

BCIRG 001 Study



**Phase III Trial Comparing
TAC with FAC
in the Adjuvant Treatment of
Node Positive Breast Cancer Patients:
Interim Analysis**

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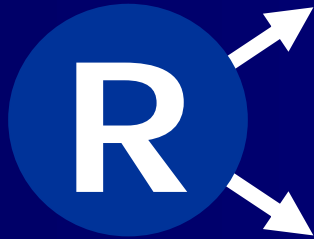
Study Rationale

- Anthracycline-based regimens are standard adjuvant treatments in node positive breast cancer patients
- Docetaxel-containing regimens have shown superior activity over standard regimens in MBC
 - ✓ Anthracycline failure
 - Docetaxel versus MV (Nabholtz et al, JCO '99)
 - Docetaxel versus MF (Sjöstrom et al, EJC '99)
 - ✓ CMF failure
 - Docetaxel versus Doxorubicin (Chan et al, JCO '99)
 - ✓ First-line
 - AT versus AC (Nabholtz et al, ASCO 1999)
 - TAC versus FAC (Nabholtz et al, ASCO 2001; Mackey et al, ASCO 2002)



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Design



F	5-FU	500 mg/m ²
A	Doxorubicin	50 mg/m ²
C	Cyclophosphamide	500 mg/m ²

Every 3 weeks x 6 cycles

Stratification:

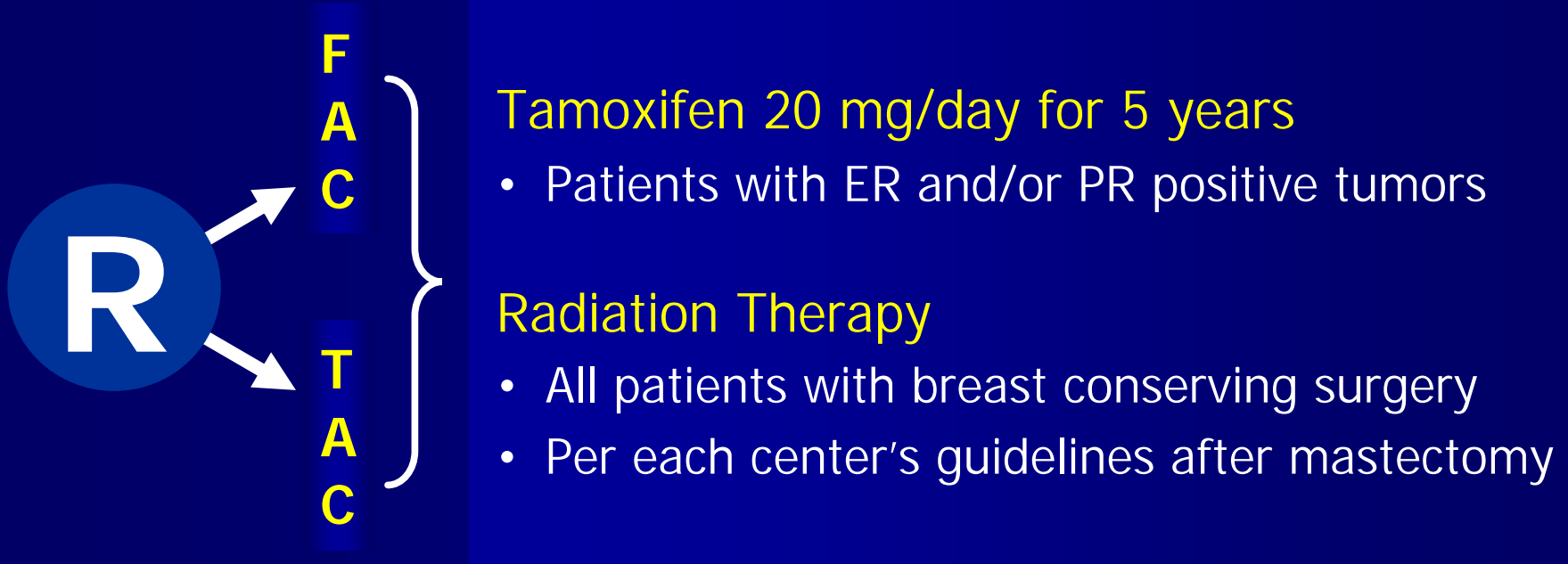
- Nodes:
 - 1-3
 - 4+
- Center

T	Docetaxel	75 mg/m ²
A	Doxorubicin	50 mg/m ²
C	Cyclophosphamide	500 mg/m ²

Dexamethasone premedication, 8 mg bid, 3 days
Prophylactic Cipro 500 mg bid, day 5-14



Post Chemotherapy Treatment



Major Eligibility Criteria

- Histologically proven node-positive breast cancer
- Stage T1-3, N1, M0
- Definitive surgery with axillary LN dissection (≥ 6 LNs)
- ≤ 60 days between surgery and randomization
- Age ≤ 70 years, KPS $\geq 80\%$
- Normal hematologic, liver, renal and cardiac function
- Informed consent



Endpoints

Primary

→ Disease-free Survival

Secondary

→ Overall Survival

→ Toxicity

→ Quality of Life, Socioeconomic Analyses

→ Pathologic & Molecular Markers

Source verification: 100% data for all patients



Patient Characteristics

Randomized (n=1,491)	TAC n= 745	FAC n= 746
Median Age	49	49
Median KPS	100%	100%
Premenopausal	51%	50%
Mastectomy	60%	59%
Radiotherapy	68%	71%
Tamoxifen	68%	69%

Enrollment: June 1997 to June 1999



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Tumor Characteristics

	TAC n= 745	FAC n= 746
Nodal Status	%	%
1-3	62	62
4-10	30	31
>10	8	7
Tumor Size (cm)		
£2	40	43
>2 and £5	53	51
>5	7	6
ER and/or PR +	69	69
HER2+ (FISH)	19	20



Exposure to Treatment

Treated (n=1,480)	TAC n= 744	FAC n= 736
Completed 6 cycles	679 (91%)	711 (97%)
Relative dose intensity		
Median	0.98	0.97
>0.90	89%	84%
Median total dose mg/m ²		
Docetaxel	446	-
Doxorubicin	297	298
Cyclophosphamide	2978	2985
5FU	-	2985



Protocol Defined Statistical Analyses Disease Free Survival and Overall Survival

→ Cohort: Intent to treat

→ First planned analysis: 3 years

✓ Main Analysis

- Log rank test stratified by nodal status

✓ Confirmatory analyses

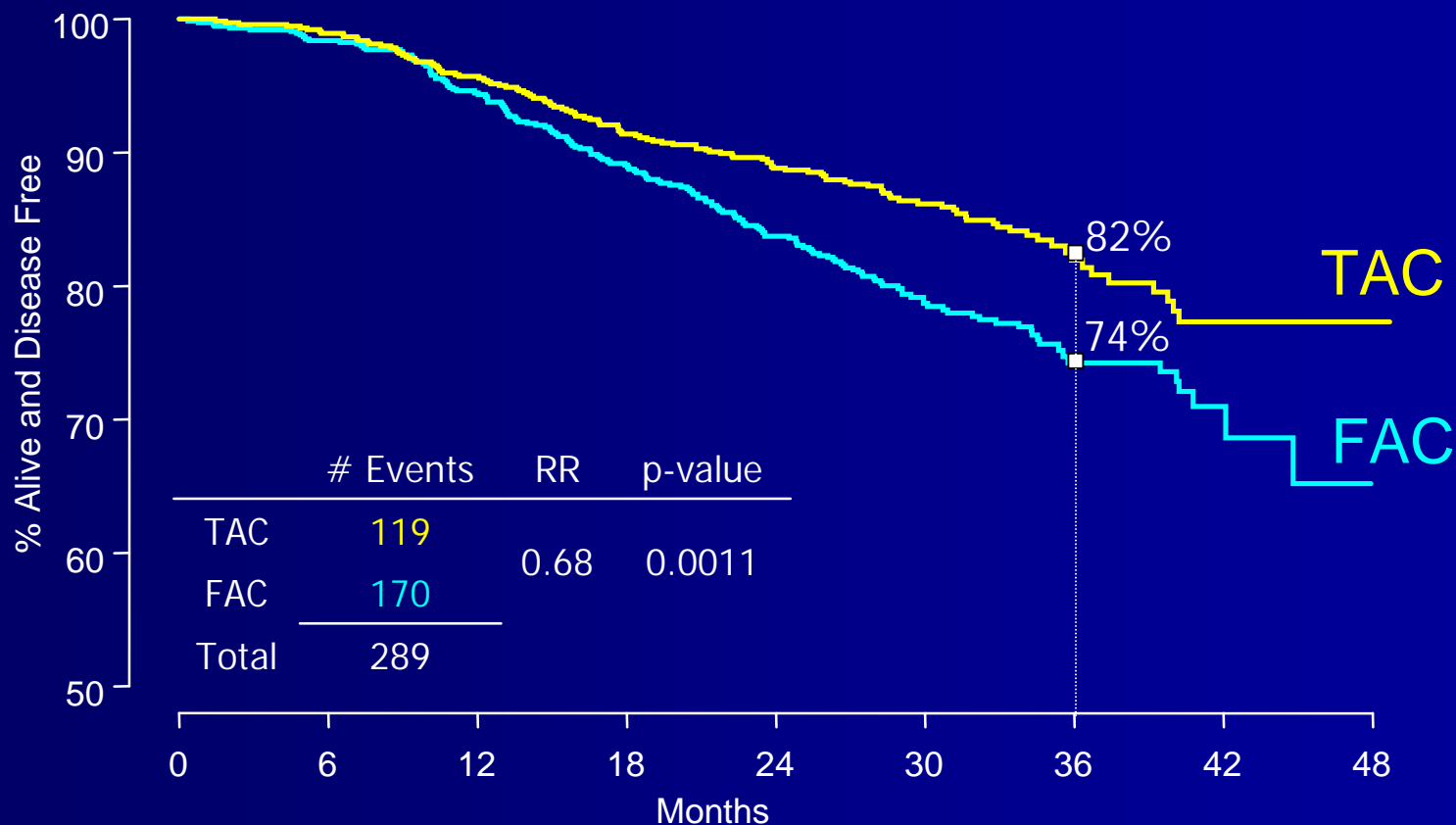
- Unadjusted
- Multivariate (Cox model)



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Disease Free Survival (ITT)

Median follow-up: 33 months



Number at Risk

TAC	745	736	710	678	654	373	152	23	1
FAC	746	729	699	656	605	334	150	31	0



Confirmatory Analyses: DFS

Analysis	Cohort	RR	p
Main Analysis (Stratified by nodes)	ITT	0.68 (0.54 – 0.86)	0.0011
Unadjusted	ITT	0.67 (0.53 – 0.85)	0.0008
Cox Model*	ITT	0.64 (0.50 – 0.81)	0.0002

*Controls for nodes, age, tumor size, histology, ER/PR, HER2



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Sites of First Events

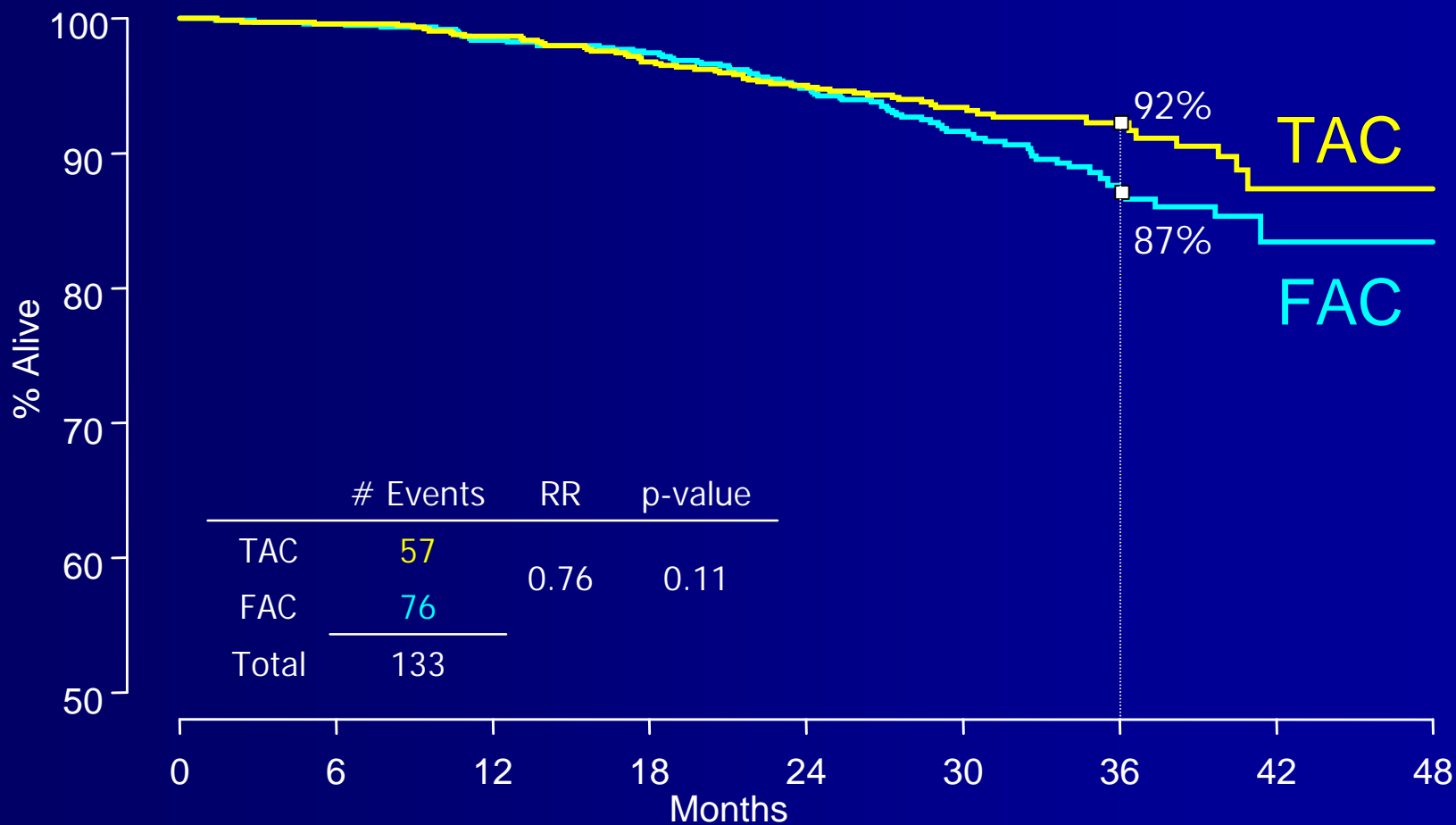
	TAC n= 745	FAC n= 746
	number of events	
Metastatic	80	119
Local/Regional	23	31
Contralateral	3	6
Other 2 nd Primary	6	10
Death NED	7	4
	119	170



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Overall Survival (ITT)

Median follow-up: 33 months



Number at Risk

TAC	745	741	732	718	700	393	171	24	1
FAC	746	738	728	713	678	375	171	33	1



Confirmatory Analyses: Overall Survival

Analysis	Cohort	RR	p
Main Analysis (Stratified by nodes)	ITT	0.76 (0.54 - 1.07)	0.11
Unadjusted	ITT	0.75 (0.53 - 1.06)	0.10
Cox Model*	ITT	0.71 (0.50 - 1.00)	0.049

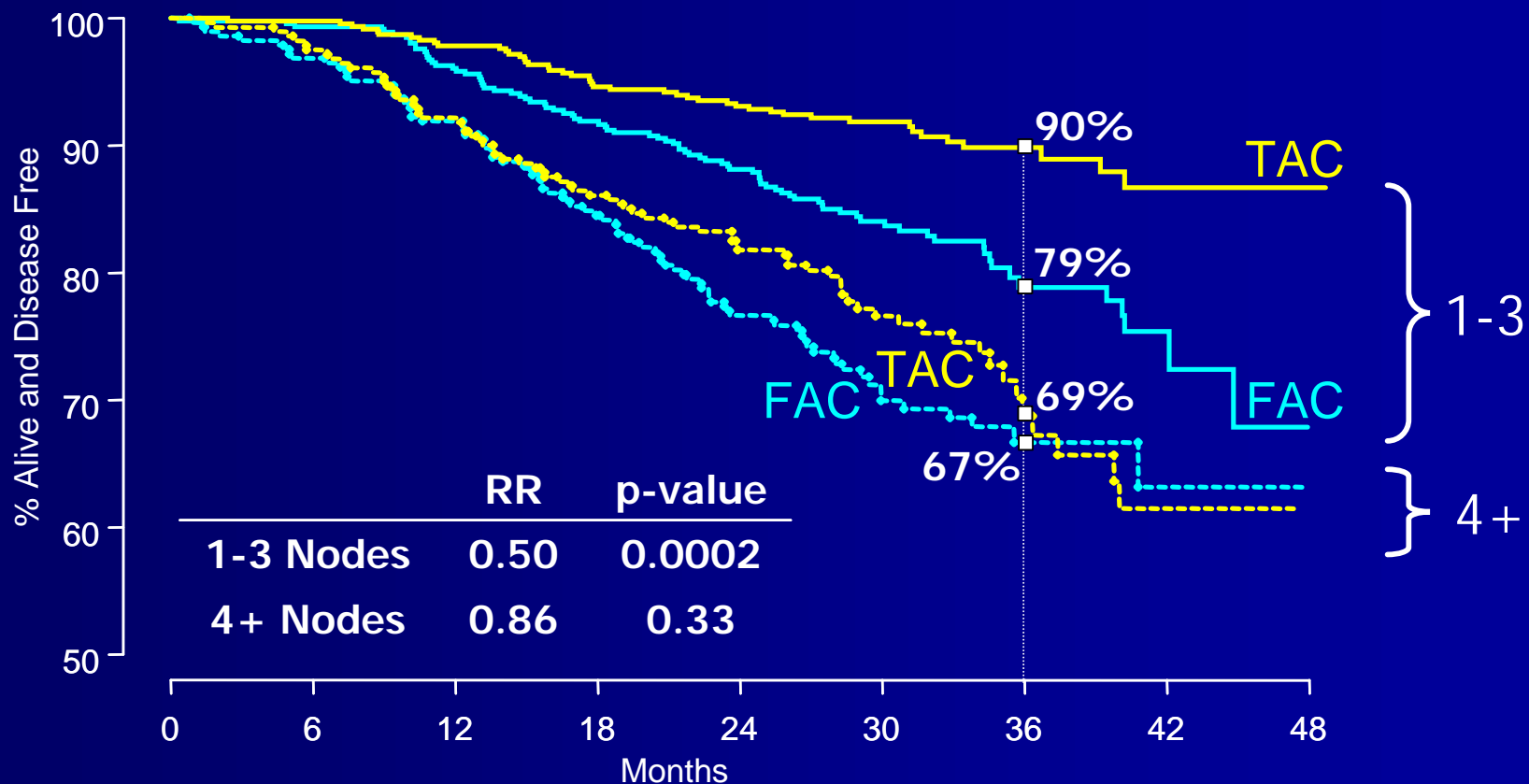
*Controls for nodes, age, tumor size, histology, ER/PR, HER2



Planned Additional Analyses Disease Free Survival and Overall Survival

- Prospectively defined and powered at 5 years
 - ✓ By nodal status
- Prospectively defined but not powered
 - ✓ By Hormonal Receptor
 - ✓ By HER2 status (FISH)

Disease Free Survival by Nodal Status

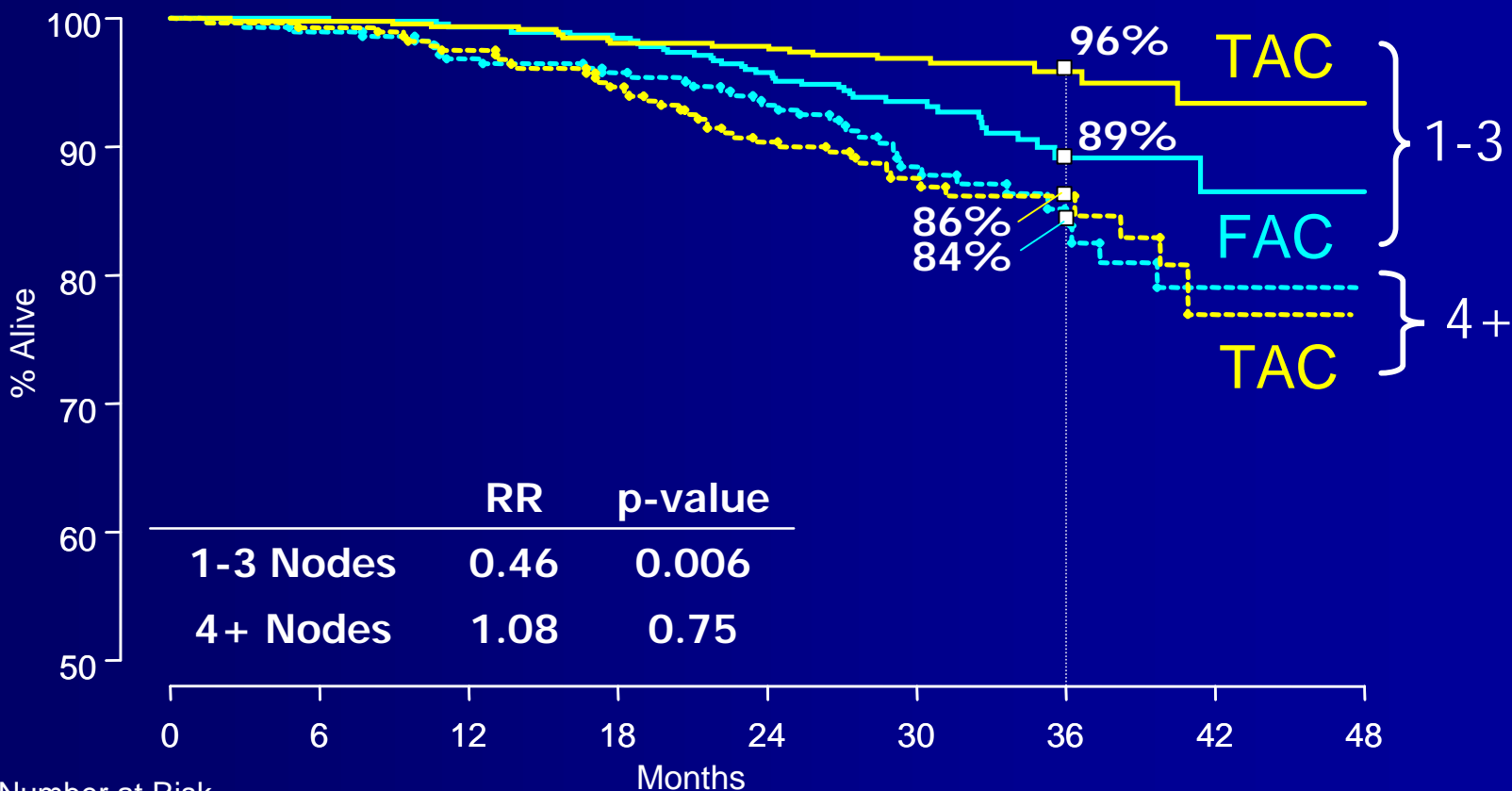


Number at Risk		0	6	12	18	24	30	36	42	48
1-3	TAC	463	462	452	437	427	250	103	14	1
	FAC	459	454	438	417	393	224	98	26	0
4+	TAC	282	274	258	241	227	123	49	9	0
	FAC	287	275	261	239	212	110	52	5	0



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Overall Survival by Nodal Status



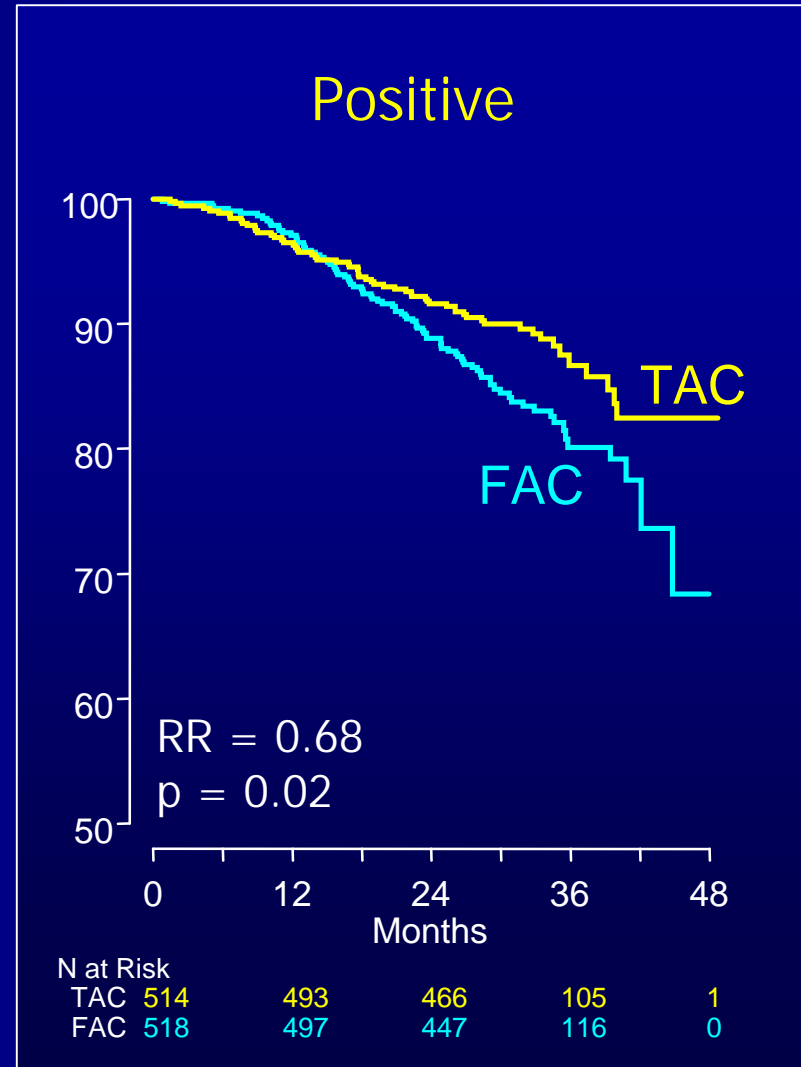
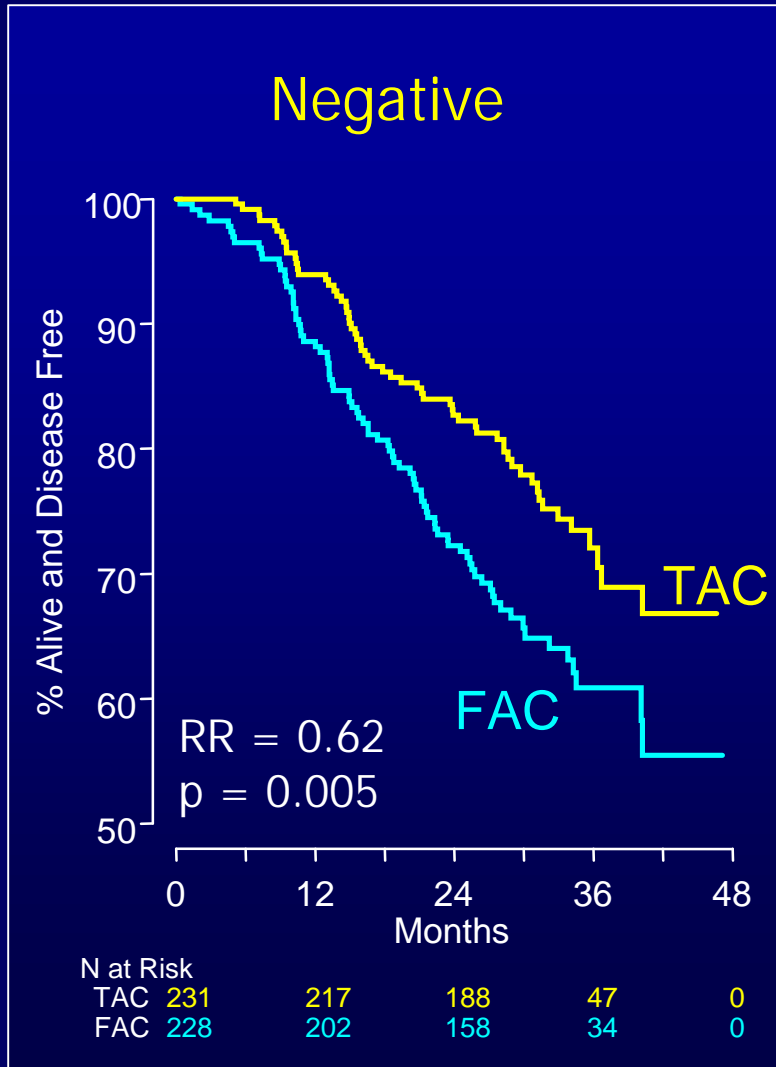
	RR	p-value
1-3 Nodes	0.46	0.006
4+ Nodes	1.08	0.75

		Number at Risk								
		0	6	12	18	24	30	36	42	48
1-3	TAC	463	462	459	453	449	261	112	14	1
	FAC	459	457	453	444	422	243	107	28	1
4+	TAC	282	279	273	265	251	132	59	10	0
	FAC	287	281	275	269	256	132	64	5	0

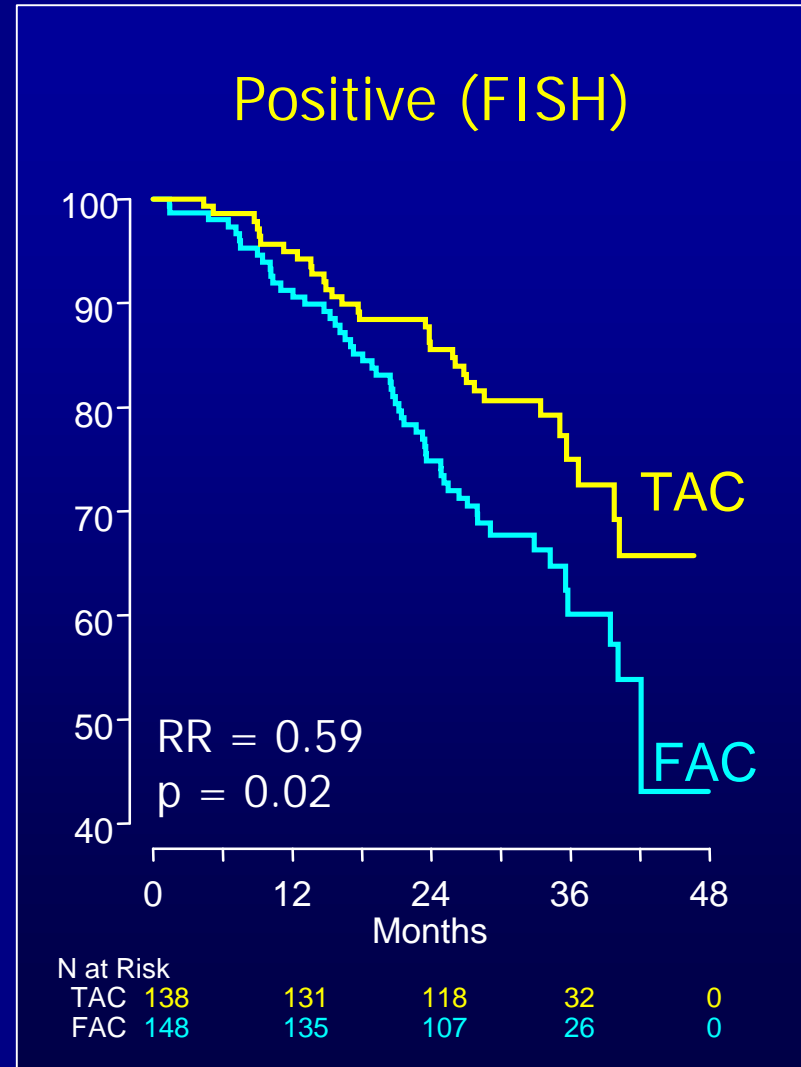
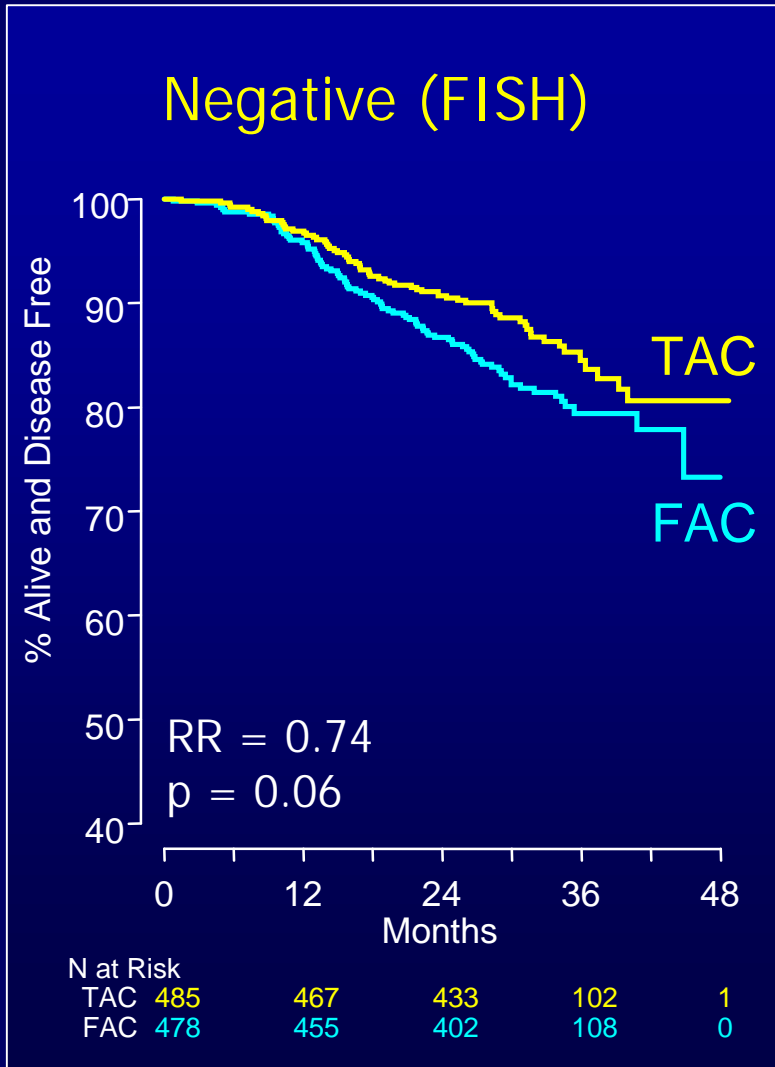


Nabholtz et. al, ASCO 2002 (abs 141)

Disease Free Survival by Hormonal Status



Disease Free Survival by HER2 status



Hematological Toxicity

Treated (n=1,480)	TAC n=744	FAC n=736
	%	%
ANC <1000 [∞]	65.1*	49.0
Febrile Neutropenia [§]	23.9*	2.4
Infection (Gr 3/4)	3.1	1.5
Septic Death	0	0
Anemia (Gr 3/4)	4.8*	2.2
Thrombocytopenia (Gr 3/4)	2.4	1.8

[∞] Protocol required blood counts every 3 weeks

[§] Gr 4 neutropenia at time of grade \geq 2 fever and i.v. antibiotics

* $p \leq 0.05$



Non-Hematological Toxicity

Grade 3 or 4 with Incidence >1%

	TAC n=744	FAC n=736
	%	%
Nausea	5.1	9.5*
Vomiting	4.3	7.3*
Diarrhea	3.4*	1.0
Stomatitis	7.1*	2.0
Asthenia	11.2*	5.3
CHF	1.6	0.7
Premenopausal pts	n=383	n=375
Amenorrhea	51.4*	32.8

*p≤0.05



Summary (I)

At 33 months median follow-up, TAC provides over FAC:

Primary endpoint: Disease-Free Survival

- Relapse rate ✓ Overall 32% reduction (p=0.0011)
 - ✓ By nodal status 1-3: 50% reduction (p=0.0002)
4+: No difference
 - ✓ By hormonal status HR- : 38% reduction (p=0.005)
HR+ : 32% reduction (p=0.02)

Secondary endpoint: Overall Survival

- Mortality rate ✓ Overall 24% reduction (p=0.11)
 - ✓ By nodal status 1-3: 54% reduction (p=0.006)
4+: No difference



Summary (II)

- Febrile neutropenia was more frequent on TAC, without increased incidence of infection and no septic deaths
- Other toxicities were acceptable and manageable in both arms

Conclusions

- The observed early benefit of TAC is large enough to be of clinical value in the adjuvant treatment of node positive breast cancer patients
- Additional follow-up is necessary to confirm the integration of TAC in this patient population



Investigators

Canada	Nabholtz, Walley, Tomiak, Guevin, Tang, Colwell, Prady, Provencher, Walde, Gelmon, Sehdev, Drolet, Dufresne , Yelle, Zibdawi, Lesperance, Verma, Cantin, Holland, Trudeau, Chang, Rubin, Allan		
USA	Vogel (CRN), Chap (UCLA network), Weaver, Hainsworth, Modiano, Erban, Graham, Harris, O'Rourke, Beck, Limentani, Robert, Tongol, Schnell, Begas, Haraf, Rosenberg, Campos, Foster, Beeker, Collin, George, Avery		
Spain	Martin Jimenez, Carrato Mena, Pelegri Sarle, Alba Conejo, Alvarez Lopez, Aranda Aguilar, Munarriz Gandia, Anton Torres, Lobo Samper, Lopez Vega, Menendez Prieto, Murias Rosales, Cassinello Espinosa, Garcia Puche		
Poland	Pienkowski, Pawlicki, Karnicka		
UK	Howell, Coleman, Whipp, Le Vay	Greece	Georgoulas
Hungary	Juhos, Pinter, Szanto	Germany	Oberhoff
France	Guastalla	So. Africa	Ruff
Brazil	Vinholes , Teixeira	Egypt	Abd-El-Azim, Gad-El-Mawla
Sweden	Fornander, Nylén	Austria	Schuller
Israel	Lurie, Merimsky, Steiner	Czech Rep	Abrahamova, Finek
Argentina	Guixa, Mickiewicz, Martinez	Portugal	Goncalves, Chumbo
Uruguay	Viola, Garbino	Slovak Rep	Koza



Development of Adjuvant Chemotherapy Breast Cancer

1970s

→ **Before anthracyclines**

- ✓ CMF, CMFVP

1980s

→ **With anthracyclines**

- ✓ Combinations: AC, FAC, AVCMF, FEC, CEF
- ✓ Sequence and Alternating
- ✓ Dose intensity, dose density

1990s

→ **Taxanes (Paclitaxel/Docetaxel)**

- ✓ Sequential: $A \Rightarrow T \Rightarrow C$ or $AC \Rightarrow T$
- ✓ Combinations: TA, TAC

2000s

Comparative Efficacy of Adjuvant Systemic Therapies

Therapies of	N	F-Up	% risk reduction in annual odds	
			Recurrence	Death
CT vs no CT	~10000	15yrs	23.5 P<0.00001	17 P<0.00001
Doxorubicin vs no doxorubicin	~7000	10yrs	10.8 P=0.0055	15.7 P<0.00001
Paclitaxel vs no paclitaxel	~3000	52mos	13.0 P=0.032	14.0 P=0.074
Docetaxel vs no docetaxel	1491	33mos	32.0 P=0.0011	24.0 P=0.11
docetaxel vs no docetaxel (1-3 lymph nodes)	~1000	33mos	50.0 P=0.0002	54.0 P=0.006