))))))))))))))))))
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (f 1 - 20 mm (T1) 21 - 50 mm (T2) >	$\begin{array}{c} 1.300000\\ 0.10000000\\ 1.3305079\\ (0.1500000000000000000000000000000000000$	$ \begin{array}{l} 5^{+}_{77}(1630)\\ (4^{+}_{77})\\ (4^{$	-33.0 -22.1 -22.1 (NS) -70.9 -63 -97.0 -63 -97.0 -63 -97.0 (NS) -61.1 -132.4 -28.6 -64.3 p=0.0 -54.8 -64.3 -64.3 -6.3 -97.2 -61.4 -6.3 -6.4 -6.4 -22.1 -56.7 -52.7 -61.8 -22.0 (NS) -61.4 -22.1 -6.5 -22.1 -23.2	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 229.8 289.9 10 322.4 303.0 150.7 349.2 598.0 247.6 2421.1 241.9 291.5 156.7 247.6 222.1 241.9 215.7 294.2 215.7 294.2 215.7 294.2 215.7 215.	·┞ᡂ┾┿╶╞╎╎╪┿ _{╈╈┿╈╶} ╒╛ ┇ _{┢┢╋} ╺╴╴╴╴╴	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-93 (st 0.04 0-94 (st 0.16 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.05 0-84 (st 0.05 0-84 (st 0.05 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-93 (st 0.06 0-
ER+ HER2+ ER+ HER2 unk. (g) <u>Tumour differentiat</u> Poorty-diff. Moderately-diff. Grade unknown (e) <u>Tumour diameter</u> (t 1 – 20 mm (T1) 21 – 50 mm (T2) > 50 mm (T2	$\begin{array}{c} 1.3 \ 0.5 \$	$\begin{array}{c} 5^{-1}_{77} (1630)\\ (14$	-33.0 -22.1 -22.1 -70.9 -70.9 -61.3 -97.0 -61.1 -132.4 -64.3 p = 0.0 -54.8 -132.4 -64.3 p = 0.0 -54.8 -132.4 -64.3 p = 0.0 -54.8 -132.4 -63.9 -61.4 -63.9 -63.7 -61.4 -64.3 -72.2 -64.3 -72.4 -74.4	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 239.9 102.7 349.2 588.0 150.7 349.2 588.0 247.6 247.6 247.6 247.6 247.6 247.6 247.6 103.0 10	╷╴┞ <u>┉</u> ┾┿╶╞╎┤┿┿ _╈ ┿┿ _┢ ╶╔ [╈] _{┢┢} ┿╶╶╌╪ ╸ ╶╌┾┿ ┉ ┿╶╒╎╁ [╈] ╶╈╴╴╒┤┿	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.03 0-85 (st 0.04 0-85 (st 0.04 0-84 (st 0.03 - 0-88 (st 0.06 0-80 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-93 (st 0.06
ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Moderately-diff. (b) Tumour diameter (t 1 - 20 mm (T1) 21 - 50 mm (T2) > 50 mm (T3) > 50 mm (T3)	$\begin{array}{c} \text{adjust} \\ \text{adjust} \\$	$\begin{array}{c} 5^{+}_{7} (1+600)\\ (4-2)^{+}_{7}(1+2)$	-33.9 -23.9 -22.1 -862 (), NS) -6.3 -97.0 -6.3 -97.0 -6.4 -7.4 -7.5	227.8 90.4 5224.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 1) 322.4 303.0 150.7 349.2 558.0 247.6 292.1 241.9 291.5 115.2 115.2 115.2 241.9 291.5 115.2 241.9 291.5 115.2 292.1 293.2 293.2 293.2 293.2 294.2 115.2 294.4 107.2 107.	ᅋᇹᇦᇔᆃᆃᇰᇦ╎╡ᆃᆃᆃᆃᆃᆠ╶ᄗ ^ᆂ ᇂ _{ᇥᇥ} ᆃ╶╌┾ ᇵ ᇔᇰᇊᆠᇔᇾ╶	- 0-88 (st 0.06 - 0-78 (st 0.06 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.02 0-85 (st 0.04 0-87 (st 0.04 0-84 (st 0.03 - 0-88 (st 0.05 0-84 (st 0.05 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-93 (st 0.06 0-81 (st 0.05 0-84 (st 0.05 0-87 (st 0.05
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (t 21 – 50 mm (T2) 21 – 50 mm (T2) 21 – 50 mm (T3/T4) 21 – 50 mm (T3/T4) 25 – 50 mm (T3/T4) 25 – 69, ER+ 35 – 69, ER+ 36 – 51, ER+ 37 – 51,	$\begin{array}{c} 1.3 \\ 0.3 \\ 0.5 \\$	$\begin{array}{c} 5^{+}_{77}(1680)\\ (475)$	-33.0 -23.0 -24.2 -70.9 -70.9 -61.3 -97.0 -61.4 -132.4 -28.6 -64.3 -64.3 -64.3 -64.3 -64.3 -64.3 -64.4 -64.3 -64.9 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -64.3 -65.4 -	227.8 904 52244 648-3 415-0 103-0 579-3 431-2 762-9 229-8 229-8 229-9 10 229-8 229-9 112-7 229-4 110-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 224-4 100-7 247-6 247-7 247-6 247-7	╙┉╶┞ <u>┉</u> ┾┿╶┾╎┤┿┿ _╈ ┿┿ _┿ ╶⋳╛ [╈] ╆ _{┷╈} ╶└┤┿ ┉ ╞┿╶╞╎┤┿	- 0-88 (st 0.06 - 0.78 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-85 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-94 (st 0.05 0-84 (st 0.05 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-96 (st 0.06 0-93 (st 0.06 0-
ER+ HER2+ ER+ HER2 unk. (g) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (h) Tumour diameter (i 21 - 50 nm (T2) 21 - 50 nm (T2) 25 - 50 ER+ 25 - 60 ER+ 26 - 60 ER+ 27 - 60 ER+ 26 - 60 ER	$\begin{array}{l} \begin{array}{l} & 1.0 \mbox{ or } 0.1 \mbox{ or } $	57916803 (2473) 2263%) 2263%) 2263%) 2263%) 2153% 2153% 2153% 21573103 1508/2226 (2473) 21172103 1508/2226 (2473) 21172103 21172100 21172100 21172100 2117210000000000	-33.0 -33.0 -22.1 -70.9 -70.9 -70.9 -6.3 -97.0 -6.3 -97.0 -6.4 -28.6 -64.3 -64.3 -64.3 -64.3 -64.3 -6.4 -7.4 -6.4 -7.4 -6.4 -7.4 -6.1 -7.4 -7.5 -	227.8 904 52244 648-3 415-0 103-0 579-3 431-2 762-9 229-8 289-9 1) 322-4 303-0 579-3 224-4 1057-3 1057-3 1040-0 579-3 229-6 229-6 229-6 229-6 229-7 229-7 229-6 229-7 200-7 2	╼┺╼╗╴┞ᡂ┾┿╶┝╎┤┿┿ _╈ ┿┾ _┿ ╶╒⋺ [╈] _{┢┢┿} ╺╴╒┙ [┿] ╋┿┿╶╒╛ [╈] ╈╸╞╴╴╒┤┿	- 0-88 (st 0.06 - 0.78 (st 0.09 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-94 (st 0.10 0-85 (st 0.04 0-94 (st 0.03 - 0-88 (st 0.05 0-80 (st 0.06 0-90 (st 0.06 0-90 (st 0.06 0-91 (st 0.06 0-93 (st 0.06) 0-93
ER+ HER2+ ER+ HER2+ ER+ HER2 unk. (a) Tumour differentiat Poorly-diff. Moderately-diff. Grade unknown (b) Tumour diameter (f (b) Tumour diameter (f (c) Tumour diameter (f (c) Tumour diameter (f (c) Tumour diameter (f (c) Tumour differentiati Poorly, ER- Poorly, ER+ Mod/Well ER-poor (c) S, ER+ (c) S, ER+ (c) S, ER, Poor	$\begin{array}{l} \begin{array}{l} & 1.0 \ or W_{1} \\ & 1.0 \ or W_{2} \\ \hline \end{array} \\ \begin{array}{l} 1.0 \ or W_{2} \\ 1.0 \ or W_{2} \\ \hline \end{array} \\ \begin{array}{l} 1.0 \ or W_{2} \\ 1.$	57916803 (2430) 2263760 (2430) 2263760 (2430) 2263760 (2430) 13772108 1580(22202) 231872108 (2430) 1102228716 (24400) 1102228716 (24400) 1102228716 (24400) 1102228716 (24400) (2570) 2318022 (24400) (2570)	-33.9 -23.9 -22.1 -70.9 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -6.3 -97.0 -6.3 -6.4 -132.4 -6.4 -7.4 -6.4 -7.4 -6.4 -7.4 -6.4 -7.4 -6.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.4 -7.5 -	257.8 90.4 524.4 648.3 415.0 103.0 579.3 431.2 762.9 229.8 289.9 10 322.4 303.0 150.7 349.2 598.0 247.6 229.1 241.9 244.6 866.5 207.11,1	╾ᡂᡂ╶┞ᡂ┾┿╶╞╎┤┿┿ _╈ ╈┿╈╶╔╛ [╈] ╆ _┢ ╸╴╴╴╴┾┿╋╈╶╒╛╁ [╈] ╈╸╴╒┤┿	- 0-88 (st 0.06 - 0.78 (st 0.09 0-85 (st 0.04 0-90 (st 0.04 0-90 (st 0.04 0-94 (st 0.03 0-85 (st 0.04 0-94 (st 0.03 - 0-84 (st 0.05 0-84 (st 0.05 0-87 (st 0.03 0-87 (st 0.03 0-87 (st 0.03 0-87 (st 0.03 0-87 (st 0.03 0-83 (st 0.03 0-83 (st 0.03 0-83 (st 0.03 0-85 (st 0.03

	A	ny re	eci	ırre	nce	
Category	Events/won Allocated taxane	Allocated I non-tax.	Lograni O-E	e events Variance of O-E	Ratio of annu Taxane	al event rates Non-tax.
(a) Same, or more, nor	n-taxane che	mo. for co	ontrols	$(\chi_3^2 = 1)$	1-2; p = 0-01)	0.04 (0.00)
Same (1×) † ie, unconfounded	1693/36543 (4-6%/y)	1897/34877 (5-4%/y)	-126-0	740-1		0-84 (SE 0-03)
More (<2×) †	613/14791 (4-1%/y)	794/14444 (5·5%/y)	-90-5	318-8	-æ¦	0.75 (se 0.05)
More (<2×) ©	1183/30976 (3-8%/y)	1332/30674 (4·3%/y)	-71.7	552-7	- +	0-88 (se 0-04)
More (=2×) †	964/18750 (5-1%/y)	1010/18477 (5-5%/y)	-19-5	442-8	r -	0-96 (se 0-05)
(b) Taxane (D/P*) sche	<u>dule</u> (χ ₃ ² = 4-8	3; p = 0·2;	NS)		i i	
4(D100) q3w †	1305/27034 (4-8%/y)	1421/26148 (5-4%/y)	-64-0	536-8	-	0-89 (se 0-04)
Other docetaxel	1420/37570 (3-8%/y)	1685/36993 (4-6%/y)	-136-5	714-8		0-83 (se 0-03)
4(P175) q3w †	875/16282 (5-4%/v)	921/15641 (5-9%/v)	-30-6	409-0		0-93 (se 0-05)
Other paclitaxel	853/20174 (4-2%/y)	1006/19690 (5-1%/v)	-76-6	393-7		0-82 (se 0-05)
(c) Concurrent endocr	ine therapy i	<u>f ER+?</u> (χ	² = 0·5;	2p = 0.5	; NS)	
Yes	130/2870 (4-5%/y)	162/2738 (5-9%/y)	-15-7	65-1	_	0.79 (se 0.11)
No (any endocrine onl after chemo ended)	y 4323/98190 (4-4%/y)	4871/95734 (5·1%/y)	-289-9	1892-4		0-86 (se 0-02)
(1) = (
(<u>d) Entry age</u> (trend χ ₁ Age < 45	1599/29442	1741/28676	-89-9	683-4		0-88 (se 0-04)
	(5-4%/y)	(6-1%/y)	-00.1	664.0		0.97 (cc 0.04)
45 - 54	(3-9%/y)	(4-5%/y)	-50-1	004-0	-	0.07 (32 0.04)
55 - 69	1254/30822 (4-1%/y)	1468/29987 (4-9%/y)	-110-4	576-1	-	0-83 (se 0-04)
70+	74/1586 (4·7%/y)	114/1560 (7-3%/y)	-15-2	34-0 —		0-64 (se 0-14)
(e) Nodal status before	(0-0%/y) chemo (trei	nd $\chi_{4}^{2} = 0.0$); 2p =	0-9; NS)	1	
N0/N-	273/12000	296/11818 (2,5%/44)	-16-4	131-2		0.88 (se 0.08)
N1-3	(3-0%/y) (3-0%/y)	(3-5%/y) (3-5%/y)	-77-5	503-7		0-86 (se 0-04)
N4+	1342/20106 (6-7%/y)	1510/19714 (7·7%/y)	-83-7	570-7		0-86 (se 0-04)
Other / unknown	1824/35123 (5-2%/v)	2062/33787 (6-1%/\)	-128-0	751-9	Ē.	0-84 (se 0-03)
(f) ER statue /~2 - 0 4 -	2n = 0.7· NP	(= · ~/y)			Ļ	
(1) ER status (2 = 0-1; ER-poor	1751/28414	2006/27845	-111-6	759-9	<u> </u>	0-86 (se 0-03)
	(6-2%/y)	(7·2%/y)				
ER+	2175/62322 (3-5%/y)	2462/61080 (4-0%/y)	-167-3	1025-0		0-85 (SE 0-03)
ER unknown	527/10324 (5-1%/v)	565/9547 (5-9%/v)	-26-7	172-6		0-86 (se 0-07)
Subsets of ER+					1	
ER+ PR-poor	440/9902	504/9452	-45-2	205-2		0-80 (se 0-06)
ER+ PR+	(3-2%/y) (3-2%/y)	1743/46525 (3·7%/y)	-124-0	727-7		0-84 (se 0-03)
ER+ N0/N-	111/6594	124/6798	-5-3	56-1		0-91 (se 0-13)
ER+ N1-3	(1.7%/y) 580/25061 (2.3%/y)	(1.8%/y) 683/24553 (2.8%/y)	-55-3	299-5		0-83 (se 0-05)
ER+ N4+	778/14355 (5-4%/y)	864/13965 (6·2%/y)	-51-1	343-4		0-86 (se 0-05)
ER10-99 fmol/mg	77/2073 (3-7%/y)	82/1872 (4-4%/y)	-5-6	33-6		
ER+, unknown	(4-0%/y) 2091/60066	(5-3%/y) 2372/59065	-157-5	994-2		0-85 (se 0-03)
level (eg, by IHC)	(3-5%/y)	(4-0%/y)			+	
ER+ HER2-	558/18751 (3-0%/y)	635/18806 (3-4%/y)	-38-5	282-5	-#-	0-87 (se 0-06)
ER+ HER2+ ER+ HER2 unk.	197/4126 (4-8%/y) 1420/39407	243/4074 (6-0%/y) 1584/38168	-22-8	97-0 643-5		- 0-79 (SE 0-09) 0-86 (SE 0-04)
	(3-6%/y)	(4·2%/y)			<u>U</u>	
(g) Tumour differentiat	$\frac{1}{1549/25964}$; 2p = 0.1; 686/25293	-74-5	703-6		0-90 (SF 0-04)
r oony ann	(6-0%/y)	(6·7%/y)	14-5	105-0	-	0.00 (02 0.04)
Moderately-diff.	958/30323 (3-2%/y)	1172/29868 (3-9%/y)	-107-3	476-1	-	0-80 (se 0-04)
Well-diff.	253/10407 (2-4%/y)	276/10090 (2·7%/y)	-9-5	122-5		0.93 (SE 0.09)
Grade unknown	(4-9%/y)	(5-7%/y)	=110-8	694-2	받	0-85 (SE 0-03)
(h) Tumour diameter (f	rend χ ₁ ² = 0-0	; 2p = 0·9	; NS)			
1 – 20 mm (T1)	1069/34736 (3-1%/y)	1224/34447 (3-6%/y)	-73-8	511-7	-	0-87 (se 0-04)
21 - 50 mm (T2)	1883/36233 (5-2%/y)	2132/35251 (6-0%/y)	-137-8	860-0		0-85 (se 0-03)
> 50 mm (T3/T4)	573/10008	612/9469 (6.5%/v)	-34-6	242-6	- -	0-87 (se 0-06)
Other / unknown	928/20056 (4-6%/v)	(5-5%/v)	-68-3	348-3	-0-	0-82 (se 0-05)
(i) Tumour differentiati	on and ER ((² ₃ = 10·2;	p = 0-0	2)	-	
Poorly, ER-poor	746/11023 (6-8%/y)	881/10730 (8·2%/y)	-59-7	342-9		0-84 (se 0-05)
Poorly, ER+	758/14309 (5-3%/y)	760/14040 (5·4%/y)	-11-6	336-5	H	0-97 (se 0-05)
Mod./Well ER-poor	371/6903 (5-4%/y)	401/7000 (5·7%/y)	-8-2	164-8	-+=	0.95 (se 0.08)
Mod./Well ER+	810/32821 (2-5%/y)	1016/32098 (3·2%/y)	-102-2	414-6	-	0-78 (se 0-04)
Any unknown	1768/36016 (4-9%/y)	1975/34614 (5·7%/y)	-122-3	713-2		0-84 (se 0-03)
(j) Entry age and ER st	$tatus (\chi_7^2 = 6.4)$	5; p = 0-5;	NS)		-	
Age < 45, ER-poor	632/9393 (6-7%/y)	707/9610 (7·4%/y)	-22-6	272-8	-4	0-92 (se 0-06)
< 45, ER+	740/16573 (4-5%/y)	828/15826 (5·2%/y)	-67-3	341-9		0-82 (se 0-05)
45 - 54, ER-poor	604/10486 (5-8%/y)	703/10123 (6·9%/y)	-46-7	262-2	-8-	0-84 (se 0-06)
45 - 54, ER+	742/24550 (3-0%/y)	798/24352 (3·3%/y)	-28-4	342-1		0-92 (se 0-05)
55 - 69, ER-poor	487/8136 (6-0%/y)	548/7692 (7·1%/y)	-36-1	212-2		0-84 (se 0-06)
33 - 08, ER+	(3-2%/y) 28/200	(4-0%/y) 48/420	-67-1	324-0 12-P -		0.61 (se 0.22)
70+, ER+	28/398 (7-0%/y) 39/1009	+8/420 (11-4%/y) 43/933	-6-2 -4-5	17-1 -	•	
Any unknown	(3-9%/y) 527/10333 (5-1%/y)	(4-6%/y) 565/9547 (5-9%/y)	-26-7	172-6		0-86 (se 0-07)
(k) Site of first recurre	<u>nce</u> (χ ₂ ² = 0·8	p = 0.7; I	NS)		I.	
Isolated local	686/98994 (0-7%/y)	831/96477 (0-9%/y)	-65-6	334-0		0-82 (se 0-05)
Contralateral Distant/Multiple	314/98976 (0-3%/y) 3230/101060	350/96474 (0-4%/y) 3583/06472	-21-0 -193-P	146-8 1373-9		0.87 (SE 0.08)
σιστατισπιατερίθ	(3-2%/y)	(3-6%/y)	- 193-8	1913-9		J+07 (SE U+U3)
Unknown	223/100718 (0.2%/4/	269/98176 (0.3% AA	-25-2	103-4		0-78 (se 0-09)
(I) Time since randomi	sation (trend	$\chi_1^2 = 0.0;$	2p = 0	•9; NS)		
Years 0 - 1	1964/41153 (4-8%/y)	2213/40791 (5·4%/y)	-118-5	844-6		0-87 (se 0-03)
2 - 4	1923/41256	2228/40024	-158-5	866-5		0-83 (se 0-03)
5-9	(561/16702	-26-P	232-9		0-89 (sr 0.06)
10+	(3-0%/y) 32/533	(3-4%/y) 31/497	-1-8	13-5 -		
-	(6-0%/y)	(6·2%/y)			1	
Total	4453/ 101060 (4-4%/v)	5033/ - 98472 (5·1%/v)	-305-6	1957-5	ŧ	0-855 (SE 0-021 2p < 0-00001
🖶 99% or 🖘 95%	confidence inte	rvals		_		L

ytotoxic regimens cetaxel 100 mg/m² at intervals of 3 weeks 21-26) give details of each trial's 4(D100) q3w means 4 doses of do

Treatment effect 2p < 0-0. pp 21-26) give details of each trial's cytotoxic regimens et, 4(b1:s) g3w means 4 doses of docetaxel 100 mg/m² at intervals of 3 weeks rilap other chemotherapy courses with antifracytic

: χ₂₅² = 38-7; p = 0-04

ane better Non-tax. better

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*.

	Deaths/	Women		y IN e deaths		iour subgro
Category	Allocated taxane	Allocated non-tax.	Logrank O-E	Variance of O-E	Ratio of annu Taxane	al death rates : Non-tax.
(a) Same, or more, non-	taxane che	mo. for co	ontrols	$\frac{1}{2}(\chi_3^2 = 2$	·0; p = 0·6; NS)	0.86 (cr. 0.04)
ie, unconfounded	(20-9%)	(23-4%)	-79-8	520-8		0.86 (SE 0.04)
More (<2×) †	339/4282 (7·9%)	407/4302 (9-5%)	-31-3	172-3		0·83 (se 0·07)
More (<2×) ©	587/7071 (8-3%)	665/7076 (9-4%)	-32-1	278-9	-#	0·89 (se 0·06)
More (≈2×) †	546/5185 (10-5%)	590/5168 (11-4%)	-15-8	259-3	-+	0·94 (se 0·06)
(b) Taxane (D/P*) sched	ule $(\chi_3^2 = 1 \cdot$	0; p = 0·8;	NS)		1	
4(D100) q3w †	816/6480	887/6476 (13-7%)	-31-6	338-1		0·91 (se 0·05)
Other docetaxel	716/8396	844/8409	-58-4	366-9		0.85 (SE 0.05)
4(P175) q3w †	(8-5%) 572/3528	612/3502	-30-1	274-4		0.90 (se 0.06)
Other paclitaxel	(16-2%) 537/3724	(17-5%) 625/3736	-38-9	251-9		0.86 (SE 0.06)
(c) Concurrent endocrir	(14-4%)	(16.7%)	² = 0.2	2n = 0.6	• NS)	
Yes	87/713	93/723	1 - 0 2, -2.7	40.5	,, ito,	
No (any endocrine only	(12-2%) 2554/21415	(12-9%) 2875/21400	-158-3	1136-0		0.87 (se 0.03)
after chemo ended)	(11-9%)	(13-4%)				
(d) Entry age (trend χ_1^2 =	= 3·5; 2p = 0	D·06)			1	
Age < 45	871/5930	928/5927 (15.7%)	-36-7	384-6	-	0·91 (se 0·05)
45 - 54	835/7747	932/7720	-41-4	372-3	_	0.89 (se 0.05)
55 - 69	(10-8%) 735/6572	(12·1%) 877/6570	-69-0	346-5		0.82 (SE 0.05)
70+	(11-2%)	(13-3%)	-11.4	24.4 -		0.63 (95 0.16)
Age unknown	(16-2%) 149/1565	(23-6%) 150/1563	-2-5	48-6		- 000 (32 0 10)
(e) Nodal status before	(9-5%) chemo (tre	(9.6%) nd χ ² = 0·	3; 2p =	0-6; NS)		
N0/N-	120/2104	132/2070	-6-0	61-0	_	0·91 (se 0·12)
N1-3	(5-7%) 520/6981 (7-4%)	(6-4%) 599/6977 (8-6%)	-41-9	262-1		0.85 (se 0.06)
N4+	783/5012	849/5062 (16.9%)	-29-9	338-8	-	0·92 (se 0·05)
Other / unknown	1218/8031	1388/8014	-83-1	514-6		0.85 (SE 0.04)
	(15-2%)	(17-3%)			145	
(f) ER status ($\chi_1^2 = 0.1$; 2	p = 0·7; NS	5)			1	
ER-poor	1087/5883 (18-5%)	1271/6027 (21-1%)	-78-0	505-0	-	0.86 (SE 0.04)
ER+	1044/12848 (8-1%)	1164/12790 (9·1%)	-67-1	502-3	-	0.87 (SE 0.04)
ER unknown	510/3397	533/3306	-15-9	169-1		0.91 (se 0.07)
	(15-0%)	(16-1%)			Р	
Subsets of ER+					1	
ER+ PR-poor	229/2056 (11-1%)	280/2064 (13-6%)	-30-2	113-7		0.77 (SE 0.08)
ER+ PR+	710/9553 (7-4%)	768/9492 (8·1%)	-29-8	340-7	-#	0-92 (SE 0-05)
ER+ N0/N-	43/1155 (3.7%)	49/1175 (4-2%)	-1-9	22-5		0.70 (ar. 0.08)
ER+ N/-3	(4-7%) (405/2460	(5-8%)	-30-7	129-5		0.95 (se 0.07)
ER10-99 fmol/mg	(11-7%)	(12-3%) 26/387	-1-4	9-9		
ER100+ fmol/mg	(5·7%) 4/29	(6·7%) 3/25	0-8	0.7		
ER+, unknown	(13-8%) 1016/12395 (8-2%)	(12-0%) 1135/12378 (9-2%)	-63-7	494-0		0.88 (se 0.04)
ER+ HER2-	273/4613	296/4656	-11-3	136-2		0.92 (se 0.08)
ER+ HER2+	(5-9%) 98/978	(6-4%) 114/1022	-6-2	47-5		0.88 (SE 0.14)
ER+ HER2 unk.	(10-0%) 673/7257	(11.2%) 754/7112	-45-2	317-5	_fh_	0.87 (se 0.05)
(a) Tumour differentiation	(9-3%) on (trend y	² = 2.5: 2n	= 0.1:	NS)	Ч	
Poorly-diff.	974/6230	1	-23-5	443-9	I	0.95 (se 0.05)
Moderately-diff	(15-6%)	(16-3%) 520/6744	-46.1	222.7		0.81 (95 0.06)
Woll diff	(6-6%)	(8-0%)	-40-1	60.0		0.86 (or 0.12)
Grade unknown	(5.9%) 1104/7112	(7.3%)	-83-5	467-9	_	0.84 (se 0.04)
	(15-5%)	(17-7%)				
(h) Tumour diameter (tr	end χ ² = 0-	7; 2p = 0·4	; NS)			
1 – 20 mm (T1)	537/6606 (8-1%)	638/6627 (9-6%)	-41-7	268-1		0.86 (SE 0.06)
21 – 50 mm (T2)	1094/7406 (14-8%)	1247/7443 (16-8%)	-78-6	520-7	-	0.86 (SE 0.04)
> 50 mm (T3/T4)	318/2578	301/2494	-7-0	130-2		0.95 (se 0.09)
Other / unknown	(12-3%) 692/5538 (12-5%)	(12-1%) 782/5559 (14-1%)	-41-1	255-6	-0-	0.85 (SE 0.06)
(i) Tumour differentiatio	on and ER ($\chi_3^2 = 12.5;$	p = 0·0	06)	1	
Poorly, ER-poor	509/2699	591/2778	-34-9	239-2		0·86 (se 0·06)
Poorly, ER+	440/3362	398/3330	14-8	189-8		<u>1·</u> 08 (se 0·08)
Mod./Well ER-poor	(13-1%) 225/1495 (15-1%)	(12.0%) 238/1494 (15.0°/)	-7-3	102-4		0.93 (SE 0.10)
Mod./Well ER+	(15-1%) 321/7053 (4-6%)	428/7025 (6·1%)	-49-0	171-6	_ _	0.75 (SE 0.07)
Any unknown	1146/7519 (15-2%)	1313/7496 (17-5%)	-86-1	480-5		0.84 (se 0.04)
(j) Entry age and ER sta	tus ($\gamma_{-}^2 = 7$	2; p = 0-2	NS) x		4	
Age < 45, ER-poor	381/1889	418/2006	-9-0	175-0		0.95 (se 0.07)
< 45, ER+	(20-2%) 334/3415	(20-8%) 373/3349	-30-2	161-5		0.83 (SE 0.07)
45 - 54, ER-poor	(9-8%) 387/2133	(11-1%) 439/2157	-22-5	175-7		0.88 (se 0.07)
45 - 54, ER+	(16-1%) 332/4901	(20-4%) 352/4874	-7-5	156-4		0.95 (SE 0.08)
55 - 69, ER-poor	(0.0%) 297/1771 (16-8%)	(7.2%) 380/1765 (21.5%)	-42-5	143-5	_ _ _+	0.74 (se 0.07)
55 - 69, ER+	355/4338 (8-2%)	(1-1-37%) 413/4368 (9-5%)	-25-8	174-5		0.86 (se 0.07)
70+, ER-poor	22/89 (24-7%)	34/99 (34-3%)	-3-9	10-8 🗲		├ →
70+, ER+	23/193 (11-9%)	26/198 (13-1%)	-3.7	9-9	۱ ۲	0-91 (0- 0.07)
Any unknown	510/3399 (15-0%)	533/3307 (16-1%)	-15-9	169-1	-0-	U-91 (SE 0-07)
(K) Time since randomis	sation (tren	$\operatorname{id} \chi_1^2 = 0.3$; 2p = (0-6; NS)	1	0.00/
rears u - 1	646/20565 (3·1%)	/15/20561 (3-5%)	-24-1	285-9		U-92 (SE 0-06)
2 - 4	1339/18838 (7·1%)	1538/18691 (8-2%)	-99-3	612-1		0.85 (SE 0.04)
5 - 9	483/8823	553/8630	-40-3	221.7		0.83 (SE 0.06)
10+	(3·5%) 24/1011 (2.4%)	(0·4%) 12/928 (1.2%)	5-3	8-0	_	
T-4-1	(2·4%)	20661				0.070 (
Iotal	2041/ 22128 (11·9%)	2908/ . 22123 (13·4%)	-161-0	1176-5	Ŷ	0.872 (SE 0.027) 2p < 0.00001
🖶 99% or 🖘 95% o	confidence inte	ervals		_		<u> </u>
Global I	neterogeneitv	r: χ ² ₂₂ = 30·3:	p=0-1		Taxane better	Non-tax. better
					Treatment effe	ct 2p < 0.00001

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

P 9: Subgroup analyses of RECURRENCE, any anthracycline-based regimen vs. standard CMF (or near-standard CMF). NB First four subgroups are as in forest plots*.

na /firat E

Category (a) Cumulative anthracyo (trend $\chi_1^2 = 6.7$; 2p = 0 A360 or E720-800: con CF/CEE		man-years	Anthr	. events		
(a) Cumulative anthracy((trend $\chi^2_1 = 6.7$; 2p = 0 A360 or E720-800:	Allocated anthr.	Allocated CMF	Logrank O-E	variance of O-E	Ratio of annual even Anthr. : CMF	nt rates
A360 or E720-800:	cline dosa	ge, if dose	e/cycle	≥ A 60/ E 90	· I	
OG CAE/CEE	381/0220	473/0028	-50.0	194.3		0.77 (SE 0.06)
eg, CAI/CEI	(4-1%/y)	(5·2%/y)	-30-9	194-3	──■─┴│	0.77 (SE 0.00)
A300 OF E400-480	608/10194 (6-0%/у)	669/9997 (6-7%/y)	-24-0	262-7	-#∎+-	U-91 (SE 0-06)
A240: standard 4AC	820/10274 (8-0%/y)	830/10090 (8-2%/y)	-8-7	355-5	-4	0.98 (SE 0.05)
White: dose/cycle	398/6194	389/6021	-10-0	170-9		0·94 (se 0·07)
< A60/E90	(6-4%/y)	(6-5%/y)				
UU Cyclophosphamide in	II UNIF OR	$\underline{w}\underline{w}\underline{v}(\chi_1^- = 1)$	-2; 2p =	- u•3; NS)	· · · · ·	
0100×14 oral	1708/26046 (6-6%/y)	1859/25377 (7-3%/y)	-87-1	768-7		0.98 (SE 0.03)
C600x2 iv	499/9845	502/9769	-6.5	214.8		0.97 (SE 0.07)
0000-211	(5-1%/y)	(5·1%/y)		214-0		001 (32 0 01)
(c) Concurrent endocrine	e therapy	if ER+? (χ	= 0·8;	2p = 0·4;	NS) I	
Yes	73/2251	70/2231 (3.1%/y)	1-9	34-2		>
No (any endocrine only a	2134/33730 (6-3%/v)	2291/32915 (7-0%/v)	-95-5	949-3		0.90 (se 0.03)
alter chemo ended)	(00/04))	(10/03)				
(d) Entry age (trend χ_1^2 =	0·1; 2p = 0)∙8; NS)			1	
Age < 45	963/13406	1067/13306	-43-7	433-2		0.90 (se 0.05)
	(7-2%/y)	(8-0%/y)				
45 - 54	802/13866 (5-8%/y)	824/13475 (6·1%/y)	-25-9	357-6	-##-	0·93 (se 0·05)
55 - 69	406/8013	430/7708	-26-2	178-9	_ 	0.86 (se 0.07)
70+	(5·1%/y) 20/427	(5-6%/y) 23/426	-0-1	8-2		
Age unknown	(4-7%/y) 16/179	(5-4%/y) 17/231	2-3	5-5	1	
(e) Nodal status (trend χ^2	² = 0·3; 2p	(7-4%/y) = 0.6; NS)				
N0/N-	558/16757	593/16587	-16-0	265-3		0.94 (SE 0.06)
	(3-3%/y)	(3-6%/y)	10-0	2000		0.00
N1-3	583/9794 (6-0%/y)	603/9587 (6-3%/y)	-13-5	259-9		0·95 (se 0·06)
N4+	613/3996	663/3798	-27-2	253-4	_ _	0·90 (se 0·06)
Other / unknown	453/5344	502/5174	-36-9	204-9		0·84 (se 0·06)
······	(8-5%/y)	(9·7%/y)				,,
(T) ER status ($\chi_1^2 = 0.0$; 2p	o = 0·9; NS	9			;	
ER-poor	1241/18040 (6-9%/v)	1304/17790 (7-3%/v)	-34-7	547-2	-	0·94 (se 0·04)
ER+	688/13272	712/13150	-17.2	305.3	<u> </u>	0-95 (SE 0-06)
	(5·1%/y)	(5-4%/y)		000-0	_,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	5 00 (32 0 00)
ER unknown	278/4479 (6-2%/y)	345/4204 (8-2%/y)	-41-6	131-0	—o—;	0·73 (se 0·07)
Subsets of FR+					1	
					1	
ER+ PR-poor	124/1805 (6-9%/y)	119/1570 (7-6%/y)	-4-0	48-4		0.00 (05 0.07)
EKT PKT	404/8942 (4-5%/y)	451/9074 (5-0%/y)	-20-1	189-8		0.90 (SE 0.07)
ER+ N0/N-	170/5561 (3-1%/y)	187/5459 (3-4%/y)	-12-1	81-1		0·86 (se 0·10)
ER+ N1-3	181/4184 (4-3%/y)	181/4197 (4-3%/y)	1.7	77.9		
ER10-00 fm c 1/m -	135/1168 (11-6%/y)	138/1061 (13-0%/y)	-4-0	56-3		0.84 (05 0 00)
ER10-99 Imol/mg	246/4549 (5-4%/y)	209/4532 (5-9%/y)	-1/-5	103-2		0.67 (SE 0.09)
ER unknown	85/1973 (4-3%/y) 357/6752	119/1876 (6-3%/y) 324/6640	-16-6	42·1 -		0.01 (SE 0.13)
level (eg, by IHC)	(5-3%/y)	324/0649 (4-9%/y)	17-0	1447-U		
(g) Tumour differentiatio	$n_{1}(\chi_{1}^{2} = 2.7)$	'; 2p = 0·10); NS)		1	
Poorly-diff.	523/9730	593/9461	-29-1	231.7	_ _	0.88 (SE 0.06)
Moderately/Well	(3-470/y) 352/7555	334/7521	7-0	150-5		<u>1</u> ·05 (se 0·08)
Grade unknown	(4-7%/y) 1332/18564	(4-4%/y) 1434/18133	-70-1	607-8	┍╼┥	0·89 (se 0·04)
	(7·2%/y)	(7-9%/y)			╘╻┟╢	,
(h) Tumour diameter (tre	and $\chi_1^2 = 0$.	3; 2p = 0·6	; NS)		<u>;</u>	
1 – 20 mm (T1)	579/13819	622/13741	-13-8	269-4		0.95 (se 0.06)
21 - 50 mm (T2)	(4-2%/y)	(4-5%/y)	-22.4	125 1		0.93 (05 0.05)
	(7·2%/y)	(7·7%/y)	32-1	420.1	-#∰-	0 00 (00 000)
> 50 mm (T3/T4)	123/1055	133/939	-6-7	42-7		0·86 (se 0·14)
Other / unknown	541/7551 (7-2%/\/)	587/7142 (8-2%/v)	-44-8	246-3		0·83 (se 0·06)
(i) Tumour differentiation	n and FR	$\gamma^2 = 2 \cdot 1 \cdot n$	= 0.6.	NS)		
(i) luiiou une en a		~3 - ', P	••,		1 1	
	Contraction of the second second			110.0	<u> </u>	0.99 (se 0.09)
Poorly, ER-poor	252/5157 (4-9%/y)	269/5235 (5-1%/y)	-1.1	112-0	_ _ + #	0.99 (se 0.09)
Poorly, ER-poor Poorly, ER+ Mod /Well ER-poor	252/5157 (4-9%/y) 183/3343 (5-5%/y) 120/2570	269/5235 (5-1%/y) 193/2970 (6-5%/y) 110/2225	-1.1 -10.5	112-0 73-9	 	0·99 (se 0·09) 0·87 (se 0·11)
Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well FR+	252/5157 (4-9%/y) 183/3343 (5-5%/y) 120/2679 (4-5%/y) 172/3769	269/5235 (5-1%/y) 193/2970 (6-5%/y) 110/2328 (4-7%/y) 171/4180	-1.1 -10.5 -2.5 6.9	112-0 73-9 50-2 77-4		0·99 (se 0·09) 0·87 (se 0·11)
Poorly, ER-poor Poorly, ER-poor Mod./Well ER-poor Mod./Well ER+ Any unknown	252/5157 (4-9%/y) 183/3343 (5-5%/y) 120/2679 (4-5%/y) 172/3768 (4-6%/y) 1480/20002	269/5235 (5-1%/y) 193/2970 (6-5%/y) 110/2328 (4-7%/y) 171/4160 (4-1%/y) 1618/20422	-1.1 -10.5 -2.5 6.9 -84.0	112-0 73-9 50-2 77-4 676-4		0.99 (SE 0.09) 0.87 (SE 0.11)
Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown	252/515/ (4-9%/y) 183/3343 (5-5%/y) 120/2679 (4-5%/y) 172/3768 (4-6%/y) 1480/20902 (7-1%/y)	269/5235 (5-1%/y) 193/2970 (6-5%/y) 110/2328 (4-7%/y) 171/4160 (4-1%/y) 1618/20422 (7-9%/y)	-1-1 -10-5 -2-5 6-9 -84-9	112-0 73-9 50-2 77-4 676-4		0·99 (se 0·09) 0·87 (se 0·11) 0·88 (se 0·04)
()) Tenhou unterendation Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (i) Entry age and ER stat	(4.9%) (4.9%) (183/3343) (5.5%) (120/2679) (4.5%) (172/3768) (4.6%) (4.6%) (1480/20902) (7.1%) (7.1%) (7.1%) (1.5%) (7.1%) (7.1%) (1.5%)	269/5235 (5-1%/y) 193/2970 (6-5%/y) 110/2328 (4-7%/y) 171/4160 (4-1%/y) 1618/20422 (7-9%/y) 8; p = 1-0.	-1.1 -10.5 -2.5 6.9 -84.9	112-0 73-9 50-2 77-4 676-4		0.99 (se 0.09) 0.87 (se 0.11) 0.88 (se 0.04)
()) Turnou uneerinato Poorly, ER+ Mod./Well ER+ Mod./Well ER+ Any unknown (j) Entry age and ER stat Ane < 45 EP=noor	$\begin{array}{c} 252/5157\\ (4.9\%/y)\\ 183/3343\\ (5.5\%/y)\\ 120/2679\\ (4.5\%/y)\\ 172/3768\\ (4.6\%/y)\\ 1480/20902\\ (7.1\%/y)\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	269/5235 (5-1%/y) 193/2970 (6-5%/y) 110/2328 (4-7%/y) 171/4160 (1618/20422 (7-9%/y) 8; p = 1-0;	-1.1 -10.5 -2.5 6.9 -84.9 NS)	112-0 73-9 50-2 77-4 676-4		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04)
()) Futnosi unerentato Poorly, ER+ Mod./Well ER+ Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor	$\begin{array}{c} 252(5157)\\ (4.9\%/y)\\ 183/3343\\ (5.5\%/y)\\ 120/2679\\ (4.5\%/y)\\ 17213768\\ (4.6\%/y)\\ 1480/20902\\ (7.1\%/y)\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	269/5235 (5.1%/y) 193/2970 (6.5%/y) 110/2328 (4.7%/y) 171/4150 (4.1%/y) 1618/20422 (7.9%/y) 8; p = 1.0; 633/7620 (8.3%/y)	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2	112-0 73-9 50-2 77-4 676-4 259-5		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06)
()) Turnou uneerinato Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+	$\begin{array}{c} 252/5157\\ (4.9\%/y)\\ 183/3343\\ (5.5\%/y)\\ 120/2679\\ (4.5\%/y)\\ 172/3768\\ (4.6\%/y)\\ 172/3768\\ (4.6\%/y)\\ 1480/20902\\ (7.1\%/y)\\ \hline \\ \underbrace{cus}_{7,7} (\chi_7^2 = 1)\\ \underbrace{cus}_{7,7} (\chi$	269/5235 (5.1%\) 193/2970 (6.5%\) 110/2328 (4.7%\) 171/4160 (4.1%\) 1618/204 (7.9%\) 8; p = 1.0; 633/7620 (8.3%\) 280/4315 (6.5%\)	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2	112-0 73-9 50-2 77-4 676-4 259-5 118-4		0.99 (se 0.09) 0.87 (se 0.11) 0.88 (se 0.04) 0.96 (se 0.06) 0.94 (se 0.09)
() Turnou uneerinato Poorly, ER+ Mod./Well ER+ Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor	$\frac{(252)5157}{(4-9\%)}$ $\frac{(323)3243}{(5-5\%)}$ $\frac{(3-5\%)}{(172)3768}$ $\frac{(4-6\%)}{(172)3768}$ $\frac{(4-6\%)}{(172)3768}$ $\frac{(4-6\%)}{(172)3768}$ $\frac{(4-6\%)}{(7-7\%)}$ $\frac{(5-2\%)}{(16-2\%)}$ $\frac{(5-2\%)}{(6-8\%)}$	269/5235 (5.1%\) 193/2970 (6.5%\) 110/2328 (4.7%\) 171/4150 (4.1%\) 1618/20422 (7.9%\) 8; p = 1 ·0; 633/7620 (8-3%\) 280/4315 (6-5%\) 444/6477 (6-9%\)	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5		0.99 (sc 0.09) 0.67 (sc 0.11) 0.88 (sc 0.04) 0.96 (sc 0.06) 0.94 (sc 0.09) 0.96 (sc 0.07)
() Tunudu unerentatio Poorly, ER+ Mod./Weil ER+ Any unknown ()) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER+	252/515/ ($4.95\%/y$) 183/3343 ($5.5\%/y$) 120/2679 ($4.5\%/y$) 120/2679 ($4.5\%/y$) 120/2679 ($4.6\%/y$) 1480/20902 ($7.1\%/y$) 269/3310 ($6.2\%/y$) 460/6754 ($6.8\%/y$) 248/5302 ($4.7\%/y$)	26992235 (5.1%/y) 19329270 (6.5%/y) 110/2328 (4.7%/y) 171/4160 (4.1%/y) 1618/20422 (7.9%/y) 8; p = 1-0; (8.3%/y) 280/4315 (6.5%/y) 444/6477 (6.9%/y) 260/516/	-1.1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-3	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6		_0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) _0-94 (se 0-09) 0-96 (se 0-07) _0-94 (se 0-09)
()) Tuniou unerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER+ 45 = 54, ER-poor 45 = 54, ER+ 55 = 69, ER-poor	252/515/ (4.99%) 183/3343 ($5.5\%\%$) 120/2679 ($4.5\%\%$) 120/2679 ($4.5\%\%$) 172/3768 ($4.5\%\%$) 172/3768 ($4.6\%\%$) 172/3768 ($7.7\%\%$) 269/430 ($7.7\%\%$) 269/430 ($6.2\%\%$) 269/4574 ($6.2\%\%$) 268/4574 ($6.2\%\%$) 248/5302 248/5302 248/5302 248/5302	26992235 (5.1%/y) 19329270 (6.5%/y) 1102328 (4.7%/y) 171/4160 (4.1%/y) 1618/20422 (7.9%/y) 8; p = 1 -0; (8.3%/y) 280/4315 (6.5%/y) 444(467) (6.5%/y) 444(57) (6.5%/y) 280/4315 (5.5%/y) 260/5145 (5.5%/y)	-1.1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-3 -15-1	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-96 (se 0-07) 0-04 (se 0-09) 0-84 (se 0-10)
() Turned unerentation Poorly, ER-poor Poorly, ER+ Mod/Well ER-poor Mod/Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER-poor 55 - 69, ER+	$\begin{array}{c} 252515/\\ (4.99\%)\\ 183(3343)\\ (5.5\%\%)\\ 120(2679)\\ (4.5\%\%)\\ 120(2679)\\ (4.5\%\%)\\ 172(3768)\\ (4.6\%\%)\\ 172(3768)\\ (4.6\%\%)\\ 172(3768)\\ (7.7\%\%)\\ 120(2679)\\ (5.2\%\%)\\ 120(2679)\\ (6.8\%\%)\\ 120(2679)\\ (6.8\%\%)\\ 190(3535)\\ 5.4\%\%)\\ 157(3803)\\ 157(380$	26992235 (5.1%/y) 19329270 (6.5%/y) 1102328 (4.7%/y) 171/4160 (4.1%/y) 1618/20422 (7.9%/y) 8; p = 1-0; (6.3%/y) 1618/20422 (6.5%/y) 444(447) (6.5%/y) 260/5145 (5.1%/y) 260/	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7 -7.3 -15.1 -3.7	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3		0.99 (sc 0.09) 0.87 (sc 0.11) 0.88 (sc 0.04) 0.96 (sc 0.06) 0.94 (sc 0.09) 0.96 (sc 0.07) 0.94 (sc 0.09) 0.94 (sc 0.10) 0.95 (sc 0.12)
() Turnud unerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 69, ER-poor 55 - 69, ER+ 70+, ER-poor	252515/ ($4.996/y$) 183/3343 ($5.596/y$) 120/2679 ($4.596/y$) 120/2679 ($4.596/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 268/4310 ($6.296/y$) 268/4310 ($6.296/y$) 248/5902 ($4.676/y$) 248/5902 ($4.576/y$) 157/3503 ($4.695/y$) 157/3503 ($4.595/y$) ($4.595/y$)	26992235 (5.1%/y) 19322970 (6.5%/y) 1102328 (4.7%/y) (4.7%/y) (4.1%/y) (4.1%/y) (6.33/7820422 (6.33/7820422 (6.33%/y) 280/4315 (6.5%/y) 280/63145 (5.1%/y) 280/6315 (5.1%/y) 200/6315 (5.1%/y) 200/6315 (5	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.2 -7.3 -15.1 -3.7 -1.5	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9		_0-99 (se 0-09) 0-87 (se 0-11)
() Turnou une entation Poorly, ER+ Mod./Weil ER+ Mod./Weil ER+ Any unknown (i) Entry age and ER stat Age < 45, ER+ 45 = 54, ER-poor 45 = 54, ER+ 55 = 69, ER+ 55 = 69, ER+ 70+, ER-poor 70+, ER+	252515/ ($4.996/y$) 183/3343 ($5.596/y$) 120/2579 ($4.596/y$) 120/2579 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 172/3768 ($4.696/y$) 268/4310 ($6.296/y$) 268/4310 ($6.296/y$) 268/4310 ($6.296/y$) 248/5302 ($4.576/y$) 248/5302 ($4.576/y$) 248/5302 ($4.576/y$) 257/54/y) 268/4310 ($6.296/y$) 268/4310 ($6.296/y$) 269/4310 ($6.296/y$) 269/4000 ($6.296/y$)	2696/2247 (5-1%/y) 192/2977 (6-5%/2) 16/5%/2977 (6-5%/2) 16/5%/2977 (6-5%/y) 16/7%/297 (6-3%/y) 16/8%/207 (6-5%/y) 16/12477 (6-9%/y) 260/5/145 (5-1%/y) 260/5/145 (5-1%/y) 16/12477 (6-9%/y) 17/285 (6-1%/y) 1	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7 -7.3 -15.1 -3.7 -1.5 0.5	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 2-8		_0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) - 0-94 (se 0-09) 0-96 (se 0-07) - 0-94 (se 0-09) 0-84 (se 0-10) _0-95 (se 0-12)
() Tunudu unerentation Poorly, ER-poor Poorly, ER+ Mod./Weil ER-poor Mod./Weil ER+ Any unknown ()) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER+ 55 - 69, ER+ 55 - 69, ER+ 55 - 69, ER+ 70+, ER-poor 70+, ER+ Any unknown	252515/ (4.9%/y) 183/3343 (5.5%/y) 14.55/26/y) 172/3768 (4.6%/y) 172/3768 (4.6%/y) 1480/20902 (7.1%/y) 200 (7.7%/y) 248/302 (4.7%/y) 157/3503 (4.5%/y) 8/218 (3.7%/y) 8/21	2696/2297 (6.57%) (6.57%) (6.57%) (6.57%) (6.57%) (6.57%) (6.57%) (6.57%) (6.57%) (6.57%) (6.57%) (1.6	-1-1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-7 -7-7 -7-7 -15-1 -3-7 -15 0-5 -41-4	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 2-8 134-7		_0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) - 0-94 (se 0-09) 0-96 (se 0-07) - 0-94 (se 0-09) 0-84 (se 0-10) 95 (se 0-12) 0-74 (se 0-07)
() Turnou uneerination Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 55 - 69, ER+ 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence	252515/ (4.9%/y) 183/3343 (5.5%/y) 120/56/y) 172/376/y) 172/376/y) 172/376/y) 172/376/y) 1480/20902 (7.1%/y) 1480/20902 (7.1%/y) 1480/20902 (7.1%/y) 268/4310 (6.2%/y) 460/8754 (6.8%/y) 244/85002 (4.9%/y) 157/3503 (4.5%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 9/17/ (5.3%/y) 8/219 (3.7%/y) 8/219 (3	269/J2235 (5-1%4/) 19-5764/ 19-5764/ 19-5764/ 11-0/2228 (4-7%4/) 11-0/2228 (4-7%4/) 11-0/2228 (4-7%4/) 161/2222 (7-9%4/) 8; p = 1-0; (6-3%4/) 280/4315 (6-5%4/) 280/4315 (6-7%4/) 280/45/(6-7%4/) 280/4315 (6-7%4/	-1-1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-7 -7-7 -7-7 -7-7 -1-5 0-5 -41-4 NS)	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 2-8 134-7		_0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) - 0-94 (se 0-09) 0-96 (se 0-07) - 0-94 (se 0-09) 0-84 (se 0-10) _0-95 (se 0-12) 0-74 (se 0-07)
(I) Turnou uneerination Poorly, ER-poor Poorly, ER+ Mod/Well ER-poor Mod/Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER-poor 55 - 69, ER-poor 55 - 69, ER+ 70+, ER-poor 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrenc Isolated local	$\begin{array}{c} 252515, \\ (4.956, y) \\ ($	269/Jo2d3 (5-1%4/) 19:526/0/ 19:526/0/ 19:526/0/ 110/2328 (4-7%4/) 110/2328 (4-7%4/) 110/2328 (4-7%4/) 1618/20422 (7-9%4/) 8: p = 1-0; 6:33/7620 (8-3%4/) 280/4315 (6-5%4/) 280/4315 (6-5%4/) 280/4315 (6-1%4/) 260/5145 (5-1%4/) (5	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7 -7.3 -15.1 -3.7 -1.5 0.5 -41.4 VS) -8.3	112-0 73-9 50-2 77-4 676-4 2559-5 118-4 197-5 112-6 83-9 69-3 4-9 2-8 134-7 130-8		_0-99 (se 0-09) 0-87 (se 0-11)
() Turnou uneerination Poorly, ER-poor Poorly, ER+ Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER+ 45 - 54, ER+ 55 - 69, ER-poor 55 - 69, ER-poor 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated Iocal	$\begin{array}{c} 222505(x)\\ 222505(x)\\ (x)\\ (x)\\ (x)\\ (x)\\ (x)\\ (x)\\ (x)\\ $	28992235 (512237) (512237) (512237) (512237) (102328 (47%)) (1102328 (47%)) (102328 (47%)) (102328 (47%)) (102328 (47%)) (102328 (77%)) (10238 (77%)) (10238 (77%)) (102388 (77%)) (10238 (77%)) (102388	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7 -7.3 -15.1 -3.7 -1.5 0.5 -41.4 NS) -8.3 S	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 2-8 134-7 130-8 78-5		_0-99 (se 0-09) 0-87 (se 0-11)
()) Turival unerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown ()) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER+ 55 - 69, ER+ 55 - 69, ER+ 55 - 69, ER+ 70+, ER-poor 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrenc Isolated local Contralateral	$\begin{array}{c} 22253156\\ 22253156\\ 163726\\ 163$	2899.2239 (5172.27) (5172.	-1-1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-3 -15-1 -3-7 -15-5 0-5 -41-4 NS) -8-3 6-3 -3-5 -8-3 -3-5 -8-3 -8-3 -8-3 -8-3 -8-3 -8-3 -8-3 -8-3 -8-3 -8-5 -8-5 -8-5 -8-5 -8-5 -8-5 -8-5 -8-5 -8-5 -8-5 -8-5 -8-5 -7-5 -7-5 -7-7	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 2-8 134-7 130-8 78-5 717-9		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 94 (se 0-09) 0-94 (se 0-09) 0-94 (se 0-01) 0-94 (se 0-07) 0-94 (se 0-07) 95 (se 0-07) 94 (se 0-07) 94 (se 0-08) 0-98 (se 0-03)
() Turnud une entation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER- d5, ER+ 45 - 54, ER-poor 45 - 54, ER-poor 55 - 69, ER+ 70+, ER+ Any unknown (k) Site of first recurrenc Isolated local Contralateral Distant/Multiple	$\begin{array}{c} 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 $	2880,625,0 1632,2270 1632,2270 1632,2270 1632,2270 1632,2270 1632,2270 1632,2270 1632,2270 1632,2270 1632,2270 1632,2270 1633,7620 (8-3%/y) 1612,20422 280,6454 (9-5%/y) 1612,2270 1612,270 1612,270 1612,2700 1612,2700 161	-1-1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-3 -15-1 -3-7 -7-5 0-5 -41-4 NS) -8-3 6-3 -93-5	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 2-8 134-7 130-8 78-5 717-8		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-96 (se 0-07) 0-94 (se 0-09) 0-84 (se 0-10) 0-95 (se 0-12) 0-74 (se 0-07) 0-94 (se 0-08) 0-88 (se 0-03)
(I) Tunindi unerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (I) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER-poor 55 - 69, ER-poor 55 - 69, ER+ 70+, ER-poor 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated local Contralateral Distant/Multiple Unknown	$\begin{array}{c} 222500\\ 222500\\ 222500\\ 222500\\ 222500\\ 220500\\$	288/30450 193/2370 193/2370 193/2370 193/2370 193/2370 193/2370 193/2370 193/2370 193/2370 193/2370 193/24	-1-1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-3 -15-1 -3-7 -1-5 0-5 -41-4 NS) -8-3 6-3 -93-5 1-9	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 69-3 132-8 134-7 130-8 78-5 717-8 56-3		_0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-96 (se 0-07) 0-94 (se 0-09) 0-84 (se 0-10) 0-95 (se 0-12) 0-74 (se 0-07) 0-74 (se 0-07) 0-94 (se 0-08) 0-88 (se 0-03)
() Tunival unerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 69, ER-poor 45 - 69, ER-poor 55 - 69, ER+ 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated Iocal Contralateral Distant/Multiple Unknown (l) Time since randomise	24250 2570 2770 2	286/2023 193/2270 193/270	-1-1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-3 -15-1 -3-7 -15-5 0-5 -41-4 -8-3 6-3 -93-5 1-9 -9022	112-0 73-9 50-2 774 676-4 259-5 118-4 197-5 118-4 1197-5 118-7 1197-5 118-7 1197-5 1		0-99 (se 0-09) 0-87 (se 0-11)
()) Tunindu dimerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER+ 55 - 69, ER-poor 55 - 69, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated local Contralateral Distant/Multiple Unknown (l) Time since randomisa Years 0 - 1	24250 242500 245000 2450000 2450000 2450000 2450000 2450000 2450000 2450000 24500000 245000000000000000000000000000000000000	288/30253 193/2277 193/2277 193/2277 193/2277 193/2277 193/2277 193/2277 193/2277 193/227 193/27 193	-1-1 -10-5 -2-5 6-9 -84-9 NS) -10-2 -7-2 -7-7 -7-3 -15-1 -3-7 -15-5 0-5 -41-4 -8-3 6-3 -93-5 1-9 -9-5 -19 -9-020 -9-5 -9-5 -9-9 -9-	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 118-4 197-5 112-6 83-9 9-9-3 4-9 2-8 134-7 130-8 78-5 717-8 56-3 490-9		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-96 (se 0-07) 0-94 (se 0-09) 0-94 (se 0-10) 95 (se 0-12) 0-74 (se 0-07) 0-94 (se 0-03) 0-88 (se 0-03)
(I) Tunuda Cinerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (I) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER+ 55 - 69, ER+ 55 - 69, ER+ 70+, ER-poor 70+, ER-poor 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated local Contralateral Distant/Multiple Unknown (I) Time since randomisa Years 0 - 1	$\begin{array}{c} 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 $	288/30245 193/2277 193/277 1	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.2 -7.7 -1.5 0.5 -41.4 NS) -8.3 6.3 -93.5 1.9 P002) -94.4	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 69-3 4-9 69-3 4-9 2-8 134-7 130-8 78-5 717-8 56-3 490-8		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-94 (se 0-09) 0-94 (se 0-10) 0-95 (se 0-12) 0-74 (se 0-07) 0-94 (se 0-08) 0-88 (se 0-03) 0-88 (se 0-04)
(1) Tumbar dimensional Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER- ds = 54, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 69, ER+ 70+, ER+ Any unknown (k) Site of first recurrence Isolated local Contralateral Distant/Multiple Unknown (j) Time since randomisa Years 0 - 1 2 - 4	222505 222505 222505 222505 222505 220257 22025	288/62/53 1932/2370	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.2 -7.2 -7.3 -15.1 0.5 -41.4 VS) -8.3 6.3 -93.5 1.9 -002) -94.4 0.8	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 69-3 4-9 2.8 69-3 4-9 2.8 134-7 130-8 78-5 717-8 56-3 490-8 490-8		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-96 (se 0-07) 0-94 (se 0-09) 0-84 (se 0-10) 0-95 (se 0-12) 0-74 (se 0-07) 0-94 (se 0-08) 0-88 (se 0-03) 0-83 (se 0-04) 1-00 (se 0-05)
() Tunivar Universitation Poorly, ER-poor Poorly, ER+ Mod./Well ER-poor Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER- tage < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER-poor 55 - 69, ER-poor 55 - 69, ER+ 70+, ER-poor 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated local Contralateral Distant/Multiple Unknown (l) Time since randomisa Years 0 - 1 2 - 4	$\begin{array}{c} 2(4) \\ 2($	288/30431 193/2370 193/2	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7 -7.3 -15.1 -3.7 -1.5 0.5 -41.4 S -93.5 1.9 -9002) -94.4 0.8	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 112-6 83-9 89-3 4-9 2.8 83-9 134-7 130-8 717-8 56-3 490-8 492-6		_0-99 (se 0-09) 0-87 (se 0-11)
() Tunida Cinerentiato Poorly, ER-poor Poorly, ER+ Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER-poor 55 - 69, ER-poor 55 - 69, ER+ 70+, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated local Contralateral Distant/Multiple Unknown (l) Time since randomisa Years 0 - 1 2 - 4 Total	$\begin{array}{c} 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 $	208170230 208170230 208170230 19322770 19322770 19322770 19322770 19322770 2081720 2	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7 -7.3 -15.1 -3.7 -1.5 0.5 -41.4 KS) -93.5 1.9 -002) -94.4 0.8 -93.6	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 118-4 197-5 118-4 197-5 118-4 9-0-3 4-9 2-8 134-7 130-8 78-5 717-8 56-3 490-8 492-6 983-5		0-99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-96 (se 0-07) 0-94 (se 0-09) 0-84 (se 0-12) 0-74 (se 0-07) 0-94 (se 0-07) 0-94 (se 0-08) 0-88 (se 0-04) 1-00 (se 0-05) 0-909 (se 0-030)
() Tunvou unerentation Poorly, ER-poor Poorly, ER+ Mod./Well ER+ Any unknown (j) Entry age and ER stat Age < 45, ER-poor < 45, ER+ 45 - 54, ER-poor 45 - 54, ER+ 55 - 69, ER-poor 55 - 69, ER-poor 70+, ER+ Any unknown (k) Site of first recurrence Isolated local Contralateral Distant/Multiple Unknown (j) Time since randomisa Years 0 - 1 2 - 4 Total	$\begin{array}{c} 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 $	2881/2025) 183/2277 183/2277 183/2277 183/2277 183/2277 183/2277 183/2277 183/2277 183/2277 193/22777 193/2277 193/277 1	-1.1 -10.5 -2.5 6.9 -84.9 NS) -10.2 -7.2 -7.7 -7.3 -15.1 -3.7 -1.5 0.5 -41.4 VS) -8.3 6.3 -93.5 1.9 -002) -94.4 0.8 -93.6	112-0 73-9 50-2 77-4 676-4 259-5 118-4 197-5 118-4 197-5 118-4 197-5 118-4 197-5 118-4 9-9-3 490-8 490-8 492-6 983-5		99 (se 0-09) 0-87 (se 0-11) 0-88 (se 0-04) 0-96 (se 0-06) 0-94 (se 0-09) 0-96 (se 0-07) 0-94 (se 0-09) 0-94 (se 0-09) 0-94 (se 0-12) 0-74 (se 0-07) 0-94 (se 0-07) 0-88 (se 0-03) 0-88 (se 0-04) 1-00 (se 0-05) 0-909 (se 0-030) 2p=0-003

Events/woman-years Anthr. events Allocated Allocated Logrank Variance CMF O-E of O-E Ratio of annual event rates Anthr. : CMF Category (a) Cumulative anthracycline dosage, if dose/cycle \ge A60/E9 (trend χ_1^2 = 4-8; 2p = 0-03) A360 or E720-800: eg, CAF/CEF 585/20175 670/19703 -51.5 288.0 (2-9%/y) (3-4%/y) 0.84 (SE 0.05) 707/12972 767/12810 -20-5 302-3 (5-5%/y) (6-0%/y) 0.93 (SE 0.06) A300 or E400-480 A240: standard 4AC 1114/21307 1105/20804 -6-8 489-9 (5-2%/y) (5-3%/y) 0.99 (SE 0.04) White: dose/cycle < A60/E90 525/10219 522/9961 -13·3 227·6 (5·1%/y) (5·2%/y) 0.94 (se 0.06) -11-1 (b) Cyclophosphamide in CMF oral/iv ($\chi_1^2 = 1.1$; 2p = 0.3; NS) Т 2293/50195 2430/48833 -87·9 1032·7 (4-6%/y) (5-0%/y) C100×14 oral 0-92 (se 0-03) C600×2 iv 638/14478 634/14445 -4-2 275-2 (4-4%/y) (4-4%/y) 0.99 (SE 0.06) (c) Concurrent endocrine therapy if ER+? ($\chi_1^2 = 2.7$; 2p = 0.1; NS) 1 Yes 101/4053 87/4067 7-6 45-2 (2.5%/y) (2.1%/y) No (any endocrine only 2830/64673 2977/59211 -99-7 1262-7 after chemo ended) (4-4%/y) (5-0%/y) 0.92 (SE 0.03) (d) Entry age (trend $\chi_1^2 = 0.2$; 2p = 0.6; NS) T Age < 45 1267/25005 1367/24995 (5-1%/y) (5-5%/y) -42.7 572.4 0.93 (se 0.04) 45 - 54 0.96 (SE 0.04) 1092/24816 1091/23939 -20-2 484-7 (4-4%/y) (4-6%/y) -55 - 69 -32-2 233-4 0.87 (SE 0.06) 526/13869 (3-8%/y) 558/13275 (4-2%/y) 70+ -0.2 11-3 28/789 (3-5%/y) 18/194 31/808 (3-8%/y) 17/261 Age unknown 3-3 6-0 $\chi_{1}^{2} = 0.9; 2p = 0.3; NS)$ (e) Nodal status (trend N0/N--8.5 375.8 0.98 (SE 0.05) 804/31296 819/30996 (2-6%/y) (2-6%/y) N1-3 -12-8 358-3 0.96 (SE 0.05) 798/17484 815/17250 (4-6%/y) (4-7%/y) N4+ 0.91 (SE 0.05) 745/7090 (10-5%/y) 795/6512 (12-2%/y) -30.6 310.0 Other / unknown 0.86 (se 0.06) -40-1 263-9 584/8803 (6-6%/y) 635/8520 (7-5%/y) -T (f) ER status ($\chi_1^2 = 0.1$; 2p = 0.8; NS) 0.96 (SE 0.04) ER-poor 1619/35068 1669/34555 -30-1 721-0 (4-6%/y) (4-8%/y) 967/22322 -24-8 418-1 (4-3%/y) ER+ 0.94 (se 0.05) 931/22500 (4-1%/y) ER unknown -37.1 168.7 -0--0.80 (SE 0.07) 381/7105 (5-4%/y) 428/6401 (6-7%/y) Subsets of ER+ 1 ER+ PR-poor 167/3412 (4-9%/y) 581/15853 (3-7%/y) 144/3053 (4-7%/y) 641/16096 (4-0%/y) 1.0 62-8 ER+ PR+ -26-8 276-7 0.91 (SE 0.06) _ ER+ N0/N 0.91 (se 0.08) 285/10464 (2-7%/y) 236/6093 (3-9%/y) 160/1615 (9-9%/y) 383/9697 (3-9%/y) -12.0 127.4 271/1058 (2-6%/y) 4 3%/y) 236/6118 (3-9%/y) 166/*-ER+ N1-3 -0.3 102.2 1.00 (SE 0.10) ER+ N4+ -0.3 67.7 (9-3%/y) 372/9657 0.92 (SE 0.08) ER10-99 fmol/mg -12.6 152.5 ÷ (3-9%/y) 147/4067 (3-6%/y) 412/8710 (4-7%/y) ER100+ fmol/mg (3-9%/y) 172/3792 (4-5%/y) 412/8755 (4-7%/y) -16-9 66-4 0.78 (SE 0.11) 1 ER+, unknown level (eg, by IHC) 3-8 177-8 1.02 (SE 0.08) I (g) Tumour differentiation ($\chi_1^2 = 2.2$; 2p = 0.1; NS) Poorly-diff. 623/13923 677/13701 -22-9 270-6 (4-5%/y) (4-9%/y) 0.92 (SE 0.06)
 (4-5%)(9)
 (4-9%)(9)

 465/11687
 445/11639
 10-6
 196-1

 (4-0%)(y)
 (3-8%/y)
 1843/39038
 1942/37924
 -78-9
 846-9

 (4-7%)(y)
 (5-1%/y)
 (5-1%/y)
 16-1
 16-1
 16-1
 Moderately/Well 1 1.06 (SE 0.07) Grade unknown 0.91 (se 0.03) (h) Tumour diameter (trend $\chi_1^2 = 0.4$; 2p = 0.5; NS) 842/255557 890/25285 -13-6 392-2 (3-3%/y) (3-5%/y) 1 - 20 mm (T1) 0.97 (SE 0.05) 21 - 50 mm (T2) 1227/24532 1282/24601 -33-8 542-2 (5-0%/y) (5-2%/y) 0.94 (SE 0.04) . 146/1942 152/1712 -6·3 50·5 (7-5%/y) (8-9%/y) 716/12612 740/11660 -42·2 320·9 (5-7%/y) (6·3%/v) 0.88 (se 0.13) > 50 mm (T3/T4) Other / unknown 0.88 (SE 0.05) (i) Tumour differe and ER ($\chi_3^2 = 2.5$; p = 0.5; NS) Poorly, ER-poor 4-8 132-8 1.04 (SE 0.09) 303/7951 (3-8%/y) 310/8207 (3-8%/y) Poorly, ER+ -10-5 86-7 0.89 (se 0.10) 218/4358 (5-0%/y) 159/4540 (3-5%/y) 227/5514 224/3890 (5-8%/y) 140/3922 (3-6%/y) 231/6223 Mod./Well ER-poor -0.8 65.1 Т Mod./Well ER+ 10.5 101.5 (4-1%/y) (3-7%/y) 2024/42285 2159/41022 (4-8%/y) (5-3%/y) 1 Any unknown -95-2 927-6 0.90 (se 0.03) F (j) Entry age and ER status (χ^2_{π} = 6.0; p = 0.5; NS) 1 764/14966 815/15437 (5-1%/y) (5-3%/y) Age < 45, ER-poor -3-3 347-1 0.99 (SE 0.05) < 45, ER+ 352/7380 (4-8%/y) 597/13157 (4-5%/y) -18-0 158-9 0.89 (SE 0.08) 380/7374 (5-2%/y) -45 - 54, ER-poo 0.95 (SE 0.06) 576/12364 (4-7%/y) -13-0 259-1 45 - 54, ER+ 5-9 158-7 1.04 (SE 0.08) 359/8860 (4-1%/y) 347/8780 (4-0%/y) -55 - 69, ER-poo -14-8 107-0 0.87 (se 0.09) (40%) 255/6186 (4-1%/y) 223/5840 (3-8%/y) 18/522 (3-4%/y) 11/208 241/6522 (3-7%/y) 202/5820 55 - 69 ER+ -11-1 93-6 0.89 (se 0.10) 202/5820 (3-5%/y) 13/382 (3-4%/y) 11/347 70+, ER-poor 1-3 6-3 1 70+, ER+ -3-0 4-3 2%/y) 2/7239 4%.4.* (3-2 392 (5-4 (5-3%/y) 439/6567 (6-7%/y) ____ Any unknown -35.9 172.9 0.81 (SE 0.07) (k) Site of first recurrence (χ^2_2 = 13·2; p = 0·001) 1 343/43329 344/42463 -8-6 159-6 (0-8%/y) (0-8%/y) 339/64648 271/63274 28-6 144-1 (0-5%/y) (0-4%/y) Isolated local 0.95 (SE 0.08) ÷ Contralateral Т Distant/Multiple (0-3 /a/y) (0-4 /a/y) 2021/64673 2227/63278 -113-5 896-7 (3-1%/y) (3-5%/y) 0.88 (SE 0.03) <u>1.</u>02 (se 0.10) $\begin{array}{c} \text{Unknown} & & 228/64618 \\ (0-4\%/y) & (0.4\%/y) & (0.4\%/y) \\ \hline \text{(I) Time since randomisation} (trend \ \chi^2_1 = 10\text{-}4; \ 2p = 0\text{-}001) \\ \end{array}$ 1 1064/16586 1257/16378 -94-4 490-8 (6-4%/y) (7-7%/y) 0.83 (SE 0.04) Years 0 - 1 -1.00 (se 0.05) 2 - 4 1143/19183 1104/18621 (6-0%/y) (5-9%/y) 0-8 492-6 -0.95 (SE 0.06) 5 - 9 535/19578 (2·7%/y) 552/19106 -12-7 247-6 (2-9%/y) -10+ 14-2 76-8 151/8766 (1-7%/y) 189/8935 (2-1%/y) +╞ 2931/ 3064/ 64673 63278 (4·5%/y) (4·8%/y) -92.0 1307.9 0.932 (SE 0.027) 2p = 0.01 Tota - 95%

Any recurrence

Treatment effect 2p = 0.003 * 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 Dreaviewel (and cumulative dosage) is given after the drug name in mg/m², AsvEso means 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin

Forest plots (webappendix pp 27-32) give details of each trial's cylotoxic regimens Anthracyclines: A = doxonbiloni (Adriamycin); E = epirubicin. Other cylotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil Dosecycle (and cumulative dosage) given after the durg name in mg/m². AwdEin means 60 mg/m² of doxonbicin or 90 mg/m² of epirubicin

Global heterogeneity: χ^2_{21} = 44.5; p = 0.002

0.5

-5 1-0 Anthr. better CMF better

Treatment effect 2p = 0.01

1.5

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*.

Cotogony	Deaths/ Allocated	Women Allocated	Anthr Logrank	deaths Varianc	e Ratio of annual de	ath rates
(a) Cumulative anthracy	cline dosa	ige, if dose	e/cycle	≥A60/Es	20*	·
(trend $\chi_1^2 = 8.0$; 2p = (A360 or E720-800:	378/2082	475/2097	-50.0	198.0	_	0.78 (SE 0.06)
eg, CAF/CEF	(18-2%)	(22.7%)	-50-0	190-0		0.92 (or 0.07)
A300 01 E400-480 A240: standard 4ΔC	(14-3%) 877/2565	472/2770 (17-0%) 886/2557	-35-9	405-6		0.98 (SE 0.07)
White dees (such	(34-2%)	(34-6%)		100 0		0.02 (0.00)
< A60/E90	(23-4%)	(23-8%)	-11-1	160-1		0.93 (SE 0.08)
(b) Cyclophosphamide i	n CMF ora	$\frac{1}{1} (\chi_1^2 = 0)$	•9; 2p =	= 0·3; N	s)	0.00 (0.00)
C100×14 01 ai	(25-3%)	(28.1%)	-98-8	/00-0		0.00 (SE 0.03)
C600×2 iv	358/2413 (14-8%)	356/2401 (14-8%)	-6-6	157-9		0.96 (se 0.08)
(c) Concurrent endocrin	e therapy	if ER+? (χ	² = 0·0;	2p = 1·	0; NS)	
Yes	57/502 (11-4%) 1952/8441	62/502 (12-4%) 2128/8424	-2-9	29-0		0.89 (se 0.03)
after chemo ended)	(23-1%)	(25-3%)	102.0	011 0		000 (02 0 00)
(d) Entry age (trend χ_1^2 =	0·0; 2p =	0·9; NS)				
Age < 45	871/3398 (25-6%)	991/3454 (28-7%)	-54-8	422-8		0.88 (SE 0.05)
45 - 54	738/3399	773/3356	-30-6	344-3		0·91 (se 0·05)
55 - 69	375/1961	396/1920	-20-2	169-3	_	0.89 (SE 0.07)
70+	(19-1%) 18/106 (17-0%)	(20-6%) 25/112 (22-3%)	-2-2	8-7	т .	
Age unknown	7/79 (8-9%)	5/84 (6-0%)	2.4	1.8		
(e) Nodal status (trend χ	- = 0·9; 2p	= 0·3; NS) _10 E	222.4	_	0.84 (c= 0.06)
N1-3	(11.9%)	(14.0%)	-40-5	233-1		0.96 (st 0.06)
N4+	(21·3%) 612/1234	(22·5%) 647/1233	-23.1	243.4		0.92 (SE 0.06)
Other / unknown	(49.6%) 416/1402	(52-5%) 459/1406	-31.9	196-8		0.85 (SE 0.07)
(f) FR status ($\gamma^2 = 0.1: 2r$	(29.7%)	(32-6%)				,
ER-poor	1201/4488	1287/4518	-43-7	564-6		0.93 (se 0.04)
ER+	(26-8%)	(28-5%)	-26 5	267.0		0.91 (e= 0.00)
ER+	(17.4%)	610/3257 (18-7%)	-26-5	267-0		0.91 (SE 0.06)
	(20.3%)	(25.5%)	-33-2	115-2		0-74 (SE 0-00)
Subsets of ER+						
ER+ PR-poor ER+ PR+	120/442 (27.1%) 323/2079	110/396 (27-8%) 390/21/6	-3-8	48-9	P	0.84 (se 0.07)
ER+ N0/N-	(15-5%) 152/1285	(18-2%) 170/1269	-12-9	74-9		0.84 (SE 0.11)
ER+ N1-3	(11.8%) 123/1028 (12.0%)	(13-4%) 126/1033 (12-2%)	-1-9	54-4		
ER+ N4+ ER10-99 fmol/mg	119/342 (34-8%) 247/1072	121/326 (37-1%)	-5.7	52-3	Ŧ	0.82 (se 0.09)
ER100+ fmol/mg	(23·0%) 86/450	(25-5%) 116/450	-15-4	42.0		0.69 (SE 0.13)
ER+, unknown level (eg. by IHC)	(19-1%) 236/1757 (13-4%)	(25-8%) 215/1713 (12-6%)	7-6	99-7	++0	
(g) Tumour differentiatio	on (trend χ	² = 0·9; 2p	= 0∙4;	NS)	1	
Poorly-diff.	395/2466 (16-0%)	455/2471 (18-4%)	-27-9	190-2	_∎+	0.86 (SE 0.07)
Moderately-diff.	221/1555 (14-2%)	238/1546 (15-4%)	-12-8	105-5		0.89 (SE 0.09)
Grade unknown	(12-3%) 1354/4604	(11-8%) 1458/4579	-67-3	659-6		0·90 (se 0·04)
	(29-4%)	(31-8%)			4	
(h) Tumour diameter (tre	and $\chi_1^2 = 0$	0; 2p = 1·0); NS)	0545	L L	0.01 (05 0.06)
1 = 20 mm (11)	(15-8%)	(17.9%)	-27.1	204-0		0.91 (SE 0.05)
21 - 30 mm (12)	(25.6%)	(27.5%)	-37-1	412-0	-###+	0.91 (SE 0.03)
> 50 mm (13/14) Other / unknown	123/311 (39-5%) 491/1930	125/296 (42-2%) 527/1884	-4-9 -35-2	45-0 231-0		0.86 (SE 0.06)
(i) Tumour differentiation	(25-4%)	(28.0%) (x ² = 0.3. n	• = 1·0·	NS)		
Mod./Well ER-poor	91/637	95/572	-5.7	40.2		0.87 (SE 0.15)
Poorly, ER-poor	(14-3%) 198/1258 (15-7%)	(16-6%) 222/1308 (17-0%)	-5.7	93-5	, 	0·94 (se 0·10)
Mod./Well ER+	125/952 (13-1%) 131/868	136/1047 (13-0%) 130/793	-1-8	58-3		
Any unknown	(15·1%) 1464/5228	(16-4%) 1607/5206	-82-8	706-1		0.89 (SE 0.04)
	(28-0%)	(30-9%)			백	
(j) Entry age and ER stat	$us_{77} = 1$	·9; p = 1·0; 629/1961	; NS)	269.2		0-93 (se 0-06)
< 45 EP+	(29.1%)	(32-1%)	-14 E	104.1		0.87 (c= 0.09)
45 - 54, ER-poor	(20-2%) 447/1663	(21.7%) 447/1626	-16-1	204-0		0.92 (SE 0.07)
45 – 54, ER+	(26-9%) 208/1282	(27.5%) 224/1255	-8-4	98-2	_	0·92 (se 0·10)
55 - 69, ER-poor	(194/865 (22-4%)	(193/844 (22-9%)	-4.7	86-0	_	0.95 (SE 0.10)
55 - 69, ER+ 70+, ER-poor	134/846 (15-8%) 7/51	140/847 (16-5%) 17/69	-3-6 -3-1	61-1 5-1		04 (32 0 12)
70+, ER+	(13·7%) 7/45 (15·6%)	(24-6%) 7/30 (23-3%)	-0.7	2.8		
Any unknown	243/1219 (19·9%)	296/1204 (24-6%)	-34-2	116-3		0.75 (SE 0.08)
(k) Time since randomis	ation (trer	$d \chi_1^2 = 0.4$; 2p = 0)·5; NS)		0.00 / 0 07
rears u = 1 2 - 4	359/8943 (4-0%) 891/8307	4U2/8926 (4-5%) 972/8216	-22-1	171-9 416.5		U-00 (SE U-U7)
5-9	(10.7%)	(11.8%)	-00.0	- 10-0	╶┲╡	0.80 (0= 0.00)
5 - 5 10+	0/9/6253 (9·3%)	041/0140 (10-4%)	-32-3	2//·1	╶╼┻┼	0.03 (SE 0.06) 0.98 (SE 0.11)
Denominators: wom	(5-6%) (5-en entering	(5-7%) (5-7%)	-1-3	01-3		
Total	2009/ 8943	2190/ - 8926	-105 ∙4	946·8	\downarrow	0.895 (SE 0.031)
	(22.5%) onfidence int	(24·5%) ervals		_		
Global h	eterogeneity	/: χ ² ₁₉ = 13·4;	p = 0·8		0·5 1·0 Anthr. better	1·5 CMF better

* Forest plots (webappendix pp 27-32) give details of each trial's cytotoxic regimens Anthracyclines: A = doxonbuicin (Adriamycin), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil Dosecycle (and cumulative dosage) is given atter the drug name in mg/m², AuxEe means 80 mg/m² of doxonblicin or 90 mg/m² of epirubicin

Treatment effect 2p = 0.0006

P 11: RECURRENCE in trials of any anthracycline-based regimen (eg, standard 4AC) vs. No chemotherapy

Early recurrence (first 5 years)

Catagony	Events/wo Allocated	man-years Allocated	Anth. Logrank	Variance	e Ratio of annua	al event rates
(a) Cumulative anthracy	cline dosa	ige, if dos	e/cycle	≥A60/Es	Antn. : 90*	Control
(χ ₁ ² = 0·1; 2p = 0·8; NS	S)				1	
A360: CAF	231/5196 (4-4%/y)	324/4785 (6-8%/y)	-26-3	55.7	_ _	0.62 (SE 0.11)
A300			(no	trials)	I	
A240/E360: standard 4AC/EC	163/3225 (5·1%/y)	233/3130 (7-4%/y)	-33-5	79-5		0.66 (SE 0.09)
<pre>White: dose/cycle < A60/E90</pre>	785/10611 (7-4%/y)	955/9649 (9-9%/y)	-125-4	354-6		0·70 (SE 0·04)
(b) Anthracycline tested	* (χ ² = 2·9;	2p = 0·09)			
Doxorubicin (A)	758/10735	968/9627	-122-9	283-4		0.65 (SE 0.05)
Enirubicin (E)	(7-1%/y) 283/4597	(10-1%/y)	-33.0	122.5		0.78 (s= 0.08)
A or E	(6·2%/y)	(7.7%/y)	=28.4	72.0		0.68 (se 0.10)
(a) Consurrant and asrin	(3.7%/y)	(5.9%/y)	² = 0.2	20 = 0.		0 00 (32 0 10)
(c) concurrent endocrin		<u>II EKT (</u>	1 - 0.2,	2p = 0	5, NS) ·	0.71 (05.0.06)
	(6·1%/y)	(8-3%/y)	-/0-1	22:3-1		0-71 (SE 0-00)
after chemo ended)	468/5563 (8-4%/y)	561/4975 (11-3%/y)	-76-9	200-2		0.68 (SE 0.06)
Random †	250/5852 (4-3%/y)	368/5539 (6-6%/y)	-32-2	64-6		0.61 (SE 0.10)
(d) Entry age (trend χ_1^2 =	0·0; 2p = 0	0·9; NS)			1	
Age < 45	133/1565 (8-5%/y)	147/1237	-20-2	50-0		0.67 (SE 0.12)
45 - 54	292/4491 (6-5%/v)	379/4463 (8-5%/v)	-43-9	122-8	_ #	0.70 (SE 0.08)
55 - 69	713/12122 (5-9%/y)	923/11063 (8-3%/y)	-115-8	306-5		0.69 (SE 0.05)
70+	35/819	56/788	-5-2	9-0	T	
Age unknown	(4-3%/y) 6/35 (17.1%/u)	(7-1%/y) 7/13 (53.8%/y)	-0-2	1.6	1	
(e) Nodal status (trend χ	² = 0·1; 2p	= 0.7; NS)			
N0/N-	136/3243	178/2966	-28-8	67-0	_	0.65 (SE 0.10)
N1-3	(4-2%/V) 393/9908 (4-0%/v)	(5-0%/V) 484/9257 (5-2%/v)	-48-2	171-0	∎	0.75 (se 0.07)
N4+	450/4775	620/4450	-73-2	174-0	_ 	0.66 (SE 0.06)
Other / unknown	200/1106	230/891	-35-0	77.9		0.64 (se 0.09)
(f) ER status (χ ₁ ² = 0·1; 2	p = 0.8; NS	(20-0%/y) 5)				
ER-poor	357/4282	437/3612	-58-4	154-1		0.68 (SE 0.07)
ER+	(8-3%/y) 658/13126	(12-1%/y) 912/12584	-112-3	274-5		0.66 (SE 0.05)
ER unknown	(5-0%/y) 164/1624	(7·2%/y) 163/1368	-14-6	61-3		0.79 (se 0.11)
	(10·1%/y)	(11-9%/y)			I Ü	,
Subsets of ER+						
ER+, chem+end.	491/11266	682/10831	-71.1	196-0		0.70 (SE 0.06)
Ditto, age < 55	(4·4 %/y) 128/2498	(0·3 ‰ry) 172/2776	-8-1	50-6	_	0·85 (se 0·13)
Ditto, 55 - 69	(5·1%/y) 331/8021	(6-2%/y) 472/7409	-59-3	137-5		0.65 (SE 0.07)
ER+ PR-poor	(4-1%/y) 163/2592	(6-4%/y) 259/2684	-41.9	77-3		0.58 (SE 0.09)
ER+ PR+	(6-3%/y) 445/9616 (4.6%/y)	(9-6%/y) 599/9207 (6-5%/y)	-71-0	186-0	_ _	0.68 (SE 0.06)
ER+ N0/N-	49/1563	80/1568	-15-1	28-3 🛪		0.59 (se 0.15)
ER+ N1-3	(3·1%/y) 240/7518 (3·2%/y)	(5-1%/y) 301/7176 (4-2%/y)	-28-8	102-5		0.76 (SE 0.09)
ER+ N4+	291/3514 (8-3%/y)	420/3369 (12-5%/y)	-47-3	106-7	—••·	0.64 (SE 0.08)
ER10-99 fmol/mg	305/5880 (5·2%/y)	455/5622 (8·1%/V)	-62-4	130-0	- e	0.62 (SE 0.07)
ER100+ fmol/mg	224/4984 (4-5%/y)	280/4957 (5-6%/y)	-16-5	82-3	<u> </u>	0.82 (se 0.10)
ER+, unknown level (eg. by IHC)	129/2174 (5·9%/y)	177/1877 (9-4%/y)	-27-9	56-1		0.61 (SE 0.11)
(g) Tumour differentiation	<u>on</u> (χ ₁ ² = 0·1	; 2p = 0·7	; NS)		I	
Poorly-diff.	223/2977 (7.5%/w)	272/2627	-35-8	96-4		0.69 (SE 0.09)
Moderately/Well	322/5564 (5-8%/y)	402/5281 (7-6%/v)	-48-5	148-5	_ _	0.72 (SE 0.07)
Grade unknown	634/10504 (6,0%/y)	838/9666 (8.7%/v)	-98-0	255-5	- <u>Ġ</u>	0.68 (SE 0.05)
(h) Tumour diameter (tre	and $\gamma_{1}^{2} = 0$	4:2p = 0·5	: NS)		Т	
1 - 20 mm (T1)	328/8420	425/7831	-53-3	147-4		0.70 (se 0.07)
21 - 50 mm (T2)	(3-9%/y) 659/8880	(5-4%/y) 865/8166	-108-8	281.0		0.68 (SE 0.05)
2. 00 mm (T2/T4)	(7-4%/y)	(10-6%/y)	100 0	2010		0 00 (02 0 00)
> 50 mm (13/14) Other / unknown	107/764 (14-0%/y) 85/065	114/693 (16-5%/y) 109/965	-3-9	31-5		0.65 (sc 0.14)
(i) Tumour differentiation	(8-8%/y)	(12-5%/y)	- 0.7	NO)	9	000(32014)
		χ ₃ - 1.4, μ	· = 0·/,	NO)	I	0.07 (0.40)
Poorly, ER-poor	87/1014 (8-6%/y) 107/1680	108/880 (12-3%/y) 143/1535	-15-1	37-4		0.66 (se 0.12)
Mod./Well ER-poor	(6-4%/y) 63/624	(9-3%/y) 62/516	-3-3	23-1		> 00 (32 0.12)
Mod./Well ER+	(10-1%/y) 207/4204	(12-0%/y) 286/4153	-39-5	104-1	_	0.68 (se 0.08)
Any unknown	(4-9%/y) 715/11523	(0-9%/y) 913/10490	-103-6	286-2	-[0.70 (se 0.05)
(i) Entry are and EP ator	(0·2%/y) hus (~ ² - ?	(ö·/%/y)	NS)		۳	
Age < 45 EB-poor	40/564	49/242	7	15.0	_ 1	0.58 (cr. 0.19)
< 45, ER+	(8-7%/y) 57/757	(14-0%/y) 68/657	-8-2	10-8 ≼ 24-5 -	-	0.72 (SE 0.17)
45 - 54, ER-poor	(7-5%/y) 95/1256	(10-4%/y) 110/1007	-15-6	39-4		0.67 (se 0.13)
45 - 54, ER+	(7.6%/y) 157/2757	(10-9%/y) 222/3094	-20-2	66-5		0.74 (se 0.11)
55 - 69, ER-poor	(5-7%/y) 211/2393 (8.8%/y)	(7-2%/y) 265/2176 (12-2%/y)	-33-2	98-1		0.71 (SE 0.09)
55 - 69, ER+	411/8860 (4-6%/y)	580/8145 (7-1%/v)	-79-6	175-2	- -	0.63 (SE 0.06)
70+, ER-poor	2/65	14/86	-0-9	0.7	1	
70+, ER+	33/748 (4-4%/y)	41/687 (6-0%/v)	-4-3	8-3		
Any unknown	164/1632 (10-0%/y)	164/1369 (12-0%/y)	-14-6	61-3		— 0·79 (se 0·11)
(k) Site of first recurrence	$\frac{1}{2} = 0.1$; p = 1·0;	NS)		I	
Isolated local	144/14360 (1.0%/y)	210/13303 (1-6%/y)	-24-7	65-6		0.69 (se 0.10)
Contralateral	73/18624 (0-4%/y)	101/17175 (0-6%/y)	-12-2	35-1		— 0.71 (se 0.14)
Istant/Multiple	ชชช/19032 (4-7%/y)	(6-3%/y)	-142-3	364-6	-∰-	ບ∙68 (SE 0∙04)
Unknown	76/18653 (0-4%/v)	86/17294 (0-5%/v)	-6-0	24-6	<u> </u>	
(I) Time since randomisa	ation $(\chi_1^2 =$	13·4; 2p =	0.0003	3)	I	
Years 0 - 1	525/8630	804/8255	-132-5	243-4		0.58 (se 0.05)
2 - 4	(0-170/y) 654/10319	708/9215	-52-7	246-4	_ 	0.81 (se 0.06)
_	(6-3%/y)	(7-7%/y)				
Total	1179/ 19032	1512/ 17564	-185-2	489·8	4	0.685 (SE 0.038) 2p < 0.00001
	(6·2%/y)	(8·6%/y)				
- <u>-</u> 3370 UI⊥> 35% CI	Contractice (ND	2		_	0.5 1.	0 1.5
Global h	eterogeneity	γ: χ ₂₁ = 21·5;	p = 0·4		Antn. better	Antn. worse

Treatment effect 2p < 0.00001

* 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. AvoEso means 60 mg/m² of doxorubicin or 90 mg/m² d epirubicin 1 in the SWOS B41 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy. ‡ chem+end. = chemo-endocrine therapy

Any	rec	urre	nce
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	Events/wo	man-years	Anth.	events	Patio of annu	al avant ratae
Category (a) Cumulative anthracy	anth.	control ge, if dose	O-E	of O−E ≥A60/E90*	Anth.	: Control
$\chi_1^2 = 1.4$; 2p = 0.2; N	S) 409/10308	552/0105	-46.8	96.8		0-62 (s⊨ 0-08)
A300	(4-0%/y)	(6-0%/y)	(no	trials)	- 1	0 02 (02 0 00)
A240/E360: standard 4AC/EC White: dose/cycle < A60/E90	278/6259 (4-4%/y) 1140/20007 (5-7%/y)	345/5787 (6-0%/y) 1300/17987 (7-2%/y)	-41.5 -138.2	128-0 505-2	₽	0·72 (se 0·08) 0·76 (se 0·04)
(b) Anthracycline tested	$d^* (\chi_1^2 = 5.9)$	2p = 0·01)			1	
Doxorubicin (A)	1166/21977 (5-3%/y)	1429/19154 (7-5%/y)	-161.7	424-0	-8-	0.68 (SE 0.04)
Epirubicin (E)	427/8215 (5-2%/y)	462/7719 (6-0%/y)	-33-0	193-7	∔∎	0·84 (se 0·07)
A or E	234/6382 (3-7%/y)	306/6096 (5-0%/y)	-31-8	112-3		0·75 (se 0·08)
(c) Concurrent endocrin Yes	763/15212	<u>π ER+7</u> (χ ₁ 895/13901	= 0·2;	2p = 0.7; 360.2	NS)	0·77 (se 0·05)
No (any endocrine only	(5-0%/y) 621/9986	(6-4%/y) 694/8763	-78.3	259-9	-	0.74 (se 0.05)
after chemo ended) Random †	(6-2%/y) 443/11376	(7-9%/y) 608/10305	-52-2	109-9 _	-0	0.62 (SE 0.08)
(d) Entry age (trend χ_1^2 =	(3-9%/y) = 0-2; 2p =	(5-9%/y) D-7; NS)			1	
Age < 45 45 - 54	176/2869 (6-1%/y) 455/8922	193/2352 (8-2%/y) 548/8542	-21-9 -53-8	68-1 181-5	ė	0·73 (se 0·10) 0·74 (se 0·06)
55 - 69	(5-1%/y) 1131/23233	(6-4%/y) 1357/20590	-140-2	464-7		0.74 (SE 0.04)
70+	(4-9%/y) 57/1493	(6-6%/y) 92/1463	-10.8	13-9 <table-cell-columns></table-cell-columns>		0·46 (se 0·19)
Age unknown	(3-8%/y) 8/57 (14-0%/y)	(6-3%/y) 7/22 (31-8%/y)	0.2	1-8	I	
(e) Nodal status (trend) N0/N-	χ ⁻ ₁ = 1·2; 2p 209/5919	= 0.3; NS) 243/5505	-29-0	97-4		0·74 (sf 0·09)
N1-3	(3-5%/y) 709/20045 (3-5%/v)	(4-4%/y) 825/18342 (4-5%/y)	-70.5	293-6		0.79 (SE 0.05)
N4+	670/8752 (7·7%/y)	873/7692 (11-3%/y)	-93-5	247-9	_ _	0.69 (se 0.05)
Other / unknown	239/1858 (12-9%/y)	256/1430 (17-9%/y)	-33-4	91-1		0.69 (SE 0.09)
$(1) \models \kappa \text{ status} (\chi_1^2 = 0.7; 2)$ ER-poor	μ = U·4; NS 484/8593	578/7009	-80-2	211-2		0.68 (se 0.06)
ER+	(5-6%/y) 1118/24872	(8-2%/y) 1408/23352	-135-2	436-5		0·73 (se 0·04)
ER unknown	(4-5%/y) 225/3109	(8-0%/y) 211/2608	-11-1	82-3		0·87 (se 0·10)
Subsets of ER+	(7-2%/y)	(8-1%/y)			1	
ER+, chem+end.	882/21412 (4-1%/v)	1121/20163 (5-6%/v)	-92-3	330-3	-	0.76 (se 0.05)
Ditto, age < 55	223/4838 (4-6%/y)	293/5256 (5-6%/y)	-16-2	84-9		0·83 (se 0·10)
Ditto, 55 - 69	607/15225 (4-0%/y)	(5-5%/y) (5-5%/y)	-66-8	232-9	₩	0.75 (SE 0.06)
ER+ PR-poor ER+ PR+	273/5019 (5-4%/y) 759/18187	369/4983 (7-4%/y) 964/17051	-44·6 -92·9	117-7 305-2		0.68 (SE 0.08) 0.74 (SE 0.05)
ER+ N0/N-	(4-2%/y) 92/2822	(5-7%/y) 121/2853	-16-9	47-6 -		0·70 (se 0·12)
ER+ N1-3	(3-3%/y) 470/14782 (3-2%/y)	(4-2%/y) 544/13971 (3-9%/y)	-36-5	184-7		0.82 (SE 0.07)
ER+ N4+ ER10-99 fmol/ma	460/6404 (7-2%/y) 540/11773	619/5786 (10-7%/y) 729/11074	-60·7	160-7 213-5		0.69 (SE 0.07) 0.70 (SE 0.06)
ER100+ fmol/mg	(4-6%/y) 398/9488	(6-6%/y) 471/9242	-25-2	139-5		0.83 (se 0.08)
ER+, unknown level (eg, by IHC)	(4-2 /a/y) 180/3530 (5-1%/y)	208/2947 (7·1%/y)	-26.7	70-5		0.68 (SE 0.10)
(g) Tumour differentiation	$on_{1}(\chi_{1}^{2} = 0.4)$	5; 2p = 0·5;	NS)	447.0	Ļ	0.74 (05 0.08)
Moderately/Well	(5-6%/y) 499/9823	(7.3%/y) 573/9205	-49-1	222-3		0.80 (SE 0.06)
Grade unknown	(3-1/a/y) 1050/21757 (4-8%/y)	(0.2 /a/y) 1307/19429 (6.7%/y)	-136-6	406-6	-11-	0·71 (se 0·04)
(h) Tumour diameter (tr	end $\chi_1^2 = 0$	6; 2p = 0·5;	NS)		Τ	
1 – 20 mm (T1)	574/16624 (3-5%/y)	720/15248 (4-7%/y)	-78-0	247-7		0.73 (SE 0.05)
21 – 50 mm (T2)	975/16645 (5-9%/y)	1188/14894 (8-0%/y)	-129-6	401-0	- # -	0·72 (se 0·04)
> 50 mm (T3/T4) Other / unknown	146/1394 (10-5%/y) 132/1904	146/1151 (12·7%/y) 143/1661	-3.0 -11.9	39-0 49-1		0·79 (se 0·13)
(i) Tumour differentiatio	(6-9%/y)	(^{8·6%/y)} χ ₃ ² = 1·1; p	= 0.8;	NS)	1	
Poorly, ER-poor Poorly, ER+	97/1789 (5-4%/y) 145/2707	120/1499 (8-0%/y) 171/2446	-17-1 -19-3	42-0 — 64-1		0.67 (SE 0.13)
Mod./Well ER-poor	(5-4%/y) 77/1090 (7-1%/v)	(7-0%/y) 79/899 (8-8%/v)	-5-1	29-1		
Mod./Well ER+ Any unknown	340/7386 (4-6%/y) 1168/23613	417/7247 (5-8%/y) 1410/20886	-41.5 -138.6	162-2 449-4		0·77 (SE 0·07) 0·73 (SF 0·04)
(i) Entry and and ED	(4-9%/y)	(6-8%/y)	NE		┶┰┢╴	
<u>u/ ⊏ntry age and ER sta</u> Age < 45, ER−poor	<u>παs</u> (χ ₇ = 5 56/1034	58/637	-11.1	19-5 ৰ—	<u> </u>	0·57 (se 0·17)
< 45, ER+	(5-4%/y) 84/1378 (6-1%/y)	(9-1%/y) 97/1240 (7-8%/y)	-9.1	36-2	 	0.78 (se 0.15)
49 - 54, ER-poor 45 - 54, ER+	138/2629 (5-2%/y) 259/5333	138/2026 (6-8%/y) 350/5812	-14-7 -31-7	54-5 104-7		0.76 (SE 0.12) 0.74 (SE 0.08)
55 - 69, ER-poor	(4-9%/y) 286/4783 (6-0%/y)	(8-0%/y) 368/4186 (8-8%/y)	-53-8	136-2	_ 	0.67 (SE 0.07)
55 - 69, ER+	722/16800 (4-3%/y)	884/15022 (5-9%/y)	-84-3	282-7	-#	0·74 (se 0·05)
70+, ER+	4/135 (3-0%/y) 53/1352 (3-9% 4-1	(8-8%/y) 76/1277 (6-0%/4/)	-0-6 -10-2	1-0 12-9 ≼ ∎		0·46 (se 0·19)
Any unknown	225/3130 (7·2%/y)	212/2609 (8·1%/y)	-11.1	82-3	- <u>-</u>	
(K) Site of first recurren Isolated local	<u>ce</u> (χ ₂ = 6·0 194/26565	<pre>; p = 0.05) 267/23918</pre>	-30-9	87-1		0·70 (se 0·09)
Contralateral	(0-7%/y) 190/36112 (0-5%/y)	(1.1%/y) 187/32556 (0.6%/y)	-5-4	75-9	- +	0.93 (SE 0.11)
Distant/Multiple	1222/36574 (3-3%/y)	1531/32969 (4-6%/y)	-188-4	504-6	H	0·69 (se 0·04)
Unknown	221/36041 (0-6%/y)	212/32644 (0.6%/y)	-1.8	62-5	T	
Years 0 - 1	525/8630	804/8255	-132-5	243-4	.	0.58 (se 0.05)
2 - 4	(6-1%/y) 654/10319 (6-3%/v)	(9·7%/y) 708/9215 (7·7%/v)	-52.7	246-4	- ⊥_	0.81 (se 0.06)
5 - 9	487/11893 (4-1%/y)	487/10385 (4-7%/y)	-20.1	174-7		0.89 (se 0.07)
10+	161/5449 (3-0%/y)	198/4819 (4-1%/y)	-21.2	65-5		0·72 (se 0·11)
Total	1827/ 36574 (5·0%/v)	2197/ _ 32969 (6·7%/v)	226-5	730-0	4	0·733 (SE 0·032) 2p < 0·00001
🖶 99% or 🖘 95% o	confidence int	ervals		<u>_</u>	<u>l.</u> 5 1	·0 1·5

Global heterogeneity: χ^2_{21} = 35·0; p = 0·03

Anth. better Anth. worse Treatment effect 2p < 0.00001

Forest plots (webappendix pp 33–38) give details of each trial's cytotoxic regimens Anthracyclines: A = doxoubicin (Adriamycin), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil Dosekycle (and cumulative dosage) is given after the dwg name in mg/m². AveExe means 60 mg/m² of doxonbicin or 60 mg/m² of epirubicin 1 In the SWOG 8814 trial of CAF in postmenopausal ER+ disease, tamoxifen started randomly with or after the chemotherapy.

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

Catagony	Deaths Allocated	Women Allocated	Anth Lograni	deaths Variance	e Ratio of annu	al death rates
(a) Cumulative anthracy	anth. cline dosa	control age, if dos	O-E e/cycle	of O−E ≥A60/E9	Anth.:	Control
(χ ₁ ² = 1·5; 2p = 0·2; Ν	S)				- 1	
A360: CAF	324/1177 (27-5%)	456/1143 (39-9%)	-35-3	80-3		0·64 (se 0·09)
A300 A240/F360	212/747	265/792	(no -25.6	trials)	<u> </u>	0.78 (SE 0.09)
standard 4AC/EC	(28-4%)	(33-5%)	-79.0	400.5	_	0.82 (SE 0.05)
< A60/E90	(31.1%)	(35-0%)	100	4000	╶┧╻┝╴	0 02 (02 0 00)
(b) Anthracycline tested	<u>i</u> * (χ ₁ ² = 1·9	; 2p = 0·2;	NS)		I.	
Doxorubicin (A)	973/2626	1185/2570 (46.1%)	-106-1	370-4		0·75 (se 0·05)
Epirubicin (E)	293/1283	318/1283	-20-5	138-4		0.86 (se 0.08)
A or E	(22-8%) 150/845	(24-8%) 198/880	-13-3	72-5		
(c) Concurrent endocrin	(17-8%) therapy	(22-5%) if ER+? (χ	² = 0·3	2p = 0∙	6; NS)	
Yes	607/2004	693/2014	-54-4	288-0		0·83 (se 0·05)
No (any endocrine only	(30-3%) 462/1431	(34-4%) 514/1398	-48-2	203-8		0.79 (SE 0.06)
after chemo ended)	(32-3%)	(36-8%)	-10 2	200 0		0.66 (az 0.00)
Random T	(26-3%)	494/1321 (37-4%)	-37-2	89-4		0.00 (SE 0.09)
(d) Entry age (trend χ_1^2 =	2·0; 2p =	0·2; NS)			I	0.91 (c= 0.13)
Age < 45	135/402 (33-6%)	127/353 (36-0%)	-4-9	53-0		0 30 (se 0 13)
45 - 54	338/1115 (30-3%)	419/11/5 (35-7%)	-34-9	139-8		0.78 (SE 0.07)
55 - 69	(30-0%)	(36-2%)	-88-5	377-0		0.79 (SE 0.05)
70+	43/225 (19-1%)	84/232 (36-2%)	-11.7	11.4 <	i	0·36 (se 0·19)
Age unknown	1/17 (5·9%)	0/17 (0-0%)	0-2	0-1	I	
(e) Nodal status (trend)	([∠] = 0·0; 2p	o = 0·9; NS)		I	
N0/N-	122/789 (15-5%)	137/761 (18-0%)	-12-0	56-9		0.81 (SE 0.12)
N1-3	513/2257 (22-7%)	604/2217 (27-2%)	-51-3	214-1	_₽_	0·79 (se 0·06)
N4+	575/1226 (46-9%)	741/1295	-53-7	222-3	- ģ	0·79 (se 0·06)
Other / unknown	206/482	219/460	-22-8	88-0	d	0·77 (se 0·09)
(f) ER status ($\chi_1^2 = 0.1; 2$	p = 0·7; NS	(*****) S)			I	
ER-poor	403/1095	464/1043	-40-5	180-4	_ 	0·80 (se 0·07)
ER+	(36-8%) 831/3100	(44-5%) 1063/3177	-84-6	328-5		0·77 (se 0·05)
ER unknown	(26-8%)	(33-5%)	-14.0	79.9		0.81 (er 0.11)
ER UIKIOWI	(32-6%)	(33-9%)	-14-9	12.3	L	0.01 (SE 0.11)
Subsets of ER+					I	
ER+, chem+end.	659/2622	853/2675	-56-2	247-0		0.80 (se 0.06)
vs end. only ‡ Ditto, age < 55	(25·1%) 166/585	(31.9%)	-6-9	62-5		0.90 (SE 0.12)
Ditto, 55 - 69	(28-4%) 455/1855	(31-5%) 575/1836	-38-8	174-1		0.80 (SE 0.07)
ER+ PR-poor	(24-5%) 215/650	(31-3%) 297/730	-26-7	93-8		0.75 (SE 0.09)
ER+ PR+	(33·1%) 546/2225	(40-7%) 699/2264	-57-0	219-9		0.77 (se 0.06)
ER+ N0/N-	(24-5%)	(30-9%)	=7.9	24.1		0.72 (s= 0.17)
ER+ N1-3	(12-2%) 320/1682	(15-5%) 375/1668	-20-7	124-3		0.85 (SE 0.08)
ER+ N4+	(19-0%) 388/872	(22-5%) 525/931	-40-1	140-7		0.75 (SE 0.07)
ER10-99 fmol/mg	(44-5%) 416/1371	(56-4%) 544/1442	-35-3	162-5		0.80 (SE 0.07)
ER100+ fmol/ma	(30-3%) 274/1146	(37-7%) 337/1160	-20-6	95-6		- 0.81 (se 0.09)
ER+, unknown	(23-9%) 141/583	(29-1%) 182/575	-25.7	62-5	<u>「</u>	0.66 (SE 0.10)
level (eg, by IHC)	(24-2%)	(31.7%) 2 ² = 0.1.2n	s = 0.8.	NS)	I	
(g) rundur unterentiation	203/020	220/00/	=21.0	02.7	<u> </u>	0.79 (s= 0.09)
Moderately-diff.	(21.9%) 308/1084	(25-3%) 354/1082	-29-5	146-6		0.82 (SE 0.07)
Well-diff.	(28-4%) 48/253	(32-7%) 56/256	-4-1	23-0		
Grade unknown	(19-0%) 857/2488	(21-9%) 1062/2491	-89-1	341-8	_بل_	0·77 (se 0·05)
	(34-4%)	(42-6%)			$\neg T$	
(h) Tumour diameter (tre	end $\chi_1^2 = 3$	6; 2p = 0·0	06)		I.	
1 – 20 mm (T1)	398/1935 (20-6%)	516/1892 (27-3%)	-53-7	174-2	_ 	0.73 (se 0.07)
21 – 50 mm (T2)	785/2221 (35-3%)	951/2240 (42-5%)	-80-1	331-0	-#	0·79 (se 0·05)
> 50 mm (T3/T4)	134/228	125/229	4-0	39-0		-
Other / unknown	(38-8%) 99/370 (26-8%)	109/372	-10-4	39-1	d	0·77 (se 0·14)
(i) Tumour differentiatio	n and ER	(χ ₃ ² = 0·6; μ	o = 0·9;	NS)	I	
Poorly, ER-poor	77/275	90/262	-6-9	34-7	, ,=	0·82 (SE 0·15)
Poorly, ER+	(20-0%) 100/461 (21-7%)	(34-4%) 120/477 (25-2%)	-12-2	45-8	e	0·77 (se 0·13)
Mod./Well ER-poor	62/167 (37-1%)	66/150 (44-0%)	-2-3	25-7	_	
Mod./Well ER+	228/985 (23-1%)	286/1026 (27-9%)	-27-8	112-8		0.78 (se 0.08)
Any unknown	949/2866 (33-1%)	1139/2818 (40-4%)	-95-2	373-2		0·77 (SE 0·05)
(j) Entry age and ER sta	<u>tus</u> ($\chi^2_7 = 8$	•0; p = 0·3	; NS)			
Age < 45, ER-poor	44/148	38/107	-2-9	15-8	,_	
< 45, ER+	(29-7%) 61/186	(35-5%) 61/175	-1.7	26-0		→
45 - 54, ER-poor	(32-8%) 105/316 (33.2%)	(34-9%) 112/281 (39.0%)	-8-0	44-2		0.83 (se 0.14)
45 - 54, ER+	(28-7%)	(33-2%)	-17.7	76-5	F	— 0·79 (se 0·10)
55 - 69, ER-poor	250/612 (40-8%)	302/626 (48-2%)	-29-0	119-8		0.78 (se 0.08)
55 - 69, ER+	542/2071 (26-2%)	677/2055 (32-9%)	-53-9	215-3		0·78 (se 0·06)
70+, ER-poor	4/18 (22-2%)	12/29 (41-4%)	-0-5	0-6	1	
70+, ER+	39/183 (21-3%)	70/178 (39-3%)	-11-2	10-8 <		0·35 (se 0·19)
Any unknown	182/561 (32-4%)	174/514 (33-9%)	-14-9	72-3	P	— υ·ชາ (se 0·11)
(K) Time since randomis	sation (tree	nd χ ₁ ² = 3·9	; 2p = (J·05)	I	
Years 0 - 1	184/4754 (3-9%)	249/4733 (5·3%)	-28-1	87-6		0.73 (se 0.09)
2 - 4	516/4305 (12-0%)	661/4216 (15-7%)	-69-3	219-5	- -	U·73 (SE 0·06)
5 - 9	499/3494 (14-3%)	560/3277 (17-1%)	-35-9	193-2		0·83 (se 0·07)
10+	217/2013 (10-8%)	231/1844 (12-5%)	-6.7	81-0	-+	0·92 (se 0·11)
Denominators: wor	nen entering	time period	400 0	E04 0	I	0.796 (0.007
Total	4754 (29·8%)	4733 (35·9%)	128.8	301-3	Ŷ	2p < 0.0001
🖶 99% or 🖘 95% c	onfidence int	ervals		_		<u>_</u>
Olat-15	eteroache'	w w ² = 22.0	n = 0.2		0.5 1	0 1-5
Giobal h	ieterogeneit	y· χ ₁₉ = 22·0;	, µ = 0·3		Treatment offe	ct 2p < 0.00001

 Forest plots (webappendix pp 33-38) give details of each trial's cytotoxic regimens Anthracyclines: A = doxorubicin (Adriamych), E = epirubicin. Other cytotoxics: C = cyclophosphamide, M = methotrexate, F = fluorouracil Dose/cycle (and cumulative doseg) is given after the drug name in mgm²: Auk/smeans 60 mg/m² of doxorubicin or 90 mg/m² of epirubicin † In the SWOC 8814 trial of CAF in postmenopeusal ER+ disease, tamoxifen started randomly with or after the chemotherapy. ‡ chem+end. = chemo-endecime therapy

P 13: RECURRENCE in trials of standard CMF (or near-standard CMF)* vs. No chemotherapy

Category (a) Standard CMF (o) Yes (shown below) No (excluded) (b) Cyclophosphami	Allocated CMF r near-standa 549/11282 (4.9%/y) 1320/1666	Allocated control rd CMF)? 748/10317 (7·3%/y)	$Logrank 0-E * (\chi_1^2 = 4-135.5$	Variance of O-E •5; 2p = 0.0	Ratio of annua CMF : 1 03)	Control	Category (a) Standard CMF (or r	Allocated CMF near-standa	Allocated control ard CMF)?	Logrank O-E * $(\chi_1^2 = 4)$	Variance of O-E I-8; 2p =	<u>Ratio of annu</u> CMF: 0∙03) 	Control
(a) Standard CMF (o Yes (shown below) No (excluded) (b) Cyclophosphami	r near-standa 549/11282 (4-9%/y) 1320/16661	rd CMF)? 748/10317 (7·3%/y)	* (χ ₁ ² = 4 -135·5	•5; 2p = 0·0)3)	0.61 (or 0.05)	(a) Standard CMF (or r	near-standa	1058/2274	$(\chi_1^2 = 4)^{-152}$	ŀ8; 2p =	0.03)	
Yes (shown below) No (excluded) (b) Cyclophosphami	549/11282 (4-9%/y) 1320/16661	748/10317 (7·3%/y)	-135-5	277.0		0.61 (or 0.05)	Vec (chown helow)	070/05/04	1058/22747	-152 1	101 0		
No (excluded) (b) Cyclophosphami	1320/16661					0.01 (SE 0.03)	res (shown below)	(3·4%/y)	(4·7%/y)	-155-1	421-6	-	0·70 (se 0·04)
(b) Cyclophosphami	[/·976/V]	1599/15588 (10-3%/y)	-185-0	553-4		0.72 (SE 0.04)	No (excluded)	1879/31866 (5·9%/y)	2053/28512 (7·2%/y)	-172-4	748-4	i 🖂 🛛	0.79 (SE 0.03)
	ido oral/iv (v ²	= 0.0: 2n =	0.Q. NS	`			(b) Cyclophosphamidd	oral/iv (v ²	= 0.1. 2n =	0.8. NS	*)		
C100×14 Oral/CVCIE	509/10922	709/10008	-134.1	261.7		0.60 (SE 0.05)	C100×14 oral/cycle	819/24897	1014/22215	-154.3	403-1		0.68 (SE 0.04)
	(4-7%/y)	(7·1%/y)	-2.0	6.2				(3·3%/y)	(4-6%/y)	4.0		-	
Optional (oral/iv)	(9-2%/y) 26/208	(16-1%/y) 19/185	1.5	9-1	1		Optional (oral/iv)	(8-8%/y) 34/372	(11.9%/y) 24/364	3.2	11.6		<u></u> ~>
(c) Concurrent endo	(12.5%/y) crine therapy	(10-3%/y) if ER+? (χ	² = 0·1;	2p = 0·8; N	S)		(c) Concurrent endocr	(9·1%/y) ine therapy	(6-6%/y) if ER+? (γ	² = 0·2;	2p = 0·7	'; NS)	
Yes	231/5873	338/5578	-61.7	121.5		0.60 (SE 0.07)	Yes	402/13665	523/12737	-78·3	204-3		0.68 (SE 0.06)
No (any endocrine o	(3.9%/y) nly 318/5409	(6.1%/y) 410/4739	-73-8	155-4	⊤ ∎—	0.62 (SE 0.06)	No (any endocrine onl	(2·9 %/y) y 470/11819	(4-1 %) 535/10010 (5,3%/v)	-74-8	217-3	_	0·71 (se 0·06)
(d) Entry age (trend	$\chi_{1}^{2} = 5.1; 2p = 0$	0.02)			т		(d) Entry age (trend χ^2_{i}	= 10·8; 2p =	= 0·001)			Ī	
Age < 45	121/3199	168/2578	-41-4	64·7 \prec 🗕	<u> </u>	0.53 (SE 0.09)	Age < 45	184/7325	234/5684	-52-8	95-2 _		0.57 (se 0.08)
45 - 54	(3-8%/y) 132/3552 (3-7%/y)	(6.5%/y) 221/3476 (6.4%/y)	-46-3	75-1	⊢	0.54 (SE 0.09)	45 - 54	(2·5%/y) 223/7992 (2·8%/y)	(4-1%/y) 324/7508 (4-3%/y)	-57-6	118-8	_∎+_	0.62 (se 0.07)
55 - 69	279/4208 (6-6%/y)	336/3838 (8-8%/y)	-47-0	129-9	╷┻──	0·70 (SE 0·07)	55 - 69	438/9491 (4-6%/y)	471/8588 (5·5%/y)	-44-9	196-9	∎	0.80 (se 0.06)
70+	17/318 (5-3%/y)	23/425 (5-4%/y)	-0-7	7.2	1		70+ A no university	26/664 (3-9%/y)	29/967 (3-0%/y)	2.2	10-6	-	→
	(0.0%/y) (0.0%/y)	- 0.02)					Age unknown	(8·3%/y)	0/0				
	102/7015	- 0.02)	70.0	400.4		0.52 (05.0.07)	NO/N-	343/17755	497/16249	-95.6	197.8	_	0.62 (SE 0.06)
N1-3	(2·4%/y) 149/2074	(4·4%/y) 206/1817	-37.5	76.1		0.61 (SE 0.09)	N1-3	(1.9%/y) 257/5164	(3·1%/y) 290/4354	-37.4	119-4		0.73 (SE 0.08)
N4+	(7·2%/y) 197/1201	(11·3%/y) 204/1002	-21.9	75-8		0·75 (SE 0·10)	N4+	(5·0%/y) 260/2360	(6-7%/y) 261/1950	-21.1	100-5		0.81 (SE 0.09)
Other / unknown	(16-4%/y) 10/92 (10-9%/y)	(20-4%/y) 8/82 (9-8%/y)	1.9	3.0	1		Other / unknown	(11-0%/y) 12/205 (5.9%/y)	(13-4%/y) 10/194 (5-2%/y)	1.0	3-8		
(f) ER status ($\chi_1^2 = 0$ ·	1; 2p = 0·7; NS	(; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;			1		(f) ER status ($\chi_1^2 = 0.0$;	2p = 0·8; N	S)			I	
ER-poor	168/2497 (6-7%/v)	236/2174 (10-9%/v)	-37-1	82-2	┍━── │	0.64 (SE 0.09)	ER-poor	216/5702 (3·8%/y)	265/4893 (5-4%/y)	-32-8	99-2		0.72 (se 0.09)
ER+	237/7352 (3·2%/y)	356/7071 (5·0%/y)	-67-4	134-7	╃── │	0.61 (SE 0.07)	ER+	439/16218 (2·7%/y)	576/15329 (3-8%/y)	-82-6	233-2		0.70 (se 0.06)
ER UNKNOWN	144/1433 (10-0%/y)	156/1072 (14-6%/y)	-31.0	60-1	 	U-60 (SE 0-10)	ER unknown	217/3564 (6·1%/y)	217/2525 (8-6%/y)	-37.7	89-1		U·66 (SE 0·09)
Subsets of ER+					.		Subsets of ER+					I	
ER+, chem+end.	172/6295 (2,7%/y)	253/6033 (4,2%/y)	-47-8	97-8	∳	0.61 (SE 0.08)	ER+, chem+end.	342/13888 (2·5%/v)	435/13147 (3·3%/v)	-59-6	180-8		0.72 (SE 0.06)
Ditto, age < 55	77/3637 (2·1%/y)	127/3410 (3.7%/y)	-31.3	47·6 <		0.52 (SE 0.11)	Ditto, age < 55	152/7994 (1-9%/y)	223/7251 (3.1%/v)	-47-2	88-6 _	- -	0.59 (se 0.08)
Ditto, 55 - 69	88/2429 (3-6%/y)	118/2340 (5-0%/y)	-16-4	46.7 —	+ •	0.70 (SE 0.12)	Ditto, 55 - 69	176/5436 (3·2%/y)	199/5277 (3-8%/y)	-14.1	85-8	╧╼	0.85 (SE 0.10)
ER+ PR-poor ER+ PR+	(4-0%/y) 149/5581	6.8%/y) 236/5350	-18-1	30-9 <		0.56 (SE 0.14) 0.59 (SE 0.08)	ER+ PR-poor ER+ PR+	93/3098 (3.0%/y) 301/12304	124/2602 (4-8%/y) 392/11714	-23.7	48-7 -		0.62 (SE 0.11) 0.72 (SE 0.07)
ER+ N0/N-	(2·7%/y) 106/5753	(4-4%/y) 208/5555	-55-4	74.4 🛹	+	0.47 (SE 0.08)	ER+ N0/N-	(2·4%/y) 222/12886	(3·3%/y) 353/12103	-76-0	137.7		0.58 (SE 0.07)
ER+ N1-3	(1-8%/y) 52/974 (5-3%/y)	(3-7%/y) 66/889 (7-4%/y)	-9-2	26.6		0·71 (se 0·16)	ER+ N1-3	(1.7%/y) 101/2177	(2.9%/y) 103/2017	-6-1	46-4		0·88 (se 0·14)
ER+ N4+	74/562 (13-2%/y)	80/576 (13-9%/y)	-3-5	32-3	· • •		ER+ N4+	(4-6%/y) 109/1020 (10-7%/y)	(3-17%/y) 116/1116 (10-4%/y)	-0-4	47-0		·
ER10-99 fmol/mg ER100+ fmol/mg	107/4036 (2-7%/y) 82/2161	194/3831 (5-1%/y) 103/2158	-45-3	64·3 < _	∔ ↓ ∎	0·49 (SE 0·09) 	ER10-99 fmol/mg	207/9391 (2·2%/y) 1/9///860	317/8563 (3-7%/y) 169/4848	-63-9	113-0 _	╶╼┼	0.57 (SE 0.07)
ER+, unknown	(3-8%/y) 48/1091	(4-8%/y) 59/1014	-8-0	23.9		0·71 (se 0·17)	ER+, unknown	(3·1%/y) 83/1915	(3·5%/y) 90/1867	-6-3	38-1		<u>0</u> ·85 (se 0·15)
(g) Tumour different) $(4.4\%/y)$ iation $(\chi_4^2 = 0.2$	(5·8%/y) 2; 2p = 0·6	; NS)		1		level (eg, by IHC) (g) Tumour differentia	(4.3%/y) tion $(\chi_4^2 = 0.$	(4·8%/y) 1; 2p = 0·8	; NS)			
Poorly-diff.	105/1906	152/1956	-23-2	56-2 —		0.66 (SE 0.11)	Poorly-diff.	155/3999	208/3927	-26-8	81-4	_	0.72 (SE 0.09)
Moderately/Well	(5-5%/y) 103/4651 (2-2%/y)	(7.8%/y) 163/4360 (3.7%/y)	-30.7	61.3	+	0.61 (SE 0.10)	Moderately/Well	207/10199 (2·0%/y)	283/9489 (3-0%/y)	-42-2	114-4	——	0.69 (SE 0.08)
Grade unknown	341/4723 (7-2%/y)	433/3995 (10∙8%/y)	-76-0	165-3 _	₽-	0.63 (SE 0.06)	Grade unknown	510/11294 (4-5%/y)	567/9331 (6·1%/y)	-76-9	233-6	-p-	0·72 (se 0·06)
(h) Tumour diameter	$\frac{1}{2}$ (trend $\chi_1^2 = 3$ ·	4; 2p = 0·0	6)		1		(h) Tumour diameter (trend $\chi_1^2 = 6$	·3; 2p = 0·0)1)		1	
1 – 20 mm (T1)	243/6462 (3-8%/y)	339/6093 (5·6%/y)	-58-0	131.9 _	╼──────	0.64 (SE 0.07)	1 – 20 mm (T1)	429/14564 (2·9%/y)	528/13350 (4-0%/y)	-68-4	219-6	_∎	0·73 (SE 0·06)
21 - 50 mm (T2)	228/3827 (6-0%/y)	313/3360 (9.3%/y)	-62-5	115-8		0.58 (SE 0.07)	21 – 50 mm (T2)	329/8840 (3-7%/y)	410/7589 (5-4%/y)	-70-3	161-1	- B -	0.65 (SE 0.06)
Other / unknown	(9.9%/y) 52/720	(23.6%/y) 55/682	-3.6	0.0 20.9 —	·	0.27 (SE 0.19)	> 50 mm (13/14) Other / unknown	37/601 (6-2%/y) 77/1477	44/375 (11.7%/y) 76/1423	-13-0	8-8 30-8	, 	0.23 (SE 0.18)
(i) Tumour differenti	(7.2%/y) ation and ER	(8.1%/y) $\chi^2 = 1.4; p$	o = 0·7;	NS)	I -		(i) Tumour differentiat	(5.2%/y) ion and ER	$(\gamma_{2}^{2} = 1.3;)$	o = 0·7;	NS)		
Poorly, ER-poor	35/470	48/413	-8-7	17·1 ≼	-	0.60 (se 0.19)	Poorly, ER-poor	45/949	54/787	-7.9	20∙8 ←		0.69 (se 0.18)
Poorly, ER+	(7-4%/y) 67/1370 (4-9%/y)	(11.6%/y) 101/1493 (6.8%/y)	-13.7	37-9	┦┲──┤	– 0·70 (se 0·14)	Poorly, ER+	(4-7%/y) 105/2925 (3-6%/y)	(6-9%/y) 150/3044 (4-9%/y)	-18-7	58-7		0·73 (se 0·11)
Mod./Well ER-poor	28/486 (5-8%/y)	35/412 (8·5%/y)	-3-8	13∙4 ←	+ • +	> 0.50 (0.44)	Mod./Well ER-poor Mod /Well ER+	37/926 (4-0%/y) 167/9151	40/804 (5-0%/y) 240/8551	-2·1	16-5 96-6		0:66 (SE 0:08)
Any unknown	(1-8%/y) 345/4839	127/3894 (3-3%/y) 437/4099	-27-1	47·4 ←	<u> </u>	0.56 (SE 0.11) 0.63 (SE 0.06)	Any unknown	(1·8%/y) 518/11541	(2-8%/y) 574/9561	-76.9	236-8		0.72 (SE 0.06)
(i) Entry ago and EP	(7.1%/y)	(10.7%/y)	NS)				(i) Entry age and ER si	(4·5%/y) tatus (γ ² = 1	(6-0%/y) 8-8: p = 0-	009)		۲ I	
Age < 45 FR-poor	39/868	48/656	-10.0	19.9 -	L	0.61 (SE 0.18)	Age < 45, ER-poor	50/2044	59/1541	-11.7	25·2 🗲		0.63 (SE 0.16)
< 45, ER+	(4-5%/y) 43/1876	(7·3%/y) 87/1644	-25-0	30.6 -	-	0.44 (SE 0.12)	< 45, ER+	(2·4%/y) 79/4180 (1-9%/y)	(3-8%/y) 133/3476 (3-8%/y)	-34-3	50·5 🖛	- →	0.51 (se 0.10)
45 – 54, ER-poor	(2·3%/y) 37/783 (4·7%/y)	(5·3%/y) 68/770 (8·8%/y)	-11.0	21·1 <	•	0.59 (SE 0.17)	45 - 54, ER-poor	51/1811 (2·8%/y)	79/1722 (4-6%/y)	-10-0	26·6 —	_ 1	0.69 (SE 0.16)
45 - 54, ER+	55/2362 (2·3%/y)	101/2384 (4·2%/y)	-24-2	35-1 ←		0.50 (SE 0.12)	45 - 54, ER- 55 - 69, ER-poor	(2.0%/y) 107/1738	(3-4%/y) 115/1471	-36-6	62-6 — 44-9		0.56 (SE 0.10)
55 - 69, ER-poor 55 - 69 ER+	85/793 (10·7%/y) 131/2856	108/676 (16-0%/y) 159/2734	-14-4	38-6	+•	0.69 (SE 0.13)	55 - 69, ER+	(6-2%/y) 241/6317	(7-8%/y) 257/6161	-13-4	113-3		0·89 (se 0·09)
70+, ER-poor	(4-6%/y) 7/48	(5-8%/y) 12/72	-1.7	2.5	-	010(02011)	70+, ER-poor	(3.8%/y) 7/97 (7.2%/y)	(4·2 ///y) 12/159 (7·5%/y)	-1.7	2.5	·	
70+, ER+	(14-6%/y) 8/258 (3-1%/y)	(16-7%/y) 9/309 (2-9%/y)	-0-1	4-0	1		70+, ER+ Any unknown	15/548 (2.7%/y) 218/3576	14/685 (2-0%/y) 217/2525	1.6 -37.7	6-9 89.1		0.66 (s= 0.09)
Any unknown	144/1438 (10-0%/y)	156/1072 (14-6%/y)	-31.0	60-1	q	0.60 (SE 0.10)	(k) Site of first recurre	(6.1%/y)	(8.6%/y) 4: n = 0.07	1	03.1		0 00 (32 0 03)
(k) Site of first recur	rence $(\chi_2^2 = 2 \cdot 0)$; p = 0·4;	NS)		1		Isolated local	207/25267	282/22576	-50.7	113-8		0.64 (se 0.08)
Isolated local	133/11128 (1·2%/y)	215/10190 (2.1%/y)	-49-2	80-8	μi	0·54 (se 0·08)	Contralateral	(0-8%/y) 111/24836	(1.2%/y) 101/22296	-3-0	49-9	-l 	
Distant/Multiple	40/10/30 (0-4%/y) 369/11282	47/9916 (0-5%/y) 480/10317	-6-0 -80-9	20.5 172.7		0·63 (se 0·06)	Distant/Multiple	(U·4%/y) 531/25484 (2·1%/y)	(U-5%/y) 662/22747 (2-9%/y)	-95-8	249-6	-#-	0.68 (SE 0.05)
Unknown	(3-3%/y) 7/11279	(4·7%/y) 6/10315	0.6	3.0	-	· · · · · /	Unknown	23/25481 (0·1%/v)	13/22756 (0-1%/v)	3.5	8-3	I	
(I) Time since rando	$misation (\gamma^2 =$	(0·1%/y) 14·8; 2p =	0.0001)	1		(I) Time since random	isation (trer	$d \chi_1^2 = 24 \cdot$	3; 2p < (D·00001)	I	1
Years 0 - 1	258/4995	431/4673	-102-3	143-7 <table-cell-columns> 💻</table-cell-columns>	<u> </u>	0·49 (se 0·06)	Years 0 - 1	258/4995 (5·2%/y)	431/4673 (9•2%/y)	-102-3	^{143.7} <	■-	0·49 (se 0·06)
2 – 4	(5-2%/y) 291/6241	(9·2%/y) 317/5594	-33-2	133-2		0·78 (se 0·08)	2 - 4	291/6241 (4·7%/y)	317/5594 (5·7%/y)	-33-2	133-2	∎	U·78 (SE 0·08)
	(4·/%/y) 549/	(5·/%/y) 748/	-12F F	277.0		0.613 (or 0.049)	3 - 9 10+	2077996 (2∙6%/y) 116/6109	210/7119 (2-9%/y) 100/5216	-10-9	ชอ.ช 48-7		(SE 0.03)
Total	0-01		133.2	LII'U '	~	0.010 (SE 0.040)		(1.9%/y)	(1-9%/y)				1
Total	11282 (4·9%/y)	10317 (7·3%/y)			I	2p < 0.00001	Total	872/	1058/	-162.4	121.0	1	0.696 (0= 0.044
Total ⊕ 99% or <>> 95	11282 (4·9%/y) 5% confidence int	10317 (7·3%/y) ervals				2p < 0.00001	Total	872/ 25484 (3·4%/y)	1058/ 22747 (4·7%/y)	-153·1	421.6	+	0.696 (SE 0.041 2p < 0.00001

 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.
 them+end. = chemo-endocrine therapy

 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.
 t chem+end. = chemo-endocrine therapy

Treatment effect 2p < 0.00001

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

Category	Deaths/ Allocated	Women Allocated	CMF Logrank	deaths Variance	Ratio of annual	death rates
(a) Standard CMF (or ne	ar-standa	rd CMF)?	$*(\chi_1^2 = -$	4·4; 2p =	0.04)	
Yes (shown below)	658/2665	790/2588	-89·1	320.1		0·76 (se 0·05)
No (excluded)	(24·7%) 1512/4378	(30.5%) 1643/4372	-81.4	611.1	─ ──	0.88 (SE 0.04)
no (oxoludou)	(34-5%)	(37.6%)	0.1	0		000 (02 0 0 1)
(b) Cyclophosphamide	oral/iv (χ_1^2 =	= 0·1; 2p =	0·7; N	S)	1	
C100×14 oral/cycle	617/2562 (24.1%)	756/2497	-89-9	305-1		0·74 (se 0·05)
C600×2 iv/cycle	15/40	18/39	-2-6	6-1		
Optional (oral/iv)	(37-5%) 26/63 (41-3%)	(46-2%) 16/52 (30-8%)	3-3	8-9	I	
(c) Concurrent endocrin	e therapy	if ER+? (χ	² = 0·3;	2p = 0·6	;NS)	
Yes	301/1342	391/1338	-47-2	151-2	_ #	0.73 (SE 0.07)
No (any endocrine only after chemo ended)	357/1323 (27·0%)	399/1250 (31.9%)	-41.9	168-9		0.78 (SE 0.07)
(d) Entry age (trend χ_1^2 =	10∙0; 2p =	0.002)			1	
Age < 45	115/739	150/635	-33-0	62·2 —		0·59 (se 0·10)
45 - 54	(15-6%) 165/803	(23.6%) 230/853	-35-5	86-1	_ _	0.66 (se 0.09)
55 - 69	(20-376) 356/1043 (34-1%)	385/994 (38-7%)	-21.8	163-0	┴┲┼	0.87 (SE 0.07)
70+	22/77 (28-6%)	25/105 (23-8%)	1.2	8-8	I	
Age unknown	0/3 (0·0%)	0/1 (0.0%)			I	
(e) Nodal status (trend χ	2 = 6·5; 2p	= 0.01)			1	
N0/N-	197/1754 (11·2%)	294/1711 (17·2%)	-54.0	117-2		0.63 (SE 0.07)
N1-3	218/513 (42·5%)	257/499 (51-5%)	-27.8	105-7		0.90 (cr 0.40)
Other / unknown	∠31/365 (63-3%) 12/33	∠30/351 (65-5%) 9/27	-10-4	3.6		— u∙ s u (se u•1u)
(f) FR status (x ² = 0.2: 2)	(36-4%)	(33-3%)	3.1	0.0		
FR-noor	167/620	209/617	-17.F	79.2		0.80 /s= 0.10)
ER+	(26·6%) 295/1646	(33-9%) 387/1635	-47.2	155.7		0·74 (se 0·07)
ER unknown	(17·9%) 196/390	(23·7%) 194/336	-24-3	85-2		0.75 (SE 0.09)
	(50-3%)	(57.7%)			+	
Subsets of ER+						
ER+, chem+end. vs end. only ‡	225/1379 (16·3%)	285/1358 (21.0%)	-34-3	117-6	_	0·75 (se 0·08)
Ditto, age < 55	85/778 (10-9%)	129/754 (17·1%)	-28-2	50·3 «		0.57 (se 0.11)
Ditto, 55 - 69	129/550 (23-5%)	146/540 (27.0%)	-6-3	62-6 29.7		0.90 (SE 0.12)
ER+ PR+	(24-5%) 180/1224	(31.6%) 246/1205	-33-3	100.2		0.72 (se 0.08)
ER+ N0/N-	(14·7%) 119/1239	(20-4%) 201/1234	-42.5	77.3 _		0.58 (SE 0.09)
ER+ N1-3	(9·6%) 77/228	(16-3%) 84/218	-5-6	35-6	_	
ER+ N4+	(33-8%) 92/162 (56-8%)	(38-5%) 99/169 (58-6%)	0-1	40.7		>
ER10-99 fmol/mg	130/884 (14·7%)	207/888 (23-3%)	-39-9	73-8 _		0.58 (SE 0.09)
ER100+ fmol/mg	100/493 (20-3%)	120/494 (24-3%)	-6-2	48-2		0·88 (SE 0·14)
level (eg, by IHC)	(24-2%)	(23.7%)		27.5		>
(g) Lumour differentiatio	on (trend χ	- = 0·0; 2p	= 0-9;	NS)	1	0.70 (0.44)
Poorly-diff. Moderately-diff	115/444 (25-9%) 101/755	160/488 (32-8%) 145/750	-17-3	64-1 58-6		0.76 (SE 0.11)
Well-diff.	(13·4%) 17/254	(19-3%) 20/221	-1.1	8.7		0 00 (32 0 11)
Grade unknown	(6·7%) 425/1212	(9.0%) 465/1129	-41.6	202-5		0·81 (se 0·06)
(h) Tumour diameter (tre	(35.1%) and $\gamma^2 = 5.1$	(41·2%) 2: 2p = 0·0	2)			
1 – 20 mm (T1)	307/1457	369/1443	-35.5	155.7		0.80 (se 0.07)
21 - 50 mm (T2)	(21·1%) 264/937	(25.6%) 329/893	-43-0	134-8		0.73 (SE 0.07)
> 50 mm (T3/T4)	(28-2%) 28/72	(36-8%) 36/68	-12.7	8.7	-	0·23 (se 0·18)
Other / unknown	(38-9%) 59/199	(52.9%) 56/184	-0.4	24-3		> <i>, , , , , , , , , , , , , , , , , , ,</i>
(i) Tumour differentiatio	(29.6%) n and ER ($\chi_{3}^{2} = 0.8; p$	= 0-8;	NS)		
Poorly, ER-poor	36/118	44/115	-5-4	17·4 «		
Poorly, ER+	(30-5%) 75/311 (24-1%)	(38-3%) 114/361 (31-6%)	-14.5	43-8	e L	0·72 (se 0·13)
Mod./Well ER-poor	28/118 (23·7%)	29/108 (26·9%)	-2-2	12.8 —		
Mod./Well ER+	89/879 (10-1%)	136/850 (16-0%)	-23.2	53-4 -		U-65 (SE 0-11)
Any unknown	(34.7%)	(40.5%)	-30-0	202-2		0 03 (32 0 00)
(j) Entry age and ER sta	$tus_{7} (\chi_{7}^{2} = 1)$	3·7; p = 0·0	06)			
Age < 45, ER-poor	30/210 (14-3%)	38/174 (21-8%)	-7-8	16·3 ←		0.62 (SE 0.20)
< 45, ER+ 45 - 54 ER-poor	42/409 (10-3%) 38/186	(19-5%) 58/206	-18-8	28.1 ←	•	0.51 (SE 0.14)
45 - 54, ER+	(20-4%) 65/513	(28-2%) 110/539	-21.9	39.0 ←	1	0.57 (SE 0.12)
55 - 69, ER-poor	(12·7%) 93/217	(20-4%) 102/213	-2-9	41.0		
55 - 69, ER+	(42-9%) 176/664 (26-5%)	(47-9%) 192/646 (29-7%)	-6-6	83-5	╶┼╴┻┼	0·92 (se 0·11)
70+, ER-poor	6/14 (42-9%)	11/23 (47-8%)	-1-0	2-3	1	
70+, ER+	12/59 (20-3%)	11/71 (15-5%)	0.2	5-1	- -	0.75 (05 0 00)
	(49-9%)	(57.6%)	-24·3	05-2		0-79 (SE 0-09)
(κ) Time since randomis	auon (tren	iu χ ₁ = 0·2;	, ∠p = 0	(0°)		0.72 /05 0.42
2-4	o2/2065 (3-1%) 224/2501	(4-3%) 270/2423	-29.5	41·7 109-6		0.72 (SE 0.13) 0.76 (SE 0.08)
5 - 9	(9·0%) 220/2146	(11·1%) 271/2047	-33.7	109-6		0·74 (se 0·08)
10+	(10-3%) 132/1513	(13-2%) 139/1442	-11.9	59-1		0.82 (se 0.12)
Denominators: won	(ö·/%) nen entering	(9.6%) time period	_			
rotal	2665 (24.7%)	2588 (30-5%)	-89-1	320.1	\uparrow	U·/57 (SE 0·049) 2p < 0·00001
🖶 99% or 🖘 95% c	onfidence inte	ervals		_		<u>.</u>
Global h	eterogeneity	r; γ ² = 41·5:	p = 0.00)2	CMF better	1·5 CMF worse

* 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. ‡ chern+end. = cherno-endocrine therapy

Treatment effect 2p < 0.00001

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



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.



-25.7 / 86.4

6.5 / 58.5

Entry age<55 or 55-69 years

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

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.



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.



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.



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



© 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.

P 22: RECURRENCE in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy



† 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.

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

۲ and	/ear code study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the controls	Cumulative doses of taxane & anthracycline	Anthra- cycline difference	Deaths Allocated taxane	Women Allocated non-tax.	<u>Taxane</u> Lograni O-E	e deaths* Variance of O-E	Ratio of annual death rates Taxane : Non-tax.
(a)	Taxane (D or P)-pl	us-anthracycline (A or E)-based regimen 1	ł						
<u> </u>	vs the SAME non-	taxane cytotoxic chemotherapy (ie, uncor	founded trials of	adding a	taxane)				
988 997 95J1 95J2 9552	 Taxit216 Italy GOIM 9902 Italy NSABP B-27* NSABP B-27* NSABP B-28 	4E; 4D100; 4CMFq4 VS 4E120; 4(C600×2M40×2F600×2) 4D100; 4EC VS 4E120C600 4AC‡; 4D100± VS 4(Ac0C600)‡ 4AC‡; 4D100 VS same control patients 4AC‡; 4D100 VS same control patients	†D100×4 E480 vS E480 †D100×4 E480 vS E480 †D100×4 A240 vS A240 †D100×4 A240 vS A240 †D100×4 A240 vS A240	0 0 0 0	50/486 26/376 170/805 177/802 333/1531	79/486 30/374 186/804 186/804 353/1529	-14·4 -3·9 -9·8 -5·2 -13·0	30.8 12.8 84.9 86.2 159.5	
94D1 94D2 94D3	CALGB 9344 2 CALGB 9344 3 CALGB 9344	4AC; 4P175 vS 4A90C600 4AC; 4P175 vS 4A75C600 4AC; 4P175 vS 4A60C600	†P175×4 A360 VS A360 †P175×4 A300 VS A300 †P175×4 A240 VS A240	0 0 0	133/531 136/525 144/534	166/526 156/528 150/526	-20·3 -11·7 -5·9	69·6 67·4 68·5	
	(a) subtotal				1169/ 5590 (20∙9%)	1306/ 5577 (23·4%)	-79.8	520·8	○ 0.86 (SE 0.04 reduction 2p = 0.0005
<u>(b)</u>	Taxane-plus-anthi vs MORE (but < d	racycline-based regimen (taxane courses g oubled) non-taxane cytotoxic chemothera	given alone) † PY						
00S 95T 00E 98D1	WSG/AGO AM-02 HORG Greece FinHer/FBCG 00-01 BIG 02-98*	4E90Ce00; 4D100 vS 6(F500E100Cs00) 4D100; 4EC vS 6(F700E7sC700) 3D(e0100); 3FEC vS 3Vrb2s-s; 3(Fe00Ee0Ce00) 3A75; 3D100; 3CMFq4 vS 4A75; 3(C100+14M40+2F600+2)q4 or 4Ae0Ce00; 3CMFq4	†D100×4 E360 vS E600 †D100×4 E300 vS E450¶ †D80×3 E180 vS E180¶ †D100×3 A225 vS A270 (240/300	E240 E150 0≠ A70	11/811 65/391 18/502 112/959	22/795 62/397 29/507 131/968	-5·7 1·9 -6·4 -6·9	8·1 28·9 10·1 57·8	
99K 97R 00F 00U 03R	GEICAM 9906 Spain HE1097 Greece NCIC MA.21* AERO B-2000 France GIM 1 Italy	4FEC; 8(P100)q1 v5 6(F600E50C600) 3Eq2; 3P250q2; 3CMFq2 v5 4(E110)q2; 4(C840M50F840)q2 6(E120C630)q2; 4P175 v5 6(C75x14E60x2F500x2)q4 4FEC; 4P175 v5 6(F600E100C500) 4E90C; 4D100 v5 6(F600E75C600)	†P100×8 E360 vS E540 †P250×3 E330 vS E440 † <i>P</i> 175×4 <i>E720 vS E720</i> †P175×4 E400 vS E600 †D100×4 E360 vS E450¶	E180 E110 <i>0≠</i> E200 E90	32/614 54/304 47/701 (837 p (1636 p	52/634 61/300 50/701 atients) patients)	-7·5 -5·2 -1·5 (no (no	19·1 25·8 22·6 data) data)	
	(b) subtotal with (data on numbers dead			339/ 4282 (7·9%)	407/ 4302 (9∙5%)	- 31·3	172-3	0.83 (SE 0.07 reduction 2p = 0.02
<u>(c)</u>	Taxane-plus-anthr vs MORE (but < d	racycline-based regimen (taxane given cor oubled) non-taxane cytotoxic chemothera	ncurrently) © P <u>y</u>						
01E1+3 97L 99% 98D2	 PACS 04 France BCIRG 001 GEICAM 9805 Spain BIG 02-98* 	6E75D75 VS 6(F500E100C500) 6D75AC VS 6(F500A50C500) 6D75AC VS 6(F500A50C500) 4(A50D75); 3CMFq4 VS 4A75; 3(C100+14M40×2F600+2)q4 or 4A6xC600:3CMFq4	©D75×6 E450 VS E600 ©D75×6 A300 VS A300¶ ©D75×6 A300 VS A300¶ ©D75×4 A200 VS A270 (240/300	E150 0≠ 0≠ A45	80/1495 79/745 18/539 137/960	79/1515 122/746 19/521 131/968	1.7 −21.7 −1.6 7.4	38·1 46·7 8·7 62·8	
99N 98T 96W1 96W2 96% 96%	RAPP-01 France ECOG EST2197 ECTO Italy* ECTO Italy* Multicentre Germany GONO Italy MIG 5	4A50D75 vs 4A60C600 4AD60 vs 4A6cC600 (4A60P200; 4CMFq4) vs 4A75; 4(C600+2M40+2F600+2)q4 (4A60P200; 4CMFq4) ‡ vs same control patients 4(EP175)q2; 3CMFq2 vs 4(EsoC600); 3(C600M40F600) 4E90P175 vs 6(F600EsoC600)	©D75×4 A200 vS A240 ©D60×4 A240 vS A240 ©P200×4 A240 vS A300¶ ©P200×4 A240 vS A300¶ ©P200×4 A240 vS A300¶ ©P175×4 E360 vS E360 ©P175×4 E360 vS E360¶	A40 0≠ A60 A60 <i>0</i> ≠ 0≠	8/311 130/1476 26/451 29/451 33/108 47/535	15/316 137/1476 42/453 42/453 38/108 40/520	-3.7 -4.3 -8.0 -6.3 -2.5 1.9	5.6 64.4 16.4 16.7 <i>12.0</i> 19.8	
	(c) subtotal				587/ 7071 (8·3%)	665/ 7076 (9·4%)	-32 ∙1	278-9	0.89 (SE 0.06 reduction 2p = 0.05
<u>(d)</u>	Taxane-plus-anthi vs DOUBLED (or	racycline-based regimen <u>†</u> ∞ doubled) non-taxane cytotoxic chemothe	erapy						
01F 01G 01T 96F 97J 97A 94E 00F2 02D	TACT UK TACT UK TACT UK LMU Munich ADEBAR Aberdeen Scotland PACS 01 France DEVA UK MD Anderson MCIC MA.21* GGG 42 / NNBC 3-Eu	4(F600E60C600); 4D100 vS 8(F600E60C600) 4(F600E60C600); 4D100 vS 4E100; 4(C600×2M40×2F600×2)q4 4 4E90C600; 4D100 vS 6(C7s+14E60×2F500×2)q4 4 4/VAC; 4D700 vS 4/VAC; 4(V: A5x0C1000) 3 FEC; 3D100 vS 6(F500E100C500) 3 Eq4; 3D100 vS 6(E50×2)q4 4 4P2s0t; 4FAC vS 4FAC‡; 4(F500×2A50C500) 4 A60C600; 4P175 vS 6(C7s+14E60×2F500x2)q4 r. 3FEC; 3D100 vS 6(F500E100C500)	†D100×4 E240 vs E480 †D100×4 E240 vs E400 †D100×4 E360 vs E720 †D100×4 E200 vs A4001 †D100×3 E300 vs E600 †D100×3 E300 vs E600 †D100×3 E300 vs A4001 †P175×4 A240 vs A700 †P175×4 A240 vs E720 †D100×3 E300 vs E600	E240 E160 E360 A200 E300 E300 A200 E720-A240 E300	165/1258 108/815 40/684 4/52 96/1003 38/406 30/265 65/702 (4149 p	164/1265 122/824 24/675 12/52 131/995 50/397 37/259 50/701 patients)	4·2 -6·0 6·9 -4·0 -14·4 -8·6 -1·3 7·5 (no	74-5 52-4 15-0 3-4 53-4 19-4 14-8 26-4 a data)	
	(d) subtotal with	data on numbers dead			546/ 5185 (10∙5%)	590/ 5168 (11∙4%)	-15∙8	259∙3	0.94 (SE 0.06 reduction 2p > 0.1; NS
	Total (a − d) w	vith data on numbers dead (some with time	e to event unknov	vn)	2641/ 22128 (11∙9%)	2968/ 22123 (13·4%)	-161.0	1176-5	
(e)	No anthracycline i	n one allocation	ity between 4 sub	totals: χ_3^2	= 2·0; p >	0·1; NS			
00S 97N	6 WSG/AGO AM-02 I USO 97-35	4E90C600; 4D100 vs 6(C600×2M40×2F600×2)q4 4D75C vs 4A60C600	D100×4 E360 vs None D75×4 None vs A240	- E 360 A 240	4/167 47/506	12/177 53/510	-3·3 -1·9	3·6 23·5	
-	- 99% or <> 95% - 99% confidence i	 confidence intervals ntervals, time to event unknown 						 0	0.5 1.0 1.5 2.0
* † ‡	For 3-way trials, "E For 95J NSABP B- 98D BIG 02-98 (O· Taxane courses do Pre-operative cher	tither active vs same control patients" (not plc 27, this (O-E) is -10.5 with variance V = 112 -E) = 0.4, V = 81.5; 00F MA.21 (O-E) = 4.0; ' not overlap with any other chemotherapy con notherapy: all patients in these trials were an	otted) is what contri ·2; 96W ECTO Ital V = 33·2 urses; hence, total alysed as unknown	butes to th y (O-E) = chemothe nodal sta	ne total. −9·3, V = rapy durat tus	20·8; ion is inc	reased		Taxane better Non-tax. better

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

≠ Same cumulative anthracycline dose, but differences in other drugs

 \P Control anthracycline dose less than E_{90} or A_{60} 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.

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

	Regimens compared and drug doses	Cumulative doses	Anthra-	Deaths/wor	man-years	Taxane	deaths*		
Year code and study name	(mg/m²) per cycle. Any unstated doses are as in the controls	of taxane & anthracycline	cycline difference	Allocated taxane	Allocated L non-tax.	.ogrank Ö−E	Variance of O-E	Ratio of annual Taxane : N	death rates Ion-tax.
a) Taxane (D or P)-pl	us-anthracycline (A or E)-based regimen	t							
vs the SAME non-	taxane cytotoxic chemotherapy (ie, uncor	founded trials of	adding a	taxane)					
98B Taxit216 Italy	4E: 4D100: 4CMF04 VS 4E120: 4(C600×2M40×2F600×2)	†D100×4 E480 VS E480	0	1/458	1/458	0.0	0.5 -		>
99T GOIM 9902 Italy	4D100; 4EC vs 4E120C600	†D100×4 E480 VS E480	0	0/350	0/339				
5J1 NSABP B-27*	4AC‡; 4D100‡ vs 4(A60C600)‡	+D100×4 A240 VS A240	0	5/789	1/783	2.0	1.5		>
5J2 NSABP B-27*	4AC‡; 4D100 vs same control patients	†D 100×4 A 240 VS A 240	0	5/779	1/783	2.0	1.5		>
95K NSABP B-28	4AC; 4P225 vs 4A60C600	†P 225×4 A 240 VS A 240	0	5/1500	4/1499	0.4	2.2		·>
4D1 CALGB 9344	4AC; 4P175 vs 4A90C600	+P175×4 A360 VS A360	0	2/513	4/508	-0.9	1.5 -		>
1D2 CALGB 9344	4AC; 4P175 VS 4A75C600	+P175×4 A300 VS A300	0	1/510	1/504	0.0	0.5 -		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
103 ONEOD 0044		11 175-4 A240 V3 A240	0	1010	1/000	00	00 -		
(a) subtotal				20/	13/	2.2	7.6		
(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				5417	5380				1·34 (SE 0·42
				(0·4%/y)	(0·2%/y)				increase
									2p > 0.1; NS
) Taxane-plus-anthr	acycline-based regimen (taxane courses	given alone) †							
vs MORE (but < d	oubled) non-taxane cytotoxic chemothera	ру							
00S WSG/AGO AM-02	4E90C600; 4D100 vs 6(F500E100C500)	†D 100×4 E360 vs E600	E 240	2/769	2/752	0.1	1.0		
95T HORG Greece	4D100: 4EC vs 6(F700E75C700)	†D100×4 E300 VS E450¶	E150	0/356	3/356	-1.2	0.7		
0E FinHer/FBCG 00-01	3D(80/100); 3FEC vs 3Vrb25×3; 3(F600E60C600)	†D80×3 E180 VS E180¶	0≠	2/449	0/452	1.0	0.5		>
D1 BIG 02-98*	3A75; 3D100; 3CMFq4 vs 4A75; 3(C100×14M40×2F600×2)q4	†D100×3 A225 VS A270	A 70	1/928	1/936	0.1	0.5 —		·>
	or 4A60C600; 3CMFq4	(240/300)	1						
9K GEICAM 9906 Spain	4FEC; 8(P100)q1 vs 6(F600E90C600)	†P100×8 E360 VS E540	E180	4/579	1/602	1.6	1.2		>
I7R HE1097 Greece	3Eq2; 3P250q2; 3CMFq2 vs 4(E110)q2; 4(C840M50F840)q2	†P 250×3 E 330 vs E 440	E 110	1/276	0/275	0.2	0.2 –		>
(b) subtotal				10/	7/	2.0	4.1		
(b) Subtotal				3357	3373	2.0	4.1		1.64 (SE 0.64
				(0·3%/y)	(0·2%/y)				increase
									2p > 0·1; NS
) Taxane-plusanth	racycline-based regimen (taxane given co	oncurrently) ©							
vs MORE (but < d	oubled) non-taxane cytotoxic chemothera	py							
1+3 PACS 04 France	6E75D75 vs 6(F500E100C500)	©D75×6 E450 VS E600	E 150	5/1451	2/1479	1.6	1.8		>
97L BCIRG 001	6D75AC vs 6(F500A50C500)	©D75×6 A300 vs A300¶	0≠	4/720	5/716	-0.2	2.2		>
9% GEICAM 9805 Spain	6D75AC VS 6(F500A50C500)	©D75×6 A300 VS A300¶	0≠	0/516	0/503	0.5	0.0		
D2 BIG 02-98"	4(A50D75); 3CMFq4 VS 4A75; 3(C100×14M40×2F600×2)q4 or 4A60C600; 3CMFq4	© U75×4 A200 VS A270 (240/300)	A45	2/931	1/936	0.2	0.8		>
9N RAPP-01 France	4A50D75 vs 4A60C600	©D75×4 A200 VS A240	A 40	2/298	0/302	1.0	0.5		
8T ECOG EST2197	4AD60 vs 4A60C600	©D60×4 A240 VS A240	0≠	6/1440	2/1445	2.0	2.0		
W1 ECTO Italy*	(4A60P200; 4CMFq4) vs 4A75; 4(C600×2M40×2F600×2)q4	©P200×4 A240 vs A300¶	A 60	2/434	1/430	0.2	0.7		
W2 ECTO Italy*	(4A60P200; 4CMFq4)‡ vs same control patients	©P200×4 A240 VS A300¶	A 60	1/437	1/430	-0.1	0.5 —	·	>
6X GONO Italy MIG 5	4E90P175 VS 6(F600E60C600)	©P175×4 E360 vs E360¶	0≠	0/507	3/488	-1.5	0∙8 ⊷		>
(c) subtotal				22/	15/	3.6	8.8		
(0) Subtotui				6734	6729		00		1.50 (SE 0.42
				(0·3%/y)	(0·2%/y)				increase
									2p > 0·1; NS
I) Taxane-plus-anthr	acycline-based regimen †								
ve DOUBLED (or a									
V3 DOUDLED (01	e doubled) non-taxane cytotoxic chemothe	erapy							
	doubled) non-taxane cytotoxic chemothe ((FreeFeeCeer)) (Due un 9/FreeFeeCeer)	erapy	Fair	5/1000	4/4007	2.2	15		
1F TACT UK	<u>doubled) non-taxane cytotoxic chemoth</u> (FeorEeoCeor); 4D100 vs 8(FeorEeoCeor) (FeorEeoCeor); 4D100 vs 4(FeorEeoCeor)	+D100×4 E240 VS E480¶	E240	5/1220 4/783	1/1227	2·2 1·5	1·5 1·2		
11F TACT UK 1G TACT UK 11T LMU Munich ADEBAR	<u>~ doubled) non-taxane cytotoxic chemoth</u> 4(Feo0Ee0Ceo0); 4D100 vs 8(Feo0Ee0Ceo0) 4(Feo0Ee0Ceo0); 4D100 vs 4E100; 4(Ceo0~2M40×2Feo0~2)q4 4Ee0Ceo0; 4D100 vs 6(C275+14Ee0x0Fe00~2)q4	+ + + D100×4 E240 vs E480¶ + D100×4 E240 vs E480 + D100×4 E270 + D100×4 E270 + D100×4 + + + + + + + + + + + + + + + + + + +	E240 E160 E360	5/1220 4/783 4/605	1/1227 1/786 5/582	2·2 1·5 -0·1	1·5 1·2 2·2		
11F TACT UK 1G TACT UK 11T LMU Munich ADEBAR 97J PACS 01 France	≃ doubled) non-taxane cytotoxic chemothe 4(F600E60C600); 4D100 vs 8(F600E60C600) 4(F600E60C600); 4D100 vs 4E100; 4(C600-2M40+2F600+2)q4 4E90C600; 4D100 vs 6(C75+14E60+2F500+2)q4 3FEC; 3D100 vs 6(F500E100C500)	+D100×4 E240 VS E480¶ †D100×4 E240 VS E480¶ †D100×4 E240 VS E400 †D100×4 E360 VS E720 †D100×3 E300 VS E600	E240 E160 E360 E300	5/1220 4/783 4/605 0/984	1/1227 1/786 5/582 0/975	2·2 1·5 −0·1	1.5 1.2 2.2		>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
11F TACT UK 1G TACT UK 11T LMU Munich ADEBAR 17T PACS 01 France 17A DEVA UK	≃ doubled) non-taxane cytotoxic chemoth: 4(FeeeEeeCeee); 4D100 vs 8(FeeeEeeCeee) 4(FeeeEeeCeee); 4D100 vs 6(FeeeEeeCeee); 4d40×2Fee0×2)q4 4EeeCeee; 4D100 vs 6(FeeeE100Ceee) 3FEC; 3D100 vs 6(FeeeE100Ceee) 3Eq4; 3D100 vs 6(Eeox2)q4	+D100×4 E240 VS E480¶ †D100×4 E240 VS E400 †D100×4 E360 VS E720 †D100×3 E300 VS E600 †D100×3 E300 VS E600	E240 E160 E360 E300 E300	5/1220 4/783 4/605 0/984 1/379	1/1227 1/786 5/582 0/975 4/368	2·2 1·5 −0·1 −1·4	1·5 1·2 2·2 1·2 —		>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
1F TACT UK 1G TACT UK 1T LMU Munich ADEBAR 17J PACS 01 France 7A DEVA UK 4B MD Anderson	≃ doubled) non-taxane cytotoxic chemoth: 4(FscoEscCscoc); 4D100 vs 8(FscoEscCscoc) 4(FscoEscCscoc); 4D100 vs 8(E100; 4(Cscoc>2M40×2Fscor>2)q4 4EsoCscoc; 4D100 vs 6(Cr5or=14560×2Fscor>2)q4 3FEC; 3D100 vs 6(FscoE1coCscoc) 3Eq4; 3D100 vs 6(Escor=2)q4 4P2sot‡; 4FAC vs 4FAC‡; 4(Fscor=2AsoCscoc)	†D100×4 E240 VS E480¶ †D100×4 E240 VS E400 †D100×4 E360 VS E720 †D100×3 E300 VS E600 †D100×3 E300 VS E600 †D100×3 E300 VS E600 †D250×4 A200 VS A4001	E240 E160 E360 E300 E300 E300	5/1220 4/783 4/605 0/984 1/379 0/242	1/1227 1/786 5/582 0/975 4/368 0/230	2·2 1·5 −0·1 −1·4	1.5 1.2 2.2 1.2 —		> > >
11F TACT UK 1G TACT UK 11T LMU Munich ADEBAR 17J PACS 01 France 17A DEVA UK 4B MD Anderson	≈ doubled) non-taxane cytotoxic chemoth: 4(F600E60C600); 4D100 vS 8(F600E60C600) 4(F600E60C600); 4D100 vS 4E100; 4(C600×2M40×2F600×2)q4 4E90C600; 4D100 vS 6(C75×14E60×2F500×2)q4 3FEC; 3D100 vS 6(F500E100C500) 3Eq4; 3D100 vS 6(E50×2)q4 4P250‡; 4FAC vS 4FAC‡; 4(F500×2A50C500)	TD100+4 E240 VS E4801 †D100+4 E240 VS E4001 †D100+4 E360 VS E7201 †D100+3 E300 VS E6001 †D100+3 E300 VS E60011 †D100+3 E300 VS E600111 †D250+4 A200 VS A4001111	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/984 1/379 0/242	1/1227 1/786 5/582 0/975 4/368 0/230	2·2 1·5 −0·1 −1·4	1-5 1-2 2-2 1-2 —		→ → →
UIF TACT UK 1G TACT UK 1T LMU Munich ADEBAR 97J PACS 01 France 97J PACS 01 France 97A DEVA UK 14B MD Anderson (d) subtotal	≃ doubled) non-taxane cytotoxic chemothi 4(F600E60C600); 4D100 vS 8(F600E60C600) 4(F600E60C600); 4D100 vS 4E100; 4(C600×2M40×2F600×2)q4 4E50C600; 4D100 vS 6(C75×14E60×2F500×2)q4 3FEC; 3D100 vS 6(F500E100C500) 3Eq4; 3D100 vS 6(E50×2)q4 4P250‡; 4FAC vS 4FAC‡; 4(F500×2A50C500)	tp100×4 E240 vs E4801 tp100×4 E240 vs E400 tp100×4 E360 vs E720 tp100×3 E300 vs E600 tp100×3 E300 vs E600 tp100×3 E300 vs E600 tp250×4 A200 vs A4001	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/884 1/379 0/242 14/ 4213	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168	2·2 1·5 −0·1 −1·4 2·2	1.5 1.2 2.2 1.2 — 6.1		
DIF TACT UK IIG TACT UK JIT LMU Munich ADEBAR 97J PACS 01 France 97A DEVA UK 94B MD Anderson (d) subtotal	≈ doubled) non-taxane cytotoxic chemothi 4(F600E60C600); 4D100 vS 8(F600E60C600) 4(F600E60C600); 4D100 vS 4E100; 4(C600×2M40×2F600×2)q4 4E50C600; 4D100 vS 6(C75×14E60×2F500×2)q4 3FEC; 3D100 vS 6(F500E100C500) 3Eq4; 3D100 vS 6(E50×2)q4 4P250‡; 4FAC vS 4FAC‡; 4(F500×2A50C500)	Prapy †D100×4 E240 vs E4801 †D100×4 E240 vs E400 †D100×4 E360 vs E720 †D100×3 E300 vs E600 †D100×3 E300 vs E600 †D100×3 E300 vs E600 †D250×4 A200 vs A4001	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0·3%/y)	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0-3%/y)	2·2 1·5 −0·1 −1·4 2·2	1.5 1.2 2.2 1.2 — 6.1		> > 1.44 (se 0.49
DIF TACT UK IG TACT UK IG TACT UK IT LMU Munich ADEBAR 97J PACS 01 France 97A DEVA UK 48B MD Anderson (d) subtotal	≃ doubled) non-taxane cytotoxic chemoth: 4(FsooEsoCsoo); 4D100 vS 8(FsooEsoCsoo) 4(FsooEsoCsoo); 4D100 vS 4E100; 4(Csoo+2M40×2Fsoo+2)q4 4EsoCsoo; 4D100 vS 6(Cr5+14Eso+2Fsoo+2)q4 3FEC; 3D100 vS 6(FsooE100Csoo) 3Eq4; 3D100 vS 6(Esox-2)q4 4P2sot; 4FAC vS 4FAC‡; 4(Fsoo+2AsoCsoo)	************************************	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0-3%/y)	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0-3%/y)	2·2 1·5 -0·1 -1·4 2·2	1.5 1.2 2.2 1.2 6.1		>> 1.44 (SE 0.49 increase 2p > 01: NS
	 ✓ doubled) non-taxane cytotoxic chemoth: 4(FaceEacCaco); 4D100 vs 8(FeceEacCaco) 4(FaceEacCaco); 4D100 vs 4E100; 4(Caco-zM40×2Face-2)q4 4EacCaco; 4D100 vs 6(C7s-14Eao-2F500-2)q4 3FEC; 3D100 vs 6(FsocE100C3co) 3Eq4; 3D100 vs 6(FsocE100C3co) 3Eq4; 3D100 vs 4FAC‡; 4(Fsoe-zAsoCsoe) 	************************************	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0·3%/y) 66/	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0-3%/y) 46/	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 6.1 26.3		> 1.44 (SE 0.49 increase 2p > 0.1; NS
1F TACT UK 1G TACT UK 1T LMU Munich ADEBAR 7J PACS 01 France 7A DEVA UK 4B MD Anderson (d) subtotal Total (a – d)	≃ doubled) non-taxane cytotoxic chemoth: 4(FsooEsoCsoo); 4D100 vs 8(FsooEsoCsoo) 4(FsooEsoCsoo); 4D100 vs 4E100; 4(Csoo+2M40+2Fs00+2)q4 4EsoCsoo; 4D100 vs 6(C7s+14E60+2Fs00+2)q4 3FEC; 3D100 vs 6(FsotE100Csoo) 3Eq4; 3D100 vs 6(Esot=100Csoo) 4P2so‡; 4FAC vs 4FAC‡; 4(Fsoo+2AsoCsoo)	TD100+4 E240 VS E4801 †D100+4 E240 VS E400 †D100+4 E360 VS E720 †D100+3 E300 VS E600 †D100+3 E300 VS E600 †D250+4 A200 VS A4001	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0·3%/y) 66/ 19721	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0-3%/y) 46/ 19650	2·2 1·5 −0·1 −1·4 2·2 9·8	1.5 1.2 2.2 1.2 - 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23
1F TACT UK 1G TACT UK 1T LMU Munich ADEBAR 1T LMU Munich ADEBAR 17 J PACS 01 France 7A DEVA UK 4B MD Anderson (d) subtotal Total (a - d)	≃ doubled) non-taxane cytotoxic chemothi 4(FsooEsoCsoo); 4D100 vS 8(FsooEsoCsoo) 4(FsooEsoCsoo); 4D100 vS 4E100; 4(Csoo-zM40×2Fs00-2)q4 3FEC; 3D100 vS 6(Cr5-14Eso-zFsoo-2)q4 3FEC; 3D100 vS 6(FsooE100Csoo) 3Eq4; 3D100 vS 6(Esoc-2)q4 4P250‡; 4FAC vS 4FAC‡; 4(Fsoo×2AsoCsoo)	************************************	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/84 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y)	1/1227 1/786 5/582 0/975 4/388 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y)	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 - 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase
IF TACT UK 1G TACT UK 1T LMU Munich ADEBAR 17 PACS 01 France 7A DEVA UK 4B MD Anderson (d) subtotal Total (a – d)	≃ doubled) non-taxane cytotoxic chemothi 4(FscoEscCscoc); 4D100 vs 8(FscoEscCscoc) 4(FscoEscCscoc); 4D100 vs 4E100; 4(Cscoc>M40x2Fscoc>2)q4 3FEC; 3D100 vs 6(C75×14E60x2Fscoc>2)q4 3FEC; 3D100 vs 6(FscoE1coCscoc) 3Eq4; 3D100 vs 6(Escx2)q4 4P250t; 4FAC vs 4FACt; 4(Fscox2AsoCscoc)	************************************	E240 E160 E360 E300 E300 A200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y)	1/1227 1/786 5/582 0/975 4/388 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y)	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 - 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06
15 DOUDLED (dr. 16 TACT UK 17 TACT UK 17 TACT UK 17 TACS 01 France 17 DEVA UK 48 MD Anderson (d) subtotal Total (a – d)	≃ doubled) non-taxane cytotoxic chemothi 4(FacoEaoCaco); 4D100 vs 8(FacoEaoCaco) 4(FacoEaoCaco); 4D100 vs 4E100; 4(Caco+2M40+2Faco+2)q4 4EsoCaco; 4D100 vs 6(C7s+14Ea0+2Faco+2)q4 3Fac; 3D100 vs 6(FacoE100Caco) 3Eq4; 3D100 vs 6(FacoE100Caco) 3Eq4; 3D100 vs 4FAC‡; 4(Faco+2AsoCaco) 4P2so‡; 4FAC vs 4FAC‡; 4(Faco+2AsoCaco)	ty between 4 subt	E240 E160 E300 E300 A200 A200	5/1220 4/783 4/605 0/944 1/379 0/242 14/ 4213 (0·3%/y) 66/ 19721 (0·3%/y) = 0·1; p >	1/1227 1/786 5/582 0/975 4/388 0/230 11/ 4168 (0-3%/y) 46/ 19650 (0-2%/y) 0.1; NS	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 – 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06
IT FACT UK 1G TACT UK 1G TACT UK 1T LMU Munich ADEBAR 37J PACS 01 France 17A DEVA UK 14B MD Anderson (d) subtotal Total (a – d)	<u>Coubled</u>) non-taxane cytotoxic chemothin (Feo0Es0Ce00); 4D100 vs 8(Feo0Es0Ce00) 4(Feo0Es0Ce00); 4D100 vs 4E100; 4(Ceo0-2M40×2F600-2)q4 3FEC; 3D100 vs 6(CFs-taEe0×2F500-2)q4 3FEC; 3D100 vs 6(F500E100C500) 3Eq4; 3D100 vs 6(Es0×2)q4 4P2s0‡; 4FAC vs 4FAC‡; 4(F500×2A50C500) Heterogenet <u>n one allocation</u>	ty between 4 subt	E240 E160 E300 E300 A200 A200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y) = 0.1; p >	1/1227 1/786 5/582 0/975 4/388 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y) 0·1; NS	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 – 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06
	<u>doubled</u>) non-taxane cytotoxic chemothi 4(FaotEaoCao0); 4D100 vs 8(FaotEaoCao0) 4(FaotEaoCao0); 4D100 vs 4E100; 4(Caoo-2M40×2Faot-2)q4 3FEC; 3D100 vs 6(CFaot-14E60×2Faot-2)q4 3FEC; 3D100 vs 6(FaotE100Cao0) 3Eq4; 3D100 vs 6(Faot-240 4P2so‡; 4FAC vs 4FAC‡; 4(Faot-2AaoCao0) Heterogenet <u>n one allocation</u> 4EaoCao0; 4D100 vs 6(Caonx2Manx2Eanx2)x4	the second	E240 E160 E360 E300 A200 A200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y) = 0.1; p >	1/1227 1/786 5/582 0/975 4/388 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y) 0·1; NS	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 – 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06
	<u>← doubled) non-taxane cytotoxic chemothi</u> 4(FsooEsoCsoo); 4D100 vS 8(FsooEsoCsoo); 4(FsooEsoCsoo); 4D100 vS 4E100; 4(Csoo+2M40+2Fsoo+2)q4 3FEC; 3D100 vS 6(C5+14E80+2Fsoo+2)q4 3FEC; 3D100 vS 6(FsoeE100Csoo); 3Eq4; 3D100 vS 6(FsoeE100Csoo); 3Eq4; 3D100 vS 6(FsoeE100Csoo); 3Eq4; 3D100 vS 6(FsoeE100Csoo); 4P2502; 4FAC vS 4FAC2; 4(F500+2A50Csoo); Heterogenei none allocation 4EsoCsoo; 4D100 vS 6(Csoo+2M40+2Fsoo+2)q4 4D75C vS 4As0Csoo; 4D75C vS 4As0Cso; 4D75C vS 4As0Csoo; 4D75C vS 4As0Csoo; 4D75C vS 4A	thereby thereby <td< td=""><td>E240 E160 E300 E300 A200 A200</td><td>5/1220 4/783 4/605 0/84 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y) = 0-1; p > 0/154 3/482</td><td>1/1227 1/786 5/582 0/975 4/388 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y) 0.1; NS</td><td>2·2 1·5 -0·1 -1·4 2·2 9·8</td><td>1.5 1.2 2.2 1.2 – 6.1 26.3</td><td></td><td>1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06</td></td<>	E240 E160 E300 E300 A200 A200	5/1220 4/783 4/605 0/84 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y) = 0-1; p > 0/154 3/482	1/1227 1/786 5/582 0/975 4/388 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y) 0.1; NS	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 – 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06
IF TACT UK 16 TACT UK 17 T LMU Munich ADEBAR 17J PACS 01 France 7A DEVA UK 4B MD Anderson (d) subtotal Total (a – d)) No anthracycline i 05 WSG/AGO AM-02 7N USO 97-35	≃ doubled) non-taxane cytotoxic chemothi 4(FscoEscCeco); 4D100 vS 8(FscoEscCsco) 4(FscoEscCsco); 4D100 vS 4E100; 4(Csco+2M40+2Fsco+2)q4 3FEC; 3D100 vS 6(Cr5+14E60+2Fsco+2)q4 3FEC; 3D100 vS 6(Esc+2)q4 4P2502; 4FAC vS 4FAC2; 4(Fsco+2A50Csco) Heterogenei n one allocation 4EsoCsco; 4D100 vS 6(Csco+2M40+2Fsco+2)q4 4D75C vS 4AsoCsco	therapy therapy <td< td=""><td>E240 E160 E300 E300 A200 Α200</td><td>5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y) = 0.1; p > 0/154 3/482</td><td>1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y) 0·1; NS 0/164 1/487</td><td>2·2 1·5 -0·1 -1·4 2·2 9·8</td><td>1.5 1.2 2.2 1.2 – 6.1 26.3</td><td></td><td>1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06</td></td<>	E240 E160 E300 E300 A200 Α200	5/1220 4/783 4/605 0/984 1/379 0/242 14/ 4213 (0-3%/y) 66/ 19721 (0-3%/y) = 0.1; p > 0/154 3/482	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y) 0·1; NS 0/164 1/487	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 – 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06
	<u>Confidence intervals 4(FaceEcocc) 4(FaceEcoccc) 4(FaceEcoCccc) 4(FaceEcoCcccc) 4(FaceEcoCcccc) 4(FaceEcoCcccc) 4(FaceEcoCcccc) 4(FaceEcoCcccccccccccccccccccccccccccccccccc</u>	therein the second se	E240 E160 E300 E300 A200 A200 A200	5/1220 4/783 4/605 0/884 1/379 0/242 14/ 4213 (0·3%/y) 66/ 19721 (0·3%/y) = 0·1; p > 0/154 3/482	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0·3%/y) 46/ 19650 (0·2%/y) 0·1; NS 0/164 1/487	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 - 6.1 26.3		1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06
	<u>Confidence intervals 4(FaceEcocc) 4(FaceEcoccc) 4(FaceEcoCccc) 4(FaceEcoCcccc) 4(FaceEcoCcccc) 4(FaceEcoCcccc) 4(FaceEcoccccc) 4(FaceEcoccccc) 4(FaceEcocccccccccccccccccccccccccccccccccc</u>	type therefore ther	E240 E160 E300 E300 A200 A200	5/1220 4/783 4/605 0/884 1/379 0/242 14/ 4213 (0·3%/y) 66/ 19721 (0·3%/y) = 0·1; p > 0/154 3/482	1/1227 1/786 5/582 0/975 4/368 0/230 11/ 4168 (0-3%/y) 46/ 19650 (0-2%/y) 0-1; NS 0/164 1/487	2·2 1·5 -0·1 -1·4 2·2 9·8	1.5 1.2 2.2 1.2 – 6.1 26.3	0.5 1.0	1.44 (SE 0.49 increase 2p > 0.1; NS 1.452 (SE 0.23 increase 2p = 0.06

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

 \P Control anthracycline dose less than \textbf{E}_{90} or \textbf{A}_{60} per cycle

D = docetaxel; P = paclitaxel. Anthracyclines: A = doxorubicin (Adriamycin); E = Epirubicin Taxanes: $\label{eq:constraint} \mbox{Other agents:} \quad \mbox{C} = \mbox{cyclophosphamide; } \mbox{F} = \mbox{fluorouracil; } \mbox{M} = \mbox{methotrexate; } \mbox{V} = \mbox{vincristine; } \mbox{Vrb} = \mbox{Vrb$

(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.

P 25: MORTALITY WITHOUT RECURRENCE in trials of taxane-plus-anthracycline-based regimen vs SAME, or MORE (< doubled or ~doubled) non-taxane cytotoxic chemotherapy

Year code and study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the controls	Cumulative doses of taxane & anthracycline	Anthra- cycline difference	Deaths/wo Allocated taxane	man-years Allocated non-tax.	<u>Taxane</u> Logrank O−E	deaths* Variance of O-E	Ratio of annual Taxane : N	death rates on-tax.
(a) Taxane (D or P)-pl	lus-anthracycline (A or E)-based regimen	•							
vs the SAME non-	-taxane cytotoxic chemotherapy (ie, uncor	founded trials of	adding a	taxane)					
98B Taxit216 Italy	4E; 4D100; 4CMFq4 vs 4E120; 4(C600×2M40×2F600×2)	†D100×4 E480 vs E480	0	7/2089	6/2007	0.4	3.2		•>
99T GOIM 9902 Italy	4D100; 4EC vs 4E120C600	†D100×4 E480 VS E480	0	0/1369	1/1280	-0.5	0.2		>
95J1 NSABP B-27*	4AC‡; 4D100‡ vs 4(A60C600)‡	†D100×4 A240 VS A240	0	34/5361	27/5127	2.5	15.0		•
95J2 NSABP B-27*	4AC‡; 4D100 VS same control patients	†D100×4 A240 VS A240	0	29/5318	27/5127	0.6	13.8		>
95K NSABP B-28	4AC; 4P225 vs 4A60C600	†P225×4 A240 VS A240	0	59/12066	64/11744	-3.7	30.0		
94D1 CALGB 9344	4AC; 4P175 vs 4A90C600	†P 175×4 A 360 VS A 360	0	19/3462	19/3190	-0.9	9.1		>
94D2 CALGB 9344	4AC; 4P175 vs 4A75C600	†P 175×4 A 300 VS A 300	0	15/3437	20/3188	-3.5	8.6		
94D3 CALGB 9344	4AC; 4P175 vs 4A60C600	†P 175×4 A 240 VS A 240	0	14/3441	20/3214	-4-4	8.0		
 (a) subtotal 				177/ 36543 (0∙5%/v)	184/ 34877 (0·5%/v)	-10∙2	78.7		0.88 (SE 0.11) reduction
(b) Taxane-plus-anth	racycline-based regimen (taxane courses	given alone) +			,				20 - 0 1, 10
vs MORE (but < d	oubled) non-taxane cytotoxic chemothera	ipy							
00S WSG/AGO AM-02	4EanCann: 4D100 VS 6(E500E100C500)	+D100×4 E360 VS E600	F 240	4/2063	4/1990	0.0	2.0		
95T HORG Greece	4D100: 4FC vs 6(F700F75C700)	D100×4 E300 VS E600	E150	0/1548	3/1423	-1.2	0.7		
00E FinHer/FBCG 00-01	3D(80/100): 3FEC vs 3Vrb25×3: 3(F600E60C600)	†D80×3 E180 VS E180¶	0≠	2/1470	1/1442	1.0	0.5		
98D1 BIG 02-98*	3A75; 3D100; 3CMFq4 vs 4A75; 3(C100×14M40×2F600×2)q4	†D100×3 A225 VS A270	A 70	3/4375	7/4289	-2.3	2.4		
	or 4A60C600; 3CMFq4	(240/300))						
99K GEICAM 9906 Spain	4FEC; 8(P100)q1 VS 6(F600E90C600)	†P 100×8 E 360 ∨S E 540	E 180	8/2265	3/2236	2.7	2.7		>
97R HE1097 Greece	3Eq2; 3P250q2; 3CMFq2 vs 4(E110)q2; 4(C840M50F840)q2	†P250×3 E330 vs E440	E 110	2/1271	1/1232	0.4	0.7		·>
∎ (b) subtotal				19/ 12992 (0·1%/y)	19/ 12612 (0·2%/y)	0∙5	8.9		1.06 (SE 0.34) increase
									2p > 0·1; NS
(c) Taxane-plus-anth vs MORE (but < d	nracycline-based regimen (taxane given c oubled) non-taxane cytotoxic chemothera	oncurrently) © Ipy							
01E1+3 PACS 04 France	6E75D75 vs 6(F500E100C500)	©D75×6 E450 vs E600	E 150	11/4952	7/5046	2.1	4.5		••••>
97L BCIRG 001	6D75AC vs 6(F500A50C500)	©D75×6 A300 vs A300¶	0≠	12/3042	8/2880	1.6	4.9		>
99% GEICAM 9805 Spain	6D75AC vs 6(F500A50C500)	©D75×6 A300 vs A300¶	0≠	3/2608	8/2504	-1.6	2.2		>
98D2 BIG 02-98*	4(A50D75); 3CMFq4 vs 4A75; 3(C100×14M40×2F600×2)q4	©D75×4 A200 VS A270	A 45	3/4270	7/4289	-1.8	2.5		>
	or 4A60C600; 3CMFq4	(240/300))						
99N RAPP-01 France	4A50D75 VS 4A60C600	©D75×4 A200 VS A240	A 40	5/1430	2/1440	1.5	1.8		>
98T ECOG EST2197	4AD60 vs 4A60C600	©D60×4 A240 VS A240	0≠	41/9235	40/9209	0.6	20.0		
96W1 ECTO Italy*	(4A60P200; 4CMFq4) vs 4A75; 4(C600×2M40×2F600×2)q4	©P200×4 A240 vs A300¶	A 60	4/1518	1/1457	1.3	1.1		>
96W2 ECTO Italy* 96X GONO Italy MIG 5	(4A60P200; 4CMFq4)‡ vs same control patients 4E90P175 vs 6(F600E60C600)	©P200×4 A240 VS A300¶ ©P175×4 E360 VS E360¶	A60 0≠	4/1510 13/2411	1/1457 15/2390	1·3 -1·8	1·2 6·6		>
			-						
■ (c) subtotal				96/ 30976 (0·3%/y)	89/ 30672 (0·3%/y)	2.5	44·4	~	
(d) Taxane-plus-anth vs DOUBLED (or	hracycline−based regimen † ≈ doubled) non−taxane cytotoxic chemoth	erapy							
01F TACT UK	4(F600E60C600); 4D100 VS 8(F600E60C600)	†D100×4 E240 vs E480¶	E240	15/4731	6/4721	4.6	5.2		~
01G TACT UK	4(F600E60C600); 4D100 vs 4E100; 4(C600×2M40×2F600×2)q4	†D100×4 E240 VS E400	E 160	10/3048	9/3006	0.6	4.7		•>
01T LMU Munich ADEBAR	4E90C600; 4D100 vs 6(C75×14E60×2F500×2)q4	†D 100×4 E360 vs E720	E 360	6/1508	10/1467	-1.5	3.9	e	>
97J PACS 01 France	3FEC; 3D100 vs 6(F500E100C500)	†D 100×3 E 300 VS E 600	E 300	4/4525	4/4347	0.0	2.0		>
97A DEVA UK	3Eq4; 3D100 vs 6(E50×2)q4	†D100×3 E300 VS E600	E 300	6/1660	9/1543	-2.5	3.3		>
94B MD Anderson	4P250‡; 4FAC vs 4FAC‡; 4(F500×2A50C500)	†P250×4 A200 vs A400¶	A 200	8/1544	1/1562	3.4	2.1		>
 (d) subtotal 				49/ 17016 (0·3%/y)	39/ 16646 (0·2%/y)	4 ∙9	21.1		1.26 (SE 0.24)
Total (a – d)				341/ 97527	331/ 94807	-0.9	151·0		2p > 0·1; NS → 0·994 (SE 0·08
				(0·3%/y)	(0·3%/y)				2p > 0·1; NS
(e) No anthracycline i	Heterogene	ity between 4 sub	totals: χ_3^2	= 2·6; p >	0·1; NS				
00S WSG/AGO AM-02 97N USO 97-35	4E90C600; 4D100 vs 6(C600×2M40×2F600×2)q4 4D75C vs 4A60C600	D100×4 E360 vs None D75×4 None vs A240	-E360 A240	0/655 8/2433	1/663 20/2427	-0·5 -6·9	0·2 6·5		
- 99% or <i><</i> -> 95%	% confidence intervals						L		
							0	0·5 1·0	1.5 2.0
* For 3-way trials, "E	Either active vs same control patients" (not plo	otted) is what contri	butes to t	he total.				Taxane better	Non-tax. better
For 95J NSABP B- 98D BIG 02-98 (O	-27, this (O-E) is 2.1 with variance V = 19.5 ; -E) = -2.8 , V = 2.8 ; 00F MA.21 (O-E) = 0.0 :	96W ECTO Italy (O V = 0.0	9−E) = 1·8	s, V = 1·9;					

† 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

 \P Control anthracycline dose less than E_{90} or A_{60} 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.

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

and	r∕ear code study name	Regimens compared and drug doses (mg/m²) per cycle. Any unstated doses are as in the controls	Cumulative doses of taxane & anthracycline	Anthra- cycline difference	Deaths Allocated taxane	Women Allocated non-tax.	Taxane Logrank O-E	e deaths* Variance of O-E	Ratio of annual death rates Taxane : Non-tax.
<u>(a)</u>	Taxane (D or P)-pl vs the SAME non-	us−anthracycline (A or E)−based regimen taxane cytotoxic chemotherapy (ie, uncoi	t nfounded trials of	f adding a	taxane)				
085	3 Tavit216 Italy	4E: 4D100: 4CMEat vs 4E120: 4(C600x2M40x2E600x2)	+D100×4 E480 VS E480	0	57/486	85/486	-14.0	34.0	
99	GOIM 9902 Italy	4D100; 4EC vs 4E120C600	†D100×4 E480 VS E480	0	26/376	31/374	-4.4	13·0	
95J	1 NSABP B-27*	4AC‡; 4D100‡ vs 4(A60C600)‡	†D100×4 A240 VS A240	0	204/805	213/804	-7.3	99.9	
95J	2 NSABP B-27*	4AC‡; 4D100 vs same control patients	†D100×4 A240 VS A240	0	206/802	213/804	-4.7	100.0	
95ł	K NSABP B-28	4AC; 4P225 VS 4A60C600	+ P 225×4 A 240 vs A 240	0	392/1531	417/1529	-16.7	189-4	
94D	1 CALGB 9344	4AC: 4P175 VS 4A90C600	† P 175×4 Δ 360 VS Δ 360	0	152/531	185/526	-21.2	78.8	
94D	2 CALGB 9344	4AC: 4P175 VS 4A75C600	†P 175×4 A 300 VS A 300	0	151/525	176/528	-14.9	76.0	
94D	3 CALGB 9344	4AC; 4P175 VS 4A60C600	+P175×4 A240 VS A240	0	158/534	170/526	-10.3	76-5	
	(a) subtotal				1346/ 5590	1490/ 5577	-89.9	599∙3	
(b)	Taxane-plus-anth	racycline-based regimen (taxane courses	s given alone) †		(24·1%)	(26·7%)			2p = 0.0002
<u> </u>	vs MORE (but < do	publed) non-taxane cytotoxic chemothera	ipy						
005	6 WSG/AGO AM-02	4E90C600; 4D100 vs 6(F500E100C500)	†D 100×4 E 360 vs E 600	E 240	15/811	26/795	-5.8	10.0	
95	F HORG Greece	4D100; 4EC vs 6(F700E75C700)	†D100×4 E300 vs E450¶	E 150	65/391	65/397	0.7	29.6	
00E	E FinHer/FBCG 00-01	3D(80/100); 3FEC vs 3Vrb25×3; 3(F600E60C600)	†D80×3 E180 vs E180¶	0≠	20/502	30/507	-5-3	10.6	
98D	1 BIG 02-98*	3A75; 3D100; 3CMFq4 vs 4A75; 3(C100×14M40×2F600×2)q4	†D 100×3 A 225 VS A 270	A 70	115/959	138/968	-9.2	60·1	
			(240/300	"_		== 100 1			
998	GEICAM 9906 Spain	4FEC; 8(P100)q1 VS 6(F600E90C600)	†P100×8 E360 VS E540	E180	40/614	55/634	-4.8	21.8	
975		6(E100C000)r02; 3CMFq2 VS 4(E110)q2; 4(C840M50F840)q2	+P250×3 E330 VS E440	E110	20/304 47/701	62/300 50/701	-4.9	20.0	
00/	LAERO B-2000 France	4FEC: 4P175 VS 6(E500E100C500)	+P175x4 E400 VS E600	€200	47/707 (837 n	ationts)	(10	data)	
03F	R GIM 1 Italy	4E90C; 4D100 vs 6(F600E75C600)	†D100×4 E360 VS E450¶	E 90	(1636 p	atients)	(no	data)	
	(b) subtotal with c	lata on numbers dead			358/ 4282 (8·4%)	426/ 4302 (9·9%)	-30.8	181·2	0.84 (SE 0.07) reduction 2p = 0.02
(c)	Taxane-plus-anth	racycline-based regimen (taxane given co	oncurrently) ©						
<u>(-)</u>	vs MORE (but < do	oubled) non-taxane cytotoxic chemothera	ipy						
01E1+	3 PACS 04 France	6E75D75 vs 6(F500E100C500)	©D75×6 E450 VS E600	E 150	91/1495	86/1515	3.8	42.5	
971	BCIRG 001	6D75AC vs 6(F500A50C500)	©D75×6 A300 vs A300¶	0≠	91/745	130/746	-20.0	51.6	
99%	6 GEICAM 9805 Spain	6D75AC vs 6(F500A50C500)	©D75×6 A300 VS A300¶	0≠	21/539	27/521	-3.1	11.0	_
98D	2 BIG 02-98*	4(A50D75); 3CMFq4 vs 4A75; 3(C100×14M40×2F600×2)q4	©D75×4 A200 vs A270	A 45	140/960	138/968	5.6	65-3	
		OF 4A60C600; 3CMFq4	(240/300)					
991	N RAPP-01 France	4A50D75 VS 4A60C600	©D75×4 A200 VS A240	A 40	13/311	17/316	-2.2	7.4	
98	ECTO Italu#	4AD60 VS 4A60C600 (4AcoBoos: 4CME+4) Vo 4A75: 4(Coose-Mase-Ecose)-4	©D60×4 A240 VS A240	U≠	20/451	1///14/0	-3.0	84·4	
9000	a ECTO Italy*	(4A60P200, 4CMFq4) VS 4A75, 4(C600×2M40×2F600×2)q4	©P200×4 A240 VS A300	A60	33/451	43/453	-0.0	18.0	
9000	6 Multicentre Germany	4(EP175)a2: 3CMEa2 vs 4(EpaCeon): 3(CeonMapEcon)	© P200×4 A240 VS A3001	A00	33/401	38/108	-2.5	12.0	
96>	GONO Italy MIG 5	4E90P175 vs 6(F600E60C600)	©P175×4 E360 vs E360¶	0≠	60/535	55/520	0.5	26.4	
	(c) subtotal				683/ 7071 (9·7%)	754/ 7076 (10·7%)	-29·5	323-2	O·91 (SE 0·05) reduction 2p > 0·1; NS
<u>(</u> d)	Taxane-plus-anth	racycline-based regimen †	orany						
018			+D100×4 E240 VS E480	F 240	180/1258	170/1265	8.8	79-6	
010	G TACT UK	4(F600E60C600); 4D100 VS 4E100; 4(C600×2M40×2E600×2)n4	+D100×4 E240 VS E400	E160	118/815	131/824	-5.4	57.1	
01	LMU Munich ADEBAR	4E90C600; 4D100 vs 6(C75×14E60×2F500×2)q4	+D100×4 E360 vs E720	E 360	46/684	34/675	5.4	18.9	
96	Aberdeen Scotland	4VAC‡; 4D100 vs 4VAC‡; 4(V1.5A50C1000)	+D100×4 A200 VS A4001	A 200	4/52	12/52	-4.0	3.4	
97.	J PACS 01 France	3FEC; 3D100 vs 6(F500E100C500)	†D100×3 E300 vs E600	E 300	100/1003	135/995	-14-4	55-4	— —
97/	A DEVA UK	3Eq4; 3D100 VS 6(E50×2)q4	†D 100×3 E 300 VS E 600	E 300	44/406	59/397	-10.8	22.7	
94E	3 MD Anderson	4P250‡; 4FAC vs 4FAC‡; 4(F500×2A50C500)	†P 250×4 A 200 vs A 400¶	A 200	38/265	38/259	2.0	16.8	
00F	2 NCIC MA.21*	4A60C600; 4P175 VS 6(C75×14E60×2F500×2)q4	†P175×4 A240 VS E720	E720-A240	65/702	50/701	7.5	26-4	
UZL			D100×3 E300 VS E600	E 300	(4149 p	auerns)	(110	uala)	
	(d) subtotal with (data on numbers dead			595/ 5185 (11∙5%)	629/ 5168 (12·2%)	−10 ·9	280-4	0.96 (SE 0.06) reduction 2p > 0.1; NS
	Total (a – d) v	vith data on numbers dead (some with tim	e to event unkno	wn)	2982/ 22128	3299/ 22123	-161.9	1327-3	♦ 0.885 (SE 0.026)
				. 2	(13.5%)	(14.9%)			2p < 0.00001
(e)	No anthracycline i	Heterogenei n one allocation	ity between 4 sub	totals: χ_3^2	= 3·1; p >	0·1; NS			
			_						
008 971	5 WSG/AGO AM-02 N USO 97-35	4E90C600; 4D100 vS 6(C600×2M40×2F600×2)q4 4D75C vs 4A60C600	D100×4 E360 vs None D75×4 None vs A240	-E360 A240	4/167 55/506	13/177 73/510	-3·8 -8·7	3∙9 30∙0	
-	+ 99% or <→ 95% + 99% confidence in	o confidence intervals itervals, time to event unknown						0	0.5 1.0 1.5 2.0
*	For 3-way trials, "E For 95J NSABP B-: 98D BIG 02-98 (O-	ither active vs same control patients" (not plo 27, this (O−E) is −8·4 with variance V = 131·6 ·E) = −2·3, V = 84·2; 00F MA.21 (O−E) = 4·0;	otted) is what contri 6; 96W ECTO Italy ; V = 33·2	ibutes to th (O-E) = -	he total. -7·5, V = 2	2.7;			Taxane better Non-tax. better

+ 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

 \P Control anthracycline dose less than E_{90} or A_{60} 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.

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/m²) per cycle	Cumulative dosage, E/A	Events/wor Allocated anthr.	man-years Adjusted CMF	Anthr Lograni O-E	. events Variance of O-E	Ratio of A	annual e nthr. : CN	vent rates IF
(a) Anthracycline dose/c	<u>ycle ≥ A60 or E90</u>								
i. Cumulative anthra	cycline dosage A360 or E720-800								
88R Brussels Belgium	8E100C830 VS 6(C100×14M40×2F600×2)q4	E 800	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			
89B2 SWOG 8897	6(C100×14A30×2F500×2)q4 VS 6(C100×14Wi40×2F600×2)q4	A 360	182/0725	223/0087	-19.0	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 anthra	acycline dosage A300 or E400-480								
86S GOCCNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E 480	47/363	54/334	-3.7	20.6			
97G FM Italy GMB1	4E120; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 480	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		-	
96N GOCSI MAM2 Italy	4F110: 4CMFq4, [E/5×2V1·4×2]q3) VS 6(C100×14W140×2F600×2)q4 4F110: 4CMFq4, VS 6(C600×2M40×2F600×2)q4	E450 E440	57/320 91/2019	85/2030	3.0 1.9	21·4 40·2	_	_	
96A NEAT. UK	4E100: 4CMFa4 vs 6(C100×14M40×2F600×2)a4	E400	188/3481	225/3316	-20.6	91·8			
97U1+2 IBIS 03 Italy *	4E100; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 400	76/1682	2(38/795)	-0.5	23.0			
91Q GOCSI MAM1 Italy	4A75; 6CMFq4 vs 6(C100×14M40×2F600×2)q4	A 300	66/701	73/702	-0.3	25.8			
Subtotal ii			608/ 10194 (6·0%/y)	669/ 9997 (6·7%/y)	−24 ·0	262.7			0·91 (SE 0·06) reduction 2p > 0·1; NS
iii. Cumulative anthr	acycline dosage A ₂₄₀								•
84B1 NSABP B-15	4A60C600 vs 6(C100×14M40×2F600×2)a4	A 240	350/2843	347/2799	0.4	146-4			
84B2 NSABP B-15	4(A60C600)a3: 3CMEa4 vs 6(C100×14M40×2E600×2)a4	A240	326/2907	347/2799	-13.3	141.7			
91H NSABP B-23	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	144/4524	136/4492	4.2	67.3			
Subtotal iii			820/ 10274 (8∙0%/y)	830/ 10090 (8·2%/y)	-8·7	355-5		\Leftrightarrow	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		\Leftrightarrow	0·90 (SE 0·03) reduction 2p = 0·003
	Trend between 3 st	ubtotals: χ	² = 6·7; 2p ∺	= 0·010					
(b) Anthracycline dose/c	ycle < A60 or E90								
78L2 ONCOFRANCE	12(F400×4 A 30C300×4V1)g4 vs 12(C100×14M40×2F600×2)g	4 A 360¶	48/537	54/385	-11·5	21.4			
88R Brussels Belgium	8E60C500 VS 6(C100×14M40×2F600×2)q4	E 480¶	94/1064	82/1073	4.4	35.7			
J1+2+3 GOIRC SANG 2B R1	$6({C}_{M}F_{V1\cdot 4}{E}_{40\times 2})_{q4} \text{ vs } 6({C}_{600\times 2}M_{40\times 2}{F}_{600\times 2})_{q4}$	E 480¶	40/1105	38/1092	0.0	17.6			
84L ICCG C/2/84 UK	8(FE50C)q4 vs 8(C600×2M40×2F600×2)q4	E 400¶	136/1465	142/1403	-7.0	61.3			_
80C1 SE Sweden BCG A 84N ICCG C/6/89 UK	8A40C200×4 vs 8(C100×14M40×2F600×2)q4 6FE50Ca4 vs 6(C600×2M40×2F600×2)a4	A320¶ E300¶	7/77 73/1946	8/79 65/1989	0·6 3·6	2·2 32·8			·>
					00	02.0		-	
(b) subtotal			398/ 6194 (6·4%/y)	389/ 6021 (6∙5%/y)	-10∙0	170-9			0·94 (SE 0·07) reduction 2p > 0·1; NS
Total (a + b)			2207/ 35891 (6·1%/y)	2361/ 35146 (6·7%/y)	-93·6	983-5		\Leftrightarrow	0·909 (SE 0·030 reduction 2p = 0·003
-∎- 99% or <-> 95% co	nnidence intervals	ibtotale: ~ ²	² = 7·4· n =	0.06		0	0.5	1.0	1.5 2.0
	Hotorogonaity within a	ibtotale: ~	₃ - τ, μ - ² = 12.0. η	5 0.1 · NO	5		Anthr. bette	r	CMF better
			16 - 13.9, p	> 0-1, N			Treatme	nt effect	2p = 0.003
* 97U was (4 E ; 4 C with highly prolife	MF) vs (4CMF; 4E) vs (6CMF), and its co arative disease, and slightly updated result	zu triais: χ) ntrols count ts from it ha	19 = ∠1·3; p t twice in su ave recently	been pul	5 d in tot blished	al of ever (webapp	nts/woman-yea	rs; the stu	dy included women

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

 \P Dose less than E90 or A60 per cycle of anthracycline

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

Year co and study	ode name	Regimens compared and drug doses (mg/m²) per cycle	Cumulative dosage, E/A	Events/wom Allocated / anthr.	<u>an-years</u> Adjusted CMF	<u>Anthr</u> Lograni O-E	<u>events</u> Variance of O-E	Ratio o	f annual e Anthr. : CM	event rates MF
(a) Anthr	racyclina dosa	$\Delta c = c + c + c$								
<u>(a) Anun</u> i Cu	imulative anth	$\frac{1}{1000} = \frac{1}{1000} = \frac{1}{1000}$								
			_							
88R Bruss	sels Belgium	8E100C830 VS 6(C100×14M40×2F600×2)q4	E800	104/2293	116/21/2	-9.4	46.2			-
89R NCIC 89B2 SWO	о ма.5 ОG 8897	6(C100×14E60×2F500×2)q4 VS 6(C100×14M40×2F600×2)q4 6(C100×14A30×2F500×2)q4 VS 6(C100×14M40×2F600×2)q4	A360	308/15597 3	51/15416	-19·4 -22·6	82·5 159·4			
Sub	total i			585/ 20175 (2·9%/y) (670/ 19703 3∙4%/y)	− 51·5	288·0		\Rightarrow	0.84 (SE 0.05) reduction 2p = 0.002
ii. Ci	umulative anth	hracycline dosage A300 or E400-480								-p
865 GOC	CNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E 480	59/500	65/456	-2.9	25.6		_	
97G FM It	aly GMB1	4E120; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 480	39/1025	53/1001	-4.8	20.7		-	
90Z GOIR	RC SANG 2 Italy	16(E30)q1 vs 6(C600×2M40×2F600×2)q4	E 480	66/1518	66/1598	0.4	28.5	_		
84K1 GUN	-3 Naples	$3(CMF_{q4}; [E_{75\times2}V_{1\cdot4\times2}]_{q3}) \text{ vs } 6(C_{100\times14}M_{40\times2}F_{600\times2})_{q4}$	E 450	66/497	78/561	-0.1	26.0			
96N GOC	SI MAM2 Italy	4E110; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 440	124/2881	102/2933	10·1	51·9		_ +	
96A NEAT	T, UK	4E100; 4CMFq4 vs 6(C100×14M40×2F600×2)q4	E 400	193/3634 2	241/3448	-24.3	95.7			
7U1+2 IBIS (91Q GOC	03 Italy * SI MAM1 Italy	4E100; 4CMFq4 vs 6(C600×2M40×2F600×2)q4 4A75; 6CMFq4 vs 6(C100×14M40×2F600×2)q4	E400 A300	90/2159 2 70/758	(42/1026) 78/761	1·1 0·1	26·5 27·5	_		
Sub	total ii			707/ 12972 (5∙5%/y) (767/ 12810 6∙0%/y)	− 20·5	302·3			0.93 (SE 0.06) reduction 2p > 0.1; NS
iii. C	Cumulative ant	hracycline dosage A ₂₄₀								- F ,
84B1 NSAE	BP B-15	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	468/6501 4	465/6323	-2.9	202.3			_
84B2 NSAF	BP B-15	4(A60C600)03: 3CME04 VS 6(C100x14M40x2E600x2)04	A 240	444/6643	165/6323	-17.6	196-4			
91H NSAE	BP B-23	4A60C600 vs 6(C100×14M40×2F600×2)q4	A240	202/8163	175/8158	13.8	91.2			
Sul	btotal iii			1114/ 21307 (5·2%/v) (1105/ 20804 5·3%/v)	-6-8	489·9		\Leftrightarrow	0.99 (SE 0.04) reduction
s	Subtotal (i + ii ⊦	+ iii)		2406/ 54454 (4·4%/v) (2542/ 53317 4·8%/v)	−78 •8	1080.3		\Leftrightarrow	0.93 (SE 0.03) reduction
		Trend between 3 su	ubtotals: χ_1^2	² = 4·8; 2p =	0.03					2p = 0.02
(b) Anthi	racycline dose	e/cycle < A₀₀ or E₀₀								
78I 2 ONC	OFRANCE	12(F400×4A30C300×4V1)04 vs 12(C100×14M40×2F600×2)0	4 A 360¶	67/989	66/671	-10.8	28.2			
88R Bruss	sels Belgium	8E60C500 vs 6(C100×14M40×2F600×2)q4	E480¶	129/2049	116/2172	9.0	48.6	-		
J1+2+3 GOIR	RC SANG 2B R1	6(C§M§F§V1 4E40×2)q4 vs 6(C600×2M40×2F600×2)q4	E480¶	48/1669	57/1646	-5.9	23.8		-	
84L ICCG	G C/2/84 UK	8(FE50C)q4 vs 8(C600×2M40×2F600×2)q4	E 400¶	178/2527	190/2426	-10.4	82·0	-		-
80C1 SE S	weden BCG A	8A40C200×4 vs 8(C100×14M40×2F600×2)q4	A 320¶	10/286	11/257	-0.6	3.2			>
84N ICCG	G C/6/89 UK	6FE50Cq4 vs 6(C600×2M40×2F600×2)q4	E300¶	93/2699	82/2789	5∙5	41·8			
(b) s	subtotal			525/ 10219 (5·1%/y) (522/ 9961 5·2%/y)	− 13·3	227.6			0·94 (SE 0·06) reduction 2p > 0·1; NS
	Total (a + b)			2931/ 64673 (4·5%/y) (3064/ 63278 4∙8%/y)	-92·0	1307-9		¢	0·932 (SE 0·027) reduction 2p = 0·01
- 99%	% or ⊲>> 95%	confidence intervals	ubtotolou w ²	2 - 5.0 0	.4. NO		0	0.5	1.0	1.5 2.0
			ubtotals: χ_3	² − 31.0, p > 0	- 1, NO		-	Anthr. bett	er	CMF better
		Heterogeneity within St	20 triale: χ^2	₁₆ - 21.0; p 2 2 = 26.0; p 3	- 0-1; NS	2		Treatm	ent effect	2p = 0.01
*	97U was (4 E ; 4 with highly prol	4CMF) vs (4CMF; 4E) vs (6CMF), and its co iferative disease, and slightly updated result	ntrols count	t twice in sub t e recently h	total and	d in tota blished	al of even (webapp	ts/woman-yea	ars; the stu	idy included women

Anthracyclines: \mathbf{A} = doxorubicin (Adriamycin); \mathbf{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

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

Year code	Regimens compared and	Cumulative	Deaths Allocated	/Women Adjusted	<u>Anthr</u> Lograni	<u>. deaths</u> « Variance	Ratio of	annual c	leath rates	
and study name	drug doses (mg/m²) per cycle	losage, E/A	anthr.	CMF	0-Е	of O-E	Ar	ithr. : Cr	VIF	
(a) Anthracycline dos	e/cycle ≥ A60 or E90									
i. Cumulative ant	hracycline dosage A360 or E720-800							i l		
88R Brussels Belgium	8E100C830 vs 6(C100×14M40×2F600×2)q4	E 800	73/265	91/267	-10·6	35∙0				
89R NCIC MA.5	$6(C_{75\times14}E_{60\times2}F_{500\times2})_{q4} \text{ vs } 6(C_{100\times14}M_{40\times2}F_{600\times2})_{q4}$	E 720	130/356	151/360	-11·2	64·3			-	
89B2 SWOG 8897	6(C100×14A30×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4	A 360	175/1461	233/1470	-28.2	98.6				
Subtotal i			378/ 2082 (18·2%)	475/ 2097 (22·7%)	-50 ∙0	198·0	<		0·78 (Si reduc 2p = 0	≣ 0·06) tion ∙0004
ii. Cumulative ant	thracycline dosage A300 or E400-480							i		
86S GOCCNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E 480	39/103	47/104	-2.8	18·5				
97G FM Italy GMB1	4E120; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 480	17/226	21/224	-0.7	9.0				>
90Z GOIRC SANG 2 Italy	16(E30)q1 vs 6(C600×2M40×2F600×2)q4	E 480	40/170	46/178	-3.5	18·7				
84K1 GUN-3 Naples	3(CMFq4; [E75×2V1·4×2]q3) vs 6(C100×14M40×2F600×2)q4	E 450	41/105	55/115	-3.5	18.7		- in		
96N GOCSI MAM2 Italy	4E110; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E440	41/521	48/523	-4.1	20.8		-		
90A NEAT, UK	4E100, 4CMFq4 VS 6(C600×240440×2F600×2)q4	E400	52/398	2(21/188)	-21.3	14.5				
91Q GOCSI MAM1 Italy	4A75; 6CMFq4 vs 6(C100×14M40×2F600×2)q4	A300	32/232	38/234	-2.6	13.6		-		
Subtotal ii			396/ 2766	472/ 2770	-35·9	183·1	<	-	0·82 (Si	≣ 0·07)
			(14·3%)	(17·0%)					2p = 0	008
iii. Cumulative an	thracycline dosage A240									
84B1 NSABP B-15	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	385/781	381/776	0.2	175·2				
84B2 NSABP B-15	4(A60C600)q3; 3CMFq4 vs 6(C100×14M40×2F600×2)q4	A 240	371/781	381/776	-6.2	170·7		_	-	
91H NSABP B-23	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	121/1003	124/1005	-2.4	59.7				
Subtotal iii			877/ 2565 (34·2%)	886/ 2557 (34·6%)	-8·5	405·6		\Leftrightarrow	0·98 (Si reduc 2p > 0·	≣ 0·05) tion 1; NS
Subtotal (i + ii -	+ iii)		1651/ 7413 (22:3%)	1833/ 7424 (24·7%)	-94·3	786.7		\Leftrightarrow	0.89 (Si reduc	≡ 0.03)
	Trend between 3 su	ıbtotals: χ	² = 8·0; 2p	= 0·005					2p = 0	0000
(b) Anthracycline dos	e/cvcle < Aco or Eso									
		. A	50/129	EC/112	-11 6	22.6	_			
88R Brussels Belgium	12(F400×4A30C300×4V1)q4 VS 12(C100×14V140×2F600×2)q 8F60C500 VS 6(C100×14M40×2F600×2)q4	4 A360¶ F480¶	92/272	91/267	2.9	37.6				
J1+2+3 GOIRC SANG 2B R1	6(C§M§F§V1:4E40×2)q4 vs 6(C600×2M40×2F600×2)q4	E480¶	29/245	30/244	-0.7	13·2				
84L ICCG C/2/84 UK	8(FE50C)q4 vs 8(C600×2M40×2F600×2)q4	E 400¶	133/380	125/379	0.0	60·2	-			
80C1 SE Sweden BCG A	8A40C200×4 vs 8(C100×14M40×2F600×2)q4	A 320¶	8/22	11/22	-1.6	3.8				>
84N ICCG C/6/89 UK	6FE50Cq4 vs 6(C600×2M40×2F600×2)q4	E300¶	46/473	44/477	-0.5	21.6				
(b) subtotal			358/ 1530 (23·4%)	357/ 1502 (23·8%)	-11.1	160-1			0·93 (SI reduc 2p > 0·	E 0·08) tion 1; NS
Total (a + b)			2009/ 8943 (22·5%)	2190/ 8926 (24·5%)	−105·4	946-8		\Diamond	0·895 (SP reduc 2p = 0	E 0·031 tion ∙0006
- ₽ 99% or <⇒ 95%	confidence intervals Heterogeneity between 4 su	ıbtotals: ν ²	² = 8·9: p =	0.03		o	0.5	1.0	1.5	2.0
	Heterogeneity within su	ubtotals: v	² = 9·3: n	> 0·1: NS			Anthr. better	r	CMF better	
	Heterogeneity hetween 3	20 trials: $\sqrt{2}$	$16^{2} = 18.2 \cdot r$	> 0.1. N	s		Treatmen	t effect :	2p = 0·0006	
* 97U was (4 E ; with highly pro	4CMF) vs (4CMF; 4E) vs (6CMF), and its co bliferative disease, and slightly updated result	ntrols counts from it ha	t twice in su twice in su	ubtotal an been pu	d in tot	al of deat (webapp	hs/women; the s endix p66)	study inc	luded women	

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

 $\label{eq:constraint} \mbox{Other agents:} \quad \mbox{C} = \mbox{cyclophosphamide; } \mbox{F} = \mbox{fluorouracil; } \mbox{M} = \mbox{methotrexate; } \mbox{V} = \mbox{vincristine}$

(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

P 30: MORTALITY WITHOUT RECURRENCE IN FIRST YEAR 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/m²) per cycle	Cumulative losage, E/A	Allocated anthr.	Adjusted CMF	Logrank O-E	Variance of O-E	Ratio of annual of Anthr. : C	death rates MF
(a) Anthracycline dos	se/cycle ≥ A₀₀ or E₀₀							
i. Cumulative and	thracycline dosage A360 or E720-800							
88R Brussels Belgium	8E100C830 vs 6(C100×14M40×2F600×2)q4	E 800	0/230	0/229				
89R NCIC MA.5	6(C75×14E60×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4	E 720	1/340	0/341	0.5	0.2 –		>
89B2 SWOG 8897	6(C100×14A30×2F500×2)q4 VS 6(C100×14M40×2F600×2)q4	A 360	3/1432	6/1438	-1.5	2.2		>
. Subtotal i			4/ 2002 (0·2%/y)	6/ 2008 (0∙3%/y)	−1 ·0	2.2		0.66 (SE 0.52) reduction 2p > 0.1: NS
ii. Cumulative an	thracycline dosage A300 or E400-480							
86S GOCCNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E 480	1/93	1/91	-0.2	0·5 —	•	>
97G FM Italy GMB1	4E120; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 480	0/215	1/214	-0.5	0.2		>
90Z GOIRC SANG 2 Italy	16(E30)q1 vs 6(C600×2M40×2F600×2)q4	E 480	2/145	2/156	0.0	1.0		>
84K1 GUN-3 Naples	$3(CMF_{q4}; [E_{75\times 2}V_{1\cdot 4\times 2}]_{q3}) \vee 8.6(C_{100\times 14}M_{40\times 2}F_{600\times 2})_{q4}$	E 450	1/87	1/92	-0·1	0·5 —		>
96N GOCSI MAM2 Italy	4E110; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 440	1/448	1/445	0.1	0.5 -		>
96A NEAT, UK	4E100; 4CMFq4 vs 6(C100×14M40×2F600×2)q4	E400	2/965	10/965	-4.2	3.0 -	•	
910 GOCSI MAM1 Italy	4E100; 4CMFq4 VS 6(C600×2M40×2F600×2)q4 4A75: 6CMFq4 VS 6(C100×14M40×2F600×2)q4	E400 A300	2/301	2(1/1/3) 0/178	-0.1	0.6 -	•	>
		A 300		0/1/0	00	02		
 Subtotal ii 			10/ 2485 (0·4%/y)	18/ 2487 (0∙7%/y)	-4.8	6.4		0·47 (SE 0·28) reduction 2p = 0·06
iii. Cumulative ar	nthracycline dosage A240							
84B1 NSABP B-15	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	2/746	0/740	1.0	0.2		>
84B2 NSABP B-15	4(A60C600)q3; 3CMFq4 vs 6(C100×14M40×2F600×2)q4	A 240	1/741	0/740	0.6	0.2 -		>
91H NSABP B-23	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	2/982	3/978	-0.6	1.2 -		>
. Subtotal iii			5/ 2469 (0·2%/y)	3/ 2458 (0·1%/y)	1∙0	2.0		1.62 (SE 0.91)
								2p > 0·1; NS
 Subtotal (i + ii + i 	11)		19/ 6956 (0·3%/y)	27/ 6953 (0·4%/y)	-4.9	10·9		- 0.64 (SE 0.24) reduction 2p > 0.1; NS
	Trend between 3 su	btotals: ;	χ ² ₁ = 0·7; 2p 3	> 0·1; NS				
(b) Anthracycline dos	se/cycle < A₀₀ or E₃₀							
78L2 ONCOFRANCE	12(F400×4A30C300×4V1)a4 vs 12(C100×14M40×2F600×2)a	A360¶	1/131	0/103	0.5	0.2 -		
88R Brussels Belgium	8E60C500 vs 6(C100×14M40×2F600×2)q4	E 480¶	0/236	0/229				
J1+2+3 GOIRC SANG 2B R1	$6(C_{S}M_{S}F_{S}V_{1:4}E_{40\times2})q_{4} \text{ vs } 6(C_{600\times2}M_{40\times2}F_{600\times2})q_{4}$	E 480¶	0/219	0/214				
84L ICCG C/2/84 UK	8(FE50C)q4 vs 8(C600×2M40×2F600×2)q4	E 400¶	1/360	0/355				
80C1 SE Sweden BCG A	8A40C200×4 vs 8(C100×14M40×2F600×2)q4	A320¶	0/11	0/10				
84N ICCG C/6/89 UK	6FE50Cq4 VS 6(C600×2M40×2F600×2)q4	E 300¶	2/445	0/457	1.0	0.2		>
(b) subtotal			4/	0/	1.6	0.8		
. (b) cubicital			1402 (0·3%/y)	1368 (0∙0%/y)	10			8·00 (SE 3·89) increase 2p = 0·07
			23/ 8358	27/ 8321	-3.3	11·7		
■ Total (a + b)			(0·3%/y)	(0·3%/y)				2p > 0·1; NS
■ Total (a + b) ■ 99% or <-> 95%	% confidence intervals		(0·3%/y)	(0·3%/y)				2p > 0·1; NS
■ Total (a + b) ■ 99% or <>> 95%	% confidence intervals Heterogeneity between 4 sι	btotals: ;	(0·3%/y) χ ₃ ² = 6·8; p =	(0·3%/y) 0·08		0	0.5 1.0	2p > 0·1; NS 1·5 2·0
■ Total (a + b) ■ 99% or <>> 95%	% confidence intervals Heterogeneity between 4 sւ Heterogeneity within sւ	ibtotals: ; ibtotals: ;	(0.3%/y) $\chi_3^2 = 6.8; p = \chi_{11}^2 = 8.5; p = 3.5$	(0·3%/y) 0·08 • 0·1; NS		0	0·5 1·0 Anthr. better	2p > 0·1; NS 1·5 2·0 CMF better

Anthracyclines: \mathbf{A} = doxorubicin (Adriamycin); \mathbf{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

P 31: MORTALITY WITHOUT RECURRENCE 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/m²) per cycle	Cumulative losage, E/A	Deaths/wo Allocated anthr.	man-years Adjusted CMF	Anthr Logranl O-E	. deaths Variance of O-E	Ratio of ani Anth	nuald r.:CN	eath rates IF	
(a) Anthracycline dose	e/cycle ≥ A₀o or E₀o									
i. Cumulative anth	racycline dosage A360 or E720-800									
88R Brussels Belgium	8E100C830 vs 6(C100×14M40×2F600×2)q4	E 800	18/2293	10/2172	2.7	6.6				>
89R NCIC MA.5 89B2 SWOG 8897	6(C75×14E60×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4 6(C100×14A30×2F500×2)q4 vs 6(C100×14M40×2F600×2)q4	E720 A360	4/2285 105/15597	2/2115 84/15416	0·9 10·1	1·5 45·2		_		\longrightarrow
Subtotal i			127/ 20175	96/ 19703	13·7	53·2			1·29 (SE	0·16
". 0			(0·6%/y)	(U'5%/Y)					increa 2p = 0	se 06
II. Cumulative anti	nracycline dosage A300 or E400-480									
86S GOCCNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E480	3/500	2/456	0.0	1.1				\longrightarrow
9/G FM Italy GMB1 907 COIRC SANG 2 Italy	4E120; 4CMFq4 VS 6(C600×2IVI40×2F600×2)q4 16(E20)a1 VS 6(C600×2M40×2E600×2)q4	E480	1/1025	2/1001	-0.4	0·7 - 1.8	•	-		\rightarrow
84K1 GUN-3 Nanles	3(CMEq4: [E75x2V1.4x2]q3) VS 6(C100x14M40x2E600x2)q4	E460	4/497	3/560	0.2	1.2		-		
96N GOCSI MAM2 Italy	4E110: 4CMFr4 vs 6(C600×2M40×2F600×2)r4	E440	9/2881	13/2933	-1.9	5.3				Ś
96A NEAT. UK	4E100; 4CMFq4 vs 6(C100×14M40×2F600×2)q4	E400	7/3634	14/3448	-3.8	5·1				
U1+2 IBIS 03 Italy *	4E100; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 400	4/2159	2(4/1026)	-1.4	1.7	.			\rightarrow
91Q GOCSI MAM1 Italy	4A75; 6CMFq4 vs 6(C100×14M40×2F600×2)q4	A 300	2/758	5/759	-1.4	1.2 -	•	+		\longrightarrow
Subtotal ii			40/ 12972 (0·3%/y)	57/ 12807 (0∙4%/y)	-8·3	21·1		-	0·68 (SE reduct 2p = 0	0·18 ion ·07
iii. Cumulative ant	thracycline dosage A ₂₄₀									
34B1 NSABP B-15	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	23/6501	22/6323	0.3	11·1				>
4B2 NSABP B-15	4(A60C600)q3; 3CMFq4 vs 6(C100×14M40×2F600×2)q4	A 240	20/6643	22/6323	-1.8	10.2		—		-
91H NSABP B-23	4A60C600 vs 6(C100×14M40×2F600×2)q4	A 240	38/8163	42/8158	-2.6	19.8		_		
Subtotal iii			81/ 21307 (0∙4%/y)	86/ 20804 (0·4%/y)	-4·1	41·1			 0.90 (SE reduct 2p > 0.1 	0.15 ion ; NS
Subtotal (i + ii + iii)		248/ 54454 (0∙5%/y)	239/ 53314 (0·4%/y)	1.3	115-5	-		 1.01 (SE increa 2p > 0.1 	0.09 se ; NS
	Trend between 3 su	ıbtotals: χ	² = 3·4; 2p	= 0.07						
(b) Anthracycline dose	e/cycle < A60 or E90									
78L2 ONCOFRANCE	12(F400×4A30C300×4V1)a4 vs 12(C100×14M40×2F600×2)a	4 A 360¶	2/989	2/671	-0.2	1.0				>
88R Brussels Belgium	8E60C500 vs 6(C100×14M40×2F600×2)q4	E 480¶	10/2049	10/2172	2.3	4.2				>
+2+3 GOIRC SANG 2B R1	6(C§M§F§V1·4E40×2)q4 vs 6(C600×2M40×2F600×2)q4	E 480¶	1/1669	3/1646	-0.9	1.0 -	•	—		\longrightarrow
84L ICCG C/2/84 UK	8(FE50C)q4 vs 8(C600×2M40×2F600×2)q4	E 400¶	3/2528	2/2426	-0.4	0.9	·	—		\longrightarrow
OC1 SE Sweden BCG A	8A40C200×4 VS 8(C100×14M40×2F600×2)q4	A 320¶	2/286	4/256	-0.6	1.2				\longrightarrow
84N ICCG C/6/89 UK	6FE50Cq4 vs 6(C600×2M40×2F600×2)q4	E300¶	5/2699	3/2789	1.0	2.0		+		\longrightarrow
(b) subtotal			23/	24/	1.2	10·2		+-	1.10.1	
			10220 (0·2%/y)	9960 (0·2%/y)					1·12 (SE increa 2p > 0·1	0·33 se ; NS
Total (a + b)			271/ 64674 (0·4%/y)	263/ 63274 (0∙4%/y)	2.5	125.7	-		- 1·020 (SE increa 2p > 0·1	0·09 se ; NS
- ■ 99% or <>> 95%	confidence intervals	ubtotale: v ²	² = 7.3 · n =	0.06		0	0.5	1.0	1.5	2.0
	Heterogeneity within s	ibtotale: ~	$r^2 = 7.2 \cdot n^2$	> 0.1. NS			Anthr. better		CMF better	
		20 triale: χ	16 ⁻¹ ·2, μ· ² = 14.5· ∽	5 0.1. NG			Treatment effect	2p > 0	1; NS, advers	e
* 97U was (4 E ; 4	4CMF) vs (4CMF; 4E) vs (6CMF), and its co	ntrols coun	t twice in su	ibtotal and	, d in tot	al of dea	ths/woman-years; t	he stu	dy included wor	nen

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

 \P Dose less than $E_{90} \text{ or } A_{60}$ per cycle of anthracycline

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/m²) per cycle	Cumulative losage, E/A	Deaths Allocated anthr.	Women Adjusted CMF	Anthr Lograni O-E	deaths Variance of O-E	Ratio of A	annual on the annual of an	leath rates MF
(a) Anthracycline dos	e/cycle ≥ A60 or E90								
i. Cumulative ant	hracycline dosage A360 or E720-800								
88R Brussels Belgium	8E100C830 VS 6(C100x14M40x2E600x2)o4	Eson	91/265	101/267	-7.8	41.6			
89R NCIC MA.5	6(C75×14E60×2F500×2)a4 vs 6(C100×14M40×2F600×2)a4	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	A 360	280/1461	317/1470	-18·1	143.7	-	- i	
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 ant	hracycline dosage A300 or E400-480							i	
86S GOCCNE Italy	4E120C600 vs 6(C100×14M40×2F600×2)q4	E 480	42/103	49/104	-2.8	19.6			
97G FM Italy GMB1	4E120; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 480	18/226	23/224	-1.1	9.7			
90Z GOIRC SANG 2 Italy	16(E30)q1 vs 6(C600×2M40×2F600×2)q4	E 480	50/170	56/178	-3.0	23.5		-	
84K1 GUN-3 Naples	$3(CMF_{q4}; [E_{75\times 2}V_{1\cdot 4\times 2}]_{q3}) \vee s 6(C_{100\times 14}M_{40\times 2}F_{600\times 2})_{q4}$	E 450	45/105	58/115	-3.0	19.9			
96N GOCSI MAM2 Italy	4E110; 4CMFq4 vs 6(C600×2M40×2F600×2)q4	E 440	50/521	61/523	-6.0	26.1		•	
96A NEAT, UK	4E100; 4CMFq4 vs 6(C100×14M40×2F600×2)q4	E 400	141/1011	189/1016	-25.1	74.5		H	
17U1+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(C100×14W40×2F600×2)q4	A 300	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 an	thracycline dosage A240								-
84B1 NSABP B-15	4460 C600 VS 6(C100x14M40x2E600x2)04	A 240	408/781	403/776	0.8	186-4			
		A	204/701	400/770	0.0	100 4			
0462 NOADP 0-13	4(AbuGbuu)ds, SCMIFd4 VS 6(C100×14M40×2F600×2)d4	A240	150/1002	403/170	-0.4	70.5			-
9TH NOABP B-23	4A60C600 VS 0(C100×1410140×2F600×2)q4	A 240	159/1003	100/1005	-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		\Leftrightarrow	0·90 (SE 0·03 reduction 2p = 0·002
	Trend between 3 su	ibtotals: χ	2 ² = 2·9; 2p	= 0.09					_p
(b) Anthracycline dos	e/cycle < A₀₀ or E₀₀								
	12(Eres, (AssCass, (Mr), (12, 12(Cres, (Mrs, Eres, s)))	. A	E0/120	50/112	_11 7	24.6	_		
88R Brussels Belgium	12(F400×4A30C300×4V1)q4 VS 12(C100×14IVI40×2F600×2)q	+ A3601 E4906	102/130	101/267	5.1	24·0 /1.0			
J1+2+3 GOIRC SANG 2B R1	6(CsMsFsV1.4E40×2)a4 vs 6(C600×2M40×2F600×2)a4	E480¶	30/245	33/244	-1.7	41 0 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	A 320¶	10/22	15/22	-2.1	5.0			
84N ICCG C/6/89 UK	6FE50Cq4 vs 6(C600×2M40×2F600×2)q4	E 300¶	51/473	47/477	0.8	23.6			
(b) subtotal			381/ 1530	381/ 1502	-10∙0	170·3			0·94 (se 0·07
			(24.9%)	(25.4%)					2p > 0·1; NS
Total (a + b)			2280/ 8943 (25·5%)	2453/ 8926 (27·5%)	−103·0	1072·4		¢	0·908 (SE 0·02 reduction 2p = 0·002
- ■ 99% or <>> 95%	confidence intervals		2			0	0.5	1.0	1.5 2.0
	Heterogeneity between 4 su	iptotals: χ	/ ₃ = 5·8; p >	0.1; NS	_	v	Anthr hotte	, IV	CME bettor
	Heterogeneity within su	ibtotals: χ	; _ = 10·0; p) > 0·1; N	S		Antin. Delle		
			2	-	-		Tranter	nt offoot	2n = 0.002

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

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

P 34: 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; MeI = 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

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

			Deaths	/Women	Anth.	deaths		
Year code and study name	Anthracycline regimens and drug doses per cycle	Cumulative dosage, E/A	Allocated anth.	Adjusted control	Logrank O-E	Variance of O-E	Ratio of annu Anth.	al death rates : Control
(a) Anthracycline dos	se/cycle exactly A₀₀ or E	90						
89B1 SWOG 8814 *	6(C 100×14 A 30×2 F 500×2)q4	A 360	324/1177	3(152/381)	-35.3	80·3		
92D Amsterdam C9203	4(E90C600)	E 360	6/49	6/53	-0.3	2.8		>
93H IBCSG 11-93	4([A60/E90]C600)	A240/E360	10/89	10/85	0.2	4.6		•>
93M1+2 IBCSG 12-93 *	4([A60/E90]C600)	A240/E360	27/180	2(25/110)	-4.5	11·2		
84C NSABP B-16	4(A 60 C 600)	A 240	169/429	199/434	- 21·3	81·9		+
(a) subtotal			536/ 1924 (27·9%)	721/ 1935 (37·3%)	-60·9	180-8		0·71 (SE 0·06) reduction 2p < 0·00001
(b) Anthracycline do	se/cycle < A60 or E90, so	rted by cumu	lative dos	age				
76H1 West Midlands UK	8(C250M150F250V1A50)	A 400¶	197/294	205/274	− 19·3	84·2		
76L1 Cologne	10(A 40 C 150×3)q3-4	A 400¶	(61 pa	atients)	(no	data)	1	
74D1 DFCI 74-063	6/12(A40C150×3)	A 240/480¶	1/4	2/4			1	
80B3+4 N Sweden BCG	8(A 40 C 100×4)	A 320¶	60/92	68/95	-10.0	25.9	— B	<u>+</u>
80C2 SE Sweden BCG B	8(A 40 C 200×4)	A 320¶	7/21	13/21	-2.6	4.0		
80S1 Helsinki	8(F20×14A40C500)q4	A 320¶	22/47	30/50	-4.7	7.0		
84C2 NSABP B-16	10 A 30 © 17(Mel 4 F 300)q6	A 300¶	148/358	165/360	-9.3	70.4		<u> </u>
80Z Southampton UK	6(V1·4 A 40 C 200×4)	A 240¶	19/48	23/45	-1·8	7.8		
94F JCOG 9401	6(A 40 C 500)	A 240¶	7/65	12/64	-3·5	3.8		
89D IGR Paris	6(F500[A50/E50††]C500)q3-4	E300¶	113/576	138/575	-9.2	56.7		
83B GROCTA I Italy	6(C500M40F600); 4E75	E 300¶	93/171	89/171	0.2	41.4		
86P2 FASG GFEA 02	6(F500E50C500)	E 300¶	133/384	142/392	-10.1	60·7		
86P3 FASG GFEA 03	6(F500E50C500)	E 300¶	35/167	34/161	-0.2	16.1		
89@1 Bari Italy	6(F500×2E50C500)	E 300¶	11/123	23/121	-5.1	7.8		
90C6 FASG GFEA 07	6(F500E50C500)	E 300¶	14/169	23/166	-4.8	9.0		
96E Austrian BCSG IX	4(F600E60C600)	E 240¶	1/220	1/219	-0.5	0.5 —	• •	→
82F MD Anderson8227 *	4(F400×2A40C400V1·5)q4	A 160¶	19/91	2(6/40)	1.7	5.0		• • •
(b) subtotal with	ı data §		880/ 2830 (31·1%)	980/ 2798 (35∙0%)	-79 ∙0	400·5		0·82 (SE 0·05) reduction 2p = 0·00008
Total (a + b)			1416/ 4754 (29·8%)	1701/ 4733 (35∙9%)	-139·9	581·3	÷	0·786 (SE 0·037) reduction 2p < 0·00001
(c) Lower cumulative	anthracycline dosage						1	
84Q4+5 Austrian BCSG 4	A20V1; C300×2M25×2F600×2	A 20¶	34/131	31/129	2.5	13·4		
- 99% confidence inter	vals					 0	0.5 1	·0 1·5 2·0
						•	Anth bottor	Anth worse
							Antri, better	Anui. worse

§ 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

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

			Deaths/wo	man-years	Anth.	deaths		
Year code Anthracycline regimens and study name and drug doses per cycle		Cumulative dosage, E/A	Allocated anth.	Adjusted control	Logrank O-E	Variance of O-E	Ratio of annua Anth. :	il death rates Control
(a) Anthracycline	e dose/cycle exactly A₀₀ or	E90						
89B1_SWOG 8814 *	6(C100×14 A 30×2 F 500×2)o4	∆ 360	11/1154	3(0/363)	2.5	1.9		
92D Amsterdam C92	203 4(E90C600)	E360	1/35	1/40	0.1	0.5 -		
93H IBCSG 11-93	4([A60/E90]C600)	A240/E360	0/82	0/79				-
3M1+2 IBCSG 12-93 *	4([A 60/ E 90] C 600)	A240/E360	0/160	2(0/93)				
84C NSABP B-16	4(A 60 C 600)	A 240	2/402	2/402	-0.1	1.0 -		>
. (a) subtotal			14/ 1833 (0∙8%/y)	3/ 1796 (0·2%/y)	2.2	3∙4		2·10 (SE 0·81) increase
(b) Anthracycline	e dose/cycle < A₀₀ or E₀₀, so	orted by cumu	lative dos	age				2p > 0·1; NS
76H/ West Midlands I		A 1005	1/270	0/226	0.5	0.2		<u>,</u>
	10(A40C150×2)=2-4	A400¶	1/2/0	0/230	0.5 (no.)	- 2.0 (1949		>
	6/12(A 40C 150×3)	A 240/480			(100)	data)		
80Baur N Sweden BCC	8(A40C100×4)	A 2240/4801	0/81	3/70	-1.6	0.7 .		
80Co SE Sweden BCC	$C B = 8(\Lambda_{40}C_{200\times4})$	A 3201	1/14	0/13	0.5	0.2		(
80S1 Heleinki	8(E20×14A40C500)=4	A 3201	0/31	0/31	0.5	02 -		
	10 A ao @ 17(Mol4Eaoa)-c	A0005	1/244	2/220	-0.5	0.9		
807 Southampton III		A3001	1/34	1/33	0.5	0.2		~
	6(4 40 C 500)	A2401	0/57	0/58	0.5	02 -		~
80D ICP Paris	6(Esop[Aso/Eso++]Csop)=2-4	R2401	4/536	3/520	0.7	1.7		
83B GROCTA Litaly	6(C500M40E600): 4E75	E300¶	0/163	0/155	07			
86P2 EASC GEEA 02		E300¶	1/343	2/342	-0.8	0.7		
86P3 FASG GEEA 03	6(F500E50C500)	E300¶	0/156	0/147	00	07 -		
89@1 Bari Italy	6(F500×2F50C500)	E300¶	0/112	0/110				
	6(F500F50C500)	E300¶	0/160	0/156				
96F Austrian BCSG	IX 4(F600F60C600)	E240¶	1/80	0/86	0.6	0.2 –		>
82F MD Anderson82	227 * 4(F 400×2 A 40 C 400 V 1⋅5)q4	A160¶	0/82	2(0/28)	00	02		
. (b) subtotal y	with data &		10/	11/	-0.1	4.9		、
			2463 (0·4%/y)	2369 (0∙5%/y)		40		0·97 (SE 0·45) reduction 2p > 0·1; NS
Total (a + b)			24/	14/	2.4	8.2		
			4296 (0·6%/y)	4165 (0·3%/y)	24	02		1.331 (SE 0.403 increase
(c) Lower cumula	ative anthracycline dosage							2p > 0.1; NS
84Q4+5 Austrian BCSG	4 A 20 V 1; C 300×2 M 25×2 F 600×2	A 20¶	4/114	2/115	0.2	1.2		·>
- 99% confidence	e intervals					L		
						0	0.5 1.0	0 1.5 2.0
							Anth. better	Anth. worse

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

			Deaths/wo	man-years	Anth.	deaths				
Year code and study name	Anthracycline regimens and drug doses per cycle	Cumulative dosage, E/A	Allocated anth.	Adjusted control	Logrank O-E	Variance of O-E	Ratio	of annual d Anth. : Co	<u>eath rates</u> ntrol	
(a) Anthracycline dos	e/cycle exactly A₀₀ or E	90								
89B1 SWOG 8814 *	6(C100×14A30×2F500×2)a4	A 360	162/10308	3(33/3065)	11·9	33.3				>
92D Amsterdam C9203	4(E90C600)	E 360	2/177	2/174	0.2	0.9				>
93H IBCSG 11-93	4([A60/E90]C600)	A240/E360	0/628	1/608	-0.4	0.2			1	>
93M1+2 IBCSG 12-93 *	4([A60/E90]C600)	A240/E360	8/1353	2(1/684)	2.4	1.7	_		1	>
84C NSABP B-16	4(A 60 C 600)	A 240	61/4101	51/3632	0.7	24.7	-		 	
■ (a) subtotal			233/ 16567 (1·4%/y)	155/ 14977 (1∙0%/y)	14.8	60·9			1·27 (s incr 2p =	E 0·14) ease ≅ 0·06
(b) Anthracycline dos	se/cycle < A60 or E90, so	rted by cumu	lative dosa	age						
76H1 West Midlands UK	8(C250M150F250V1A50)	A 400¶	6/2324	4/1691	0.3	2.4			 	>
76L1 Cologne	10(A 40 C 150×3)q3-4	A400¶			(no	data)				
74D1 DFCI 74-063	6/12(A 40 C 150×3)	A240/480¶	2/46	1/16	·	,			1	
80B3+4 N Sweden BCG	8(A 40 C 100×4)	A320¶	14/721	11/616	1.3	5·6				>
80C2 SE Sweden BCG B	8(A 40 C 200×4)	A320¶	7/272	3/187	1.2	1·2			1	>
80S1 Helsinki	8(F20×14A40C500)a4	A320¶	2/308	6/249	-0.2	0.4 -			i	>
84C2 NSABP B-16	10 A 30 © 17(Mel 4 F 300)₀6	A300¶	46/3330	43/2948	-0.1	20.5	_		i	_
80Z Southampton UK	6(V1·4A40C200×4)	A240¶	5/452	2/391	1.9	1.4				>
94F JCOG 9401	6(A 40 C 500)	A 240¶	1/235	2/210	0.1	0.5			1	>
89D IGR Paris	6(F500[A50/E50++]C500)g3-4	E300¶	25/4401	21/4116	2.1	11·2			-	>
83B GROCTA I Italy	6(C500M40F600); 4E75	E300¶	1/1668	0/1526	0.5	0.5				>
86P2 FASG GFEA 02	6(F500E50C500)	E300¶	13/2780	20/2619	-3.8	7·2				
86P3 FASG GFEA 03	6(F500E50C500)	E300¶	9/1185	6/1078	1.6	3.7				>
89@1 Bari Italy	6(F500×2E50C500)	E300¶	5/1058	6/1090	1.3	2.0				>
90C6 FASG GFEA 07	6(F500E50C500)	E300¶	5/1134	3/1010	0.4	1.8				>
96E Austrian BCSG IX	4(F600E60C600)	E 240¶	1/212	1/217	0.2	0.3			1	>
82F MD Anderson8227 *	4(F400×2A40C400V1.5)q4	A 160¶	2/596	2(2/259)	0.0	0.6			1	>
■ (b) subtotal with	data §		144/ 20722 (0∙7%/y)	133/ 18482 (0·7%/y)	7·0	59·2			1-13 (s incr 2p > 0	E 0·14) ease ⊡1; NS
Total (a + b)			377/ 37289 (1·0%/y)	288/ 33459 (0∙9%/y)	21.7	120·1			1-198 (s incr 2p =	E 0.100) ease 0.05
(c) Lower cumulative	anthracycline dosage								1	
84Q4+5 Austrian BCSG 4	A20V1; C300×2M25×2F600×2	A 20¶	20/764	16/761	1·5	7.5				>
99% confidence interv	vals					ر 0	0.5	 1·0	1.5	2.0
						-	Anth. bet	ter	Anth. worse	e

§ 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 **A**60 or **E**90 per cycle

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

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



Anthracyclines: \mathbf{A} = doxorubicin (Adriamycin); \mathbf{E} = Epirubicin

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; MeI = 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

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



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

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

			Deaths	/Women	Chemo	o. deaths		
Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Allocated chemo.	Adjusted control	Lograni O-E	k Variance of O-E	Ratio of annu Chemo.	ial death rates : Control
(a) Anthracycline dos	e/cycle exactly A60 or E	90					Ĩ	
89B1 SWOG 8814 *	6(C100×14A30×2F500×2)q4	A 360	324/1177	3(152/381)	-35.3	80.3		
92D Amsterdam C9203	4(E90C600)q3	E 360	6/49	6/53	-0.3	2.8		>
93H IBCSG 11-93	4([A 60/ E 90] C 600)q3	A240/E360	10/89	10/85	0.5	4.6		>
93M1+2 IBCSG 12-93 *	4([A60/E90]C600)q3	A240/E360	27/180	2(25/110)	-4.5	11.2		
84C NSABP B-16	4(A 60 C 600)q3	A 240	169/429	199/434	-21.3	81.9		+
(a) subtotal			536/ 1924 (27·9%)	721/ 1935 (37·3%)	-60-9	180 ∙8	\rightarrow	0·71 (SE 0·06) reduction 2p < 0·00001
(b) Anthracycline dos	se/cycle < A60 or E90, soi	ted by cumu	lative dos	age §			1	
76H1 West Midlands UK	8(C250M150F250V1A50)	A 400¶	197/294	205/274	-19.3	84-2		-
76L1 Cologne	10(A 40 C 150×3)q3-4	A 400¶	(61 pa	atients)	(no	data)		
74D1 DFCI 74-063	6/12(A40C150×3)q3	A240/480¶	1/4	2/4				
80B3+4 N Sweden BCG	8(A 40 C 100×4)q3	A 320¶	60/92	68/95	-10.0	25.9		<u> </u>
80C2 SE Sweden BCG B	8(A 40 C 200×4)q3	A 320¶	7/21	13/21	-2.6	4.0		
80S1 Helsinki	8(F20×14A40C500)q4	A 320¶	22/47	30/50	-4.7	7.0		
84C2 NSABP B-16	10 A 30 © 17(Mel 4 F 300)q6	A 300¶	148/358	165/360	-9.3	70.4		<u> </u>
80Z Southampton UK	6(V1.4A40C200×4)q3	A 240¶	19/48	23/45	-1.8	7.8		
94F JCOG 9401	6(A 40 C 500)q3	A 240¶	7/65	12/64	-3.5	3.8		
89D IGR Paris	6(F500[A50/E50††]C500)q3-4	E 300¶	113/576	138/575	-9.2	56.7		<u> </u>
83B GROCTA I Italy	6(C500M40F600)q3; 4E75q3	E 300¶	93/171	89/171	0.5	41.4		•
86P2 FASG GFEA 02	6(F500E50C500)q3	E300¶	133/384	142/392	-10-1	60.7		<u> </u>
86P3 FASG GFEA 03	6(F500E50C500)q3	E300¶	35/167	34/161	-0.5	16-1		
89@1 Bari Italy	6(F500×2E50C500)q3	E300¶	11/123	23/121	-5-1	7.8		
90C6 FASG GFEA 07	6(F500E50C500)q3	E300¶	14/169	23/166	-4.8	9.0		
82F MD Anderson8227 *	4(F600E60C600)q3 4(F400×2 A 40C400V1⋅5)q4	E240¶ A160¶	1/220	2(6/40)	-0·2 1·7	0.5 – 5.0		• • • • • •
(b) subtotal with	data §		880/ 2830 (31·1%)	980/ 2798 (35·0%)	- 79∙0	400 ∙5		0.82 (SE 0.05) reduction 2p = 0.00008
(c) Standard CMF (or	near-standard CMF)						:	
73B INT Milan 7205	12(C100x14M40x2F600x2)q4		141/210	134/181	-16.5	60.8		
78K3 IBCSG/Ludwig III	12(C100×14M40×2F600×2)q4		84/171	105/164	-10.2	39.3		
78V2 ECOG EST6177	12(C100×14M40×2F600×2)q4		58/87	66/95	2.5	24.5		-
79U1+3 Vienna Gyn.	6(C100×14M50×2F750×2)q4		16/30	11/29	3.4	4.1		
81H EST1180/SW.8294	6(C100×14 M 40×2 F 600×2)q4		53/276	79/265	-15.7	31.6		
86H2 IBCSG VII	6(C100×14M40×2F600×2)q4		120/312	146/318	-15.6	58.9		+-
88C NSABP B-20	6(C100×14M100×2F600×2)q4		66/789	111/788	-22.2	42.9		
89A2 SITAM-01	6([C100×14/C600×2]M40×2F600×2	2)q4	26/63	16/52	3.4	8-9		•
89E4+9 GROCTA V Italy	6(C600×2M40×2F600×2)q4		15/40	18/39	-2.6	6.1		
89V Romagnolo Italy	6(C 100×14 M 40×2 F 600×2)q4		22/138	35/143	-6.3	13.5		
90P Amsterdam C8913	6(C100×14M40×2F600×2)q4		12/149	15/122	-3.9	6·3		
903 IBC30 VIII	0(C100x14W40x2F600x2)q4		45/400	54/592	-0.0	23.2		
(c) subtotal			658/	790/	−89 ·1	320·1	\Leftrightarrow	0·76 (SE 0·05)
_			(24·7%)	(30·5%)				reduction 2p < 0·00001
Total (a + b + c	:)		2074/ 7419 (28∙0%)	2491/ 7321 (34·0%)	−229 ∙0	901·4	\diamond	0·776 (SE 0·029 reduction 2p < 0·00001
-∎- 99% or <⇒ 95%	6 confidence intervals	2	- 0 -	0.4.110			0.5 1	•0 1.5 2.0
н	eterogeneity between 3	SUDIOTAIS: χ_2^2	= 2·/; p >	0-1; NS	•	Ŭ	Chemo better	Chemo worse
	neterogeneity within	subtotals: χ^{-}_{2}	9 = 32·5; p) > U·1; N	5		Troatmont offo	r = 2n < 0.00001
	Heterogeneity betwee	n 32 trials: χ_3^2	, = 35·2; p	o > 0·1; N	S		i realitietit ette	οι 2p < 0.0000 Ι
§ 1 trial with no	data does not contribute	o subtotals or	to the ove	erall total.				

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

Other agents: C = cyclophosphamide; F = fluorouracil; M = methotrexate; MeI = 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

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

			Deaths/wor	man-years	Chemo	. deaths		
Year code and study name	Regimens and drug doses per cycle	Cumulative dosage, E/A	Allocated chemo.	Adjusted control	Logrank O-E	Variance of O-E	<u>Ratio of annua</u> Chemo. :	ll death rates Control
(a) Anthracycline dos	e/cycle exactly A60 or E	90						
89B1 SWOG 8814 *	6(C100×14A30×2F500×2)q4	A 360	11/1154	3(0/363)	2.5	1.9		>
92D Amsterdam C9203	4(E90C600)q3	E 360	1/35	1/40	0.1	0.5 —		>
93H IBCSG 11-93	4([A 60/ E 90] C 600)q3	A240/E360	0/82	0/79				
93M1+2 IBCSG 12-93 *	4([A 60/ E 90] C 600)q3	A240/E360	0/160	2(0/93)				
84C NSABP B-16	4(A 60 C 600)q3	A 240	2/402	2/402	-0.1	1.0 –		>
. (a) subtotal			14/	3/	2.5	3.4		
			1833 (0·8%/y)	1796 (0·2%/y)	_ •	•		2·10 (SE 0·81 increase 2p > 0·1; NS
(b) Anthracycline dos	e/cycle < A₀₀ or E₀₀, sor	ted by cumu	lative dosa	age §				
76H1 West Midlands UK	8(C250M150F250V1A50)	A 400¶	1/270	0/236	0.5	0.2 —		>
76L1 Cologne	10(A 40 C 150x3)q3-4	A 400¶			(no	data)		
74D1 DFCI 74-063	6/12(A40C150x3)q3	A240/480¶			(no	data)		
80B3+4 N Sweden BCG	8(A40C100×4)q3	A 320¶	0/81	3/79	-1.6	0.7 ⊷		
80C2 SE Sweden BCG B	8(A40C200×4)q3	A 320¶	1/14	0/13	0.5	0.2 —		>
80S1 Helsinki	8(F20×14A40C500)q4	A 320¶	0/31	0/31				
84C2 NSABP B-16	10 A 30 © 17(Mel 4 F 300)q6	A 300¶	1/344	2/338	-0.5	0.8 —		
80Z Southampton UK	6(V1·4A40C200×4)q3	A 240¶	1/34	1/33	0.5	0.2 —		>
94F JCOG 9401	6(A 40 C 500)q3	A 240¶	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	E 300¶	0/156	0/147				
89@1 Bari Italy	6(F500×2E50C500)q3	E 300¶	0/112	0/110				
90C6 FASG GFEA 07	6(F500E50C500)q3	E 300¶	0/160	0/156				
96E Austrian BCSG IX	4(F600E60C600)q3	E 240¶	1/80	0/86	0.6	0.2 -		>
82F MD Anderson8227 *	4(F400×2A40C400V1.5)q4	A 160¶	0/82	2(0/28)				
■ (b) subtotal with (data §		10/	11/	-0·1	4.9		>
			2463 (0∙4%/y)	2369 (0·5%/y)				0·97 (SE 0·45 reduction 2p > 0·1; NS
(c) Standard CMF (or	near-standard CMF)							
73B INT Milan 7205	12(C100×14M40×2F600×2)a4		1/198	1/160	-0.1	0.5 —		
78K3 IBCSG/Ludwig III	12(C100×14M40×2F600×2)q4		6/148	1/138	2.5	1.7		
78V2 ECOG EST6177	12(C100×14M40×2F600×2)q4		1/78	0/77	0.5	0.2 —		· · · · · · · · · · · · · · · · · · ·
79U1+3 Vienna Gyn.	6(C100×14M50×2F750×2)q4		0/18	0/19				
81H EST1180/SW.8294	6(C100×14M40×2F600×2)q4		3/258	1/248	0.9	1.0		>
86H2 IBCSG VII	6(C100×14M40×2F600×2)q4		3/292	2/289	0.7	1.2		·>
88C NSABP B-20	6(C100×14M100×2F600×2)q4		1/774	0/777	0.5	0.2 —		>
89A2 SITAM-01	6([C100×14/C600×2]M40×2F600×2	2)q4	0/45	0/39				
89E4+9 GROCTA V Italy	6(C600×2M40×2F600×2)q4		0/32	0/28				
89V Romagnolo Italy	6(C100×14M40×2F600×2)q4		1/132	0/137	0.5	0.2 —		>
90P Amsterdam C8913	6(C100×14M40×2F600×2)q4		0/141	0/112				
90S IBCSG VIII	6(C100×14M40×2F600×2)q4		0/377	0/371				
. (c) subtotal			16/	5/	5.5	5.2		
. (0) 000000			2493	2395	00	02		2.88 (SF 0.78
			(0·6%/y)	(0·2%/y)				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 0.37 increase 2p = 0.03
-∎- 99% or <-> 95%	6 confidence intervals							
н	eterogeneity between 3	subtotals: χ_2^2	= 3·1; p >	0·1; NS		0	0.5 1.0	J 1·5 2·0
	Heterogeneity within	subtotals: χ ₁	5 ₅ = 12·9; p	> 0·1; NS	6		Chemo. better	Chemo. worse
	Heterogeneity betweer	n 18 trials: χ_1^2	₇ = 16∙0; p	> 0·1; NS	3		Treatment effect 2	p = 0·03, adverse
8 2 trials with no	o data do not contribute to	subtotals or	to the overa	all total.				

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

Other agents: **C** = cyclophosphamide; **F** = fluorouracil; **M** = methotrexate; **MeI** = 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

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



Anthracyclines: \mathbf{A} = doxorubicin (Adriamycin); \mathbf{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

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



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

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

				Events/wo	man-years	Trt. 'A	' events				
Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosages, E/A	Difference	Allocated trt. 'A'	Allocated trt. 'B'	Logrank O-E	Variance of O-E	Ratio of anı Trt. 'A	ual event V : Trt. 'B'	rates	
(a) Unconfounded c	omparisons										
86P1 FASG GFEA 01	3(FE75C) vs 3(F500E50C500)	E225 VS E150¶	E 75	93/713	93/702	-0.5	38·2				
90C3+5 FASG GFEA 05	6(FE100C) vs 6(F500E50C500)	E600 VS E300¶	E 300	94/1031	135/951	-23.3	46.4	_			
92N ICCG C/9/91 UK	8(FE75C) vs 8(F600E50C600)	E600 VS E400¶	E 200	-/1549	-/1556	blind	35.0				
94D1 CALGB 9344 *	4(A90C) vs 4(A60C600)	A360 VS A240	A 120	177/2040	164/2084	5.5	75.7	_		_	
94D2 CALGB 9344 *	4(A90C); 4P vs 4(A60C600); 4P175	A360 VS A240	A 120	152/2195	154/2165	-4-4	69.6				
(a) subtotal				591/ 7528 (7∙9%/y)	634/ 7458 (8∙5%/y)	−27 ·1	264·9		> 0	• 90 (SE reduc 2p = 0	: 0·06) tion)·10
(b) Confounded con	nparisons										
85A CALGB CLB-8541	4(F600A60C600)q4 vs 4(F300A30C300)q4	A240 VS A120¶	A 120≠	170/2131	225/1881	-39.9	85·0	_ _			
88R Brussels Belgium	8(E100C830) vs 8(E60C500)	E800 VS E480¶	E 320≠	64/1131	94/1064	-14·9	32.4		_		
00F NCIC MA.21 6(C75×	14E60×2F500×2)q2; 4P vs 4A60C600; 4P175	E720 VS A240	E 720 −A 240≠	81/1825	116/1731	-20.5	44·7		-		
🖶 99% or 🖘 95	5% confidence intervals						<u> </u>				
							0	0.2	1.0	1.2	2.0
								Trt. 'A' better	Trt.	B' better	

 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

P 46: RECURRENCE in trials of anthracycline dosage

				Events/wo	man-years	<u>s Trt. '/</u>	' events				
Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosages, E/A	Difference	Allocated trt. 'A'	Allocated trt. 'B'	Logran O-E	k Variance of O−E	Ratio of an Trt. 1	nual e A' : Trt	vent rates t. 'B'	
(a) Unconfounded o	comparisons								:		
86P1 FASG GFEA 01	3(FE75C) vs 3(F500E50C500)	E225 VS E150¶	E 75	119/1313	116/1280	0.1	48.4		<u>.</u>		
90C3+5 FASG GFEA 05	6(FE100C) vs 6(F500E50C500)	E600 VS E300¶	E 300	127/1510	156/1325	-19·5	57·5		<u> </u>		
92N ICCG C/9/91 UK	8(FE75C) vs 8(F600E50C600)	E600 VS E400¶	E 200	-/2280	-/2269	blind	48·0				
94D1 CALGB 9344 *	4(A90C) vs 4(A60C600)	A360 VS A240	A 120	208/3190	214/3214	-2.8	94·7		÷ =		
94D2 CALGB 9344 *	4(A90C); 4P vs 4(A60C600); 4P175	A360 VS A240	A 120	184/3462	192/3441	-8.2	86.5		-	-	
(a) subtotal				737/ 11755 (6·3%/y)	803/ 11529 (7∙0%/y)	-41·2	335·2	<		0·88 (redu 2p :	SE 0·05) uction = 0·02
(b) Confounded cor	nparisons										
85A CALGB CLB-8541	4(F600A60C600)q4 vs 4(F300A30C300)q4	A240 VS A120¶	A 120≠	269/5037	306/4341	-39.4	126.5		_		
88R Brussels Belgium	8(E100C830) vs 8(E60C500)	E800 VS E480¶	E 320≠	104/2293	129/2049	-18·8	47·5		_		
00F NCIC MA.21 6(C75×	14E60×2F500×2)q2; 4P vs 4A60C600; 4P175	E720 VS A240	E 720 −A 240≠	82/1829	116/1732	-20.5	44.7		-		
- 99% or <> 95	5% confidence intervals						_				
							0	0.2	1.0	1.2	2.0
								Trt. 'A' better		Trt. 'B' bett	er

(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

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

				Deaths	Women	Trt. 'A	' deaths					
Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosages, E/A	Difference	Allocated trt. 'A'	Allocated trt. 'B'	Logrank O-E	Variance of O-E	Ratio of Tr	annua t. 'A' :	l death ra Trt. 'B'	ites	
(a) Unconfounded c	omparisons											
86P1 FASG GFEA 01	3(FE75C) vs 3(F500E50C500)	E225 VS E150¶	E 75	77/200	82/209	-5.9	35.7		-			
90C3+5 FASG GFEA 05	6(FE100C) vs 6(F500E50C500)	E600 VS E300¶	E 300	88/276	108/289	− 13·8	42.3		⊢ – –	-		
92N ICCG C/9/91 UK	8(FE75C) vs 8(F600E50C600)	E600 VS E400¶	E 200	-/390	-/395	blind	26.8					
94D1 CALGB 9344 *	4(A90C) vs 4(A60C600)	A360 VS A240	A 120	166/526	150/526	7.4	72.6				-	
94D2 CALGB 9344 *	4(A90C); 4P vs 4(A60C600); 4P175	A360 VS A240	A 120	133/531	144/534	-7.5	64·8					
(a) subtotal				521/ 1923 (27·1%)	548/ 1953 (28·1%)	−19 ·6	242·2			0.	92 (SE reduct 2p > 0·*	tion I; NS
(b) Confounded con	nparisons											
85A CALGB CLB-8541	4(F600A60C600)q4 vs 4(F300A30C300)q4	A240 VS A120¶	A 120≠	220/528	265/522	-35.7	110.3					
88R Brussels Belgium	8(E100C830) vs 8(E60C500)	E800 VS E480¶	E 320≠	73/265	92/272	-11.4	33-2		-	_		
00F NCIC MA.21 6(C75x	14E60×2F500×2)q2; 4P vs 4A60C600; 4P175	E 720 VS A 240	E 720 −A 240≠	50/701	65/702	-7.5	26.4					
🖶 99% or 🖘 95	5% confidence intervals										. <u> </u>	
							0	0.2	1.0) 1	·5	2.0
								Trt. 'A' bette	er	Trt. 'B	' better	

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

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

				Deaths/wo	man-years	<u>Trt. 'A'</u>	deaths				
Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosages, E/A	Difference	Allocated trt. 'A'	Allocated I trt. 'B'	Logrank O-E	Variance of O-E	Ratio of an Trt. 1	nual death A' : Trt. 'B'	rates	
(a) Unconfounded of	comparisons										
86P1 FASG GFEA 01	3(FE75C) vs 3(F500E50C500)	E225 VS E150¶	E 75	0/183	1/183	-0.2	0·2				>
90C3+5 FASG GFEA 05	6(FE100C) vs 6(F500E50C500)	E600 vs E300¶	E 300	2/244	1/245	0.5	0.8				→
92N ICCG C/9/91 UK	8(FE75C) vs 8(F600E50C600)	E600 VS E400	E 200	-/339	-/343						
94D1 CALGB 9344 *	4(A90C) vs 4(A60C600)	A360 VS A240	A 120	4/508	1/506	1.2	1.2				>
94D2 CALGB 9344 *	4(A90C); 4P vs 4(A60C600); 4P175	A 360 vs A 240	A 120	2/513	1/518	0.4	0.7				\longrightarrow
. (a) subtotal				8/ 1787 (0∙4%/y)	4/ 1795 (0·2%/y)	1.7	3∙0			I· 79 (SE increa	0·79)
(b) Confounded cor	mparisons		•	0/400	0/400	10	0.5			2p > 0·1	; NS
85A CALGE CLE-8541	4(F600A60C600)q4 VS 4(F300A30C300)q4	A240 VS A120	A120≠	0/498	2/483	-1.0	0.5 ⊷				\longrightarrow
00F NCIC MA.21 6(C75)	8(E100C830) VS 8(E60C500) x14E60x2F500x2)q2; 4P vS 4A60C600; 4P175	E800 VS E480¶ E720 VS A240	E320≠ E720−A240≠	0/230	0/236	(no c	lata)				
-∎- 99% or <-> 98	5% confidence intervals						0	0.5	1.0	1.5	2.0
								Trt. 'A' better	Trt.	'B' better	

§ 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

P 49: MORTALITY WITHOUT RECURRENCE in trials of anthracycline dosage

				Deaths/wo	man-years	Trt. 'A'	deaths				
Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosages, E/A	Difference	Allocated trt. 'A'	Allocated trt. 'B'	Logrank O−E	Variance of O-E	Ratio of Tr	annual t. 'A' : T	death rates rt. 'B'	
(a) Unconfounded of	comparisons										
86P1 FASG GFEA 01	3(FE75C) vs 3(F500E50C500)	E225 VS E150¶	E 75	3/1312	4/1278	-0.9	1.6 -				>
90C3+5 FASG GFEA 05	6(FE100C) vs 6(F500E50C500)	E600 VS E300¶	E 300	6/1509	7/1324	-1.0	3.2				>
92N ICCG C/9/91 UK	8(FE75C) vs 8(F600E50C600)	E600 VS E400¶	E 200	-/2280	-/2268	blind	0.9				
94D1 CALGB 9344 *	4(A90C) vs 4(A60C600)	A360 VS A240	A 120	19/3190	20/3214	-0.7	9.5				>
94D2 CALGB 9344 *	4(A90C); 4P vs 4(A60C600); 4P175	A360 VS A240	A 120	19/3462	14/3441	2.6	7.7				>
■ (a) subtotal				49/ 11753 (0∙4%/y)	47/ 11525 (0·4%/y)	0∙1	22.9	_	-	1-00 (s incr 2p > 0	SE 0·21) ease)·1; NS
(b) Confounded cor	mparisons										
85A CALGB CLB-8541	4(F600A60C600)q4 vs 4(F300A30C300)q4	A240 VS A120	A 120≠	39/5037	25/4340	4.2	14.4	_			>
88R Brussels Belgium	8(E100C830) vs 8(E60C500)	E800 VS E480¶	E 320≠	18/2293	10/2049	2.9	6.3				>
00F NCIC MA.21 6(C75)	×14 E 60×2 F 500×2)q2; 4P vs 4A 60 C 600; 4P 175	E720 VS A240	E 720 −A 240≠			(no	data)				
🖶 99% or <> 98	5% confidence intervals						L				
							0	0.2	1.0	1.2	2.0
								Trt. 'A' bette	r	Trt. 'B' bette	ər

§ 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

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

P 50: OVERALL MORTALITY in trials of anthracycline dosage

				Deaths	/Women	<u>Trt. 'A</u>	' deaths				
Year code and study name	Regimens compared and drug doses (mg/m ²) per cycle	Cumulative dosages, E/A	Difference	Allocated trt. 'A'	Allocated trt. 'B'	Logrank O-E	Variance of O-E	Ratio of a Trt.	A' : Trt.	eath rates 'B'	
(a) Unconfounded of	comparisons										
86P1 FASG GFEA 01	3(FE75C) vs 3(F500E50C500)	E225 VS E150¶	E 75	80/200	86/209	-6.8	37.4		-	_	
90C3+5 FASG GFEA 05	6(FE100C) vs 6(F500E50C500)	E600 VS E300¶	E 300	94/276	115/289	-14·9	45.5				
92N ICCG C/9/91 UK	8(FE75C) vs 8(F600E50C600)	E600 VS E400¶	E 200	-/390	-/395	blind	27.7				
94D1 CALGB 9344 *	4(A90C) vs 4(A60C600)	A360 VS A240	A 120	185/526	170/526	6.7	82·0				
94D2 CALGB 9344 *	4(A90C); 4P vs 4(A60C600); 4P175	A360 VS A240	A 120	152/531	158/534	-4.8	72·5			_	
(a) subtotal				570/ 1923 (29∙6%)	595/ 1953 (30·5%)	−19 ·4	265·1		\Leftrightarrow	0·93 (s redu 2p > 0	E 0·06) ction 0·1; NS
(b) Confounded co	mparisons										
85A CALGB CLB-8541	4(F600A60C600)q4 vs 4(F300A30C300)q4	A240 VS A120¶	A 120≠	259/528	290/522	- 31·5	124·7				
88R Brussels Belgium	8(E100C830) vs 8(E60C500)	E800 VS E480¶	E 320≠	91/265	102/272	-8.5	39.5			-	
00F NCIC MA.21 6(C75	×14 E 60×2 F 500×2)q2; 4 P vs 4 A 60 C 600; 4 P 175	E 720 VS A 240	E 720 −A 240≠	50/701	65/702	-7.5	26.4			_	
- ∎ - 99% or <⇒ 9	5% confidence intervals						<u> </u>	<u> </u>			
							0	0·5	1.0	1.5	2.0
								Trt. 'A' better		Trt. 'B' bette	ər

 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

P 51: EARLY RECURRENCE (first 5 years) 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 events/woman-years.

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

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

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

		Events/wo	man-years	CMF	events				
Year code and study name	CMF regimens and doses per cycle	Allocated CMF	Adjusted control	Lograni O-E	Variance of O-E	Ratio of	annual e CMF : Co	vent rates ontrol	
(a) Standard CMF (or r	near-standard CMF) regimens								
73B INT Milan 7205	12(C 100×14 M 40×2 F 600×2)q4	153/2210	140/1472	-20·9	60·5		1		
78K3 IBCSG/Ludwig III	12(C100×14M40×2F600×2)q4	91/1558	118/1236	-18·0	42·1	_	1		
78V2 ECOG EST6177	12(C100×14M40×2F600×2)q4	63/559	70/622	-1·9	25.1				
79U1+3 Vienna Gyn.	6(C100×14M50×2F750×2)q4	16/251	12/267	0.8	4.5		1		\longrightarrow
81H EST1180/SW.8294	6(C100×14 M 40×2 F 600×2)q4	76/3385	108/2758	-23·2	42·3		-		
86H2 IBCSG VII	6(C 100×14 M 40×2 F 600×2)q4	152/2554	175/2360	-18·2	72·3				
88C NSABP B-20	6(C100×14 M 100×2 F 600×2)q4	124/9087	198/8706	-41.0	78.5		-		
89A2 SITAM-01	6([C100×14/C600×2]M40×2F600×2)q4	34/372	24/364	3.2	11.6				\longrightarrow
89E4+9 GROCTA V Italy	6(C600×2M40×2F600×2)q4	19/215	20/168	-1.9	6.9				
89V Romagnolo Italy	6(C100×14M40×2F600×2)q4	40/1358	54/1283	-7.6	22.2				
	6(C100×14W40×2F600×2)q4	22/030	28/448	-6.9	11.2				
903 IBC3G VIII	0(C100×14W140×2F600×2)q4	02/3305	111/3003	-17.3	44'4				
(a) subtotal		872/ 25484 (3∙4%/y)	1058/ 22747 (4·7%/y)	-153·1	421·6	\Leftrightarrow	 	0·70 (S reduc 2p < 0·	E 0·04) ction 00001
(b) Other CMF regimer	<u>15</u>								
75E2 Manchester I	12(C 80×14 M 32×2 F 480×2)a4	35/426	34/430	-0.8	12.3				
76C Glasgow	12(C 300×2 M 40×2 F 600×2)q4	67/828	73/618	-13·2	23.9				
76E EORTC 09771	24(C50×14M15×2F350×2)q4	134/1482	132/1232	-9.8	57.5			_	
77B1+2 Danish BCG 77b	12(C80×14M30×2F500×2)q4	108/2590	133/1964	-19·3	41·9				
78E UK/Asia Collab.	8(C50M25F600)q3; 16(C100×4M25F600)q4	118/1310	132/1176	-7.7	42·2			_	
79E Guy's/Manch. II	6(C80×14M32×2F480×2)q4	118/1751	160/1209	-33·2	45.8				
79H Paris	6(C 400×2 M 40×2 F 400×2)q4	49/1111	63/983	− 10·4	24.8				
80F FM Italy 8004	12(C 600 M 40 F 600)q3	20/725	30/454	-8·2	10.3				
82C DBCG 82c postmenop.	9(C 600 M 40×2 F 400×2)q4	490/5039	498/4839	− 19·0	198·6				
84D NCIC MA.4	8(C 600 M 40 F 600)q3	164/1828	168/1707	-7.4	72·9	_		_	
86H2 IBCSG VII *	3(C100×14M40×2F600×2)q4	335/5135	2(175/2360)	-18·4	96·2				
87D3 GABG 3 Germany	6(C500×2M40×2F600×2)q4	56/1064	59/911	-5.3	25.9				
88D IBCSG IX	3(C100×14M40×2F600×2)q4	147/7488	178/7157	− 18·4	78·5				
89J1 CRCRAMS Moscow	6(C550×2M25×2F500×2)q3-4	2/38	4/25	-1·1	1.4 —	•			\longrightarrow
90X1 Tokyo CIH	6(C500M30F500)q3	20/608	17/632	2.0	8.0			-0	\longrightarrow
90£ Sweden-Finland	9(C 600 M 40 F 600)q3			(no	data)				
93S Hamburg, Germany	6(C 500×2 M 40×2 F 600×2)q4	15/397	22/428	-2.5	8.1				-
93X INC Brazil	6(C600M40F600)q3			(no	data)		1		
94P Charles U Prague	6(C 500×2 M 40×2 F 600×2)q4			(no	data)				
(b) subtotal with	ı data §	1878/ 31820 (5·9%/y)	2053/ 28485 (7·2%/y)	-172·5	748·3			0·79 (S reduc 2p < 0·	E 0·03) ction 00001
Total (a + b)		2750/ 57304 (4·8%/y)	3111/ - 51232 (6·1%/y)	-325·6	1169·9	<		0·757 (S reduc 2p < 0 [.]	E 0·026 ction 00001
■ 99% or <>> 95%	confidence intervals				 ∩	0.5	1.0	1.5	2.0
Differen treat	ice between tment effects in 2 subtotals: v ²	= 4·7: 2n	= 0.03		U		.	1.2 CML	2'0
Hete	erogeneity within subtotals: γ^2	. = 41·5: n	= 0.03			CMF better	t offeet 2		
Lista	regencity between 29 triples 2	6 - 46-21 -	- 0.04			reatmen	it enect 2	h < 0.0000.1	
	dete de pet contribute te cultate	7 – 40'3; p	- 0.0.1						

§ 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)

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

		Deaths	/Women	CMF	deaths				
Year code and study name	CMF regimens and doses per cycle	Allocated CMF	Adjusted control	Lograni O-E	√Variance of O−E	Ratio o	f annual o CMF : Co	leath rates ontrol	
(a) Standard CMF (or	near-standard CMF) regimens						1 1 1		
72B INT Miles 7205	12(C100	1/1/210	124/101	-16.5	60.9				
73B INT Milan 7205	12(C100×14W40×2F600×2)q4	141/210 04/171	105/161	-10.2	00·0				
	12(C100×14W40×2F600×2)q4	59/97	66/05	-10.2	24.5			-	
	12(C100×14W40×2F600×2)q4	16/20	11/20	2.0	24.5	_			-
	6(C100×14W150×2F750×2)q4	10/30 53/276	70/265	-15.7	4'I 31.6	_	1		
96Ho IPCSC VII	6(C100×14 14 140×2F600×2)q4	120/212	1 9/200	-15.6	59.0				
	6(C100×14W140×2F600×2)q4	66/790	140/310	- 10.0	42.0	-			
00C NSABF B-20	6(C100×14W100×2F600×2)q4	00//09	16/50	-22.2	42.9		1	_	
	6(Coopered to a 5000 × 2) W40 × 2F600 × 2) q4	20/03	10/02	-2.6	6.1		1		
80\/ Bomognolo Italy	6(C400+211140+2F600+2)+4	10/40	25/142	-2.0	12.5	_	-		_
00P Amstordam C8013	6(C100×14W40×2F600×2)q4	12/130	35/143	-3.0	6.3				
	6(C100×141440×2F600×2)q4	12/149	10/122 E4/202	-5.9	0.0				
903 IBC3G VIII	0(C100×141440×2F600×2)q4	45/400	04/39Z	-5.2	23.2				
(a) subtotal		658/ 2665 (24·7%)	790/ 2588 (30∙5%)	−89 ·1	320·1	<		0·76 (SE reduc 2p < 0·0	tion
(b) Other CMF regime	ns		. ,					- p · • •	
75E2 Manchester I	12(C 80×14 M 32×2 F 480×2)q4	35/55	30/54	3.5	11.3	_			\longrightarrow
76C Glasgow	12(C 300×2 M 40×2 F 600×2)q4	64/112	71/103	− 10·8	23.5				
76E EORTC 09771	24(C50×14M15×2F350×2)q4	86/229	99/223	− 12·9	42·0				
77B1+2 Danish BCG 77b	12(C 80×14 M 30×2 F 500×2)q4	103/201	126/196	− 13·1	41·2	———			
78E UK/Asia Collab.	8(C50M25F600)q3; 16(C100×4M25F600)q4	98/247	94/241	6.6	35.8				-
79E Guy's/Manch. II	6(C 80×14 M 32×2 F 480×2)q4	110/185	152/207	-24·9	45.8				
79H Paris	6(C 400×2 M 40×2 F 400×2)q4	20/172	19/163	1.2	8.6				\longrightarrow
80F FM Italy 8004	12(C 600 M 40 F 600)q3	14/49	24/47	− 6·1	8.3			_	
82C DBCG 82c postmenop	. 9(C 600 M 40×2 F 400×2)q4	458/708	457/737	4.8	192.3		· · · · · ·		
84D NCIC MA.4	8(C 600 M 40 F 600)q3	117/381	120/377	-4.6	52.5	_			
86H2 IBCSG VII *	3(C100×14 M 40×2 F 600×2)q4	277/636	2(146/318)	-10.1	82·0	_		-	
87D3 GABG 3 Germany	6(C 500×2 M 40×2 F 600×2)q4	25/278	26/248	-2.0	11.7				
88D IBCSG IX	3(C100×14 M 40×2 F 600×2)q4	85/853	110/862	-13·2	46.9				
89J1 CRCRAMS Moscow	6(C 550×2 M 25×2 F 500×2)q3-4	0/11	1/10	-0.4	0.2				\longrightarrow
90X1 Tokyo CIH	6(C 500 M 30 F 500)q3	10/144	7/143	1.9	4.0				\rightarrow
90£ Sweden-Finland	9(C600M40F600)q3	(≈100	oatients)	(no	data)				
93S Hamburg, Germany	6(C500×2M40×2F600×2)q4	8/117	14/125	-1.7	4.7				\longrightarrow
93X INC Brazil	6(C600M40F600)q3	(45 pi	atients)	(no	data)				
94P Charles U Prague	6(C500×2M40×2F600×2)q4	(103 p	atients)	(no	data)		i		
(b) subtotal with	n data §	1510/ 4378 (34·5%)	1642/ 4372 (37·6%)	− 81·7	610 ∙8		\operational	0·87 (SE reduc 2p = 0·	tion 0010
Total (a + b)		2168/ 7043 (30·8%)	2432/ 6960 (34·9%)	-170·7	930·8			0·832 (SE reduc 2p < 0·0	tion 00001
- 99% or <> 95%	o confidence intervals				L		. !		
Differer	nce between				0	0∙5	1.0	1.2	2.0
trea	itment effects in 2 subtotals: χ^2_1	= 4·4; 2p	= 0.04			CMF bette	er	CMF worse	
Het	terogeneity within subtotals: χ^2_2	_ = 48·6; p	o = 0·005			Treatme	nt effect ?	n < 0.00001	
Hote	r_{2}	= 53.0 r	n = 0.002			incaulle		P - 0 00001	
C 2 triple with no	χ_2	$7 = 000, \mu$		atal					

§ 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)

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

		Deaths/wo	man-years	CMF	deaths		
Year code and study name	CMF regimens and doses per cycle	Allocated CMF	Adjusted control	Logrank O-E	Variance of O-E	Ratio of annual CMF : 0	l death rates Control
(a) Standard CMF (or r	near-standard CMF) regimens						
73B INT Milan 7205	12(C100×14M40×2F600×2)04	1/198	1/160	-0.1	0.5 -		
78K3 IBCSG/Ludwig III	12(C100×14M40×2F600×2)q4	6/148	1/138	2.5	1.7		
78V2 ECOG EST6177	12(C100×14M40×2F600×2)q4	1/78	0/77	0.5	0.2		
OU1+3 Vienna Gyn	6(C100×14M50×2F750×2)q4	0/18	0/19	00	02		2
81H EST1180/SW 8294	6(C100×14 M 40×2 F 600×2)q4	3/258	1/248	0.9	1.0		>
86H2 IBCSG VII	6(C 100×14 M 40×2 F 600×2)q4	3/292	2/289	0.7	1.2		
88C NSABP B-20	6(C100×14M100×2F600×2)a4	1/774	0/777	0.5	0.2		
89A2 SITAM-01	6([C100×14/C600×2]M40×2F600×2)q4	0/45	0/39				
E4+9 GROCTA V Italy	6(C 600×2 M 40×2 F 600×2)q4	0/32	0/28				
89V Romagnolo Italy	6(C100×14 M 40×2 F 600×2)q4	1/132	0/137	0.5	0.2		>
90P Amsterdam C8913	6(C 100×14 M 40×2 F 600×2)q4	0/141	0/112				
90S IBCSG VIII	6(C 100×14 M 40×2 F 600×2)q4	0/377	0/371				
▪ (a) subtotal		16/ 2493 (0∙6%/y)	5/ 2395 (0·2%/y)	5.2	5∙2		2.88 (SE 0.78)
(b) Other CMF regimer	15						2p = 0·02
755 Manahastar I	10/Can ((Man all (an a)))	1/04	0/25	0.0	0.0		
	12(C80×14W32×2F480×2)q4	1/34	0/35	0.6	0.2		>
76C Glasgow	12(C300×2W40×2F600×2)q4	0/212	0/205	0.2	0.5		>
	24(C50×14W15×2F350×2)d4	0/212	0/205				
79E LIK/Asia Callab	12(C80×14W30×2F500×2)q4	0/148	0/100	_0.9	0.7		
70E OR/Asia Collab.	8(C50W125F600)q3, T6(C100×4W125F600)q4	0/129	0/151	-0.9	0.7 -	•	
	6(C400+141W132*2F480*2)q4 6(C400+2M40+2F480*2)q4	0/130	1/15/	-0.6	0.2		
POE EM Italy 2004	12(CsooM40Esoo)=2	0/44	0/42	00	02		
82C DBCG 82c postmenon	Q(CeooM40×3E400×3)~4	4/651	6/656	-0.6	2.5	_	
	8(CeooM40Eeoo)o2	1/356	0/3/0	0.4	0.2		~
86H2 IBCSG VII *	3(C100×14M40×2F600×2)r4	2/592	2(2/289)	-0.6	0.0	_	
87D3 GABG 3 Germany	6(C500x2M40x2F600x2)q4	0/250	3/220	-1.3	0.7	-	~
88D IBCSG IX	3(C100×14M40×2F600×2)q4	6/832	3/836	1.6	2.2		
89.11 CRCRAMS Moscow	6(C550×2M25×2F500×2)q3-4	0/7	0/6	10			->
90X1 Tokyo CIH	6(C500M30E500)a3	0/132	0/132				
90f Sweden-Finland	9(C600M40E600)q3	0,102	0,102	(no	data)		
93S Hamburg Germany	6(C500x2M40x2F600x2)q4	1/110	0/119	0.5	0.2		
93X INC Brazil	6(C600M40E600)a3		0,110	(no	data)		
94P Charles U Prague	6(C 500×2 M 40×2 F 600×2)q4			(no	data) data)		
 (b) subtotal with d 	ata §	17/	20/	-0.3	8·2		
		3936 (0∙4%/y)	3883 (0∙5%/y)				0·97 (SE 0·34) reduction 2p > 0·1; NS
■ Total (a + b)		33/	25/	5·2	13·4		
		6429 (0·5%/y)	6278 (0∙4%/y)				1·472 (SE 0·333 increase 2p > 0·1; NS
- ₽ 99% or <>> 95%	confidence intervals					0.5 4.0	4.5 0.0
Differen treat	ce between the subtotals: γ^2	= 3·8: 2p	= 0·05		0		1.5 2.0
Hete	erogeneity within subtotals: χ^2_1	_ = 12·2; p) > 0·1; N	S		Treatment effect 2n 3	ONF WORSE
Hete	rogeneity between 17 trials: γ^2	_= 15·9; p) > 0·1; N\$	S		reatment eneor 20	v 1, 110, uuveise
		6	,				

§ 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)

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

		Deaths/wo	man-years	CMF	deaths	
Year code and study name	CMF regimens and doses per cycle	Allocated CMF	Adjusted control	Logrank O-E	Variance of O-E	e Ratio of annual death rates CMF : Control
(a) Standard CMF (or r	ear-standard CMF) regimens					
73B INT Milan 7205	12(C100×14M40×2F600×2)a4	24/2210	19/1472	0.7	8·2	
78K3 IBCSG/Ludwig III	12(C 100×14 M 40×2 F 600×2)g4	37/1558	20/1235	4·0	11.6	
78V2 ECOG EST6177	$12(C_{100\times14}M_{40\times2}F_{600\times2})q^4$	8/559	7/622	1.8	3.0	
'9U1+3 Vienna Gvn.	6(C100×14 M 50×2 F 750×2)g4	4/250	10/266	0.7	1.0	
81H EST1180/SW.8294	6(C100×14M40×2F600×2)a4	31/3385	25/2758	0.7	12.5	
86H2 IBCSG VII	6(C100×14M40×2F600×2)a4	40/2554	28/2359	5.9	16.0	
88C NSABP B-20	6(C100×14M100×2F600×2)q4	54/9087	51/8706	2.1	25.9	
89A2 SITAM-01	6([C100×14/C600×2]M40×2F600×2)q4	5/370	3/364	-0.2	1.3	· · · · · · · · · · · · · · · · · · ·
9E4+9 GROCTA V Italy	6(C600×2M40×2F600×2)q4	0/215	1/167	-0.6	0.2 -	
89V Romagnolo Italy	6(C 100×14 M 40×2 F 600×2)a4	8/1358	4/1283	1.8	2.9	•_>
90P Amsterdam C8913	6(C100×14M40×2F600×2)a4	0/630	0/448			
90S IBCSG VIII	6(C 100×14 M 40×2 F 600×2)q4	4/3305	2/3063	1.4	1.4	
(a) subtotal		215/	170/	18·1	84·0	
		25481 (0∙8%/y)	(0·7%/y)			1·24 (SE 0·1) increase 2p = 0·05
(b) Other CMF regimer	<u>15</u>					
75E2 Manchester I	12(C80×14M32×2F480×2)q4	6/426	3/430	1.4	1.6	
76C Glasgow	12(C300×2M40×2F600×2)q4	14/827	6/616	1.7	4.1	
76E EORTC 09771	24(C50×14M15×2F350×2)q4	9/1482	7/1232	0.6	3.6	
7B1+2 Danish BCG 77b	12(C80×14M30×2F500×2)q4	19/2590	14/1963	0.1	5.8	
78E UK/Asia Collab.	8(C50M25F600)a3: 16(C100×4M25F600)a4	14/1432	16/1234	0.0	5.6	
79E Guv's/Manch, II	6(C80×14M32×2F480×2)g4	17/1751	15/1203	-2.3	6.2	
79H Paris	6(C 400×2 M 40×2 F 400×2)q4	0/1111	4/983	-2.0	0·9 ⊶	
80F FM Italy 8004	12(C600M40F600)a3	2/725	3/454	-0.8	1.2	
82C DBCG 82c postmenop.	9(C 600 M 40×2 F 400×2)q4	78/5039	96/4837	-6.4	39.9	
84D NCIC MA.4	8(C600M40F600)a3	15/1827	17/1707	-2.2	7.4	
86H2 IBCSG VII *	3(C100×14 M 40×2 F 600×2)a4	51/5135	2(28/2359)	-2.4	16.6	
87D3 GABG 3 Germany	6(C500×2M40×2F600×2)g4	11/1064	9/911	-0.6	4.5	
88D IBCSG IX	3(C100×14 M 40×2 F 600×2)g4	61/7488	69/7157	-6.6	32.0	
89.11 CRCRAMS Moscow	6(C550×2M25×2F500×2)q3-4	0/38	0/25		02 0	-
90X1 Tokyo CIH	6(C500M30E500)a3	3/608	2/632	0.6	1.2	
90£ Sweden-Finland	9(C 600 M 40 F 600)g3			(no	data)	
93S Hamburg, Germany	6(C500×2M40×2F600×2)g4	4/397	1/428	1.6	1.2	
93X INC Brazil	6(C600M40F600)g3			(no	data)	
94P Charles U Praque	6(C500×2M40×2F600×2)q4			(no (no	data)	
(b) subtotal with d	ata §	304/ 31940 (1∙0%/y)	318/ 28530 (1·1%/y)	-17.1	132.0	0.88 (SE 0.0 reduction 2n > 0.1: NS
Total (a + b)		519/ 57421	488/ 51273	1∙0	216·0	1.005 (SE 0.0) increase
	confidence intervala	(0·9%/y)	(1·0%/y)			2p > 0·1; NS
■ 99% UI <1> 95%					0	0.5 1.0 1.5 2.0
treat	ment effects in 2 subtotals: χ_1^2	= 6·1; 2p	= 0.01		Ū	CMF better CMF worse
Hete	erogeneity within subtotals: χ^2_2	₄ = 16·8; p	o > 0·1; N	S		Treatment effect 2p > 0⋅1; NS, adverse
Heter	rogeneity between 26 trials: χ^2_2	₅ = 22·9; p	o > 0·1; N	S		

§ 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)

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

		Deaths	/Women	CMF	deaths		
Year code and study name	CMF regimens and doses per cycle	Allocated CMF	Adjusted control	Logranl O-E	Variance of O-E	Ratio of annual CMF : 0	death rates Control
(a) Standard CMF (or n	ear-standard CMF) regimens						
73B INT Milan 7205	12(C100×14 M 40×2 F 600×2)a4	165/210	153/181	-15.8	69·0		
78K3 IBCSG/Ludwig III	12(C100×14M40×2F600×2)g4	121/171	125/164	-6.1	50·9		
78V2 ECOG EST6177	12(C100×14M40×2F600×2)q4	66/87	73/95	4.3	27.5		
79U1+3 Vienna Gyn.	6(C 100×14 M 50×2 F 750×2)q4	20/30	21/29	4·1	5.1		>
81H EST1180/SW.8294	6(C100×14 M 40×2 F 600×2)q4	84/276	104/265	− 15·0	44·1		
86H2 IBCSG VII	6(C100×14 M 40×2 F 600×2)q4	160/312	174/318	-9.7	74·9		
88C NSABP B-20	6(C100×14 M 100×2 F 600×2)q4	120/789	162/788	-20.2	68·7		
89A2 SITAM-01	6([C100×14/C600×2]M40×2F600×2)q4	31/63	19/52	3·1	10.3		— — — →
39E4+9 GROCTA V Italy	6(C 600×2 M 40×2 F 600×2)q4	15/40	19/39	-3.2	6.3		
89V Romagnolo Italy	6(C 100×14 M 40×2 F 600×2)q4	30/138	39/143	-4.5	16.4		
90P Amsterdam C8913	6(C100×14M40×2F600×2)q4	12/149	15/122	-3.9	6.3		
90S IBCSG VIII	6(C100×14M40×2F600×2)q4	49/400	56/392	-4.0	24.6		
(a) subtotal		873/ 2665 (32·8%)	960/ 2588 (37∙1%)	−70 ·9	404·1		0·84 (SE 0·05) reduction 2p = 0·0004
(b) Other CMF regimer	IS						
75E2 Manchester I	12(C 80×14 M 32×2 F 480×2) ₀ 4	41/55	33/54	4.9	12.9		>
76C Glasgow	12(C 300×2 M 40×2 F 600×2)q4	78/112	77/103	-9.1	27.6		
76E EORTC 09771	24(C50×14M15×2F350×2)q4	95/229	106/223	-12·3	45·6		_
7B1+2 Danish BCG 77b	12(C80×14M30×2F500×2)q4	122/201	140/196	− 13·0	47·0		_
78E UK/Asia Collab.	8(C50M25F600)q3; 16(C100×4M25F600)q4	112/247	110/241	6.6	41·5		
79E Guy's/Manch. II	6(C80×14M32×2F480×2)q4	127/185	167/207	-27·2	52·0	 _	
79H Paris	6(C400×2M40×2F400×2)q4	20/172	23/163	-0.8	9.5		>
80F FM Italy 8004	12(C 600 M 40 F 600)q3	16/49	27/47	-6.8	9.5		_
82C DBCG 82c postmenop.	9(C600M40×2F400×2)q4	536/708	553/737	− 1·6	232.3		
84D NCIC MA.4	8(C600M40F600)g3	132/381	137/377	-6.7	59.9		
86H2 IBCSG VII *	3(C100×14M40×2F600×2)q4	328/636	2(174/318)	− 12·4	98·6		_
87D3 GABG 3 Germany	6(C500×2M40×2F600×2)q4	36/278	35/248	-2.6	16·2		
88D IBCSG IX	3(C100×14 M 40×2 F 600×2)q4	146/853	179/862	− 19·7	78·8		
89J1 CRCRAMS Moscow	6(C550×2M25×2F500×2)q3-4	0/11	1/10	-0.4	0·2		>
90X1 Tokyo CIH	6(C500M30F500)q3	13/144	9/143	2.5	5.2		>
90£ Sweden-Finland	9(C600M40F600)q3	(≈100 µ	oatients)	(nc	data)		
93S Hamburg, Germany	6(C500×2M40×2F600×2)q4	12/117	15/125	0.0	5.9		>
93X INC Brazil	6(C600M40F600)q3	(45 pa	atients)	(nc	data)		
94P Charles U Prague	6(C 500×2 M 40×2 F 600×2)q4	(103 p	oatients)	(nc	data)		
(b) subtotal with	data §	1814/ 4378 (41·4%)	1960/ 4372 (44·8%)	−9 8·7	742·8		0.88 (SE 0.03) reduction 2p = 0.0003
Total (a + b)		2687/ 7043 (38·2%)	2920/ 6960 (42·0%)	-169·7	1146·9	\$	0·862 (SE 0·027 reduction 2p < 0·00001
- ■ - 99% or <>> 95%	confidence intervals						
Difference between treatment effects in 2 subtotals: γ^2 =			> 0·1; NS	;	U	u·s 1·0 CMF better	1·5 2·0 CMF worse
Hete	erogeneity within subtotals: χ_2^2	_e = 43·6; p	o = 0·02			Treatment effect	2p < 0.00001
Hete	rogeneity between 28 trials: γ^2	_ = 44·1: p	o = 0·02				-r · · · · · ·
§ 3 trials with no	data do not contribute to subtota	7 Is or to the	e overall t	otal			
* For balance or	and as not commute to sublot	rial etrata	count half	f or twic	o in subto	tal/c)	

* 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)

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



and in final total of events/woman-years.

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



* 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.

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



and in final total of deaths/women.

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



and in final total of deaths/woman-years.

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



and in final total of deaths/woman-years.

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



and in final total of deaths/women.

	Treatments compared	Entry age	Deaths/w	oman-years
	(Active vs Control)	(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%)

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

* 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. J Clin Oncol 2005; 23: 3686-96.
94D1-3	CALGB 9344	Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential pacitaxel 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/cyclo- phosphamide 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 - epirubicine-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. Cancer Res 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	Martín 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, Krocker 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 Intergruppo Group. <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.
		marker in a trial assessing sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT). <i>Cancer</i> <i>Res</i> 2009; 69: A607 (abstract).
01T	LMU Munich ADEBAR	Sommer HL, Jueckstock JK, Genss 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. Cancer Res
		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 cyclophsphamide: 7-year follow-up of US Oncology Research Trial 9735. <i>J Clin Oncol</i> 2009; 27 : 1177-83.

(a) Anthracycline dose/cycle ≥ 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>HER</i> 2 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	Personal communication
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: <u>http://clinicaltrials.gov/ct2/show/study/NCT01031030?term=ibis+03&rank=1</u> 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. Proc Annu Meet Am Soc Clin Oncol 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	Trial name	Publication(s)
Code		
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	Personal communication
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	Hrafnkelsson 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).

(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 PHTh; 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.
		Br J Cancer 1989; 60: 911-18.
76L1	Cologne	Personal communication
74 D1	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 reucrrence: A randomized trial. Proc Ann Meet Am Soc Clin Oncol 1982: C-290
		(abstract).
80B3+4	N Sweden BCG	Personal communication
80C2	SE Sweden BCG B	Hrafnkelsson J, Nilsson K, Soderberg M. Tolerance of radiotherapy combined with adjuvant chemotherapy in
		breast cancer. Acta Oncol 1987; 26: 269-72.
80S1	Helsinki	Blomqvist C, Tiusanen K, Elomaa I, et al. The combination of radiotherapy, adjuvant chemotherapy
		(cyclophosphamide doxorubicin ftorafur) and tamoxifen in stage II breast cancer. Long term follow up results of a
		randomised trial. Br J Cancer 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. J Clin Oncol
		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	Personal communication
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. Ann Oncol 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. Acta Oncol 2005; 44: 458-466
		Andre F, Khalil A, Slimane K, et al. Mitotic index and benefit of adjuvant anthracycline-based chemotherapy in
	000074144	patients with early breast cancer. J Clin Oncol 2005; 23: 2996-3000.
83B	GROCIAIItaly	Boccardo F, Rubagotti A, Amoroso D, et al. Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative
		Group Trials. GROCTA Trials. Recent Results Cancer Res 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 tamoxiren alone in one to three node-positive, estrogen-receptor-positive,
		postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. Ann Oncol 2006;
000-		17:05-73.
86P3	FASG GFEA 03	Hery M, Bonneterre J, Rocne 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 that. Buil Cancer
	Dari Italy	2000, 90: E109-14.
09@1	ban italy	Paradiso A, Schittum F, Cenamare G, et al. Randomized clinical that of adjuvant nuclouracit, epitublicin, and
		cyclophosphanide chemotherapy for patients with hast-prometating, node-negative bleast cancer. J Clin Oricol
9006	EASC CEEA 07	2001, 19, 3923-37.
9006	TASS OF LA UT	value int, i algoti r, roche h, et al. improved disease the survival with epitubicit-based chemoethor hadding
		adjuvant uterapy compared with tamohien alone in one to three hode-positive, estudyer-receptor-positive, postmenoposities breast cancer patients: results of Erench Adjuvant Study Group 02 and 07 trials. App Oncol 2006:
		17.65-73
96E	Austrian BCSG IX	Taucher S, Salat A, Gnant M, et al. Imnact of pretreatment thromhocytosis on survival in primary breast cancer
50L		Throm Haemost 2003: 89: 1098-1106
82F	MD Anderson 8227	Personal communication
021		

(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. J Clin Oncol 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. J Clin Oncol 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, Knuiman 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	Personal communication
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, prediminant comparing the comparing three adjuvant regiments.
000015		Premininary results. All Orleo 1992, 3. 205 (austract).
9003+5	FASG GFEA US	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).
		Bonneterre JM, French Adjuvant Study Group. Long-term efficacy and toxicity of the FEC100 regimen. <i>Oncology</i> (<i>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, Cirrincione 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

EBCTCG, Lancet 2011



*Mean of annual rates in the seven component 5-year age groups WHO (& 2008 US NCHS) mortality and UN population estimates EBCTCG, Lancet 2011 Reliable assessment of MODERATE differences in LONG-TERM survival by the 5-yearly worldwide overview (with tens of thousands randomised)

Need <u>all</u> 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

EBCTCG, Lancet 2011
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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Berlin Buch Akademie der Wissenschaften, Germany U Peek, Birminaham General Hospital, UK G D Oates, J Powell. Bordeaux Institut Bergonié, France M Durand, L Mauriac. Bordet Institute, Brussels, Belgium A Di Leo, S Dolci, D Larsimont, J M Nogaret, C Philippson, M J Piccart. Bradford Royal Infirmary, UK M B Masood, D Parker, J J Price. Breast Cancer International Research Group (BCIRG) M A Lindsay, J Mackey, M Martin, Breast Cancer Study Group of the Comprehensive Cancer Centre, Limburg, Netherlands P S G J Hupperets. British Association of Surgical Oncology BASO II Trialists, London, UK T Bates, R W Blamey, U Chetty, I O Ellis, E Mallon, D A L Morgan, J Patnick, S Pinder. British Columbia Cancer Agency, Vancouver, Canada I Olivotto, J Ragaz. Cancer and Leukemia Group B, Washington DC, USA D Berry, G Broadwater, C Cirrincione, H Muss, L Norton, R B Weiss. Cancer Care Ontario, Canada H T Abu-Zahra. Cancer Research Centre of the Russian Academy of Medical Sciences, Moscow, Russia S M Portnoi, Cancer Research UK Clinical Trials Unit (CRCTU), NCRI, Birmingham, UK S Bowden, C Brookes, J Dunn, I Fernando, M Lee, C Poole, D Rea, D Spooner. Cardiff Trialists Group, UK P J Barrett-Lee, R E Mansel, I J Monypenny. Case Western Reserve University, Cleveland, OH, USA N H Gordon. Central Oncology Group, Milwaukee. WI. USA H L Davis. Centre for Cancer Prevention. Wolfson Institute of Preventive Medicine, Queen Marv. University of London. UK J Cuzick. Centre Léon-Bérard. Lvon. France Y Lehingue, P Romestaing. Centre Paul Lamarque, Montpellier, France J B Dubois. Centre Regional Francois Baclesse, Caen, France T Delozier, B Griffon, J Mace Lesec' h. Centre René Huquenin, Paris, St Cloud, France P Rambert, Centro Oncologico, Trieste, Italy G Mustacchi, Charles University in Prague, First Faculty of Medicine, Department of Oncology of the First Faculty of Medicine and General Teaching Hospital, Czech Republic L Petruzelka, O Pribylova. Cheltenham General Hospital, UK J R Owen. Chemo NO Trial Group, Germany N Harbeck, F Janicke, C Meisner, M Schmitt, C Thomssen. Chicago University, IL, USA P Meier. Chinese Academy of Medical Sciences, Beijing, People's Republic of Ching (in collaboration with the Oxford CTSU) Y Shan, Y F Shao, X Wang, D B Zhao (CTSU: Z M Chen, H C Pan). Christie Hospital and Holt Radium Institute, Manchester, UK A Howell, R Swindell. Clinical Trial Service Unit, Oxford, UK (ie, EBCTCG Secretariat) J A Burrett, M Clarke, R Collins, C Correa, D Cutter, S Darby, C Davies, K Davies, A Delmestri, P Elphinstone, V Evans, L Gettins, J Godwin, R Gray, C Gregory, D Hermans, C Hicks, S James, A Kerr, E MacKinnon, M Lay, P McGale, T McHugh, R Peto, J Sayer, C Taylor, Y Wang. Coimbra Instituto de Oncologia, Portugal J Albano, C F de Oliveira, H Gervasio, J Gordilho. Copenhagen Radium Centre, Denmark H Johansen, H T Mouridsen, Dana-Farber Cancer Institute, Boston, MA, USA R S Gelman, J R Harris, D Hayes, C Henderson, C L Shapiro, E Winer. Danish Breast Cancer Cooperative Group, Copenhagen, Denmark P Christiansen, B Ejlertsen, M Ewertz, M-B Jensen, S Moller, H T Mouridsen. Danish Cancer Registry, Copenhagen, Denmark B Carstensen, T Palshof. Düsseldorf University, Germany H J Trampisch. Dutch Working Party for Autologous Bone Marrow Transplant in Solid Tumours, Amsterdam & Groningen, Netherlands O Dalesio, E G E de Vries, S Rodenhuis, H van Tinteren. Eastern Cooperative Oncology Group, Boston, MA, USA R L Comis, N E Davidson, R Gray, N Robert, G Sledge, L J Solin, J A Sparano, D C Tormey, W Wood, Edinburgh Breast Unit, UK D Cameron, U Chetty, J M Dixon, P Forrest, W Jack, I Kunkler. Elim Hospital, Hamburg, Germany J Rossbach. Erasmus MC/Daniel den Hoed Cancer Center, Rotterdam, Netherlands J G M Kliin, A D Treurniet-Donker, W L J van Putten, European Institute of Oncology, Milan, Italy N Rotmensz, U Veronesi, G Viale. European Organization for Research and Treatment of Cancer, Brussels, Belgium H Bartelink, N Bijker, J Bogaerts, F Cardoso, T Cufer, J P Julien, E Rutgers, C J H van de Velde. Evanston Hospital, IL, USA M P Cunningham, Finnish Breast Cancer Group, Finland R Huovinen, H Joensuu, Fondazione Maugeri Pavia, Italy A Costa, C Tinterri. Fondazione Michelangelo, Milan, Italy G Bonadonna, L Gianni, P Valagussa. Fox Chase Cancer Center, Philadelphia, PA, USA L J Goldstein. French Adjuvant Study Group (GFEA), Guyancourt, France J Bonneterre, P Fargeot, P Fumoleau, P Kerbrat, E Luporsi, M Namer, German Adjuvant Breast Group (GABG), Frankfurt, Germany W Eiermann, J Hilfrich, W Jonat, M Kaufmann, R Kreienberg, M Schumacher,

German Breast Cancer Study Group (BMFT), Freiburg, Germany G Bastert, H Rauschecker, R Sauer, W Sauerbrei, A Schauer, M Schumacher. German Breast Group (GBG), Neulsenburg, Germany J U Blohmer, S D Costa, H Eidtmann, B Gerber, C Jackisch, S Loibl, G von Minckwitz. Ghent University Hospital, Belgium A de Schryver, L Vakaet. GIVIO Interdisciplinary Group for Cancer Care Evaluation, Chieti, Italy M Belfiglio, A Nicolucci, F Pellegrini, M C Pirozzoli, M Sacco, M Valentini. Glasgow Victoria Infirmary, UK C S McArdle, D C Smith, S Stallard. Groote Schuur Hospital, Cape Town, South Africa D M Dent, C A Gudgeon, A Hacking, E Murray, E Panieri, ID Werner. Grupo Español de Investigación en Cáncer de Mama (GEICAM), Spain E Carrasco, M Martin, M A Segui. Gruppo Oncologico Clinico Cooperativo del Nord Est, Aviano, Italy E Galligioni. Gruppo Oncologico Dell'Italia Meridionale (GOIM), Rome, Italy M Lopez, Guadalaiara Hospital de 20 Noviembre, Mexico A Erazo, J Y Medina. Gunma University, Japan J Horiguchi, H Takei Guy's Hospital, London, UK I S Fentiman, J L Hayward, R D Rubens, D Skilton. Heidelberg University I, Germany H Scheurlen. Heidelberg University II, Germany M Kaufmann, H C Sohn, Helios Klinikum Berlin-Buch, Germany M Untch, Hellenic Breast Surgeons Society. Greece U Dafni, C Markopoulos. Hellenic Cooperative Oncology Group, Athens, Greece U Dafni, G Fountzilas. Hellenic Oncology Research Group, Greece D Mavroudis. Helsinki Deaconess Medical Centre, Finland P Klefstrom. Helsinki University, Finland C Blomgvist, T Saarto. Hospital del Mar, Barcelona, Spain M Gallen. Innsbruck University, Austria R Margreiter. Institut Claudius Regaud, Toulouse, France B de Lafontan, J Mihura, H Roche. Institut Curie, Paris, France B Asselain, R J Salmon, J R Vilcog, Institut Gustave-Roussy, Paris, France R Arriagada, C. Bourgier, C Hill, S Koscielny, A Laplanche, M G Le, M Spielmann. Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU, NCRI), 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 Chilvers, 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, Isrgel 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 Pannuti. 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 Institute of Oncology, Poland S Korzeniowski, J Skolvszewski, Kumamoto University Group, Japan M Ogawa, J Yamashita, Leiden University Medical Center, Netherlands E Bastiaannet, 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

S Anderson, G Bass, A Brown (deceased), J Bryant (deceased), J Costantino, J Dignam, B Fisher, C Geyer, E P Mamounas, S Paik, C Redmond, S Swain, L Wickerham, N Wolmark. Nolvadex Adjuvant Trial Organisation, London, UK M Baum, I M Jackson (deceased), M K Palmer. North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN, USA E Perez, J N Ingle, V J Suman, North Sweden Breast Cancer Group, Umeå, Sweden N O Bengtsson, S Emdin, H Jonsson. North-West Oncology Group (GONO), Italy L Del Mastro, M Venturini. North-Western British Surgeons, Manchester, UK J P Lythgoe, R Swindell. Northwick Park Hospital, London, UK M Kissin. Norweaian Breast Cancer Group, Oslo, Norway B Erikstein, E Hannisdal, A B Jacobsen, J E Varhaug. Norwegian Radium Hospital, Oslo, Norway B Erikstein, S Gundersen, M Hauer-Jensen, H Host, A B Jacobsen, R Nissen-Meyer. Nottingham City Hospital, UK R W Blamey, A K Mitchell, D A L Morgan, J F R Robertson, Oita Prefectural Hospital, Japan H Ueo. Oncofrance, Paris, France M Di Palma, G Mathe (deceased), J L Misset. Ontario Clinical Oncology Group, Hamilton, Canada M Levine, K I Pritchard, T Whelan. Osaka City University, Japan K Morimoto. Osaka National Hospital, Japan K Sawa, Y Takatsuka, Oxford Radcliffe Hospitals NHS Trust, Churchill Hospital, Oxford, UK E Crossley, A Harris, D Talbot, M Taylor. PACS Adjuvant Study Group, France A L Martin, H Roche. Parma Hospital, Italy G Cocconi, B di Blasio. Petrov Research Institute of Oncology, St Petersburg, Russia V Ivanov, R Paltuev, V Semiglazov. Piedmont Oncology Association, Winston-Salem, NC, USA J Brockschmidt, M R Cooper. Pretoria University, South Africa CI Falkson. Royal Marsden NHS Trust, London and Sutton, UK R A' Hern, S Ashley, M Dowsett, A Makris, T J Powles, I E Smith, J R Yarnold, St George's Hospital, London, UK J C Gazet.

St George Hospital, Sydney, Australia L Browne, P Graham. St Luke's Hospital, Dublin, Ireland N Corcoran. Sardinia Oncology Hospital A Businico, Cagliari, Sardinia N Deshpande, L di Martino. SASIB International Trialists, Cape Town, South Africa P Douglas, A Hacking, H Host, A Lindtner, G Notter. Saskatchewan Cancer Foundation, Regina, Canada A J S Bryant, G H Ewing, L A Firth, J L Krushen-Kosloski. Scandinavian Adjuvant Chemotherapy Study Group, Oslo, Norway R Nissen-Meyer. South Sweden Breast Cancer Group, Lund, H Anderson, F Killander, P Malmstrom, L Ryden. South-East Sweden Breast Cancer Group, Linköping, Sweden L-G Arnesson, J Carstensen, M Dufmats, H Fohlin, B Nordenskjold, M Soderberg. South-Eastern Cancer Study Group and Alabama Breast Cancer Project, Birmingham, AL, USA J T Carpenter. Southampton Oncology Centre, UK N Murray, G T Royle, P D Simmonds. Southwest Oncology Group, San Antonio, TX, USA K Albain, W Barlow, J Crowley, D Hayes, J Gralow, S Green, G Hortobagyi, R Livingston, S Martino, C K Osborne, P M Ravdin. Stockholm Breast Cancer Study Group, Sweden J Adolfsson, J Bergh, T Bondesson, F Celebioglu,

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Comparisons between different polychemotherapy 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) Published online December 6, 2011 in The Lancet

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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.



Taxane-plus-anthracycline-based regimens vs (L) the SAME, or (R) MORE, non-taxane chemo. 11167 women 33084 women 50 50 RR 0.86 (0.79-0.93) **Breast cancer mortality** RR 0.88 (0.81-0.95) **Breast cancer mortality** Logrank 2p = 0.001 Logrank 2p = 0.000540 40 5-y gain 1.4% (se 0.4) 8-y gain 2.8% (se 0.9) 30 30 Control 23.9% 21.1% 20 20 16.7% Tax + anth % ± se % ± se Control **11**.5% 10 10 10.1% Tax + anth 0 0 3 4 5 3 8 5 years 2 4 6 2 years Death rates (% / year: total rate - rate in women without recurrencYEUbX``c[fUb_'UbU'mgYg Allocation Year 5+ Year 5+ Years 0 – 4 Years 0 – 4 Tax + anth 3.21 SE 0.11 2.48 SE 0.13 2.01 SE 0.06 2.37 SE 0.20 3.58 SE 0.13 3.06 SE 0.16 2.26 SE 0.21 Control 2.30 SE 0.07 Rate ratio 0.88 SE 0.05 0.82 SE 0.07 0.87 SE 0.04 0.97 SE 0.13 (O-E) / V -46·4 / 348·5 –33·3 / 172·3 -77·0 / 549·5 -1·7 / 57·4



Taxane comparisons, subdivided according to:

(a) how the non-taxane treatments compare
(active = control, active = ½ control,
or an intermediate ratio), and

(b) whether the cycles of taxane are given <u>concurrently</u> (©) with the anthracycline, or whether taxanes are given alone (†).

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

	Deaths	Women	Taxar	e deaths		
Category	Allocated	Allocated	Logran	k Variance	e <u>Ratio of annu</u> Taxane	ual death rates
outegory	taxane	non tax.	0 2	010 2		
(a) Same, or more, n	on-taxane ch	emo, for d	control	$s^* (\gamma^2 = 2)$	2·0: p = 0·6: NS)	
<u>(u) ounie, er mere, n</u>				<u> </u>		
Same (1×) † ie, unconfounded	1169/5590 (20·9%)	1306/5577 (23·4%)	-79.8	520.8	-#-	0·86 (se 0·04)
More (<2×) †	339/4282 (7·9%)	407/4302 (9·5%)	-31.3	172.3		0·83 (se 0·07)
More (<2×) ©	587/7071 (8·3%)	665/7076 (9·4%)	-32.1	278.9		0·89 (se 0·06)
More (≈2×) †	546/5185 (10·5%)	590/5168 (11·4%)	−15·8	259.3		0·94 (se 0·06)
(b) Taxane (D/P*) scl	hedule $(\chi_3^2 = 1)$	•0; p = 0·8	; NS)		1	
4(D100) q3w †	816/6480 (12·6%)	887/6476 (13•7%)	-31.6	338-1	-#	0·91 (se 0·05)
Other docetaxel	716/8396 (8·5%)	844/8409 (10·0%)	-58.4	366.9		0·85 (SE 0·05)
4(P175) q3w †	572/3528 (16·2%)	612/3502 (17·5%)	-30.1	274.4		0·90 (se 0·06)
Other paclitaxel	537/3724 (14·4%)	625/3736 (16·7%)	-38.9	251.9		0·86 (se 0·06)
(c) Concurrent endo	crine therapy	<u>if ER+?</u> (χ	$x_1^2 = 0.2$; 2p = 0·	6; NS)	
Yes	87/713 (12·2%)	93/723 (12·9%)	-2.7	40.5		
No (any endocrine o after chemo ended	nly 2554/21415) (11·9%)	2875/21400 (13·4%)) -158.3	1136.0		0·87 (se 0·03)
Total	2641/ 22128 (11·9%)	2968/ 22123 (13·4%)	−161·0	1176.5	÷	0·872 (SE 0·027) 2p < 0·00001
- - 99% or <-> 95	5% confidence int	ervals		_		
01-1	hal hatana na				Towana hatter	Non tax better
Giol	bai neterogeneity	y: χ ₁₀ = /·1;	p = 0∙7		Taxane better	
					i reatment effe	ect ∠p < 0·00001

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 NODAL STATUS before chemotherapy



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

Catagony	Deaths Allocated	Women Allocated	Taxan Logran	e deaths k Variance	e <u>Ratio</u>	of annual of	death rates
Calegory	taxane	non-tax.	0-E	OF U-E			
(d) Entry age (trend	d χ_1^2 = 3.5; 2p =	0·06)					
Age < 45	871/5930 (14·7%)	928/5927 (15·7%)	-36.7	384.6			0·91 (se 0·05)
45 - 54	835/7747 (10·8%)	932/7720 (12∙1%)	-41.4	372.3			0·89 (se 0·05)
55 - 69	735/6572 (11·2%)	877/6570 (13·3%)	-69.0	346.5	-		0·82 (SE 0·05)
70+	51/314 (16·2%)	81/343 (23·6%)	-11.4	24∙4 ←			0·63 (se 0·16)
Age unknown	149/1565 (9·5%)	150/1563 (9·6%)	-2.5	48.6			
(e) Nodal status be	fore chemo (tre	and $\chi_1^2 = 0$	3; 2p =	0·6; NS)		
N0/N-	120/2104 (5·7%)	132/2070 (6·4%)	-6.0	61.0			0·91 (se 0·12)
N1-3	520/6981 (7·4%)	599/6977 (8·6%)	-41.9	262.1	_		0·85 (SE 0·06)
N4+	783/5012 (15·6%)	849/5062 (16·8%)	-29.9	338.8			0·92 (SE 0·05)
Other / unknown	1218/8031 (15•2%)	1388/8014 (17·3%)	-83.1	514.6	-		0·85 (se 0·04)
Total	2641/ 22128 (11·9%)	2968/ - 22123 (13·4%)	-161.0	1176-5		$\left \right\rangle$	0·872 (SE 0·027) 2p < 0·00001
- ■ - 99% or <⊃	95% confidence int	ervals		_	0.5	1.0	1.5
GI	obal heterogeneit	y: $\chi^2_{10} = 7.1$;	o = 0·7		Taxane be	etter	Non-tax. better
	0				Treatm	ent effect 2	2p < 0·00001



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

	Deaths	Women	Taxan	e deaths		
Catagory	Allocated	Allocated	Logran	k Varianc	e Ratio of ann	ual death rates
Category	laxane	non-tax.	0-E	01 U-E	Taxane	i Non-lax.
(f) ER status ($\chi_1^2 = 0.1$;	; 2p = 0·7; NS	5)			I	
ER-poor	1087/5883 (18·5%)	1271/6027 (21·1%)	-78.0	505.0	-	0·86 (se 0·04)
ER+	1044/12848 (8·1%)	1164/12790 (9·1%)	0 -67.1	502.3	-	0·87 (se 0·04)
ER unknown	510/3397 (15·0%)	533/3306 (16·1%)	-15.9	169-1		0·91 (se 0·07)
Subsets of ER+					I	
ER+ HER2-	273/4613 (5·9%)	296/4656 (6·4%)	-11.3	136-2	_ _ _ _	0·92 (se 0·08)
ER+ HER2+	98/978 (10-0%)	114/1022 (11·2%)	-6.2	47.5	_	0·88 (se 0·14)
ER+, age < 55	666/8316 (8·0%)	725/8223 (8·8%)	-37.7	317.9	-#	0·89 (se 0·05)
ER+, 55 - 69	355/4338 (8·2%)	413/4368 (9·5%)	-25.8	174.5		0·86 (se 0·07)
ER+, poorly differentiated	440/3362 (13·1%)	398/3330 (12·0%)	14-8	189.8	I—	<u>1·</u> 08 (se 0·08)
ER+, moderately differentiated	273/5552 (4·9%)	354/5595 (6·3%)	-38-0	143-0	#	0·77 (se 0·07)
ER+, well differentiated	48/1501 (3·2%)	74/1430 (5·2%)	-11.1	28.7 _		0·68 (SE 0·16)
Total	2641/ 22128 (11·9%)	2968/ 22123 (13·4%)	−161·0	1176·5	↓	0·872 (SE 0·027) 2p < 0·00001
-∎- 99% or <⇒ 95%	% confidence int	ervals		_	0.2	1·0 1·5
Globa	al heterogeneity	$\chi^2_{10} = 7.1;$	p = 0·7		Taxane better	Non-tax. better
					Treatment eff	ect 2p < 0.00001

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 C100x14 oral M40x2 iv F600x2 iv

Standard 4AC:

Four 3-weekly cycles of A60 iv C600 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



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

(mg/m² x frequency/cycle)

CAF:

Six 4-weekly cycles of C100x14 oral A40x2 iv F500x2 iv

CEF:

Six 4-weekly cycles of C75x14 oral E60x2 iv F500x2 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



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

Category	Deaths/ Allocated anthr.	/ <u>Women</u> Allocated CMF	Anthr Logranl O-E	<u>deaths</u> Variand of O-E	ce	Ratio of annu Anthr.	al death rates : CMF
(a) Cumulative anthracy	cline dosa	age, if dos	e/cycle	e ≥ A 60/E	<u>90</u> *	I	
(trend χ ₁ ² = 8⋅0; 2p =	0·005)						
A360 or E720-800: eg, CAF/CEF	378/2082 (18·2%)	475/2097 (22·7%)	-50-0	198-0		∎†-	0·78 (se 0·06)
A300 or E400-480	396/2766 (14·3%)	472/2770 (17∙0%)	-35-9	183-1		∎∔	0·82 (se 0·07)
A240: standard 4AC	877/2565 (34·2%)	886/2557 (34·6%)	-8.5	405-6		-1	— 0·98 (se 0·05)
White: dose/cycle < A60/E90	358/1530 (23·4%)	357/1502 (23·8%)	-11.1	160-1			0·93 (se 0·08)
(b) Cyclophosphamide	in CMF ora	$\frac{\mathrm{al/iv}}{\mathrm{al/iv}} \left(\chi_1^2 = 0\right)$)·9; 2p	= 0·3; N	IS)	I	
C100×14 oral/cycle	1651/6530 (25·3%)	1834/6525 (28·1%)	-98-8	788-8			0·88 (se 0·03)
C600×2 iv/cycle	358/2413 (14·8%)	356/2401 (14·8%)	-6.6	157.9			0·96 (se 0·08)
(c) Concurrent endocrin	e therapy	<u>if ER+?</u> (χ	$2^{2}_{1} = 0.0$; 2p = 1	·0; NS)	I	
Yes	57/502 (11·4%)	62/502 (12·4%)	-2.9	29-0		•	
No (any endocrine only after chemo ended)	1952/8441 (23·1%)	2128/8424 (25·3%)	-102.5	917.8			0·89 (se 0·03)
Total	2009/ 8943 (22·5%)	2190/ 8926 (24·5%)	−105·4	946·8			0·895 (SE 0·031 2p = 0·0006
- ■ - 99% or <=> 95% o	onfidence int	ervals		-	0.5	1	•0 1.5
Global h	eterogeneity	y: χ _e ² = 9·9; μ	0 = 0·1		Ant	hr. better	CMF better
		U			1	reatment effe	ect 2p = 0·0006

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

0-1	Deaths Allocated	/Women Allocated	Anth Logran	r. deaths k Varianc	e <u>Ratio o</u>	f annual d	eath rates
Category	anthr.	CMF	0-E	of O-E	Α	Nnthr. : CN	IF
(d) Entry age (trend	$\chi_1^2 = 0.0; 2p =$	0·9; NS)				I	
Age < 45	871/3398 (25·6%)	991/3454 (28•7%)	-54.8	422.8	-	—	0·88 (se 0·05)
45 - 54	738/3399 (21·7%)	773/3356 (23·0%)	-30.6	344-3	_		0·91 (se 0·05)
55 - 69	375/1961 (19·1%)	396/1920 (20·6%)	-20.2	169.3			0·89 (se 0·07)
70+	18/106 (17·0%)	25/112 (22·3%)	-2.2	8.7			
Age unknown	7/79 (8·9%)	5/84 (6·0%)	2.4	1.8			
<u>(e) Nodal status</u> (tro	end χ <mark>²</mark> = 0·9; 2p	o = 0·3; NS	5)			1	
N0/N-	461/3865 (11·9%)	541/3869 (14·0%)	-40.5	233-1	—		0·84 (se 0·06)
N1-3	520/2442 (21·3%)	543/2418 (22·5%)	-10.0	243-4	-		– 0·96 (se 0·06)
N4+	612/1234 (49·6%)	647/1233 (52·5%)	-23.1	273-4	_		0·92 (se 0·06)
Other / unknown	416/1402 (29·7%)	459/1406 (32∙6%)	-31.9	196.8	—[0·85 (se 0·07)
Total	2009/ 8943 (22·5%)	2190/ 8926 (24·5%)	−105·4	946·8		$\left \right\rangle$	0·895 (SE 0·031) 2p = 0·0006
- ■ - 99% or <>>	95% confidence int	tervals		_	0.5	1.0	1.5
Gl	obal heterogeneit	y: χ ₆ ² = 9·9; ι	o = 0·1		Anthr. bette	er	CMF better
		v			Treatme	nt effect 2	p = 0·0006

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

Category	Deaths/ Allocated anthr.	Women Allocated CMF	Anth Logran O-E	r. deaths k Varianc of O−E	e <u>Ratio</u>	of annual d Anthr. : CM	eath rates IF
(f) ER status ($\chi_1^2 = 0.1$; 2p	o = 0∙8; NS	5)					
ER-poor	1201/4488 (26·8%)	1287/4518 (28·5%)	3 -43.7	564.6			0·93 (se 0·04)
ER+	569/3279 (17·4%)	610/3257 (18·7%)	-26.5	267.0			0·91 (se 0·06)
ER unknown	239/1176 (20·3%)	293/1151 (25·5%)	-35-2	115-2		-+	0·74 (se 0·08)
Subsets of ER+							
ER10–99 fmol/mg	247/1072 (23·0%)	279/1094 (25·5%)	-21.2	108-3			0·82 (se 0·09)
ER100+ fmol/mg	86/450 (19·1%)	116/450 (25⋅8%)	- 15·4	42.0	B		0·69 (se 0·13)
ER+, age < 55	426/2359 (18∙1%)	461/2345 (19·7%)	-22.9	202.3	_		0·89 (se 0·07)
ER+, 55 - 69	134/846 (15·8%)	140/847 (16·5%)	-3.6	61.1			0·94 (se 0·12)
ER+, poorly differentiated	131/868 (15·1%)	130/793 (16·4%)	-4-1	52.7			
ER+, moderately/well differentiated	125/952 (13•1%)	136/1047 (13·0%)	-1.8	58.3			
Total	2009/ 8943 (22·5%)	2190/ 8926 (24·5%)	−105·4	946·8		$\left \right\rangle$	0·895 (SE 0·031) 2p = 0·0006
- ■ - 99% or <>> 95% co	onfidence int	ervals		_	0.5	1.0	1.5
Global h	eterogeneity	γ: χ ₆ ² = 9·9; ∣	p = 0·1		Anthr. be	tter	CMF better
		-			Treatn	nent effect 2	2p = 0·0006

Trials of chemotherapy vs no adjuvant chemotherapy

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

- Standard CMF vs nil







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

	Deaths	/Women	Chem	o. deaths			
Category	Allocated	Allocated	Logran	k Varianc	e Ratio o	f annual death	rates
Oalegoly	chemo.	control	0-1	010-2			·
(a) Cumulative anthracy	cline dosa	age. if dos	e/cvcle	e >A60/E	90*		
$(\chi_1^2 = 1.5; 2p = 0.2; N)$	S)						
A360: CAF	324/1177 (27·5%)	456/1143 (39·9%)	-35.3	80-3	_∎_†	-	0·64 (se 0·09)
A300			(no	o trials)	I		
A240/E360: standard 4AC/EC	212/747 (28·4%)	265/792 (33·5%)	-25.6	100.5			0·78 (se 0·09)
White: dose/cycle < A60 or E90	880/2830 (31·1%)	980/2798 (35·0%)	-79-0	400.5]-	0·82 (se 0·05)
(Excludes CMF trials)					· ·		
(b) Anthracycline tested	!* (χ ₂ ² = 2·1	; 2p = 0·4;	NS)		I		
Doxorubicin (A)	973/2626 (37·1%)	1185/2570 (46∙1%)	-106-1	370.4	-#	-	0·75 (se 0·05)
Epirubicin (E)	293/1283 (22·8%)	318/1283 (24·8%)	-20.5	138-4	<u> </u>		0·86 (se 0·08)
A or E	150/845 (17·8%)	198/880 (22·5%)	-13-3	72.5]	0·83 (se 0·11)
No anthracycline							
(standard CMF or near-standard CMF)	658/2665 (24·7%)	790/2588 (30·5%)	-89-1	320-1	-#	_	0·76 (se 0·05)
(c) Concurrent endocrin	e therapy	<u>if ER+?</u> (χ	2 ² = 0·0	; 2p = 1·	0; NS)		
Yes	922/3515 (26·2%)	1107/3518 (31·5%)	-106-4	448-2	-	\mathbf{F}	0·79 (se 0·04)
No (any endocrine only after chemo ended)	805/2585 (31·1%)	890/2482 (35·9%)	-85-4	363.7	-		0·79 (se 0·05)
Random †	347/1319 (26·3%)	494/1321 (37·4%)	-37-2	89-4		_	0·66 (se 0·09)
Total	2074/ 7419 (28·0%)	2491/ 7321 (34·0%)	-229 ∙0	901·4	÷	. 0	•776 (SE 0•029) 2p < 0∙00001
- ■ 99% or <>> 95% o	onfidence inf	tervals		-	0.5	1.0	1.5
Global h	eterogeneit	y: χ ² = 8·4; p	o = 0·3		Chemo. bet	ter Che	mo. worse
	J	,			Treatme	nt effect 2p < 0	0.00001

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



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





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

0-1	Deaths Allocated	/Women Allocated	Anth Logran	<u>. deaths</u> k Variance	Ratio of	annual	death rates
Category	anth.	control	0-Е	of O-E	/	Anth. : C	Control
(d) Entry age (tre	nd $\chi_1^2 = 2.0$; 2p =	0·2; NS)			I		
Age < 45	135/402 (33·6%)	127/353 (36·0%)	-4.9	53-0		-	0·91 (se 0·13)
45 - 54	338/1115 (30·3%)	419/1175 (35·7%)	-34.9	139.8	#		0·78 (se 0·07)
55 - 69	899/2995 (30·0%)	1071/2956 (36·2%)	-88.5	377.0	-	_	0·79 (se 0·05)
70+	43/225 (19·1%)	84/232 (36·2%)	-11.7	11∙4 ←	اا		0·36 (se 0·19)
Age unknown	1/17 (5·9%)	0/17 (0·0%)	0.2	0.1	l l		
(e) Nodal status ((trend $\chi_1^2 = 0.0$; 2p	o = 0·9; NS	5)		Ι		
N0/N-	122/789 (15·5%)	137/761 (18·0%)	-12.0	56-9			0·81 (se 0·12)
N1-3	513/2257 (22·7%)	604/2217 (27·2%)	-51.3	214.1	-#		0·79 (se 0·06)
N4+	575/1226 (46·9%)	741/1295 (57·2%)	-53.7	222.3	-#		0·79 (se 0·06)
Other / unknown	206/482 (42·7%)	219/460 (47·6%)	-22.8	88.0			0·77 (se 0·09)
Total	1416/ 4754 (29·8%)	1701/ 4733 (35∙9%)	-139∙9	581·3	\Rightarrow		0·786 (SE 0·037) 2p < 0·00001
- - 99% or <i><</i> ⊐	> 95% confidence int	tervals			0.5	1.0	1.5
	Global heterogeneit	y: χ <mark>²</mark> = 5·8; p	o = 0·4		Anth. bette	r	Anth. worse
		0			The stars are	4 . 66 4	0

Treatment effect 2p < 0.00001



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

Category	Deaths/ Allocated anth.	Women Allocated control	Anth Logran O-E	<u>. deaths</u> k Varianc of O-E	e <u>Ratio of a</u> An	nnual death rates ith. : Control	
(f) ER status ($\chi_1^2 = 0.1$; 2p	o = 0∙7; NS	5)					
ER-poor	403/1095 (36·8%)	464/1043 (44·5%)	-40.5	180-4	-#	0.80 (se 0·07)
ER+	831/3100 (26·8%)	1063/3177 (33·5%)	-84.6	328.5		0.77 (se 0·05)
ER unknown	182/559 (32·6%)	174/513 (33·9%)	-14.9	72.3	—	0·81 (se 0·11)
Subsets of ER+							
ER+, chemo+end. vs end. only ‡	659/2622 (25·1%)	853/2675 (31.9%)	-56-2	247.0		0.80 (se 0·06)
ER10–99 fmol/mg	416/1371 (30·3%)	544/1442 (37·7%)	-35.3	162.5		0·80 (se 0·07)
ER100+ fmol/mg	274/1146 (23·9%)	337/1160 (29·1%)	-20.6	95.6	P	0·81 (se 0·09)
ER+, age < 55	250/845 (29·6%)	316/943 (33·5%)	-19.4	102-4		0·83 (se 0·09)
ER+, 55 - 69	542/2071 (26·2%)	677/2055 (32·9%)	-53.9	215.3		_ 0·78 (se 0·06)
ER+, poorly differentiated	100/461 (21·7%)	120/477 (25•2%)	-12.2	45∙8	_	0·77 (se 0·13)
ER+, moderately/well differentiated	228/985 (23·1%)	286/1026 (27·9%)	-27.8	112.8		0.78 ((se 0·08)
Total	1416/ 4754 (29·8%)	1701/ 4733 (35∙9%)	−139·9	581·3	\Rightarrow	0∙786 (₂p <	SE 0·037) 0·00001
- ■ - 99% or <-> 95% co	onfidence int	ervals		_	0.5	1.0	1.5
Global he	eterogeneit	y: χ ₆ ² = 5·8; μ	o = 0·4		Anth. better	Anth. wors	se
		-			Treatment	effect 2p < 0.00001	


EBCTCG, Lancet 2011

Halving <u>big</u> risks and halving <u>small</u> risks by chemotherapy

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