### Adjuvant polychemotherapy in oestrogen-receptor-poor breast cancer: meta-analysis of individual patient data from the randomised trials

### The Lancet 2008; 371: 29-40

# Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

### Web site figures

Each figure is in three parts, corresponding to the three endpoints: (i) recurrence, (ii) breast cancer mortality and (iii) death from any cause.

- **Web Fig. 1** Polychemotherapy versus not in ER-poor disease, subdivided first by type of comparison (absence or presence of tamoxifen in both treatment groups) and then by age at randomisation: event rate ratios for recurrence, breast cancer mortality and death from any cause
- **Web Fig. 2** Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of tamoxifen in both treatment groups): event rate ratios for recurrence, breast cancer mortality and death from any cause
- Web Fig. 3 Tamoxifen versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of chemotherapy in both treatment groups): event rate ratios for recurrence, breast cancer mortality and death from any cause
- **Web Fig. 4** Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) and age at randomisation: 10-year probabilities of recurrence, breast cancer mortality and death from any cause
- Web Fig. 5Polychemotherapy versus not in ER-poor disease, by type of comparison<br/>(absence or presence of tamoxifen in both treatment groups) for patients with<br/>entry age < 50: 10-year probabilities of recurrence, breast cancer mortality and<br/>death from any cause
- Web Fig. 6 Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) for patients with entry ages 50-69: 10-year probabilities of recurrence, breast cancer mortality and death from any cause
- Web Fig. 7 Polychemotherapy versus not in ER-poor disease, subdivided first by age at

randomisation and then by nodal status: event rate ratios for recurrence, breast cancer mortality and death from any cause

- Web Fig. 8Polychemotherapy versus not in ER-poor disease, by various subgroups: event<br/>rate ratios for recurrence, breast cancer mortality and death from any cause
- **Web Fig. 9** Polychemotherapy versus not in ER-poor disease: trial details and recurrence, breast cancer mortality and all-cause mortality rate ratios in each of 46 separate trials
- **Web Fig. 10** Tamoxifen versus not in ER-poor disease: trial details and recurrence, breast cancer mortality and all-cause mortality rate ratios in each of 50 separate trials
- **Web Fig. 11** Perioperative polychemotherapy versus no adjuvant cytotoxic in ER-poor disease, subdivided by nodal and menopausal status: trial details and recurrence, breast cancer mortality and all-cause mortality rate ratios in each of 4 separate trials

Web Fig. 1(i). Polychemotherapy versus not in ER-poor disease, subdivided first by type of comparison (absence or presence of tamoxifen in both treatment groups) and then by age at randomisation: event rate ratios for recurrence



Web Fig. 1(ii). Polychemotherapy versus not in ER-poor disease, subdivided first by type of comparison (absence or presence of tamoxifen in both treatment groups) and then by age at randomisation: event rate ratios for breast cancer mortality

Entry age	Deaths/ Allocated	Women Allocated	Polychei Logrank	MO. deaths	Ratio of annual death	rates
Entry age	Foly	control	0-L	010-2	Poly Control	
(a) Polychemothera	apy alone v	ersus no	adjuva	<u>nt</u> (trend'	* χ <sub>1</sub> <sup>2</sup> = 0·0; 2p = 0·99; Ν	S)
< 50	217/915 (23·7%)	260/807 (32·2%)	-28.4	97.8		0·75 (se 0·09)
50 – 59	146/464 (31·5%)	182/479 (38·0%)	–13·8	65·3		0-81 (se 0-11)
60 – 69	96/264 (36·4%)	114/275 (41·5%)	-11·2	40.4		0·76 (se 0·14)
70+	5/14	7/21	_1·5	2∙0		
Unknown	1/4	0/1				
(a) subtotal	465/ 1661 (28·0%)	563/ 1583 (35-6%)	-54-9	205-5		0· <b>77 (</b> SE <b>0·06</b> ) 2p = 0·0001
(b) Polychemothera	apy plus ta	moxifen v	ersus t	tam alone	<u>e</u> (trend* $\chi_1^2 = 3.8$ ; 2p =	0.05)
< 50	24/100 (24·0%)	27/85 (31·8%)	_5·7	8-1		0·49 (se 0·25)
50 – 59	274/756 (36·2%)	210/496 (42·3%)	-30·9	92.4		0·72 (se 0·09)
60 – 6 <del>9</del>	323/733 (44·1%)	224/498 (45 <b>·</b> 0%)	-3.7	107.5		0·97 (se 0·09)
70+	21/61	23/55	-3.7	6-9		
Unknown	0/0	0/1				
(b) subtotal	642/ 1650 (38·9%)	484/ 1135 (42·6%)	-44·0	214-8		0· <b>81 (</b> SE <b>0·06</b> ) 2p = 0·003
(a+b) All polychem	otherapy v	ersus not	(trend	$\chi_1^2 = 1.9;$	2p = 0·17; NS)	
< 50	241/1015 (23·7%)	287/892 (32·2%)	<b>_34</b> ∙1	105.9		0·72 (se 0·08)
50 – 59	420/1220 (34·4%)	392/975 (40·2%)	_44·7	157.7		0·75 (se 0·07)
60 – 69	419/997 (42·0%)	338/773 (43·7%)	_14·9	147.8		0·90 (se 0·08)
70+	26/75	30/76	<i>_</i> 5·2	8-9		
Unknown	1/4	0/2				
(a+b) Total	1107/ 3311 (33·4%)	1047/ 2718 (38-5%)	-98·9	420-3	↓ 0	0· <b>79 (se 0·04</b> ) 2p < 0·00001
-∎- 99% or <->> 95% co * Difference betwe	nfidence intervals <b>Ben</b>			0 P	0-5 1-0 olychemo. better Polych	1.5 2.0 emo. worse

Web Fig. 1(iii). Polychemotherapy versus not in ER-poor disease, subdivided first by type of comparison (absence or presence of tamoxifen in both treatment groups) and then by age at randomisation: event rate ratios for death from any cause

Entry age	Deaths/wom Allocated Poly	an-years Allocated control	Polychei Logrank O-E	mo. deaths Variance of O-E	Ratio of annual de Poly : Co	eath rates ntrol
(a) Polychemothe	rapy alone v	ersus no	adjuva	<u>nt</u> (trend*	$\chi_1^2 = 0.0; 2p = 0.98$	; NS)
< 50	238/9967 (2·4%/y)	276/8356 (3·3%/y)	-28.7	106.0		0·76 (se 0·09)
50 – 59	173/5197 (3·3%/y)	208/4745 (4·4%/y)	_13·9	75 <b>·</b> 8		0·83 (se 0·10)
60 – 69	123/2614 (4∙7%/y)	144/2494 (5·8%/y)	_13·9	51.8		0·76 (se 0·12)
70+	8/144	12/179	-1·7	3.3		
Unknown	1/31	0/0				
(a) subtotal	543/ 17953 (3∙0%/y)	640/ 15774 (4-1%/y)	<b>-58</b> ∙2	236-9	$\diamond$	0·78 (se 0·06) 2p = 0·0002
(b) Polychemothe	rapy plus ta	moxifen v	ersus t	tam alone	$\chi_1^2 = 4.2; 2$	p = 0·04)
< 50	25/702 (3·6%/y)	27/560 (4·8%/y)	-5.7	8.0		– 0·49 (se 0·25)
50 – 59	310/6480 (4·8%/y)	222/3750 (5·9%/y)	–28·9	101.0		0·75 (se 0·09)
60 – 69	390/5893 (6·6%/y)	262/3799 (6·9%/y)	-3.6	128.3		– 0.97 (se 0.09)
70+	31/387	30/308	-2·6	10.1		
Unknown	0/0	0/21				
(b) subtotal	756/ 13462 (5⋅6%/y)	541/ 8438 (6·4%/y)	-40.9	247.3	$\rightarrow$	0·85 (SE 0·06) 2p = 0·009
(a+b) All polycher	notherapy v	ersus not	(trend	$\chi_1^2 = 2.3; 2$	2p = 0·13; NS)	
< 50	263/10669 (2·5%/y)	303/8916 (3∙4%/y)	-34·4	114.0		0·74 (se 0·08)
50 – 59	483/11677 (4∙1%/y)	430/8495 (5∙1%/y)	_42·8	176.8		0·78 (se 0·07)
60 – 69	513/8507 (6∙0%/y)	406/6293 (6·5%/y)	_17·6	180.1		0·91 (se 0·07)
70+	39/531	42/487	_4·2	13.4		
Unknown	1/31	0/21				
(a+b) Total	1299/ 31415 (4.1%/y)	1181/ 24212 (4·9%/y)	<b>-99</b> ∙0	484·2	$\Diamond$	0·82 (se 0·04) 2p < 0·00001
-∎ 99% or <>> 95% o	confidence intervals			0 Pc	0.5 1.0 Diychemo. better Pc	1.5 2.0 lychemo. worse

Web Fig. 2(i). Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of tamoxifen in both treatment groups): event rate ratios for recurrence

Catagony	Events/ Allocated	Women Allocated	Polycher Logrank	no. event	e <u>Ratio of annu</u>	al event rates
Category	POly	CONTROL	0-E	01 O-E	Poly	
<u>(a) Age &lt; 50</u>						
Poly alone vs. Nil	307/915 (33∙6%)	374/807 (46·3%)	-60.6	133.6	-	0·64 (se 0·07)
Poly + Tam vs. Tam	30/100 (30·0%)	36/85 (42·4%)	<b>-9</b> ∙3	10.1		0·40 (se 0·21)
(a) subtotal	337/ 1015 (33-2%)	410/ 892 (46·0%)	-70.0	143.7	$\diamond$	0·61 (SE 0·07) 2p < 0·00001
Difference between treatment effects	in 2 catego	ries: χ <sub>1</sub> <sup>2</sup> = 2·	1; 2p = 0	·15; NS		
<u>(b) Age 50 – 59</u>						
Poly alone vs. Nil	180/464 (38·8%)	230/479 (48∙0%)	<i>–</i> 25·7	78·5		0·72 (se 0·10)
Poly + Tam vs. Tam	325/756 (43∙0%)	247/496 (49·8%)	–45·3	1 <b>03·0</b>		0·64 (se 0·08)
(b) subtotal	505/ 1220 (41-4%)	477/ 975 (48-9%)	<b>-71</b> ∙0	181.5	$\diamond$	0·68 (SE 0·06) 2p < 0.00001
Difference between treatment effects	in 2 catego	ries: χ <sub>1</sub> <sup>2</sup> = 0·	6; 2p = 0	-46; NS		
<u>(c) Age 60 – 69</u>						
Poly alone vs. Nil	117/264 (44·3%)	134/275 (48·7%)	–16·9	46.1		0·69 (se 0·12)
Poly + Tam vs. Tam	368/733 (50·2%)	263/498 (52·8%)	–16·7	119.1		— 0·87 (se 0·09)
(c) subtotal	485/ 997 (48·6%)	397/ 773 (51.4%)	-33-6	165-2	$\diamond$	0·82 (SE 0·07) 2p = 0·009
Difference between treatment effects	in 2 catego	ries: χ <sub>1</sub> <sup>2</sup> = 1.	7; 2p = 0	·19; NS		
- <b></b> 99% or <->> 95% conf	idence intervals			 0	0.5 1	-0 1.5 2.0
(a+b+c): Difference bei presence/absence of tar	tween polyc n: age–strat	hemotheraj ified $\chi_1^2 = 0$ .	oy effects 0; 2p = 0	s in •84; NS	Polychemo. better	Polychemo. worse

Web Fig. 2(ii). Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of tamoxifen in both treatment groups): event rate ratios for breast cancer mortality

Category	<u>Deaths/</u> Allocated Poly	Women Allocated control	Polycher Logrank O–E	no. deaths Variance of O–E	Ratio of annu Poly	ial death rates : Control
<u>(a) Age &lt; 50</u>						
Poly alone vs. Nil	217/915 (23·7%)	260/807 (32·2%)	<b>-28</b> ∙4	97.8	-	0·75 (SE 0·09)
Poly + Tam vs. Tam	24/1 <b>00</b> (24 <b>·0%</b> )	27/85 (31·8%)	<i>_</i> 5·7	8.1		0·49 (SE 0·25)
(a) subtotal	241/ 1015 (23·7%)	287/ 892 (32-2%)	-34.1	105.9	- 🔶	0·72 (SE 0·08) 2p = 0·0009
Difference between treatment effects	in 2 catego	ries: χ <sub>1</sub> <sup>2</sup> = 1·	3; 2p = 0	·25; NS		
<u>(b) Age 50 – 59</u>					:	
Poly alone vs. Nil	146/464 (31·5%)	182/479 (38·0%)	–13·8	65·3		0⋅81 (se 0⋅11)
Poly + Tam vs. Tam	274/756 (36·2%)	21 <b>0</b> /496 (42·3%)	-30.9	92·4		0·72 (SE 0·09)
(b) subtotal	420/ 1220 (34-4%)	392/ 975 (40-2%)	-44.7	157.7	- 🔶	0·75 (SE 0·07) 2p = 0·0004
Difference between treatment effects	in 2 catego	ries: χ² = 0·	6; 2p = 0	-45; NS		
<u>(c) Age 60 – 69</u>					:	
Poly alone vs. Nil	96/264 (36·4%)	114/275 (41·5%)	-11·2	4 <b>0</b> ·4		— 0·76 (se 0·14)
Poly + Tam vs. Tam	323/733 (44·1%)	224/498 (45 <b>·</b> 0%)	<i>_</i> 3·7	1 <b>0</b> 7·5		0·97 (se 0·09)
(c) subtotal	419/ 997 (42·0%)	338/ 773 (43·7%)	-14.9	147.8	$\leftarrow$	> 0.90 (SE 0.08) 2p = 0.22; NS
Difference between treatment effects	in 2 catego	ries: χ <sub>1</sub> <sup>2</sup> = 1.	7; 2p = 0	·19; NS		
- <b></b> - 99% or 🖘 95% conf	idence intervals			0	0.5 1	-0 1.5 2.0
(a+b+c): Difference be presence/absence of tar	tween polyc n: age–strat	hemothera ified $\chi_1^2 = 0$ .	py effect 0; 2p = 0	P sin ·94; NS	olychemo. better	Polychemo. worse

Web Fig. 2(iii). Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of tamoxifen in both treatment groups): event rate ratios for death from any cause

<u> </u>	Deaths/wom	nan-years F	Polycher	no. death	S Detio of onnu	al death rates
Category	Poly	control	Ö–E	of O-E	Poly	: Control
<u>(a) Age &lt; 50</u>						
Poly alone vs. Nil	238/9967 (2·4%/y)	276/8356 (3·3%/y)	–28·7	106.0	-	0·76 (se 0·09)
Poly + Tam vs. Tam	25/702 (3·6%/y)	27/560 (4·8%/y)	<b>_5</b> ∙7	8∙0		0·49 (se 0·25)
(a) subtotal	263/ 10669 (2-5%/y)	303/ 8916 (3·4%/y)	-34.4	114.0	$\diamond$	0·74 (SE 0·08) 2p = 0·001
Difference between treatment effects	in 2 catego	ries: χ <sub>1</sub> <sup>2</sup> = 1.ξ	5; 2p = 0	·23; NS		
<u>(b) Age 50 – 59</u>						
Poly alone vs. Nil	173/5197 (3·3%/y)	208/4745 (4·4%/y)	_13·9	75 <b>·</b> 8		— 0·83 (se 0·10)
Poly + Tam vs. Tam	310/6480 (4·8%/y)	222/3750 (5·9%/y)	–28·9	101.0		0·75 (se 0·09)
(b) subtotal	483/ 11677 (4·1%/y)	430/ 8495 (5⋅1%/y)	-42.8	176-8	-	0·78 (SE 0·07) 2p = 0·001
Difference between treatment effects	in 2 catego	ries: χ² = 0.\$	5; 2p = 0	.50; NS		
<u>(c) Age 60 – 69</u>					:	
Poly alone vs. Nil	123/2614 (4·7%/y)	144/2494 (5·8%/y)	_13·9	51 <i>·</i> 8		0.76 (se 0.12)
Poly + Tam vs. Tam	390/5893 (6∙6%/y)	262/3799 (6·9%/y)	<i>–</i> 3·6	128.3		—— 0·97 (se 0·09)
(c) subtotal	513/ 8507 (6∙0%/y)	406/ 6293 (6·5%/y)	-17.6	180-1	$\Leftrightarrow$	> 0.91 (SE 0.07) 2p = 0.19; NS
Difference between treatment effects	in 2 catego	ries: χ <sub>1</sub> <sup>2</sup> = 2.∙	1; 2p = 0	·14; NS		
- <b>-</b> - 99% or <i>&lt;</i> → 95% confi	dence intervals			 0	0.5 1	
(a+b+c): Difference bet presence/absence of tan	tween polyc n: age–strat	hemotherap ified $\chi_1^2 = 0.0$	oy effect ); 2p = 0	in ∙91;NS	Polychemo. better	Polychemo. worse

Web Fig. 3(i). Tamoxifen versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of chemotherapy\* in both treatment groups): event rate ratios for recurrence

Category	<u>Events</u> Allocated Tam	Women Allocated control	Tamoxif Lograni O–E	en events Variance of O–E	<u>Ratio of annu</u> Tam	al event rates : Control
<u>(a) Age &lt; 50</u>						
Tam alone vs. Nil	180/440 (40·9%)	147/326 (45·1%)	-16·3	50.6		– 0·72 (se 0·12)
Tam + Poly vs. Poly	951/2819 (33·7%)	879/2727 (32·2%)	13·6	<b>38</b> 4·1	-	– 1·04 (se 0·05)
(a) subtotal	1131/ 3259 (34·7%)	1026/ 3053 (33.6%)	-2.8	434.7	<	> 0.99 (se 0.05) 2p = 0.89; NS
Difference between treatment effect	ts in 2 catego	ories: χ <sub>1</sub> <sup>2</sup> = 5·	7; 2p = 0	.02		
<u>(b) Age 50 – 59</u>						
Tam alone vs. Nil	261/555 (47 <b>·0</b> %)	246/486 (50·6%)	_19·1	92·2		0.81 (se 0.09)
Tam + Poly vs. Poly	483/1477 (32·7%)	498/1532 (32·5%)	_11 <b>·</b> 9	201.8		— 0·94 (se 0·07)
(b) subtotal	744/ 2032 (36-6%)	744/ 2018 (36-9%)	-30.9	294.0	$\diamond$	0.90 (SE 0.06) 2p = 0.07
Difference between treatment effect	ts in 2 catego	ories: $\chi_1^2 = 1$ .	4; 2p = 0	-24; NS		
<u>(c) Age 60 – 69</u>		•			I	
Tam alone vs. Nil	253/547 (46·3%)	254/55 <b>0</b> (46·2%)	<b>_</b> 3·1	1 <b>00</b> ·2		0.97 (se 0.10)
Tam + Poly vs. Poly	226/794 (28·5%)	316/859 (36·8%)	-28·7	109.4		0·77 (se 0·08)
(c) subtotal	479/ 1341 (35·7%)	570/ 1409 (40·5%)	-31.8	209.7	$\diamond$	0.86 (SE 0.06) 2p = 0.03
Difference between treatment effect	ts in 2 catego	pries: $\chi_1^2 = 2$ .	8; 2p = 0	.09		
- <b>■</b> - 99% or <_> 95% co	nfidence intervals	3		0	0.5 1	0 1.5 2.0
(a+b+c): Difference b esence/absence of cher	etween tamo no: age-stra	xifen effects tified $\chi_1^2 = 1$ .	s in 1; 2p = 0	⊤ ⊷29; NS	amoxifen better	Tamoxifen worse

\* In the tamoxifen versus not analyses, 3 of the 32 trials were of single-agent chemotherapy.

Web Fig. 3(ii). Tamoxifen versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of chemotherapy\* in both treatment groups): event rate ratios for breast cancer mortality

Category	<u>Deaths</u> Allocated Tam	Women Allocated control	Tamoxif Lograni O–E	en deaths Variance of O–E	Ratio of annual death rates Tam : Control		
<u>(a) Age &lt; 50</u>							
Tam alone vs. Nil	132/440 (30·0%)	114/326 (35·0%)	-11·2	42 <b>·</b> 0		— 0·77 (se 0·14)	
Tam + Poly vs. Poly	718/2819 (25 <sup>.</sup> 5%)	673/2727 (24·7%)	6·6	297.7	-	— 1.02 (se 0.06)	
(a) subtotal	850/ 3259 (26.1%)	787/ 3053 (25.8%)	-4.6	339.7	$\triangleleft$	> 0.99 (SE 0.05) 2p = 0.80; NS	
Difference between treatment effect	ts in 2 catego	ories: $\chi_1^2 = 3$ .	1; 2p = 0	-08			
<u>(b) Age 50 – 59</u>		-					
Tam alone vs. Nil	220/555 (39·6%)	201/486 (41 ·4%)	–1 <b>0</b> ·3	82·2		0·88 (se 0·10)	
Tam + Poly vs. Poly	381/1477 (25·8%)	398/1532 (26·0%)	–12·6	164-1		— 0·93 (se 0·08)	
(b) subtotal	601/ 2032 (29.6%)	599/ 2018 (29.7%)	-22.9	246-2	$\Leftrightarrow$	O·91 (SE 0·06) 2p = 0·14; NS	
Difference between treatment effect	ts in 2 catego	ories: $\chi_1^2 = 0$ .	1; 2p = 0	•72; NS			
<u>(c) Age 60 – 69</u>							
Tam alone vs. Nil	220/547 (40·2%)	226/55 <b>0</b> (41 ·1%)	-8·3	88.9		0.91 (se 0.10)	
Tam + Poly vs. Poly	190/794 (23·9%)	256/859 (29·8%)	-15·7	90·2	∎	— 0·84 (se 0·10)	
(c) subtotal	410/ 1341 (30.6%)	482/ 1409 (34.2%)	-24.0	179.1	$\diamond$	0.87 (SE 0.07) 2p = 0.07	
Difference between treatment effect	ts in 2 catego	ories: $\chi_1^2 = 0$ .	3; 2p = 0	-59; NS			
- <b>■</b> - 99% or < <b>-&gt;</b> 95% cor	nfidence intervals	;		 0	0.5 1.	.0 1.5 2.0	
(a+b+c): Difference b	etween tamo	xifen effects	s in	Т	amoxifen better	Tamoxifen worse	

\* In the tamoxifen versus not analyses, 3 of the 32 trials were of single-agent chemotherapy.

Web Fig. 3(iii). Tamoxifen versus not in ER-poor disease, subdivided first by age at randomisation and then by type of comparison (absence or presence of chemotherapy\* in both treatment groups): event rate ratios for death from any cause

Allocated Tam 146/4354 (3·4%/y) 763/23516 (3·2%/y)	Allocated control 126/3175 (4·0%/y) 721/23081 (3·1%/v)	Logrank O–E –12·8	47.6	Ratio of annu Tam	0.76 (sc 0.13)
146/4354 (3·4%/y) 763/23516 (3·2%/y)	126/3175 (4·0%/y) 721/23081 (3·1%/v)	-12·8	47·6	<b></b>	0.76 (er 0.13)
146/4354 (3·4%/y) 763/23516 (3·2%/y)	126/3175 (4·0%/y) 721/23081 (3·1%/v)	–12·8	47·6		0.76 (er 0.13)
146/4354 (3·4%/y) 763/23516 (3·2%/y)	126/3175 (4·0%/y) 721/23081 (3·1%/y)	_12·8	47·6		0.76 (e= 0.13)
763/23516 (3·2%/y)	721/23081 (3·1%/v)				— 0.70 (SE 0.13)
		4·8	317·5	-	— 1.02 (se 0.06)
909/ 27870 (3.3%/v)	847/ 26256 (3·2%/v)	-8.0	365-0	$\triangleleft$	> 0.98 (SE 0.05) 2p = 0.67; NS
in 2 catego	ries: $\chi_{1}^{2} = 3.4$	4; 2p = 0	-07		
_	1				
263/591 <b>0</b> (4·5%/y)	235/5074 (4·6%/y)	-12·2	96.3		0·88 (se 0·10)
434/11588 (3·7%/y)	448/11852 (3∙8%/y)	–11 <b>·3</b>	186.5		0·94 (se 0·07)
697/ 17498 (4₊0%/y)	683/ 16926 (4·0%/y)	-23.5	282.7	$\Leftrightarrow$	> 0.92 (SE 0.06) 2p = 0.16; NS
in 2 catego	ries: χ <sup>2</sup> = 0.3	3; 2p = 0	.60; NS		
316/5854 (5·4%/y)	323/5728 (5∙6%/y)	-2·1	127 <b>∙0</b>		0·98 (se 0·09)
239/5638 (4·2%/y)	315/6102 (5·2%/y)	_17·2	112.4		0.86 (se 0.09)
555/ 11492 (4·8%/y)	638/ 11830 (5·4%/y)	-19.3	239-4	$\Leftrightarrow$	> 0.92 (SE 0.06) 2p = 0.21; NS
in 2 catego	ries: $\chi_1^2 = 1$ .	1; 2p = 0	-29; NS		
dence intervals			 0	0.5 1	0 1.5 2.0
			т,	movifen better	
	909/ 27870 (3.3%/y) in 2 catego 263/5910 (4-5%/y) 434/11588 (3-7%/y) 697/ 17498 (4-0%/y) in 2 catego 316/5854 (5-4%/y) 239/5638 (4-2%/y) 555/ 11492 (4-8%/y) in 2 catego dence intervals ween tamoo	909/ 847/ 27870 26256 (3.3%/y) (3.2%/y) in 2 categories: $\chi_1^2 = 3.4$ 263/5910 235/5074 (4.5%/y) (4.6%/y) 434/11588 448/11852 (3.7%/y) (3.8%/y) 697/ 683/ 17498 16926 (4.0%/y) (4.0%/y) in 2 categories: $\chi_1^2 = 0.3$ 316/5854 323/5728 (5.4%/y) (5.6%/y) 239/5638 315/6102 (4.2%/y) (5.2%/y) 555/ 638/ 11492 11830 (4.8%/y) (5.4%/y) in 2 categories: $\chi_1^2 = 1.3$ dence intervals ween tamoxifen effects : ace-stratified $\chi^2 = 0.4$	909/ 847/ -8.0 27870 26256 (3.3%/y) (3.2%/y) in 2 categories: $\chi_1^2 = 3.4$ ; 2p = 0 263/5910 235/5074 -12·2 (4·5%/y) (4·6%/y) 434/11588 448/11852 -11·3 (3·7%/y) (3·8%/y) 697/ 683/ -23.5 17498 16926 (4.0%/y) (4·0%/y) in 2 categories: $\chi_1^2 = 0.3$ ; 2p = 0 316/5854 323/5728 -2·1 (5·4%/y) (5·6%/y) 239/5638 315/6102 -17·2 (4·2%/y) (5·2%/y) 555/ 638/ -19·3 11492 11830 (4·8%/y) (5·4%/y) in 2 categories: $\chi_1^2 = 1.1$ ; 2p = 0 dence intervals ween tamoxifen effects in 2 age-stratified $\chi^2 = 0.4$ ; 2p = 0	999/ 847/ -8.0 365.0 27870 26256 (3.3%/y) (3.2%/y) in 2 categories: $\chi_1^2 = 3.4$ ; 2p = 0.07 263/5910 235/5074 -12.2 96.3 (4.5%/y) (4.6%/y) 434/11588 448/11852 -11.3 186.5 (3.7%/y) (3.8%/y) 697/ 683/ -23.5 282.7 17498 16926 (4.0%/y) (4.0%/y) in 2 categories: $\chi_1^2 = 0.3$ ; 2p = 0.60; NS 316/5854 323/5728 -2.1 127.0 (5.4%/y) (5.6%/y) 239/5638 315/6102 -17.2 112.4 (4.2%/y) (5.2%/y) 555/ 638/ -19.3 239.4 11492 11830 (4.8%/y) (5.4%/y) in 2 categories: $\chi_1^2 = 1.1$ ; 2p = 0.29; NS dence intervals 0 ween tamoxifen effects in $\chi$ age-stratified $\chi^2 = 0.4$ ; 2p = 0.54; NS	909/97 847/ -8-0 365-0 27870 26256 (3.3%/y) (3.2%/y) in 2 categories: $\chi_1^2 = 3.4$ ; 2p = 0.07 263/5910 235/5074 -12·2 96·3 (4.5%/y) (4.6%/y) 434/11588 448/11852 -11·3 186·5 (3.7%/y) (3.8%/y) 697/ 683/ -23.5 262.7 17498 16926 (4.0%/y) (4.0%/y) in 2 categories: $\chi_1^2 = 0.3$ ; 2p = 0.60; NS 316/5854 323/5728 -2·1 127·0 (5.4%/y) (5.6%/y) 239/5638 315/6102 -17·2 112·4 (4·2%/y) (5.6%/y) 239/5638 315/6102 -17·2 112·4 (4·2%/y) (5.2%/y) 5555/ 638/ -19·3 239.4 11492 11830 (4.8%/y) (5.4%/y) in 2 categories: $\chi_1^2 = 1.1$ ; 2p = 0.29; NS dence intervals 0 0.5 1. Tamoxifen better ween tamoxifen effects in : ane-stratified $\chi^2 = 0.4$ ; 2p = 0.54; NS

\* In the tamoxifen versus not analyses, 3 of the 32 trials were of single-agent chemotherapy.

Web Fig. 4(i). Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) and age at randomisation: 10-year probabilities of recurrence



Web Fig. 4(ii). Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) and age at randomisation: 10-year probabilities of breast cancer mortality



Web Fig. 4(iii). Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) and age at randomisation: 10-year probabilities of death from any cause



Web Fig. 5. Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) for patients with entry age < 50: 10-year probabilities of (i) recurrence, (ii) breast cancer mortality and (iii) death from any cause

#### (i) Recurrence

#### (ii) Breast cancer mortality

(iii) Death from any cause



Web Fig. 6. Polychemotherapy versus not in ER-poor disease, by type of comparison (absence or presence of tamoxifen in both treatment groups) for patients with entry ages 50-69: 10-year probabilities of (i) recurrence, (ii) breast cancer mortality and (iii) death from any cause

#### (i) Recurrence

#### (ii) Breast cancer mortality

(iii) Death from any cause



Web Fig. 7(i). Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by nodal status: event rate ratios for recurrence

	Events/	Women	Polyche	mo. evente	<u>S</u>	
Category	Allocated Poly	Allocated control	Logrank O–E	variance of O-E	Poly :	al event rates Control
$(a) \Delta a a < 50$						
(a) Age < 50						
N0/N-	240/811 (29∙6%)	300/718 (41∙8%)	-55·2	116 <b>·0</b>	-	0.62 (SE 0.07)
N+/N?	97/204 (47·5%)	11 <b>0</b> /174 (63·2%)	_14·8	27.7		0·59 (se 0·15)
(a) subtotal	337/ 1015 (33-2%)	410/ 892 (46·0%)	-70·0	143-6	- 🔶	0.61 (SE 0.07) 2p < 0.00001
Difference between treatment effect	ts in 2 catego	ories: χ <sup>2</sup> = 0·	1; 2p = 0	-78; NS		
<u>(b) Age 50 – 59</u>						
N0/N-	12 <b>0</b> /473 (25·4%)	169/467 (36·2%)	-26·1	62·9		0·66 (se 0·10)
N+/N?	385/747 (51 ·5%)	308/508 (60·6%)	_44·9	118.6	-	0.68 (se 0.08)
(b) subtotal	505/ 1220 (41-4%)	477/ 975 (48·9%)	-71.0	181.5	$\rightarrow$	0·68 (SE 0·06) 2p < 0·00001
Difference between treatment effect	ts in 2 catego	ories: $\chi_1^2 = 0$ .	1; 2p = 0	•82; NS		
<u>(c) Age 60 – 69</u>						
N0/N-	96/311 (30·9%)	106/300 (35·3%)	_12·1	44·7		— 0·76 (se 0·13)
N+/N?	389/686 (56·7%)	291/473 (61 ·5%)	–21·5	120.5	-	- 0·84 (se 0·08)
(c) subtotal	485/ 997 (48-6%)	397/ 773 (51-4%)	-33.6	165-2	$\stackrel{-}{\diamondsuit}$	0·82 (SE 0·07) 2p = 0·009
Difference between treatment effect	ts in 2 catego	pries: $\chi_1^2 = 0$ .	3; 2p = 0	-60; NS		
- <b></b> 99% or <-> 95% co	nfidence intervals			 0	0.5 1.	0 1.5 2.0
		_		. F	olychemo. better	Polychemo. worse
(a+b+c): Difference b 2 nodal status categori	etween polyc ies: age–stral	tified $\chi_1^2 = 0$	py effect 1; 2p = 0	s in •75; NS	-	-

Web Fig. 7(ii). Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by nodal status: event rate ratios for breast cancer mortality

	Deaths	Women	Polyche	no. deaths		
Category	Allocated Poly	Allocated control	Lograni O–E	of O-E	Ratio of annual de Poly : Cor	ath rates ntrol
(a) Age < 50						
N0/N-	159/811 (19∙6%)	186/718 (25·9%)	-21·5	77·3		0·76 (se 0·10)
N+/N?	82/204 (40·2%)	101/174 (58·0%)	_12·6	28.6		0·64 (se 0·15)
(a) subtotal	241/ 1015 (23·7%)	287/ 892 (32.2%)	-34.1	105- <del>9</del>	-	0·72 (SE 0·08) 2p = 0·0009
Difference between treatment effe	cts in 2 catego	ories: χ <sup>2</sup> = 0·	6; 2p = 0	-46; NS		
(b) Age 50 – 59						
N0/N-	84/473 (17·8%)	129/467 (27·6%)	_22·0	47.4		0·63 (se 0·12)
N+/N?	336/747 (45 <b>·0%</b> )	263/508 (51 ·8%)	-22·7	11 <b>0·3</b>		0·81 (se 0·09)
(b) subtotal	420/ 1220 (34-4%)	392/ 975 (40-2%)	-44.7	157.7	$\rightarrow$	0·75 (se 0·07) 2p = 0·0004
Difference between treatment effe	cts in 2 catego	pries: $\chi_1^2 = 2$ .	2; 2p = 0	-14; NS		
<u>(c) Age 60 – 69</u>						
N0/N-	69/311 (22·2%)	87/300 (29·0%)	_1 <b>0</b> ·7	35·2		0·74 (se 0·15)
N+/N?	350/686 (51 ∙0%)	251/473 (53·1%)	_4·2	112.6		- 0·96 (se 0·09)
(c) subtotal	419/ 997 (42-0%)	338/ 773 (43.7%)	-14.9	147.8		0·90 (SE 0·08) 2p = 0·22; NS
Difference between treatment effe	cts in 2 catego	pries: $\chi_1^2 = 1$ .	9; 2p = 0	-17; NS		
- <b>■</b> - 99% or <>> 95% o	confidence intervals	i		0	0.5 1.0	
(a+b+c): Difference	between polyc	:hemothera	py effect	Po sin	lychemo. better Po	lychemo. worse

(a+b+c): Difference between polychemotherapy effects in 2 nodal status categories: age–stratified  $\chi_1^2 = 1.9$ ; 2p = 0.17; NS

Web Fig. 7(iii). Polychemotherapy versus not in ER-poor disease, subdivided first by age at randomisation and then by nodal status: event rate ratios for death from any cause

	Deaths/won	nan-years F	Polycher	no. death	S D	
Category	Allocated Poly	Allocated control	Logrank O_E	variance of O–E	e <u>Ratio of annu</u> Poly	al death rates : Control
	· · · <b>,</b>					
<u>(a) Age &lt; 50</u>						
N0/N-	178/9124 (2∙0%/y)	200/7847 (2·5%/y)	_21 <b>∙0</b>	84·8		0·78 (se 0·10)
N+/N?	85/1545 (5∙5%/y)	103/1069 (9∙6%/y)	–13·3	29·3		0·63 (SE 0·15)
(a) subtotal	263/ 10669 (2·5%/y)	303/ 8916 (3·4%/y)	-34.4	114-1	- 🔶	0·74 (SE 0·08) 2p = 0·001
Difference between treatment effect	ts in 2 catego	ries: χ <sup>2</sup> = 0-9	9; 2p = 0	-33; NS		
<u>(b) Age 50 – 59</u>					1	
N0/N-	11 <b>0/5326</b> (2·1%/y)	152/4681 (3·2%/y)	_22·5	58·1		0·68 (se 0·11)
N+/N?	373/6351 (5∙9%/y)	278/3814 (7∙3%/y)	–20·3	118.7		0.84 (se 0.08)
(b) subtotal	483/ 11677 (4·1%/y)	430/ 8495 (5·1%/y)	-42.8	176-8	- 🔶	0·79 (SE 0·07) 2p = 0·001
Difference between treatment effect	ts in 2 catego	ries: χ <sup>2</sup> = 1.6	B; 2p = 0	-18; NS		
<u>(c) Age 60 – 69</u>					1	
N0/N-	98/3116 (3·1%/y)	120/2868 (4·2%/y)	_14·3	49 <b>·</b> 0		0.75 (se 0.12)
N+/N?	415/5391 (7·7%/y)	286/3425 (8·4%/y)	<u>-</u> 3·3	131.2		— 0·98 (se 0·09)
(c) subtotal	513/ 8507 (6·0%/y)	406/ 6293 (6-5%/y)	-17.6	180.1	- 🔶	> 0·91 (SE 0·07) 2p = 0·19; NS
Difference between treatment effect	ts in 2 catego	ries: χ <sup>2</sup> = 2.5	5; 2p = 0	⊷11; NS		
- <b></b> - 99% or <->> 95% co	nfidence intervals			 0	0.5 1	-0 1.5 2.0
(a+b+c): Difference b 2 nodal status categori	etween polyc es: age–stral	themotherap ified $\chi_1^2 = 1.9$	oy effect 9; 2p = 0	sin ⊡17;NS	<sup>o</sup> olychemo. better	Polychemo. worse

19

# Web Fig. 8(i). Polychemotherapy versus not in ER-poor disease, by various subgroups: event rate ratios for recurrence

	Events/	Nomen I Allocated	Polycher Logrank	no.eve Varian	oe Ratio of annu	al event rates
(a) Type of polychen	Poly	control $fy^2 = 2.8$	0-E	of O-I S9:NS	E Poly	Control
CMF alone	471/1150	450/970	-57.1	178.6		0.73 (SE 0.06)
FAC/FEC alone	(41 0%) 146/420	(46-4%) 170/348	-32-8	67-6		0.62 (SE 0.10)
CMF plus non-anth.	(34·8%) 126/307	(48-9%)	-15-9	56-8		- 0.75 (SE 0.12)
Other anth.	(41 0%) 376/731	(46·1%) 257/427	-32.7	120.1		0.76 (SE 0.08)
Other non-anth.	(51-4%) 239/703	(60.2%) 303/676	-49.5	121.7		0.67 (SE 0.07)
(h) Entry age (trend	(34·0%) v <sup>2</sup> - 3.9· 2i	(44/6%) n – 0.05)				
(D) Entry age (Liena	1 an/aen	1 = 0.00)	- ac	E1.0	_	0.60 (c= 0.11)
40 - 44	(36·1%) 97/294	(51-0%)	-17-9	41.9		0.65 (SE 0.13)
45 - 49	(33·0%) 110/361	(44·1%) 141/330	-25.9	49.9		0.60 (SE 0.11)
50 - 54	(30-5%) 239/596	(42-7%) 223/481	-27.1	85.9		0.73 (SE 0.09)
55 – 59	(40·1%) 266/624	(46.4%) 254/494	-43-8	95.7		0.63 (SE 0.08)
60 - 64	(42·6%) 304/626	(51 4%) 261/497	-26-3	1054		0.78 (SE 0.09)
65 - 69	(48-6%) 181/371	(52-5%) 136/276	-7.3	59.9		
70+	(48.8%) 29/75	(49/3%) 33/76	-5-8	90		0.53 (SE 0.25)
Unknown	2/4	0/2				
(c) Menopausal statu	<u>us</u> (age-st	rat.* $\chi_1^2 =$	0·5; 2p	= 0.49	; NS)	
Pre/peri	397/1138	449/1006	-66-0	174.7		0.69 (SE 0.06)
(78% age < 50y) Post	(34·9%) 952/2148	(44-6%) 850/1684	-111-4	357.7	<b>—</b>	0·73 (se 0·05)
(6% age < 50y)	(44·3%)	(50-5%)			The second se	
(d) Nodal status (age	9/25 →strat.* χ	= 0.1; 2p	-5·1 5 = 0·74	; NS)		
N0/N-	463/1621	566/1521	-100.1	238 0		0.66 (SE 0.05)
(49% age < 50y) N±/N2	(28·6%)	(38-7%)		204.0	<b>–</b>	0.74 (c= 0.05)
(12% age < 50y)	(53·0%)	(60.9%)	-07.4	294.0		0-74 (SE 0-05)
(e) Absence or prese	ence of tar	n (age-st	trat.* $\chi_1^2$	= 0.0;	2p = 0.84; NS)	
Poly alone vs. Nil	611/1661	746/1583	-105.6	260.0		0.67 (SE 0.05)
(53% age < 50y) Poly + Tam vs. Tam	747/1650	571/1135	-74.8	2394		0·73 (SE 0·06)
(6% age < 50y)	(45·3%)	(50 3%)			<b>.</b>	
(1) Tumour size (tren	$d \chi_1^- = 0.1;$	2p = 0.82	2; NS)			
1–20mm (T1)	438/1254 (34-9%)	393/975 (40 3%)	-57.9	167.7	-#	0·71 (SE 0·07)
21–50mm (T2)	597/1456 (41·0%)	620/1245 (49.6%)	-88-9	246-2	-#-	0·70 (se 0·05)
> 50mm (T3+T4)	89/156	80/137	-4.7	22.2		0·81 (SE 0·19)
Other / unknown	234/445	224/361	-31.5	82.2	-d	0.68 (SE 0.09)
(g) Tumour size, N0/	N– only (ti	rend $\chi_1^2 =$	0·1; 2p	= 0.78	i; NS)	
1–20mm (T1)	158/671	212/643	-36-6	84 <i>-</i> 5		0.65 (SE 0.09)
21–50mm (T2)	236/771	314/731	-57.5	121.6		0.62 (SE 0.07)
> 50mm (T3+T4)	22/53	17/47	-D·1	7.0		
Other / unknown	47/126	45/100	-3·6	18-8	Ne.	
(II) Tulliour unlerent		10 k <sub>1</sub> = 2.	1, zp =	0.14,1	13)	
Well-differentiated	(39·5%)	(40.3%)	1.6	9.6	_	
Roorly	(43·6%)	(51-0%)	-30.9	115.4		0.71 (se 0.08)
Unknown	(41·1%)	(47.4%)	-127.4	320.2		0.67 (SE 0.05)
	(40.4%)	(48.6%)	127 4	OLC L	L)	000 (02000)
(i) Tumour differenti	ation, N0/N	v– only (t	rend $\chi^2_1$	= 0.0;	2p = 0.86; NS)	
Well-differentiated	10/35 (28·6%)	7/31 (22:6%)	D-1	2.9		•••••
Moderately	57/229 (24·9%)	72/201 (35-6%)	-13-3	27.0		0.61 (SE 0.15)
Poorly	135/472 (28-6%)	163/436 (37-4%)	-20.9	61.7		0.71 (SE 0.11)
Unknown	261/885 (29·5%)	346/853 (40.6%)	-64 •4	1403	-0+-	U-63 (SE U-U7)
(j) PR status ( $\chi_1^2 = 0.3$	5; 2p = 0·5	0; NS)				
PR-poor	624/1903 (43·3%)	783/1571 (49 <sup>.</sup> 6%)	-105.0	325-1	<b>#</b>	0·72 (SE 0·05)
PR+	271/705	256/516	-39-1	97.7		0.67 (SE 0.08)
PR unknown	263/703	278/631	-36-9	109.6	- <u></u>	0·71 (SE 0·08)
(k) Years from entry	(trend χ <sup>2</sup> =	= 15·7; 2p	= 0.00	008; de	enominator: survi	vors)
0 – 1	570/3311	704/2718	-137.7	2514		0.58 (SE 0.05)
2 - 4	(17·2%) 458/2658	(25-9%) 372/1932	-33-4	1724		0.82 (SE 0.07)
5-9	(17.2%)	(19:3%)	14.1	07.6		0.84 (c= 0.10)
10+	(11·3%) 105/1256	(11-6%) 76/850	- 14-1	0210 38/3		0.93 (SE 0.16)
	(8·4%)	(8-9%)	- NE			(0-0-10)
() Type of recurrence	e (χ <sub>2</sub> = 2·9	; p = 0.24	; NS)	<i></i>		0.01/
Isolated local	204/2254 (9·1%)	242/1959 (12:4%)	-43-4	97.2		0.64 (SE 0.08)
Isol. contralateral	123/3045 (4·0%)	104/2446 (4·3%)	-8-3	52.6		0.85 (SE 0.13)
uistant/mixed/unk.	1031/3311 (31·1%)	971/2718 (35·7%)	-136-3	394-9		U-71 (SE 0-04)
Total	1358/	1317/	120 0	544 0		0.709 /
	3311 (41-0%)	2718 (48-5%)	-100.0	~ <del>~~</del>	\$	2p < 0.00001
-∎- 99% or -<±>- 95% confi	dence intervals					
				c	Polychemo hetto-	u 1.5 2.0
* Ch+01	E0 E0 -	80 8C ·			Treatment effect	ct 2p < 0.00001
Stratmed for age < 50	, 30–39 and	on pa ou h				• • • • • • • •

# Web Fig. 8(ii). Polychemotherapy versus not in ER-poor disease, by various subgroups: event rate ratios for breast cancer mortality

Catagony	Deaths/ Allocated	Women F Allocated	Polycher Lograni	no. deaths Variance	Ratio of annua	death rates
(a) Type of polycher	Poly	control $(\sqrt{2} - 1.3)$	0-E	610-E	Poly	Control
	200/1150	272/070	20.5	156.0		0.79 (cc 0.07)
	(34-4%)	(38.5%)	-30-5	1502		0.73 (az 0.07)
CME plup pop onth	(26.4%)	(35.6%)	-17-4	51.7		0.71 (SE 0.12)
Other anth	(31.9%)	(36.7%)	-10.7	47.1	_	0.80 (SE 0.13)
Other pop, onth	(44.3%)	(51.3%)	-17.9	108-3		- 0.85 (SE 0.09)
	(25.3%)	(32.8%)	-20.1	92.1		0.75 (SE 0.03)
(b) Entry age (trend	$\chi_1^2 = 1.4; 2$	p=0·23;I	NS)			
< 40 years	91/360 (25-3%)	101/306 (33-0%)	-8.6	35.9	-+	— 0·79 (se 0·15)
40 – 44	74/294 (25-2%)	77/256 (30.1%)	-6-0	32.5		
45 – 49	76/361 (21·1%)	109/330 (33·0%)	-19·5	37.5		0.59 (SE 0.13)
50 – 54	189/596 (31·7%)	180/481 (37-4%)	-19-3	71.9		0.76 (SE 0.10)
55 – 59	231/624 (37·0%)	212/494 (42·9%)	-25-4	85.8		0.74 (se 0.09)
60 – 64	262/626 (41·9%)	220/497 (44·3%)	-17·0	93-3		0.83 (SE 0.09)
65 - 69	157/371 (42·3%)	118/276 (42-8%)	2.1	54.5		1-04 (SE 0-14)
70+	26/75 (34·7%)	30/76 (39.5%)	-5.2	8.9		— 0·56 (SE 0·25)
Unknown	1/4	0/2				
(c) Menopausal stat	us (age-si	trat.* $\chi_1^2 =$	0.9; 2p	= 0·35; N	S)	
Pre/peri	284/1138 (25:0%)	315/1006	-33-9	128.6		0.77 (se 0.08)
Post	814/2148	718/1684	-71.1	316-3	- <b></b>	0.80 (SE 0.05)
(5% age < 50y) Unknown	9/25	14/28	-2.7	4.1	TI	
(d) Nodal status (age	e-strat.* $\chi$	<sup>2</sup> = 1.9; 2p	) = 0·17	'; NS)		
ND/N-	316/1621	413/1521	-62.9	169.6	- <b>B</b>	0.69 (se 0.06)
(49%) age < 50y) N+/N?	(19·5%) 791/1690	(27·2%) 634/1197	-44-6	275-2		0.85 (se 0.06)
(12% age < 50y)	(46-8%)	(53.0%)	_			. ,
(e) Absence or prese	ence of tai	<u>m</u> (age–st	rat.* χ <sub>1</sub>	= 0∙0; 2p	= 0.94; NS)	
Poly alone vs. Nil (53% age < 50v)	465/1661 (28·0%)	563/1583 (35·6%)	-54-9	205.5		0.77 (SE 0.06)
Poly + Tam vs. Tam	642/1650	484/1135	-44.0	214.8		0.81 (se 0.06)
(b% age < 50y) (f) Tumour size (tren	(30-376)	- 2n - 0.98	NS)			
1 20mm (T1)	247(1254	200/075		101.0	<u> </u>	0.80 (cc. 0.08)
1=20mm (T1)	(27.7%)	(29.7%)	-20.0	131.3		0.00 (SE 0.00)
21-50mm (12)	483/1456 (33·2%)	(40.3%)	-53-3	208-0		0.77 (SE 0.08)
> 59mm (T3+T4)	77/156 (49·4%)	69/137 (50-4%)	-2.9	22.7		0-88 (SE 0-20)
Other / Unknown	200/445 (44·9%)	186/361 (51-5%)	-17-9	72.4	-0	0.78 (SE 0.10)
(g) Tumour size, N0/	N– only (t	rend $\chi_1^2 =$	0·0; 2p	= 0·93; N	IS)	
1–20mm (T1)	107/671	138/643	-19-3	56.8		0.71 (SE 0.11)
21–50mm (T2)	166/771	236/731	-41.0	92.7		0.64 (se 0.08)
> 50mm (T3+T4)	17/53 (32·1%)	13/47	0.8	5.9		•>
Other / unknown	26/126	26/100	-2·5	10-7		
(n) rumour anierent	lation (tre	nu χ <sub>1</sub> = 20	o; ∠p =	U-TU; NS)	'	
	28/81 (34·6%)	24/72 (33·3%)	3.5	9.2		• • • • •
Moderately	172/493 (34·9%)	170/404 (42·1%)	-8-8	65-1		- 0.87 (SE 0.12)
Pooriy	(34.7%)	(39.5%)	-26.5	103-3		0.77 (SE 0.09)
Unknown	(32.5%)	(37.4%)	-72.9	260.0	나비	0.76 (SE 0.05)
(i) Tumour differenti	ation, NO/I	N– only (t	rend $\chi^2_1$	<sup>2</sup> = 0·1; 2p	o = 0·80; NS)	
Well-differentiated	7/35	4/31	0.8	2.2		>
Moderately	(20.0%) 36/229	(12.9%) 49/201	-8-9	18.9		0.62 (se 0.18)
Poorly	(15·7%) 98/472	(24.4%) 127/436	-16-9	48.0		0.70 (se 0.12)
Unknown	175/885	233/853	-38-3	96.6	-0+	0.67 (SE 0.08)
(j) PR status ( $\chi^2 = 0.3$	(19 <sup>-</sup> 0-%) 7;2p = 0-3	9;NS)				
PR-poor	678/1903	615/1571	-54.7	268.7	<u>i</u>	0.82 (se 0.06)
<b>DD</b>	(35.6%)	(39.1%)				
PH+	209/705 (29·6%)	196/516 (38.0%)	-24.6	78-8		0.73 (SE 0.10)
Ph unknown	(31.3%)	(37.4%)	-24-9	82.8	-4-1	0.77 (SE 0.09)
(k) Years from entry	(trend $\chi_1^2$	= 0·2; 2p =	= D·63;	NS; deno	minator: survivo	ors)
0 – 1	264/3311 (8·0%)	271/2718 (10·0%)	-28.7	112.6		0.77 (se 0.08)
2 – 4	463/2958 (15-7%)	450/2355 (19-1%)	-45-2	192-1		0.79 (SE 0.06)
5 – 9	262/2258	229/1733	-31.3	105-7	_ <b>_</b>	0.74 (se 0.08)
10+	(118/1450 /8-19/1	97/1066	-4.0	45-1		0.91 (se 0.14)
Total	1107/	1047/	100.1			0 787 (~~ 0 040)
Iotai	3311 (33-4%)	2718	-109-1	400.0		2p < 0.00001
- <b>E</b> -99% or <_> 95% confi	dence intervals	, • ·•,				
				۰_	0.5 1.0	1.5 2.0
				P	Treatment effect	- orycnemo, worse
<ul> <li>Stratified for age &lt; 50</li> </ul>	, 50-59 and	60-69 only	,			

# Web Fig. 8(iii). Polychemotherapy versus not in ER-poor disease, by various subgroups: event rate ratios for death from any cause

	Deaths/won Allocated	nan-years Allocated	olyche Lograni	mo. deat Variano	hs Ratio of annual death rates
Category	Poly	control	0-E	of O-E	Poly : Control
(a) Type of polycnel	nomerapy	$\chi_4 = 2.0;$	p = 0∙.	(4;NIS)	
CMF alone	442/9060 (4·9%/γ)	408/7115 (5·7%/γ)	-39.7	173-2	U-80 (SE U-07)
FAC/FEC alone	122/3392 (3∙6%/y)	133/2697 (4·9%/y)	-16.9	56-1	0.74 (se 0.12)
CMF plus non-anth	119/3796 (3.1%/v)	129/3430 (3-8%/y)	-11.4	56.7	0·82 (se 0·12)
Other anth.	400/7131 (5-6%/v)	251/3683 (6-8%/y)	-15.9	129.9	0.66 (SE 0.06)
Other non-anth.	216/8174 (2.6%/v)	260/7418 (3-5%/y)	-30.5	110.4	0.76 (se 0.08)
(b) Entry age (trend	$\chi_1^2 = 1.6; 2$	p = 0·21; l	NS)		
< 40 years	94/3774	102/3176	-8·5	36.4	0.79 (se 0.15)
40 – 44	(2 5%/y) 79/2987	(3·2%/y) 80/2684	-5.0	34-4	0.86 (se 0.16)
45 – 49	(2·6%/y) 90/3908	(3·0%/y) 121/3056	-20·9	43-3	0.62 (se 0.12)
50 – 54	(2·3%/y) 217/6036	(4·0%/γ) 196/4472	-16.7	80.6	0.61 (se 0.10)
55 – 59	(3·6%/y) 266/5641	(4-4%/y) 234/4023	-26·1	96-2	0.76 (se 0.09)
50 – 64	(4·7%/y) 310/5563	(5-8%/y) 252/4057	-16·9	110-3	0.86 (se 0.09)
55 - 69	(5·6%/y) 203/2944	(6·2%/γ) 154/2236	-0.7	69·7	0.99 (se 0.12)
70+	(6·9%/y) 39/531	(6·9%/γ) 42/487	-4·2	13.4	0.73 (se 0.23)
Jnknown	(7·3%/y) 1/31	(8·6%/γ) 0/21			
c) Menoneusel stat		trat $\star \sqrt{2}$ –	0.8.20	- 0.36	NS)
c) wenopausarstat	us (age-s	ιαι. χ <sub>1</sub> =	u∙o, zp	= 0.30	, NG)
-re/pen _(78% age < 50y)	313/12169 (2·6%/y)	332/9955 (3·3%/γ)	-33-3	138-1	0.79 (se 0.08)
ost (6% age < 50v)	976/19176 (5·1%/y)	831/14145 (5·9%/y)	-76.3	375-9	0.82 (se 0.05)
Jnknown	10/191	18/224	-3·5	5.0	
d) Nodal status (ag	e-strat.* χ	<sup>2</sup> = 1.9; 2p	o = 0·17	';NS)	
ND/N-	393/17862	489/15732	-68.3	204.6	0.72 (se 0.06)
(49%) age < 50y) N+/N?	(2·2%/¥) 906/13657	(3·1%/γ) 692/8574	-41·2	308-1	0.87 (se 0.05)
(12% age < 50y)	(6·6%/γ)	(8·1%/ <b>y</b> )			
e) Absence or pres	ence of ta	<u>m</u> (age-st	rat.* χ <sup>2</sup>	= 0.0;	2p = 0.90; NS)
Poly alone vs. Nil	543/17953	640/15774	-58.2	236-9	0.78 (se 0.06)
(53% age < 5∪y) Poly + Tam vs. Tam	(5 6 /0/y) 756/13462	541/8438	-40·9	247-3	0.85 (se 0.06)
(6% age < 50y)	(5·6%/γ)	(6·4%/γ)			
<del>f) Tumour size</del> (trer	nd $\chi_1^2 = 0.0$	; 2p = 0·94	1; NS)		
1–20mm (T1)	416/12886 (3:2%/v)	336/9577 (3:5%/y)	-30.5	155-6	0·82 (se 0·07)
21–50mm (T2)	576/13464	566/10866	-54·5	242.8	0.80 (se 0.06)
⊳ 50mm (T3+T4)	(4-3.0/y) 83/1312	(3·2 /0/) 72/1013	-2.4	24.4	
Other / unknown	(6·3%/γ) 224/3822	(7·1%/γ) 207/2826	-19·8	80.9	0.78 (se 0.10)
a) Tumour size, NO	(5·9%/y) /N only (1	(7·3%/y)	0 2 . 20	- 0.67	- NG)
(g) Turriour size, Nu			0.2, Zh		, 143)
1-20mm (11)	(1·7%/y)	(2·4%/γ)	-24.6	69.3	
21-50mm (12)	208/8268 (2·5%/γ)	(3·7%/y)	-43.3	112.4	U-00 (SE U-00)
> 50mm (13+14)	20/608 (3·3%/y)	16/497 (3·2%/γ)	0.7	7.2	
Other / unknown h) Tumour differen:	34/1246 tiation (tre	29/980 nd v <sup>2</sup> – 1.1	–1·6 2·2n –	12-6 0.28- N	191
Nell differentieted		10 x <sub>1</sub> = 1.	c, zp =		
Mederately	(4·1%/γ)	29/687 (4·2%/γ)	2.9	71.0	0.85 (at 0.11)
	(4·4%/γ)	(5·7%/y)	-11-0	11.0	
-oony	(5·0%/y)	(5·8%/y)	-21.2	111-0	
Jnknown	/82/20499 (3·8%/γ)	699/15/06 (4·5%/γ)	-80.6	313-2	0.77 (SE 0.05)
i) Tumour different	iation, NO/	N– only (t	rend χ <sup>2</sup>	² = 0·2;	2p = 0.67; NS)
Vell-differentiated	7/423	6/365	0.4	2.4	·
Moderately	(1·7%/y) 41/2292	(1-6%/y) 60/1950	-12.3	22.5	0.58 (se 0.16)
Poorly	(1·8%/y) 111/4040	(3·1%/γ) 135/3347	-15·0	52.9	0.75 (se 0.12)
Jnknown	(2·7%/y) 234/11091	(4·0%/y) 288/10052	-43·9	123-1	0.70 (se 0.08)
	(2·1%/γ)	(2·9%/γ)			
$\frac{ ) \text{ PR status}}{  } (\chi_1^- = 0)$	6;2p = 0.4	14; NS)			
PR-poor	792/18774 (4·2%/v)	694/14599 (4·8%/γ)	-55.5	310.6	0.84 (se 0.05)
'R+	255/7039	222/4833	-25.0	92.8	0.76 (se 0.09)
R unknown	(3·6%/y) 252/5705	(4-6%/y) 265/4868	-28.9	108.5	0.77 (se 0.08)
k) Years from entry	(4·4%/γ) (trend γ <sup>2</sup>	(5·4%/γ) - 0.5:2n-	- 0.49-	NS	
			- <del></del>	100.0	0.90 (~~ 0.09)
	∠87/6310 (4·5%/γ)	∠85/5128 (5-6%/γ)	-21.1	120.9	
2 – 4	492/7704 (6·4%/y)	467/5978 (7·8%/γ)	-45·4	202.2	0.60 (se 0.06)
5 – 9	310/9103 (3.4%/w)	263/6718	-34-9	123-6	0.75 (se 0.08)
10+	(3·+%/y) 210/8278	(3-5%/y) 166/6380	-6.2	79·6	0.93 (se 0.11)
<b>—</b> –	(2·5%/ <b>y</b> )	(2·6%/ <b>y</b> )			
Total	1299/ 31553	24343	-114-1	526-3	0-805 (SE 0-039) 2p < 0-00001
	(4·1%/ <b>y</b> )	(4·9%/y)			
- <b>■</b> aa.∞or <t> ao.∞cou</t>	naence intervala			a	0.5 1.0 1.5 2.0
					Polychemo better Polychemo worse

\* Stratified for age < 50, 50–59 and 60–69 only

Polychemo. better | Polychemo. worse Treatment effect 2p < 0.00001 Web Fig. 9(i). Polychemotherapy versus not in ER-poor disease: trial details and recurrence rate ratios in each of 46 separate trials

Y	ear code	Months &	Events/ Allocated	Women Allocated	Polycher Lograni	no. events Variance	s Ratio of annu	al event rates
and	study name	treatment	Poly	control	Ő-Е	of O-E	Poly :	Control
<u>(a)</u> (	CMF alone							
75E₂ 76C 7781+2 785 799H 80J1 80J1 80J1 8042 87Da 884D 87Da 8842 87Da 8842 87Da 89A2 89449 89A49 89A49 89A49 89A9 89A1 90P 90S1 90S1	Manchester I Graggew IBCSG-Ludwq III BCSG-Ludwq III BCSG-Ludwq III Guys March. II Paris INT Mian 8004 Viennah GKC 820 RGC A 282 RGC A 4 IBCSG VI GABG 3 Germany SABP B-20 IBCSG VI BCRC VI Haly CRCRAMS Moscow GROCTA V Italy CRCRAMS Moscow BCROCTA VI Amsterdam C8913 BCSC OLI Hamburg, Germany	$\begin{array}{c} 12 \ \text{CMF} \\ 13 \ \text{CMF} \\ 14 \ \text{CMF} \ \text{CMF} \ 14 \ 14 \ 14 \ 14 \ 14 \ 14 \ 14 \ 1$	9/12 27/40 9/19 26/40 14/48 20/49 20/49 20/49 20/49 26/40 26/40 32/20 32	13/20 19/28 13/14 26/31 36/44 18/36 30/47 6/11 64/83 17/28 44/72 4/17 0/2 60/196 12/22 20/38 2/4 16/50 11/50 11/50 13/31 13/95 13/51	$\begin{array}{c} 0.9\\ -1.4\\ -2.0\\ -7.1\\ -7.8\\ -9.2\\ 0.2\\ -2.2\\ -2.2\\ -2.2\\ -2.2\\ -2.1\\ -0.3\\ -0.3\\ -2.4\\ -2.9\\ -2.4\\ -2.9\\ -2.4\\ -2.9\\ -3.0\\ -3.2\end{array}$	$\begin{array}{c} 4 \cdot 0 \\ 8 \cdot 9 \\ 3 \cdot 4 \\ 6 \cdot 7 \\ 1 \cdot 1 \\ 1 \cdot 1 \\ 2 \cdot 7 \\ 1 \cdot 9 \\ 2 \cdot 4 \\ 3 \cdot 2 \\ - 6 \cdot 8 \\ 4 \cdot 7 \\ 5 \cdot 4 \\ 4 \cdot 0 \\ \end{array}$		
	(a) subtotal		471/ 1150 (41-0%)	450/ 970 (46·4%)	-57.1	178-6	<b>A</b>	0-73 (SE 0-06) reduction 2p = 0-00002
<u>(b)</u> I	FAC/FEC alone							
80S1 86P2+3 89@ 89B1 89D 90C6 96E	Helsinki FASG France Bari Italy SWOG 8814 IGR Paris FASG GFEA 07 Austrian BCSG IX	8 FAC + 6 FEC 6 FEC + 6 FAC + 6 FAC/FEC + 6 FEC + 4 FEC	8/22 79/199 12/54 20/55 27/79 0/1 0/10	15/18 92/190 9/40 12/18 42/76 0/0 0/6	-5·1 -12·9 0·1 -4·9 -10·1	4.2 38.5 4.9 5.1 14.9		<b>&gt;</b>
	(b) subtotal		146/ 420 (34-8%)	170/ 348 (48-9%)	-32-8	67-6	A	0.62 (SE 0.10) reduction 2p = 0.00007
(c) (	Other CMF regin	nens without	anthracy	clines				
77G1 78V2 79B1 79C 81H 85J1+3	Vienna ECOG EST6177 SWOG 7827 A Case Western B EST1180/SW.8294 PetrovStPetersb'g	36 CMEV 12 CMEPr 12 CMEVPr 12 CMEVPr 6 CMEPr † 4 CME; 2TtME	18/20 23/31 9/17 5/12 64/211 7/16	17/19 31/35 8/15 3/8 72/204 6/16	0.0 -6.5 -1.6 -1.0 -7.5 0.7	6.6 10.1 3.7 1.3 32.1 3.0		`
•	(c) subtotal		126/ 307 (41-0%)	137/ 297 (46-1%)	-15-9	56-8		0.76 (SE 0.12) reduction
(d) (	Other anthracyc	line regimens	3	,				2p = 0.00
76H	West Midlands LIK	6 CMEVAEol	49/61	63/73	-5.9	20.7		
80C2 80Z 82F 83B 84C 84Q4+5 92D 93H 93M1+2 94F	SE Sweden BCG B Southampton UK MD Anderson 8227 GROCTA I Italy NSABP B-16 Austrian BCSG 4 Amsterdam C9203 IBCSG 11-93 IBCSG 12-93 JCCG 9401	6 AC + 6 VAP/VAC + FACVPr + 6 CMF: 4 E + 6 CMF: 4 E + 24 MelF±A3AC + 6 CMFVA + 4 EC + 4 AC + 4 AC + 6 AC	2/2 20/34 16/53 1/1 275/539 4/10 5/14 0/5 0/4 4/8	2/4 22/36 5/23 2/2 152/252 3/5 5/19 0/1 0/3 3/9	0.7 -1.1 1.3 -0.5 -26.7 -1.5 0.0	0.6 9.0 3.9 0.3 - 81.2 0.6 - 2.3		
	(d) subtotal		376/ 731	257/ 427	-32.7	120-1		0.76 (SE 0.08)
			(51.4%)	(60-2%)				2p = 0.003
<u>(e)</u> (	Other polychem	otherapy						
76H2 76K 78M3 81E 88C 92B2 92G1245	West Midlands UK HD 1 W. Germany NCCTG-773051 NSABP B-13 NSABP B-20 HE1092 Greece NCRI ABC	6 ChIMF 24 ChIF 10 CFPr 11 MFFol †?? MFFol †6 CM2F various	28/78 0/1 21/26 111/373 0/0 5/13 74/212	25/60 0/0 28/31 168/380 0/2 0/5 82/198	-2.6 -4.2 -34.9 1.8 -9.5	12·1 9·7 65·5 1·0 33·3		 
	(e) subtotal		239/ 703 (34-0%)	303/ 676 (44-8%)	-49-5	121.7	-	0-67 (SE 0-07) reduction 2p < 0.00001
	Total (ae)		1358/ 3311 (41.0%)	1317/ 2718 (48·5%)	-188-0	544-8	 ♦	0-708 (SE 0-036) reduction 2p < 0-00001
-	99% or 🖘 95%	6 confidence inter	vals				0.5 1	0 1.5 2.0
He	Hotors acrost	ween 5 subto	tals: $\chi_4^2$ =	= 2·8;p>	0-1; N	5 <sup>J</sup> NG	Polychemo. better	Polychemo. worse
	Heterogeneity	within subto between 46 tr	ials: $\chi_{41}^2$	= +1·1; p = 50·5: r	> 0.1;	NS	Treatment effe	2t 2p < 0.00001
	genery		~45					

+ Chemotherapy plus tamoxifen versus same tamoxifen alone

Web Fig. 9(ii). Polychemotherapy versus not in ER-poor disease: trial details and breast cancer mortality rate ratios in each of 46 separate trials

			Deaths/	Women	- Polycher	no. deaths	<u> </u>
Y and	ear code study name	Months & treatment	Allocated Poly	Allocated control	Logrank O-E	Variance of O–E	Ratio of annual death rates Poly : Control
(a) (	CMF alone						
75E2 76CC 77B1+2 79H 80F1 80F1 84D2 86H2 87D3 88CD 88A2 87D3 89A2 89E4+9 89A2 89E4+9 89A2 89E4+9 89A2 89E4+9 89A2 89E4+9 89V 90S1 90S1 93S	Manchester I Glasgow Danish BCG 77b IBCSG/Ludwig III GUYS Manch, II WIT Milan 8004 Vienna Gyn. Danish BCG 82c Vienna Gyn. CaBC 32 Germany IBCSG IX STAKC-10 VIENCA 10 GRCRAMS Moscow STAKC-10 IBCSG VIII Tokyo CIH Hamburg, Germany (a) subtotal	$\begin{array}{c} 12 \ \text{CMF} \\ 14 \ \text{CMF} \ \text{CMF} \ 14 \ 14 \ 14 \ 14 \ 14 \ 14 \ 14 \ 1$	9/12 26/40 9/17 8/19 24/40 6/48 14/49 7/11 57/55 7/55 11/225 4/41 11/225 6/41 11/225 6/203 9/5 9/5 9/5 9/5 9/5 6/80 8/92 4/39 <b>396/</b> 1150	11/20 19/28 11/14 25/31 35/44 10/36 24/47 6/83 39/72 0/2 48/196 48/22 18/38 1/4 13/50 7/50 7/50 7/51 6/95 10/510 10/51 1	2:43 -1:49 -7:55 -3:46 -7:25 -1:1 -0:8 -3:46 -2:26 -2:30 -2:4 -2:4 -2:4 -3:65 -2:4 -2:4 -3:65 -2:4 -2:4 -2:4 -2:4 -2:4 -2:4 -2:4 -2:4	37 92 367 11-8 847 23-27 26-1 1-9 379 7-2 26-1 1-9 379 7-2 26-1 1-9 379 3-2 3-2 3-2 3-2 3-2 3-2 3-2 3-2 3-2 3-2	0.79 (SE 0.07)
			(34-4%)	(38-5%)			2p = 0.003
<u>(</u> b)	FAC/FEC alone						
80S1 86P2+3 89@ 89B1 89D 90C6 96E	Helsinki FASG France Bari Italy SWOG 8814 IGR Paris FASG GFEA 07 Austrian BCSG IX	8 FAC + 6 FEC 6 FEC + 6 FAC + 6 FAC/FEC + 6 FEC + 4 FEC	8/22 59/199 4/54 18/55 22/79 0/1 0/10	13/18 63/190 6/40 9/18 33/76 0/0 0/6	-3:4 -4:8 -1:2 -2:3 -5:7	3.8 28.5 2.4 4.8 12.3	
	(b) subtotal		111/ 420 (26·4%)	124/ 348 (35-6%)	-17.4	51.7	0.71 (SE 0.12) reduction 2p = 0.02
(c) (	Other CMF regin	nens without	anthracy	clines			
77G1 78V2 79B1 79C 81H	Vienna ECOG EST6177 SWOG 7827 A Case Western B EST1180/SW.8294 PetrovSIPetersbin	36 CMFV 12 CMFPr †12 CMFVPr †12 CMFVPr 6 CMFPr 4 4 CMF: 211MF	12/20 22/31 9/17 5/12 45/211	13/19 29/35 8/15 3/8 52/204 4/16	-1·4 -2·5 -1·2 -0·9 -5·2	5:3 11:3 3:7 1:3 - 23:6 2:0	
	(c) subtotal	1 . 0.01 , 21.00	98/ 307 (31.9%)	109/ 297 (36.7%)	-10.7	47.1	0.80 (SE 0.13) reduction
(d) (	Other anthracyc	line regimens	3	(00-1 /0)			2p > 0.1; NS
76H	Wast Midlands LIK	6 CMEVAEol	47/61	61/72	2.2	22.4	
80C2 80Z 80Z 82F 83B 84C 84Q4+5 92D 93H 93M1+2 94F	SE Sweden BCG B Southampton UK MD Anderson8227 GROCTA I Italy NSABP B–16 Austrian BCSG 4 Amsterdam C9203 IBCSG 11–93 IDCSG 12–93 JCCG 9401	6 AC + 6 VAP/VAC 4 FACVPr + 6 CMF; 4 E + 24 MelF±A/3A( + 6 CMFVA + 4 EC + 4 AC + 4 AC + 4 AC + 6 AC	2/2 13/34 13/53 1/1 237/539 3/10 4/14 0/5 0/4 4/8	0/7/3 2/4 17/36 3/23 1/2 127/252 3/5 4/19 0/1 0/3 1/9	-3-2 0-9 -0-8 -0-5 -16-4 -1-1 -0-1	22-4 0-8 6-6 3-1 0-3 — 71-6 0-6 — 1-9	
	(d) subtotal		324/ 731	219/ 427	-17.9	108-3	0.85 (SE 0.09)
			(44-3%)	(51-3%)			2p = 0.09
<u>(e)</u> (	Other polychem	otherapy					
76H₂ 76K 78M₃ 81E 88C 92B₂ 92G1₂45	West Midlands UK HD 1 W. Germany NCCTG-773051 NSABP B-13 NSABP B-20 HE1092 Greece NCRI ABC	6 ChIMF 24 ChIF 10 CFPr 11 MFFol 4?? MFFol 6 CMzF Various	21/78 0/1 21/26 77/373 0/0 4/13 55/212	21/60 0/0 24/31 108/380 0/2 0/5 69/198	-3·4 0·5 -15·7 1·3 -9·4	9·9 9·2 44·6 0·8 27·6	
	(e) subtotal		178/ 703 (25-3%)	222/ 676 (32-8%)	-26.7	92-1	0.75 (SE 0.09) reduction 2p = 0.005
	Total (ae)		1107/ 3311 (33-4%)	1047/ 2718 (38-5%)	-109-1	455-5	<ul> <li>0.787 (se 0.042)</li> <li>reduction</li> <li>2p &lt; 0.00001</li> </ul>
	99% or	6 confidence inter	vals tolor <sup>2</sup>	1 2	0.1. 14		0.5 1.0 1.5 2.0
пe	Heterogeneity Heterogeneity	within subto	tals: $\chi_4 =$	= 45.1:n	0-1; NR > 0-1-	NS F	Polychemo. better Polychemo. worse
	Heterogeneity	between 46 tr	tals: $v^2$	= 46.4: n	> 0.1	NS	Treatment effect 2p < 0.00001
† Cr	nemotherapy plus tam	noxifen versus sar	ne tamoxife	en alone	,		

Web Fig. 9(iii). Polychemotherapy versus not in ER-poor disease: trial details and all-cause mortality rate ratios in each of 46 separate trials

Y and	ear code study name	<u>E</u> Months & treatment	eaths/wom Allocated Poly	an-years Allocated control	Polychei Lograni O-E	mo. death: Variance of O-E	s Ratio of a	innual Poly : (	l death rates Control
(a) (	CMF alone								
75E2 77B1+2 78K3 79H 80F1 80F1 82C 84D2 86H2 87D3 884D2 884D2 8924 8924 8924 8924 8924 8924 8924 892	Manchester I Glasgow Danish BCG 77b IBCSGLuchwg III Guy's Manch. II Parls Guy's Manch. II Parls Chiller Mark Janes Construction Chiller Mark BCSG VII GABC 3 Germany NSABP B-20 GABC 3 Germany NSABP B-20 GRCRAMS Moscow Romagnolo Italy Amsterdam C8913 IBCSG VIII Jokyo CIH Hamburg, Germany	$\begin{array}{c} 12 \ \text{CMF} \\ 14 \ \text{CMF} \ \text{CMF} \ 14 \ 14 \ 14 \ 14 \ 14 \ 14 \ 14 \ 1$	10/98 29/312 11/196 6/363 16/837 7/104 6/4/401 25/241 134/1679 4/82 0/13 40/1900 10/164 14/243 0/567 10/567 6/301 6/348 9/420 4/129	12/216 21/178 11/147 25/233 37/244 11/234 8/133 65/550 0/28 59/1702 9/153 13/521 7/192 5/312 13/521 7/192 8/344 6/454 11/173 408/	2:2 -1:4 -4:5 -399 -900 0:2 5:5 1:1 1:9 0:2 -1:2 -1:2 -1:8 -1:8 -2:7 -1:1 1:7 -2:7	39 103 34 74 127 39 95 329 76 239 76 239 16 239 44 755 30 44 35 30 43 33 34 35 30			
-	(a) Subiotai		9060 (4-9%/y)	7115 (5·7%/y)	-39.1	173-2			reduction 2p = 0.003
(b) l	FAC/FEC alone								<b>_</b> p _ 0 000
80S1 86Pa+3 89@ 89B1 89D 90C6 96E	Helsinki FASG France Bari Italy SWOG 8814 IGR Paris FASG GFEA 07 Austrian BCSG IX	8 FAC + 6 FEC + 6 FAC + 6 FAC + 6 FAC/FEC + 6 FEC + 4 FEC	9/169 64/1646 6/508 21/488 22/562 0/6 0/13	16/111 67/1512 8/438 9/146 33/477 0/0 0/13	-3·7 -4·6 -1·2 -1·7 -5·7	4-5 30-7 3-3 5-3 12-3			
	(b) subtotal		122/ 3392	133/ 2697	-16-9	56-1			0.74 (SE 0.12) reduction
(0) (	Other OME regin	aan a with a ut	(3·6%/y)	(4·9%/y)					2p = 0-02
(C) (	Jiner CMF regin	iens without	anthracy	clines					
77G1 78V2 79B1 79C 81H 85J1+3	Vienna ECOG EST6177 SWOG 7827 A Case Western B EST1180/SW.8294 PetrovStPetersb'g	36 CMEV 12 CMEPr 12 CMEVPr 12 CMEVPr 6 CMEPr † 4 CME; 2TtMI	12/191 23/291 11/169 6/73 61/2892 F 6/180	14/145 29/289 11/131 3/57 68/2621 4/187	-1·4 -2·1 -0·6 -6·1 0·8	5·3 11·5 4·8 1·5 31·3 2·3	*		`````````````````````````````````
	(c) subtotal		119/ 3796 (3·1%/y)	129/ 3430 (3·8%/y)	-11.4	56-7			0-82 (SE 0-12) reduction 2p > 0-1; NS
(d) (	Other anthracyc	line regimen:	s						
76H1 80C2 80Z 82F 83B 84C 84Q4+5 92D 93H 93M149 93M149	West Midlands UK SE Sweden BCG B Southampton UK MD Anderson8227 GROCTA I Italy NSABP B-16 Austrian BCSG 4 Amsterdam C9203 IBCSG 12-93 IBCSG 12-93 ICCG 9401	6 CMFVAFol 6 AC † 6 VAP/VAC † 6 CMF;4 E †24 MelF±A/3AI † 6 CMFVA † 4 EC † 4 AC † 4 AC † 6 AC	48/481 2/4 17/400 14/375 1/17 C304/5643 6/52 4/52 0/38 0/34 4/35	61/515 4/37 19/375 3/152 1/17 154/2446 3/22 4/54 0/6 1/15 1/44	-2.9 0.9 0.3 2.0 -0.5 -16.4 -0.5 -0.1	22-6 0-8 8-1 3-4 0-3 - 90-6 1-0 1-9 0-3 -			
	(d) subtotal	1 0710	400/ 7131 (5-6%/y)	251/ 3683 (6-8%/y)	-15-9	129-9	-		0-88 (SE 0-08) reduction 2p > 0-1; NS
<u>(e) (</u>	Other polychem	otherapy							
76H2 76K 78M3 81E 88C 92B2 92B2	West Midlands UK HD 1 W. Germany NCCTG_773051 NSABP B-13 NSABP B-20 HE1092 Greece NCRI ABC	6 ChIMF 24 ChIF 10 CFPr 11 MFFol †?? MFFol †6 CM2F †various	23/1505 0/14 22/229 108/5261 0/0 5/54 58/1111	23/1060 0/0 26/273 140/5018 0/28 0/36 71/1003	-3·8 0·4 -19·3 1·8 -9·3	10-9 9-7 60-0 1-1 28-8			>
	(e) subtotal		216/ 8174 (2·6%/y)	260/ 7418 (3·5%/y)	-30-2	110-4	V	-	0-76 (SE 0-08) reduction 2p = 0-004
	Total (ae)		1299/ 31553 (4·1%/y)	1181/ 24343 (4·9%/y)	-114.1	526-3	<	>	0-805 (SE 0-039) reduction 2p < 0-00001
-∎ He	99% or	6 confidence inter ween 5 subto	rvals otals: $\chi^2_{-} =$	2-0;p>	0-1; N	с с	0.5	1.0	1.5 2.0
	Heterogeneity	within subto	tals: $\chi^2_A$	= 46-8; p	> 0.1;	NS	Polychemo. bet	ter	Polychemo. worse
	Heterogeneity	between 47 ti	rials: $\chi_{46}^{\overline{2}}$	= 48-8; p	> 0.1;	NS	Treatment	effect	t 2p < 0⋅00001

† Chemotherapy plus tamoxifen versus same tamoxifen alone

Web Fig. 10(i). Tamoxifen versus not in ER-poor disease: trial details and recurrence rate ratios in each of 50 separate trials



† Tamoxifen plus chemotherapy versus same chemotherapy alone

Web Fig. 10(ii). Tamoxifen versus not in ER-poor disease: trial details and breast cancer mortality rate ratios in each of 50 separate trials

	Tamoxifen	Deaths/	Women	Tamoxif	en deaths	8	
Year code and study name	dose (mg/d) & duration (y)	Allocated Tam	Allocated control	Logrank Ö–E	Variance of O–E	, <u>Ratio of annual de</u> Tam : Cor	eath rates ntrol
(a) Tamoxifen for	average of up	to 2 (mea	an: 1.7) y	ears			
72J Copenhagen	30.2	37/80	34/67	-3.2	15.9		
74G2 Case Western A	+40 1	17/36	23/34	_4·7	8.8		
76G1458 Stockholm B	+40 2	21/45	22/47	-1-1	7.8		>
77E Danish BCG 77C	20.2	71/128	43/62 62/102	-7.0	28.0		_
77K NSABP B-09	+20 2	205/318	201/307	0.2	90·9	<b></b>	
78A <sub>2</sub> S Swedish BCG	30 1	28/51	29/63	2.4	12.8	¥	>
78B1 Toronto-Edmont.	30 2	27/40	28/39	-0.5	12.3	o	
78C GUN Naples 78H Jappbruck	†30 2 20 1	25/73	32/65	-7-3	10.8		
78J ECOG EST1178	20 2	3/5	3/6	0.5	1.3		
78M NCCTG/Mayo Clin	nic † <b>20 1</b>	64/109	64/103	-3.6	27.9		
78S12345 NKCC Japan 78V ECOC 5177/6177	+20 2 +20 1	39/322	43/325	-2.2	19.2		
79B1 SWOG 7827 A	+20 1	9/17	11/15	-2.1	4.6		>
79D1+2 GABG/HD Germa	iny †30 2	50/137	59/144	-2.4	24.7	D	
80E Toulouse France	30 2	5/14	4/14 25/54	0.3	1.5		•>
80P GABG 2 Germany	30 2	3/27	5/46	-0.1	1.3		>
80S Helsinki	+40 2	22/32	22/40	3.8	8.5		>
81A Montpellier France	e 302	0/7	4/9	-1.1	0.7 -		
82B1 Danish BCG 82b	+30 1	38/58	4/9	-2.9	17.3		
82H NBCG 1a Norway	20 2	2/2	1/1			-	
82L123456 ACETBC-1	†20 1 or 2	204/969	220/1027	-5.0	97.4	— <b>— — —</b>	-
82N Kumamoto	+20 2	2/28	1/26	0.0	0.5 -		<u> </u>
83E1+2 Oita	9 30 TOT3 +20 2	2/18	29/85 3/32	2.3	0.7		
84A1+5 GBSG 02 German	τy +30 2	25/56	26/55	-1.3	11.2		*
84Q4 Austrian BCSG 4	20 2	0/0	3/5				
84S1 Kawasaki 2 84U S/SE Sweden BC	†201 G 20/402	0/1 /3/90	0/1 //2/95	3.4	18-0		
85H8dfhkra ACETBC-2	+30 2	45/241	37/251	2.0	17.2		
85J123578 PetrovStPetersbig	† <b>20</b> 1	9/26	9/21	-1-1	3.9		>
86F1 Osaka BCSG Jap	an 402	5/31	5/47	1.4	2.3		
87A1+2 ZIPP	+20 2	102/427	64/220	-7.0	34.6		
87E1 Oita	20 2	4/52	5/54	-0.3	2.1		>
89J2 CRCRAMS Mosc	ow †20 2	0/0	0/1		04.0	_	_
91J GBSG V German	v 30 2	0/7	0/5	4.4	24.8		
(a) subtotal	,	1356/	1346/	<b>45 G</b>	596 3		0.93 (s= 0.04)
		4040	3866	-43.0	300-3	4	reduction
		(33.6%)	(34-0%)				2p = 0.06
(b) Tamoxifen for	average of 3 o	r more (n	nean: 5)	years			
76G239ab Stockholm B	+40 2 or 5 20 5 or 10+	86/238 66/128	107/269 72/126	-5·4 -5·1	42·6 28·2		_
78F CRFB Caen C5	40 3	16/22	17/21	-1.2	6.8		
80H2 Marseille	† <b>30</b> 3	6/12	4/10	1.2	1.9		÷
82%1 NSABP B-14	20 5 or 10 + 20 5	3/8	4/8 3/14	-0.1	1.5		~ ~ ~
83B GROCTA I Italy	+30 5	1/1	1/2	-0·4 -0·5	0.3 -		
86M2 CRFB Caen 002	30 5	6/19	2/5	0.3	1.5		·
86P2 FASG GFEA 02	+30 3	34/71	35/79	0.4	16.0		-
89F ECOG EST5188	+20 5	19/55	18/73	4.0	8.4		
91H NSABP B-23	20 5	127/999	134/1001	-3.2	63.7		
93C5+6 GABG 4 Germany	/ †?? 5	69/374	61/360	1.1	30.3		
93N IBCSG 13-93	T ( ( 5	64/229	72/218	-7.5	31.9		_
(b) subtotal		620/	632/	_4.7	287.6		0.98 (se 0.06)
		2890	2921		207.0		reduction
		(21.5%)	(21.6%)				$2n > 0.1 \cdot NS$
		(,	(,				20 > 01, 10
Total (a + b	)	1976/	1978/	-50.3	874.0	•	0.944 (SE 0.033)
	-	6930	6787			-	reduction
<b>—</b> 00% ar <b>—</b> 0	E0/ applidance int-	(20·5%)	(∠3·1%)				2p = 0.09
Difference betwe	ero contidence inte Sen	rvais -			0	0.5 1.0	1.5 2.0
treatment eff	ects in 2 subto	otals: $\chi_{\frac{1}{2}}^2$ =	= 0.7; 2p	> 0.1; N	IS	Tamoxifen better   Ta	moxifen worse
Heterogenei	ty within subto	otals: $\chi^2_{47}$	= 34.1; p	) > 0.1;	NS	Treatment effect	2p = 0·09
Heterogeneit	y between 49 t	rials: χ <sub>48</sub>	= 34·8; p	) > 0.1;	NS		

+ Tamoxifen plus chemotherapy versus same chemotherapy alone

Web Fig. 10(iii). Tamoxifen versus not in ER-poor disease: trial details and all-cause mortality rate ratios in each of 50 separate trials



+ Tamoxifen plus chemotherapy versus same chemotherapy alone

Web Fig. 11(i). Perioperative polychemotherapy (PeCT) versus no adjuvant cytotoxic in ER-poor disease, subdivided by nodal and menopausal status: trial details and recurrence rate ratios in each of 4 separate trials

		Events	Women	PeCT	events	Dette of our	
Year code and study name	Perioperative single cycle	Allocated PeCT	Allocated control	Logrank O–E	Variance of O-E	PeCT	: Control
(a) Premenopausal*							
81F3 IBCSG/Ludwig V N-	CMFFol	80/169	37/80	0.4	24.0		<b>_</b>
85C2 INRC Genova N-	FEC	3/20	10/20	-4·4	2.9 —	-	-
85W Hamburg N-	EC	2/23	8/34	-2.0	2.1 –		>
85W Hamburg N+	EC	11/17	11/20	1.7	4.2		<b>├</b> →
86A1 EORTC 10854 N-	FAC	34/100	36/98	-1·6	16.3		
86A1 EORTC 10854 N+	FAC	13/22	19/28	-1·4	6.3	e	>
■ (a) subtotal		143/ 351 (40·7%)	121/ 280 (43·2%)	<b>_7</b> ∙3	55.8	$\triangleleft$	0.88 (se 0.13) 2p = 0.33; NS
(b) Postmenopausal						1	
81F3 IBCSG/Ludwig V N-	CMFFol †	29/102	28/58	<i>–</i> 9·1	11.8		-
85C2 INRC Genova N-	FEC	4/15	2/18	0.8	1.5		·
85W Hamburg N-	EC	8/47	14/50	-2.7	5.2		
85W Hamburg N+	EC	15/36	14/25	-1.5	5.8		
86A1 EORTC 10854 N-	FAC	23/81	25/93	- <b>0</b> ·2	11.5		•>
86A1 EORTC 10854 N+	FAC	43/89	52/85	-7·3	20.3		
■ (b) subtotal		122/ 370 (33·0%)	135/ 329 (41·0%)	-20.0	56.1	$\rightarrow$	0·70 (se 0·11) <sub>2p = 0</sub> .008
Total (a + b)		265/ 721 (36-8%)	256/ 609 (42·0%)	-27.3	111 <b>.9</b>	$\diamond$	0·784 (se 0·084) 2p = 0·010
- <b></b> 99% or <del>&lt;</del> 95% confid	lence intervals						
Difference between treatment effects in 2	subtotals: $\chi_1^2$	<sup>2</sup> = 1·4; 2p	= 0·23; N	s	U	PeCT better	PeCT worse
Heterogeneity within	subtotals: $\chi_1^2$	² ₀ = 13·5;	o > 0·1; N	s		Treatment ef	fect 2p = 0.010

\* Includes perimenopausal (and age < 50 with unknown status)

† Hypothesis generator

Web Fig. 11(ii). Perioperative polychemotherapy (PeCT) versus no adjuvant cytotoxic in ER-poor disease, subdivided by nodal and menopausal status: trial details and breast cancer mortality rate ratios in each of 4 separate trials

	Deaths/Women PeCT deaths				deaths	Datia of annu	val daath vataa
Year code and study name	Perioperative single cycle	Allocated PeCT	Allocated control	Logrank O–E	Variance of O-E	PeCT	: Control
(a) Premenopausal*							
81F3 IBCSG/Ludwig V N-	CMFFol	51/169	28/80	-2.1	16.8		
85C2 INRC Genova <i>N</i> -	FEC	2/20	8/20	-3.3	2.3 —		<u> </u>
85W Hamburg N-	EC	2/23	5/34	- <b>0</b> ·7	1.4 -		
85W Hamburg N+	EC	7/17	4/20	2.0	2.5		
86A1 EORTC 10854 N-	FAC	24/100	22/98	1.3	11.1		<b>.</b>
86A1 EORTC 10854 N+	FAC	13/22	15/28	1.6	6.0		
■ (a) subtotal		99/ 351 (28-2%)	82/ 280 (29·3%)	-1·2	40.1	<	0.97 (se 0.16) 2p = 0.85; NS
<u>(b) Postmenopausal</u>							
81F3 IBCSG/Ludwig V N-	CMFFol †	26/102	23/58	-5.5	10.6		
85C2 INRC Genova N-	FEC	2/15	2/18	0.0	1.0 -		<b>&gt;</b>
85W Hamburg N-	EC	4/47	6/50	-0.4	2.4		<b>&gt;</b>
85W Hamburg N+	EC	9/36	7/25	-0·1	3.5		>
86A1 EORTC 10854 N-	FAC	16/81	18/93	-0.4	8.2		
86A1 EORTC 10854 N+	FAC	40/89	49/85	-7.7	19.8		<u> </u>
■ (b) subtotal		97/ 370 (26·2%)	105/ 329 (31·9%)	-14.1	<b>45</b> ∙5	$\rightarrow$	0.73 (se 0.13) 2p = 0.04
■ Total (a + b)		196/ 721 (27·2%)	187/ 609 (30·7%)	-15-3	85.6	$\Leftrightarrow$	> 0.836 (se 0.099) 2p = 0.10
- 99% or - 95% confid	lence intervals				 0	0.5 1	<u> </u>
treatment effects in 2	subtotals: $\chi_1^2$	<sup>2</sup> = 1·7; 2p	-	PeCT better	PeCT worse		
Heterogeneity within	subtotals: $\chi_1^2$	Treatment e	ffect 2p = 0·10				

\* Includes perimenopausal (and age < 50 with unknown status)

† Hypothesis generator

Web Fig. 11(iii). Perioperative polychemotherapy (PeCT) versus no adjuvant cytotoxic in ER-poor disease, subdivided by nodal and menopausal status: trial details and all-cause mortality rate ratios in each of 4 separate trials

		Deaths/wo	man-years	PeCT	deaths	Datia of sum	
Year code and study name	Perioperative single cycle	Allocated PeCT	Allocated control	Logrank O–E	Variance of O-E	PeCT	: Control
<u>(a) Premenopausal*</u>							
81F3 IBCSG/Ludwig V N-	CMFFol	56/2339	28/1148	-0.4	17·9		
85C2 INRC Genova N-	FEC	2/136	8/125	-3.3	2.3 —	•	<u> </u>
85W Hamburg N-	EC	2/146	5/154	-0.7	1.4 —	•	>
85W Hamburg N+	EC	7/49	4/65	2.0	2.5		
86A1 EORTC 10854 N-	FAC	24/961	22/936	1.3	11.1		• •
86A1 EORTC 10854 N+	FAC	14/129	16/192	1.7	6.4		·>
■ (a) subtotal		105/ 3760 (2·8%/y)	83/ 2620 (3·2%/y)	0.6	41.6	<	1·01 (se 0·16) 2p = 0·93; NS adverse
(b) Postmenopausal						ł	
81F3 IBCSG/Ludwig V N-	CMFFol †	42/1454	31/734	-5.7	15.7	<b>=</b>	<u> </u>
85C2 INRC Genova N-	FEC	2/99	2/96	0.0	1.0 –		<b>→</b>
85W Hamburg N-	EC	4/225	6/275	-0.4	2.4		
85W Hamburg N+	EC	9/118	7/78	-0·1	3.5		
86A1 EORTC 10854 N-	FAC	17/797	24/838	- <b>3</b> ·7	9.9		
86A1 EORTC 10854 N+	FAC	43/637	49/549	-6.3	2 <b>0</b> ·5		
■ (b) subtotal		117/ 3330 (3·5%/y)	119/ 2570 (4·6%/y)	-16-2	53·0	$\langle \rangle$	0·74 (se 0·12) 2p = 0·03
■ Total (a + b)		222/ 7090 (3·1%/y)	202/ 5190 (3∙9%/y)	-15.6	94-6	$\Leftrightarrow$	> 0.848 (se 0.095) 2p = 0.11; NS
99% or < - 95% confic Difference between treatment effects in 2	lence intervals ${f subtotals}: \chi^2$	² = 2·4; 2p	= 0·12; N	s	0	0.5 1 ReCT better	
Heterogeneity within	subtotals: $\chi^2$	<sup>2</sup> 10 = 7·8; p	> 0 1; NS			Treatment effe	r = 0.11; NS

\* Includes perimenopausal (and age < 50 with unknown status)

† Hypothesis generator