

Supplementary Table 1a: Studies showing no benefit of anthracyclines (pre-taxanes)

Study (Year)	Ref	Regimens	N	Outcomes	P	Safety
NSABP-B12 (1989) Fisher et al	23	PAF-Tam vs PF-Tam	1106	5Y DFS: 64% vs 63% 5Y OS: 77% vs 78%	0.40 0.90	Symptomatic CHF: 0.6% vs 0% Leukemia/MPD: 0.009% vs 0.007%
NSABP-B15 (1990) Fisher et al	24	AC vs AC-CMF vs CMF	2194	3Y DFS: 62% vs 68% vs 63% 3Y DDFS: 68% vs 70% vs 68% 3Y OS: 83% vs 84% vs 82%	0.50 0.50 0.80	Symptomatic CHF: 0.1% vs 0% vs 0% Leukemia/MPD: Not reported
Moliterni et al (1991)	25	CMF-A vs CMF	486	5Y RFS: 72% vs 74% 5Y OS: 86% vs 89%	0.73 NR	Symptomatic CHF: 0% vs 0.004% Leukemia/MPD: Not reported due to size
Naples GUN-3 (1995) De Placido et al	26	CMF-EV vs CMF	220	4Y DFS: 51% vs 46% 4Y OS: 77% vs 74%	0.66 0.58	Symptomatic CHF: None reported Leukemia/MPD: None reported
Bang et al (2000)	27	AC vs CMF	124	5Y DFS: 64% vs 78% 5Y OS: 90% vs 86%	0.12 0.96	Symptomatic CHF: None reported Leukemia/MPD: None reported
Mauriac et al (1992)	28	MyTV-EVM vs CMF	228	5Y Total RFS: 80% vs 69% -Local RFS: 97% vs 94% -Distant RFS: 84% vs 83% 5Y OS: No difference	0.05 NR NR NR	Symptomatic CHF: None reported Leukemia/MPD: None reported
Budd et al (1995)	29	FAC-M vs CMFVPd	531	5Y DFS: 50% vs 55% 5Y OS: 61% vs 64%	NR 0.06	Symptomatic CHF: 0.004% vs 0% Leukemia: 0.007% vs 0%
Carpenter et al (1994)	30	CAF vs CMF	528	5Y OS: 74% vs 68%	0.41	Symptomatic CHF: Unknown Leukemia/MPD: Unknown
Levine et al (1990)	31	CMFVPd-ATam (12 wks) vs CMFVPd (36 wks)	437	3Y RFS: 55% vs 64% 3Y OS: 78% vs 85%	0.003 0.04	Symptomatic CHF: None reported Leukemia: 0% vs 0.005%
Coombes et al (1996)	32	FEC vs CMF	759	8Y RFS: 65% vs 64% 8Y OS: 82% vs 79%	0.61 0.13	Symptomatic CHF: 0.003% vs 0% Leukemia: None reported
TAX 303 Piccart et al (2001)	33	EC vs EC (high dose) vs CMF	777	3Y EFS: 72% vs 80% vs 78% 3Y OS: 89% vs 92% vs 91%	NR* NR*	Symptomatic CHF: 0.004% vs 0.01% vs 0% Leukemia: 0% vs 0.01% vs 0%
NSABP-B23 (2001) Fisher et al	34	AC+Tam vs CMF+Tam**	2008	5Y RFS: 87% vs 87% 5Y EFS: 82% vs 83% 5Y OS: 90% vs 89%	0.96 0.80 0.80	Symptomatic CHF: None reported Leukemia/MPD: None reported
INT-0102 (2005) Hutchins et al	9	CAF vs CMF	2690	10Y DFS: 77% vs 75% 10Y OS: 85% vs 82%	0.13 0.03 [†]	Symptomatic CHF: Similar in both arms Leukemia/MPD: Not increased in CAF arm

Supplementary Table 1b: Studies showing benefit of anthracyclines (pre-taxanes)

Study (Year)	Ref	Regimens	N	Outcomes (A v. NA)	P	Safety (A v. NA)
NSABP-B11 (1989) Fisher et al	23	PAF PF	707	5Y DFS: 51% vs 44% 5Y OS: 65% vs 59%	0.007 0.08	Symptomatic CHF: 0.6% vs 0.3% Leukemia/MPD: 0% vs 0.003%
Misset et al (1996)	37	AVCF CMF	249	16Y DFS [‡] : 53% vs 36% 16Y OS [‡] : 56% vs 41%	0.006 0.01	Symptomatic CHF: Similar in both arms Leukemia/MDS: 0% vs 0%
Ejlertsen et al (2007)	38	CEF CMF	1224	10Y DFS: 55% vs 50% 10Y OS: 62% vs 55%	0.04 <0.01	Symptomatic CHF: Not increased in CEF Leukemia/MPD: 0.003 vs 0.003
Poole et al (2006)	39	E-CMF CMF	2401	5Y RFS: 76% vs 69% 5Y OS: 82% vs 75%	<0.001 <0.001	Symptomatic CHF: None reported Leukemia/MPD: 0.0008% vs 0%
Levine et al (1998)	35	CEF CMF	710	10Y RFS: 52% vs 45% 10Y OS: 62% vs 58%	0.007 0.085	Symptomatic CHF: 1.1% vs 0.3% Leukemia/MPD: 0.014% vs 0.003%
Martin et al (2003)	40	FAC CMF	985	5Y DFS: 58% vs 50% 5Y OS: 75% vs 69%	0.056 ^f NS ^f	Cardiotoxicity: 2.1% vs 0.2% Leukemia/MPD: None reported
De Placido et al (2005)	36	A-CMF CMF	466	5Y DFS: 65% vs 54% 5Y OS: 83% vs 79%	0.044 0.26	Symptomatic CHF: None reported Leukemia/MPD: None reported

Abbreviations:

P (melphalan), A (doxorubicin), F (fluorouracil), Tam (tamoxifen), C (cyclophosphamide), M (methotrexate), E (epirubicin), V (vincristine), My (mitomycin C), T (thiotepa), Pd (prednisone)

* - No difference in EFS or OS between CMF and EC (high dose) groups, but overall p value not reported for all three groups

** - study also looked at addition of tamoxifen vs placebo to each group, which did not impact any survival outcomes. Overall p values for all 4 groups are shown, but, for simplicity, survival percentages reported here represent tamoxifen including arms only.

† - slight benefit shown in OS in CAF group based on one-sided p value, but because of greater overall toxicity authors could not conclude CAF to be superior to CMF

‡ - median follow up 16 years (range 13-17 years)

f – significant effect seen in prospectively formed node negative population, with (respectively for FAC vs CMF) 5Y DFS 75% vs 67%, P = 0.041; 5Y OS percentage not reported, but difference was significant (P = 0.034).