

**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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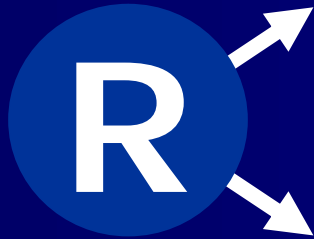
# Study Rationale

- 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



<b>F</b>	5-FU	500 mg/m <sup>2</sup>
<b>A</b>	Doxorubicin	50 mg/m <sup>2</sup>
<b>C</b>	Cyclophosphamide	500 mg/m <sup>2</sup>

Every 3 weeks x 6 cycles

## Stratification:

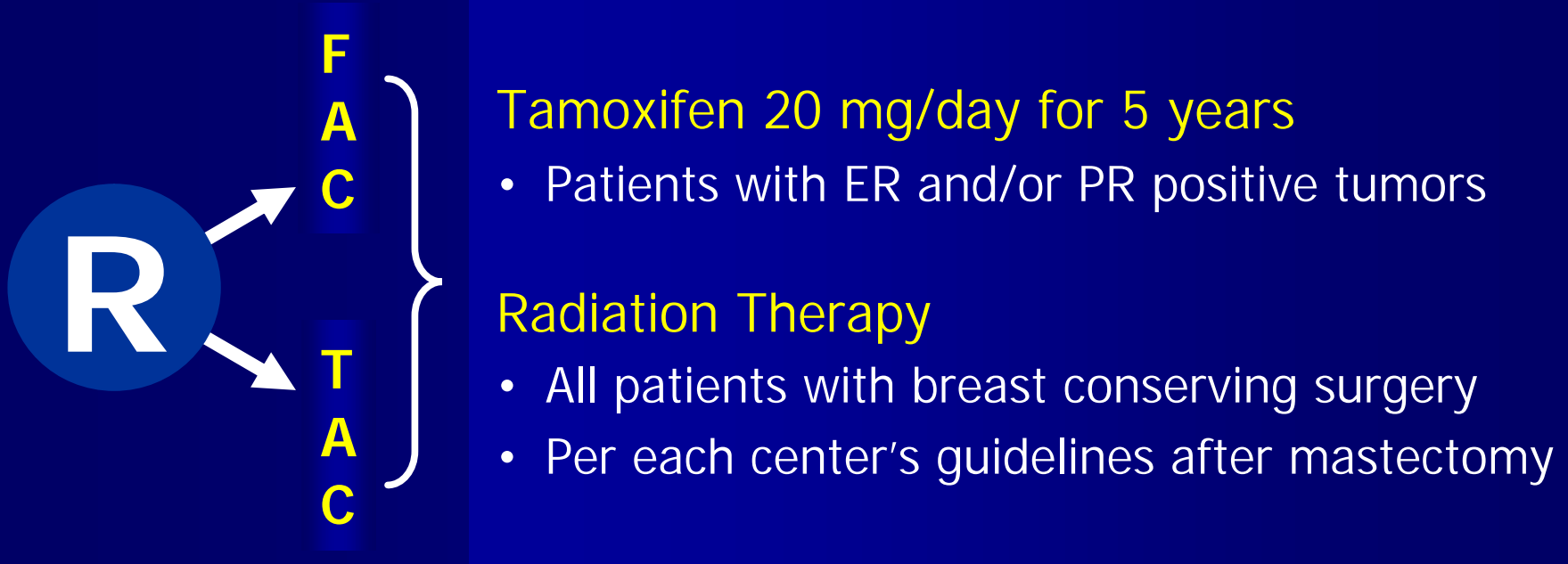
- Nodes:
  - 1-3
  - 4+
- Center

<b>T</b>	Docetaxel	75 mg/m <sup>2</sup>
<b>A</b>	Doxorubicin	50 mg/m <sup>2</sup>
<b>C</b>	Cyclophosphamide	500 mg/m <sup>2</sup>

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 ( $\geq 6$  LNs)
- $\leq 60$  days between surgery and randomization
- Age  $\leq 70$  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

	TAC n= 744	FAC n= 736
<b>Treated (n=1,480)</b>		
Completed 6 cycles	679 (91%)	711 (97%)
Relative dose intensity		
Median	0.98	0.97
>0.90	89%	84%
Median total dose mg/m <sup>2</sup>		
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

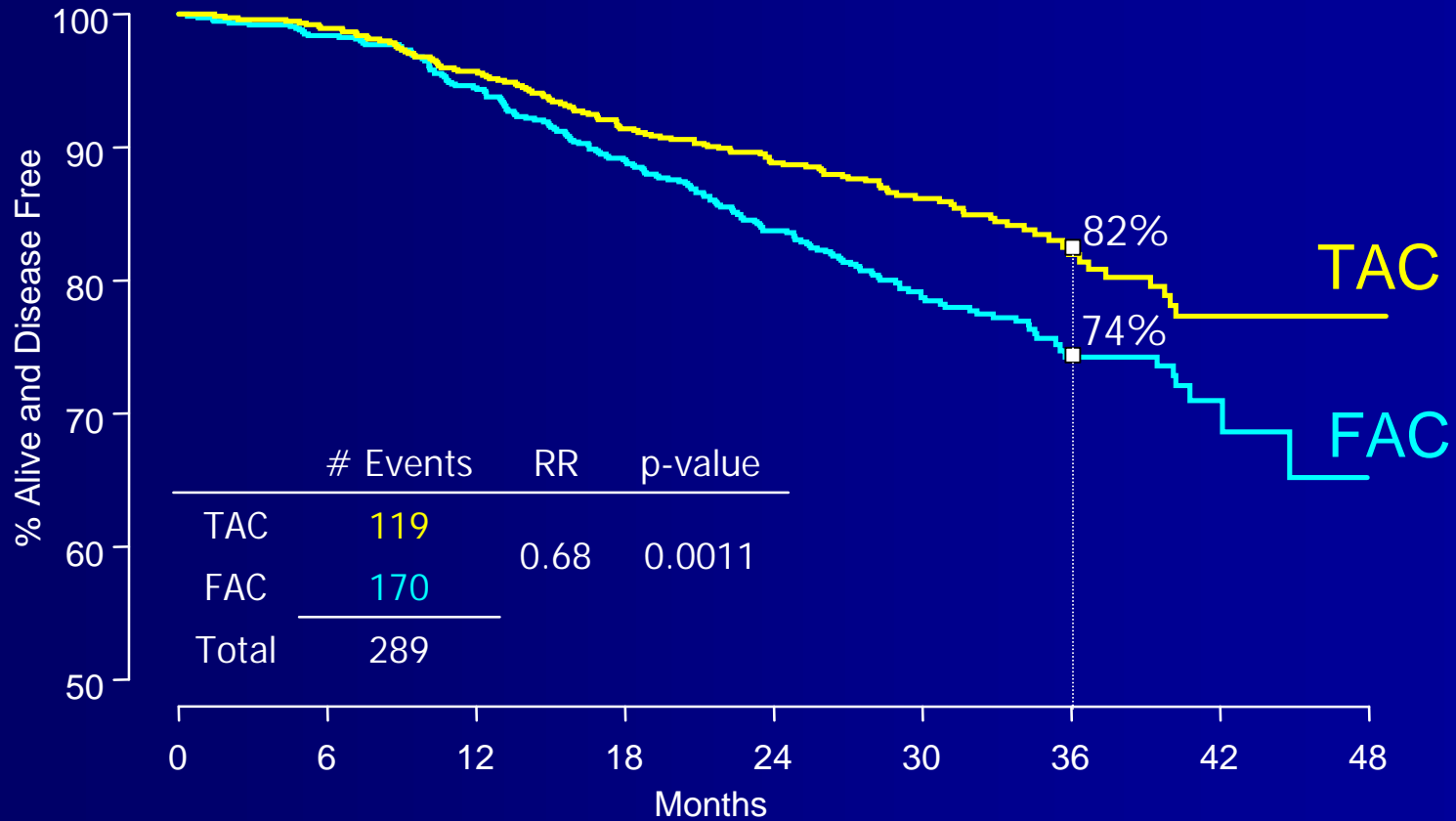
- Unadjusted
- Multivariate (Cox model)



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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	<b>0.68</b> (0.54 – 0.86)	0.0011
Unadjusted	ITT	<b>0.67</b> (0.53 – 0.85)	0.0008
Cox Model*	ITT	<b>0.64</b> (0.50 – 0.81)	0.0002

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



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# Sites of First Events

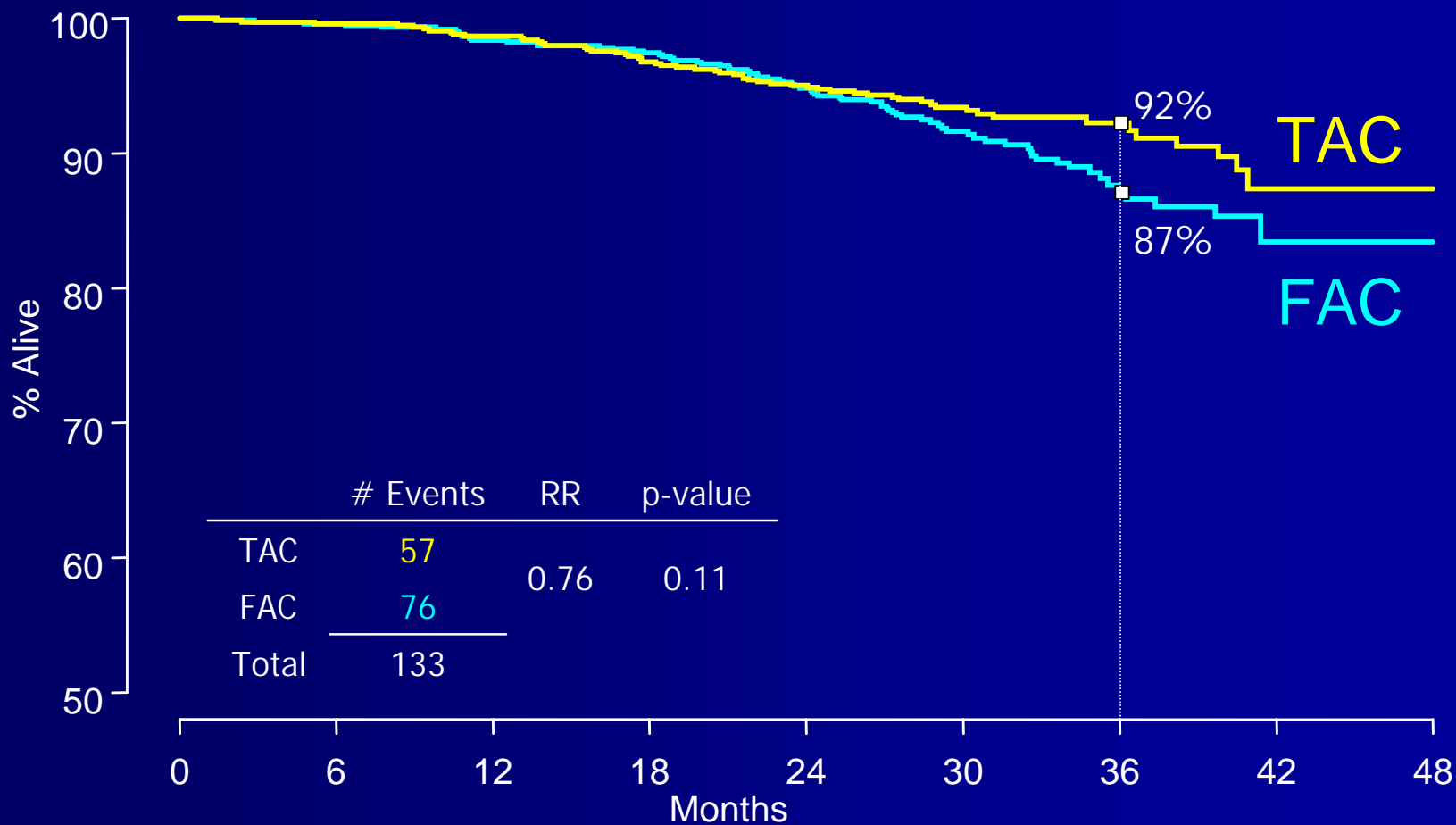
	TAC n= 745	FAC n= 746
	number of events	
Metastatic	80	119
Local/Regional	23	31
Contralateral	3	6
Other 2 <sup>nd</sup> Primary	6	10
Death NED	7	4
	119	170



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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	<b>0.76</b> (0.54 - 1.07)	0.11
Unadjusted	ITT	<b>0.75</b> (0.53 - 1.06)	0.10
Cox Model*	ITT	<b>0.71</b> (0.50 - 1.00)	0.049

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

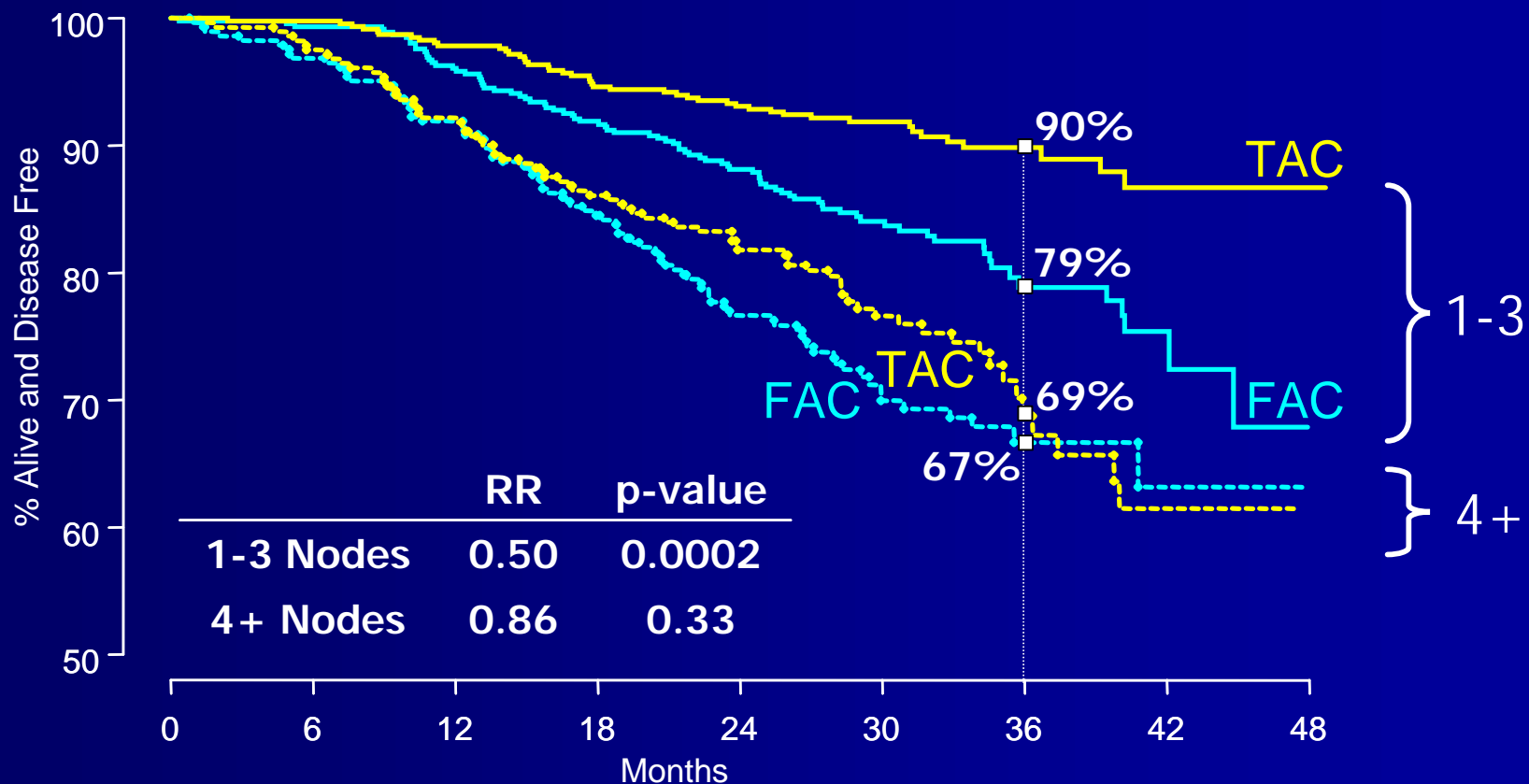


## Planned Additional Analyses Disease Free Survival and Overall Survival

- 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

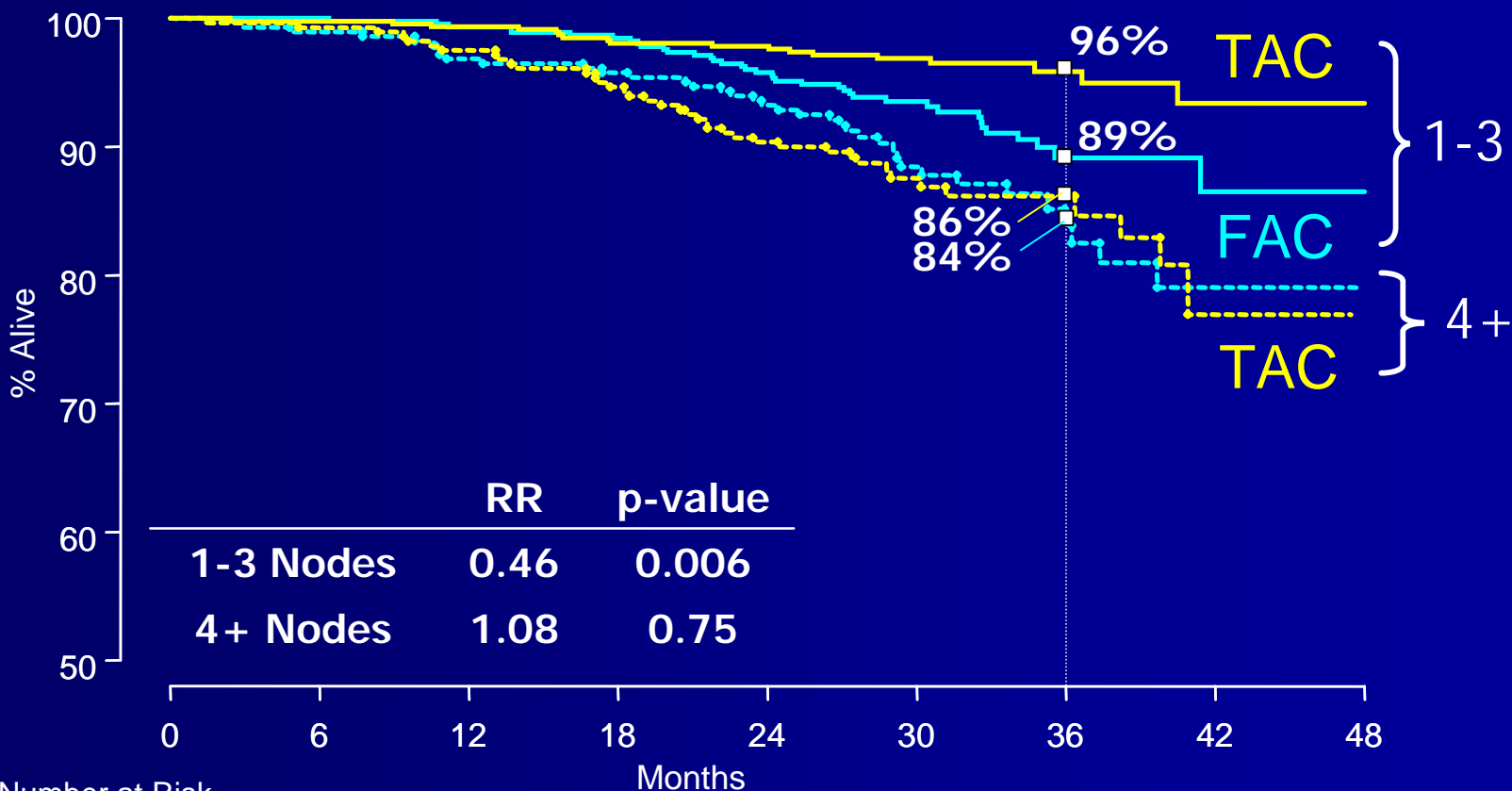


Number at Risk		0	6	12	18	24	30	36	42	48
1-3	TAC	463	462	452	437	427	250	103	14	1
	FAC	459	454	438	417	393	224	98	26	0
4+	TAC	282	274	258	241	227	123	49	9	0
	FAC	287	275	261	239	212	110	52	5	0



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# Overall Survival by Nodal Status

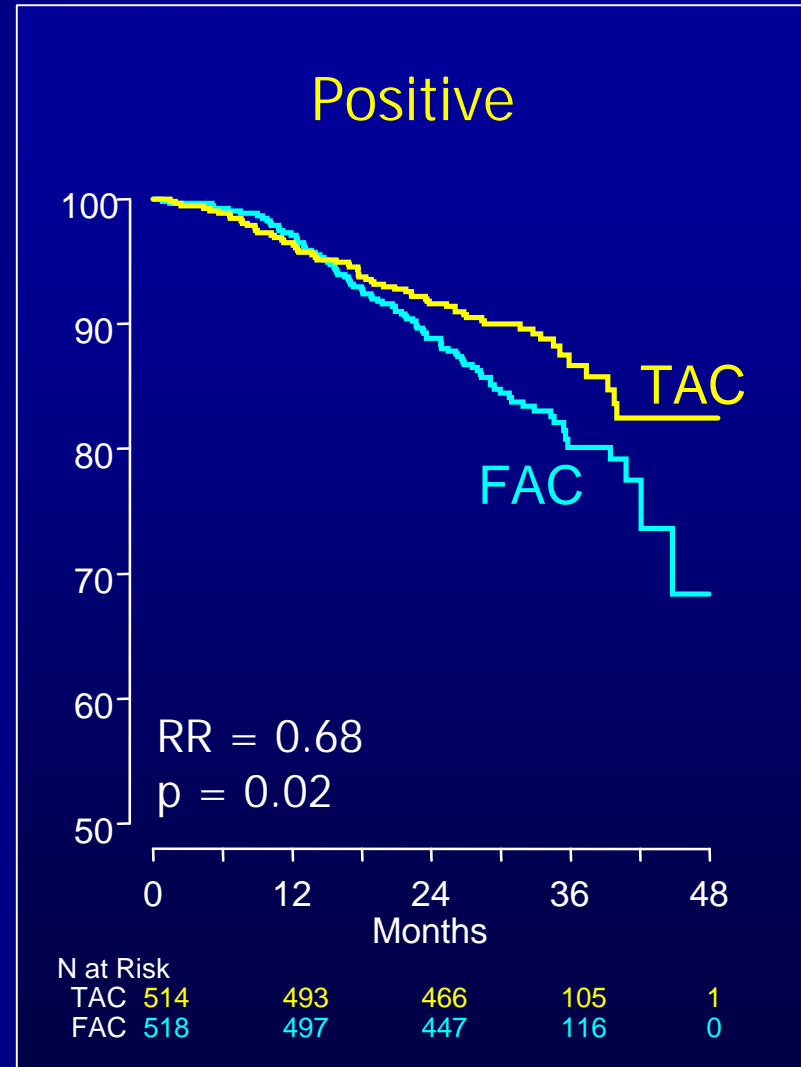
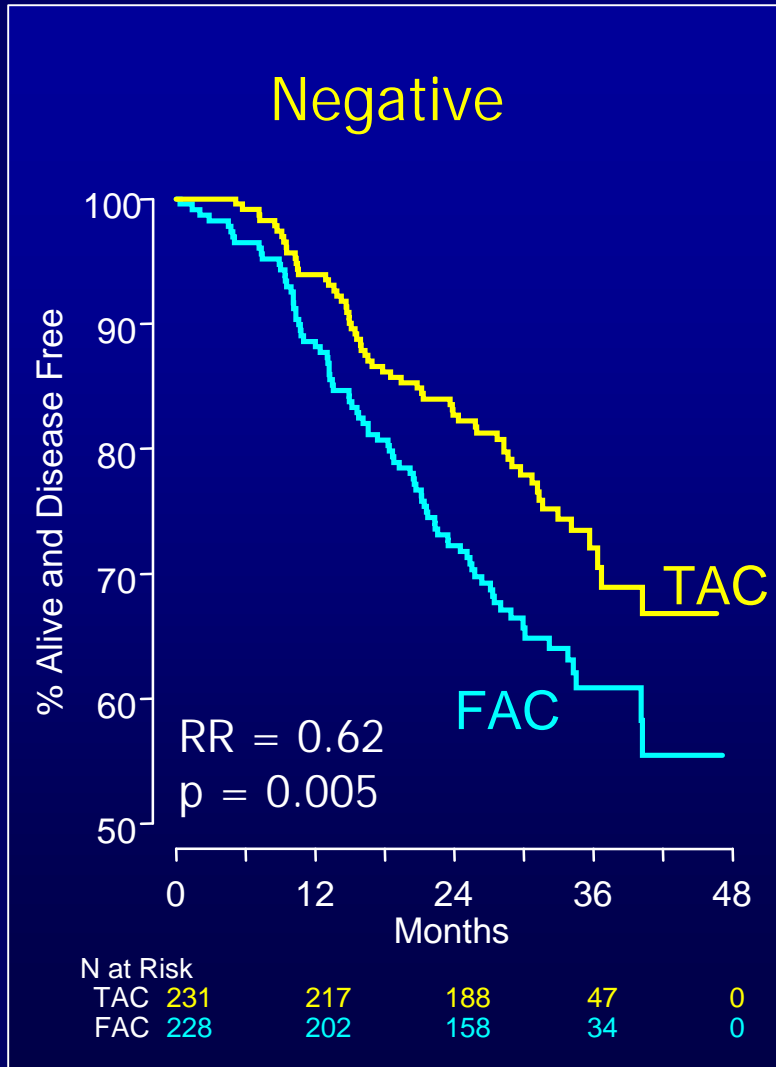


		Number at Risk								
		0	6	12	18	24	30	36	42	48
1-3	TAC	463	462	459	453	449	261	112	14	1
	FAC	459	457	453	444	422	243	107	28	1
4+	TAC	282	279	273	265	251	132	59	10	0
	FAC	287	281	275	269	256	132	64	5	0

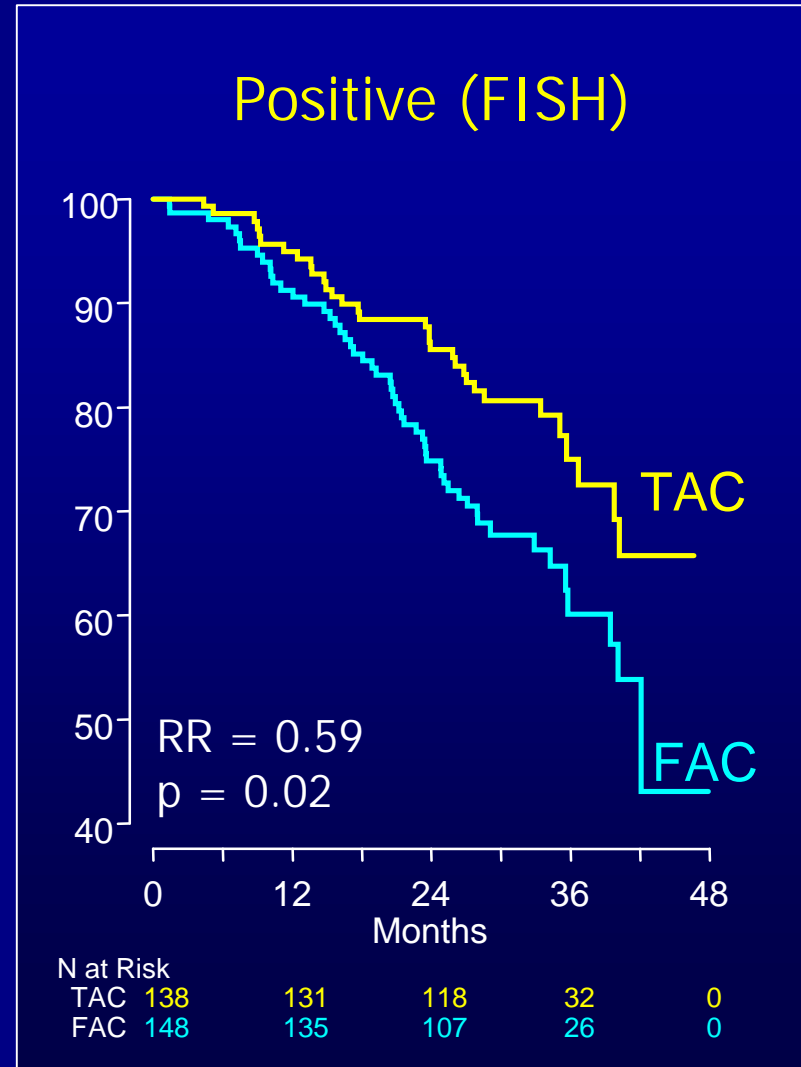
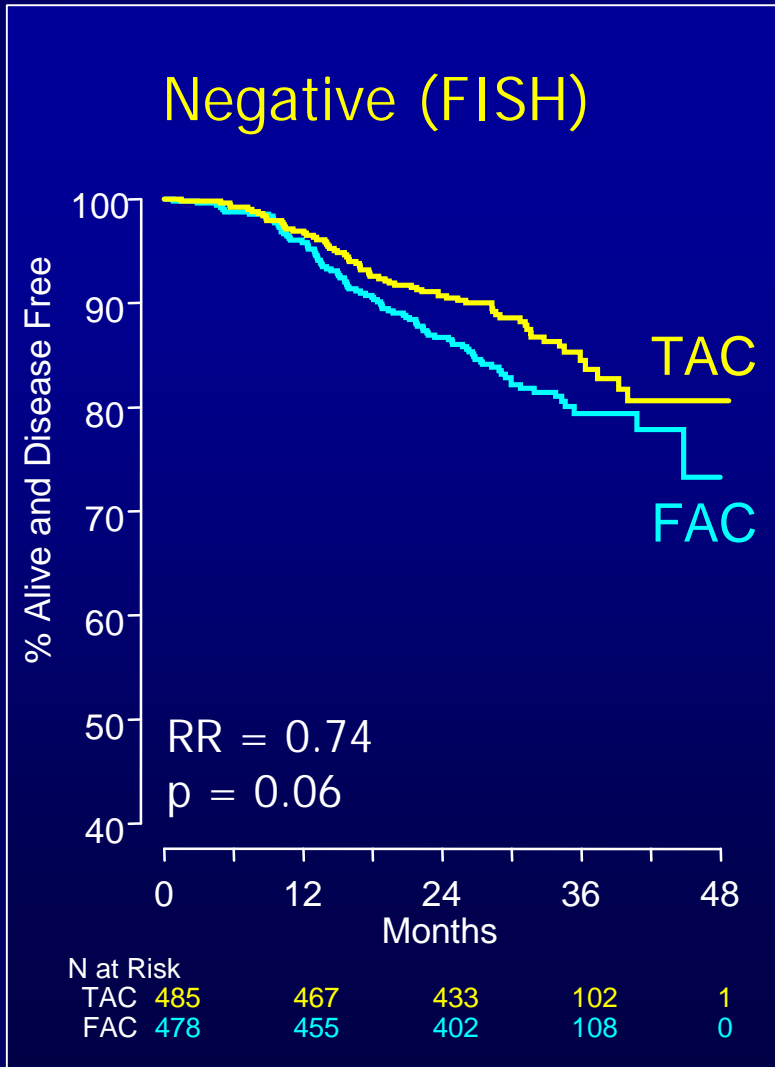


Nabholtz et. al, ASCO 2002 (abs 141)

# 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 <sup>∞</sup>	65.1*	49.0
Febrile Neutropenia <sup>§</sup>	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

<sup>∞</sup> Protocol required blood counts every 3 weeks

<sup>§</sup> 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
<b>Premenopausal pts</b>	<b>n=383</b>	<b>n=375</b>
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

<b>Canada</b>	Nabholtz, Walley, Tomiak, Guevin, Tang, Colwell, Prady, Provencher, Walde, Gelmon, Sehdev, Drolet, Dufresne , Yelle, Zibdawi, Lesperance, Verma, Cantin, Holland, Trudeau, Chang, Rubin, Allan		
<b>USA</b>	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		
<b>Spain</b>	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		
<b>Poland</b>	Pienkowski, Pawlicki, Karnicka		
<b>UK</b>	Howell, Coleman, Whipp, Le Vay	<b>Greece</b>	Georgoulis
<b>Hungary</b>	Juhos, Pinter, Szanto	<b>Germany</b>	Oberhoff
<b>France</b>	Guastalla	<b>So. Africa</b>	Ruff
<b>Brazil</b>	Vinholes , Teixeira	<b>Egypt</b>	Abd-El-Azim, Gad-El-Mawla
<b>Sweden</b>	Fornander, Nylen	<b>Austria</b>	Schuller
<b>Israel</b>	Lurie, Merimsky, Steiner	<b>Czech Rep</b>	Abrahamova, Finek
<b>Argentina</b>	Guixa, Mickiewicz, Martinez	<b>Portugal</b>	Goncalves, Chumbo
<b>Uruguay</b>	Viola, Garbino	<b>Slovak Rep</b>	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	<b>23.5</b> P<0.00001	<b>17</b> P<0.00001
Doxorubicin vs no doxorubicin	~7000	10yrs	<b>10.8</b> P=0.0055	<b>15.7</b> P<0.00001
Paclitaxel vs no paclitaxel	~3000	52mos	<b>13.0</b> P=0.032	<b>14.0</b> P=0.074
Docetaxel vs no docetaxel	1491	33mos	<b>32.0</b> P=0.0011	<b>24.0</b> P=0.11
docetaxel vs no docetaxel (1-3 lymph nodes)	~1000	33mos	<b>50.0</b> P=0.0002	<b>54.0</b> P=0.006