

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *N Engl J Med* 2006;355:1851-62.

Supplement 1 – Clinicians who recruited >1% of trial patients

			Patients
NEAT	Dr RJ Grieve	Walsgrave Hospital, Coventry	235
	Dr D Spooner	City Hospital NHS Trust, Birmingham	134
	Dr RK Agrawal	Royal Shrewsbury Hospital	96
	Dr CJ Poole	Selly Oak Hospital, Birmingham	91
	Dr IN Fernando	The Manor Hospital, Walsall	87
	Dr AM Brunt	North Staffs Royal Infirmary, Stoke on Trent	79
	Dr SM O'Reilly	Clatterbridge Hospital, Merseyside	70
	Dr SM Crawford	Airedale General Hospital	69
	Dr D Rea	Selly Oak Hospital, Birmingham	59
	Dr P Simmonds	Royal South Hampshire Hospital, Southampton	59
	Dr J Mansi	St Georges Hospital, London	58
	Dr H Earl	Addenbrookes Hospital, Cambridge	47
	Dr PA Murray	Essex County Hospital	38
	Dr VH Hall	Royal Hampshire County Hospital	34
	Dr K McAdam	Peterborough District Hospital	34
	Dr TJ Perren	St James University Hospital, Leeds	32
	Dr C Bradley	Bradford Royal Infirmary	31
	Dr M Soukop	Glasgow Royal Infirmary	30
	Dr C Price	Bristol Oncology Centre	28
	Dr RC Mehra	New Cross Hospital, Wolverhampton	27
	Dr NSA Stuart	Ysbyty Gwynedd (Bangor)	26
	Dr DA Jones	Warwick General Hospital, Coventry	24
	Dr K Benstead	Cheltenham General Hospital	23
	Dr J Joffe	Huddersfield Royal Infirmary	23
	Dr AG Goodman	Worcester Royal Infirmary	21
	Dr T Mughal	Royal Preston Hospital, Manchester	21
BR9601	Prof RCF Leonard	Western General Hospital, Edinburgh	64

Dr D Whillis	Raigmore, Inverness	41
Dr A Hutcheon	Aberdeen Royal Infirmary	37
Dr A Harnett	Beatson Oncology Centre, Glasgow	33
Dr PA Canney	Beatson Oncology Centre, Glasgow	31
Prof CJ Twelves	Beatson Oncology Centre, Glasgow	29
Dr J Dewar	Ninewells, Dundee	25
Dr AS Bulman	James Paget Hospital, Great Yarmouth	19
Dr D Cameron	Western General Hospital, Edinburgh	19
Prof R Coleman	Weston Park, Sheffield	18
Dr C Martin	James Paget Hospital, Great Yarmouth	14
Dr H Yosef	Beatson Oncology Centre, Glasgow	9
Dr DM Ritchie	Beatson Oncology Centre, Glasgow	6
Dr TRJ Evans	Beatson Oncology Centre, Glasgow	5
Dr L Mathieson	Western General Hospital, Edinburgh	4

Supplement 2 – Dose Intensity

A) Calculations

Individual drug delivered dose intensities (dDDI) were calculated using patients' body surface area, received doses and cycle duration. Cycle DDIs (cDDI) were calculated as the average of the dDDI's planned for that cycle; course DDI (CDDI) as the average of cDDIs over the planned number of cycles, per patient.

B) Results

NEAT's EcCMF patients achieved significantly higher CDDI than cCMF patients (median 94% vs 92%, $p < 0.001$). Additionally, the proportion of NEAT patients receiving an adequate CDDI ($\geq 85\%$) was significantly higher in the EcCMF arm (83% vs 76% CDDI, $p < 0.001$).

CDDI did not differ significantly between BR9601 treatments (median 96% ECMF* vs 93% CMF*, $p = 0.06$). However, the proportion of BR9601 patients receiving adequate CDDI was significantly higher for ECMF* (88% vs 74%, $p = 0.001$).

Supplement Table 3 – Tumour Characteristics

	NEAT (N=2021)		BR9601 (N=370)		OVERALL (N=2391)	
	EcCMF	cCMF	ECMF*	CMF*	ECMF	CMF
	(N=1009)	(N=1012)	(N=180)	(N=190)	(N=1189)	(N=1202)
Nodal Involvement						
0 nodes involved	315 (31)	311 (31)	21 (12)	26 (14)	336 (28)	337 (28)
1-3 nodes involved	456 (45)	459 (45)	108 (60)	106 (56)	564 (48)	565 (47)
4+ nodes involved	238 (24)	242 (24)	51 (28)	58 (30)	289 (24)	300 (25)
ER status						
Positive	517 (51)	469 (46)	106 (59)	95 (50)	623 (52)	564 (47)
Negative	312 (31)	330 (33)	56 (31)	63 (33)	368 (31)	393 (33)
Unknown	180 (18)	213 (21)	18 (10)	32 (17)	198 (17)	245 (20)
Tumour Type						
Ductal	820 (81)	814 (80)	151 (84)	149 (79)	971 (81.5)	963 (80)
Lobular	88 (9)	95 (9)	16 (9)	21 (11)	104 (8.75)	116 (10)
Medullary	14 (1)	14 (1)	0 (0)	2 (1)	14 (1)	16 (1)
Tubular	9 (1)	4 (1)	0 (0)	0 (0)	9 (1)	4 (0.25)
Papillary	1 (1)	0 (0)	2 (1)	0 (0)	3 (0.25)	0 (0)
Other	62 (6)	68 (7)	8 (4)	14 (7)	70 (6)	82 (7)
Unknown	15 (1)	17 (2)	3 (2)	4 (2)	18 (1.5)	21 (1.75)
Tumour grade						
1 - Well Differentiated	58 (6)	71 (7)	15 (8)	7 (4)	73 (6)	78 (7)
2 - Mod Differentiated	360 (36)	323 (32)	55 (31)	71 (37)	415 (35)	394 (33)
3 - Poorly Differentiated	576 (57)	608 (60)	104 (58)	106 (56)	680 (57)	714 (59)
Unknown	15 (1)	10 (1)	6 (3)	6 (3)	21 (2)	16 (1)
Tumour size						

≤2cm	432 (43)	451 (44.5)	72 (40)	66 (34)	504 (42)	517 (43)
>2 and ≤5cm	495 (49)	486 (48)	100 (56)	108 (57)	595 (50)	594 (49.5)
>5cms	54 (5)	55 (5.5)	6 (3)	9 (5)	60 (5)	64 (5.25)
Unknown	28 (3)	20 (2)	2 (1)	7 (4)	30 (3)	27 (2.25)

VL Invasion

Reported	517 (51)	516 (51)	88 (49)	99 (52)	605 (51)	615 (51)
Unreported	492 (49)	496 (49)	92 (51)	91 (48)	584 (49)	587 (49)

ER status=Estrogen Receptor Status; VL=Vascular/Lymphatic

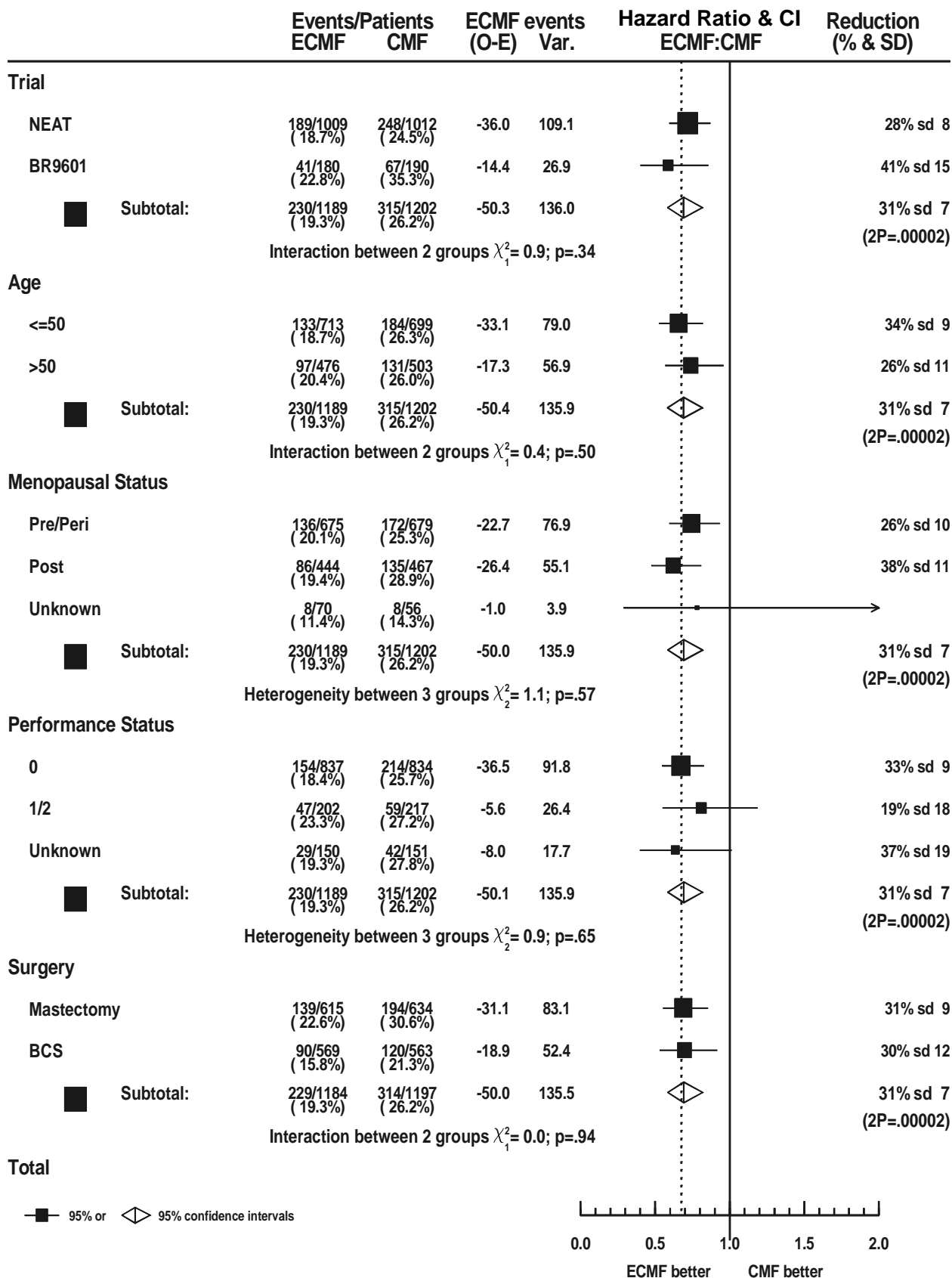
Supplement Table 4 – Relapse, Death and Second Malignancies Details

	ECMF (N=1189)		CMF (N=1202)		Total (N=2391)	
	N	%	N	%	N	%
Relapsed patients	206	17	285	24	491	21
Type of relapse*						
Loco-regional	45	4	72	6	117	5
Distant	189	16	263	22	452	19
Site of first distant relapse **						
Bone	80	42	122	46	202	45
Liver	56	30	80	30	136	30
Lung	39	21	58	22	97	21
SCF	20	11	29	11	49	11
Brain	24	13	19	7	43	10
Contralateral breast	3	2	2	1	5	1
Other	10	5	15	6	25	6
Unknown	3	2	1	1	4	1
Dead patients	171	14	242	20	413	17
Relapsed or Dead patients	230	19	315	26	545	23
Second malignancies	27	2	28	2	55	2
Site						
Contralateral breast	15	55	12	43	27	49
Endometrial	1	4	4	14	5	9
AML +/- myelodysplasia	0	0	0	0	0	0
Other	11	41	12	43	23	42

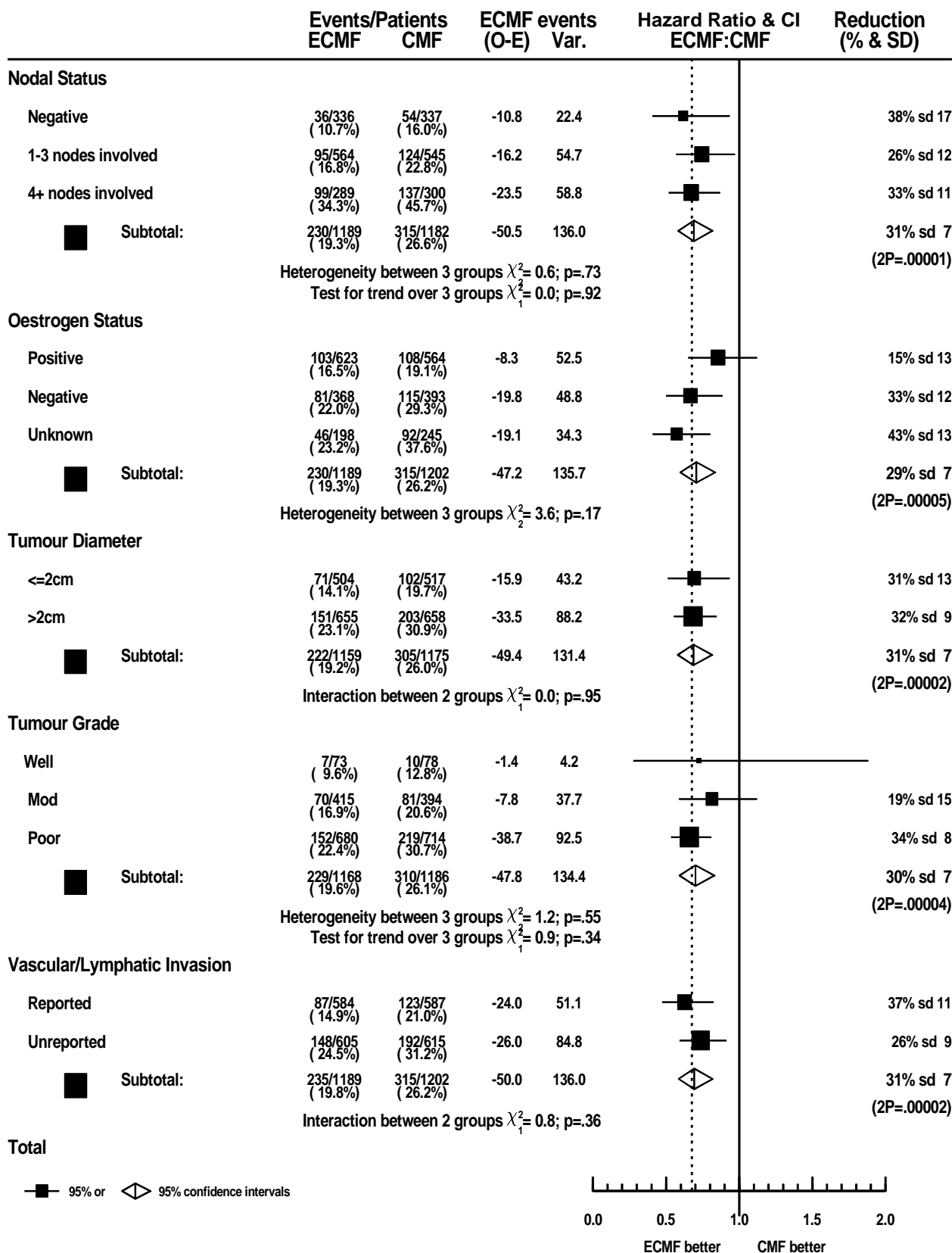
* Some patients have had loco-regional and distant relapses; ** Some patients have a first distant relapse in more than one site; AML = Acute myeloid leukaemia

Supplement Figure 5 – Relapse-free survival by treatment

A) By Patients Characteristics



B) By Tumour Characteristics



Supplement Table 6 – Cox Proportional Hazards Modelling for RFS

Factor	Grouping	HR (95%CI)	p
Nodal Status*	(Negative, Positive)	3.43 (2.63 – 4.48)	<0.001
Nodal Status*	(1-3 nodes versus other)	2.13 (1.77 – 2.58)	<0.001
Tumor grade	(Well, Mod, Poor)	1.61 (1.36 – 1.91)	<0.001
Tumor size	(≤2cm, >2cm)	1.51 (1.25 – 1.81)	<0.001
Treatment	(CMF, ECMF)	0.69 (0.58 – 0.83)	<0.001
ER Status^	(Positive, Other)	1.41 (1.17 – 1.69)	<0.001
VL Invasion	(Reported/Unreported)	0.78 (0.65 – 0.94)	0.01

* The 3 level nodal status factor is entered into the model using 2 dummy variables.

^ The estrogen factor is created using 2 dummy variables (to allow for unknowns) although only 1 is entered into the model.

Hazard ratios and p-values are from a multivariate analysis

Supplement Table 7 – Studies evaluating Epirubicin-based adjuvant chemotherapy (including Early Breast Cancer Trialists Collaborative Group meta-analysis for anthracycline-based regimens)

Study	No. Patients	Regimen (No. patients)	Relative Risk Reduction	
			Relapse/Death	Death
<i>NEAT</i>	2021	ECMF (1009) vs CMF (1012)	28%	30%
BR9601	370	ECMF (180) vs CMF (190)	41%	43%
NCIC CTG [23]	710	CEF 120 (351) vs CMF (359)	23%	18%
Subtotal	3101			
EBCTCG [25]	4840	Anthracycline (2420) vs CMF (2420)	11%	12%
TOTAL	7941			

No. patients = number of patients included in relative risk reduction analyses