# BCIRG 001 Study

BCIRG
Breast Cancer International Research Group

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

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Study sponsored by Aventis Oncology, RP56976-V-316 / TAX 316

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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)

Nabholtz et. al, ASCO 2002 (abs 141)

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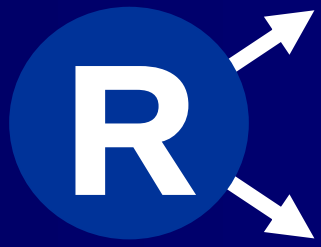
# Design

| | | |
|---|---|---|
| **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

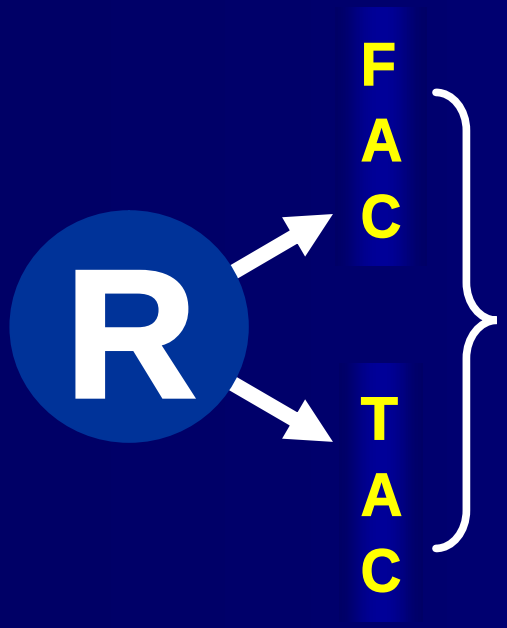
Stratification:
- Nodes:
  - 1-3
  - 4+
- Center

| | | |
|---|---|---|
| **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

Nabholtz et. al, ASCO 2002 (abs 141)

# Post Chemotherapy Treatment




## Tamoxifen 20 mg/day for 5 years

- Patients with ER and/or PR positive tumors

## Radiation Therapy

- All patients with breast conserving surgery
- Per each center's guidelines after mastectomy

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# 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 ≥ 80%
- Normal hematologic, liver, renal and cardiac function
- Informed consent

Nabholtz et. al, ASCO 2002 (abs 141)

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# Endpoints

## Primary

- → Disease-free Survival

## Secondary

- → Overall Survival
- → Toxicity
- → Quality of Life, Socioeconomic Analyses
- → Pathologic & Molecular Markers

Source verification: 100% data for all patients

Nabholtz et. al, ASCO 2002 (abs 141)

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# 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

Nabholtz et. al, ASCO 2002 (abs 141)

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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 |

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# 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 |

Nabholtz et. al, ASCO 2002 (abs 141)

# 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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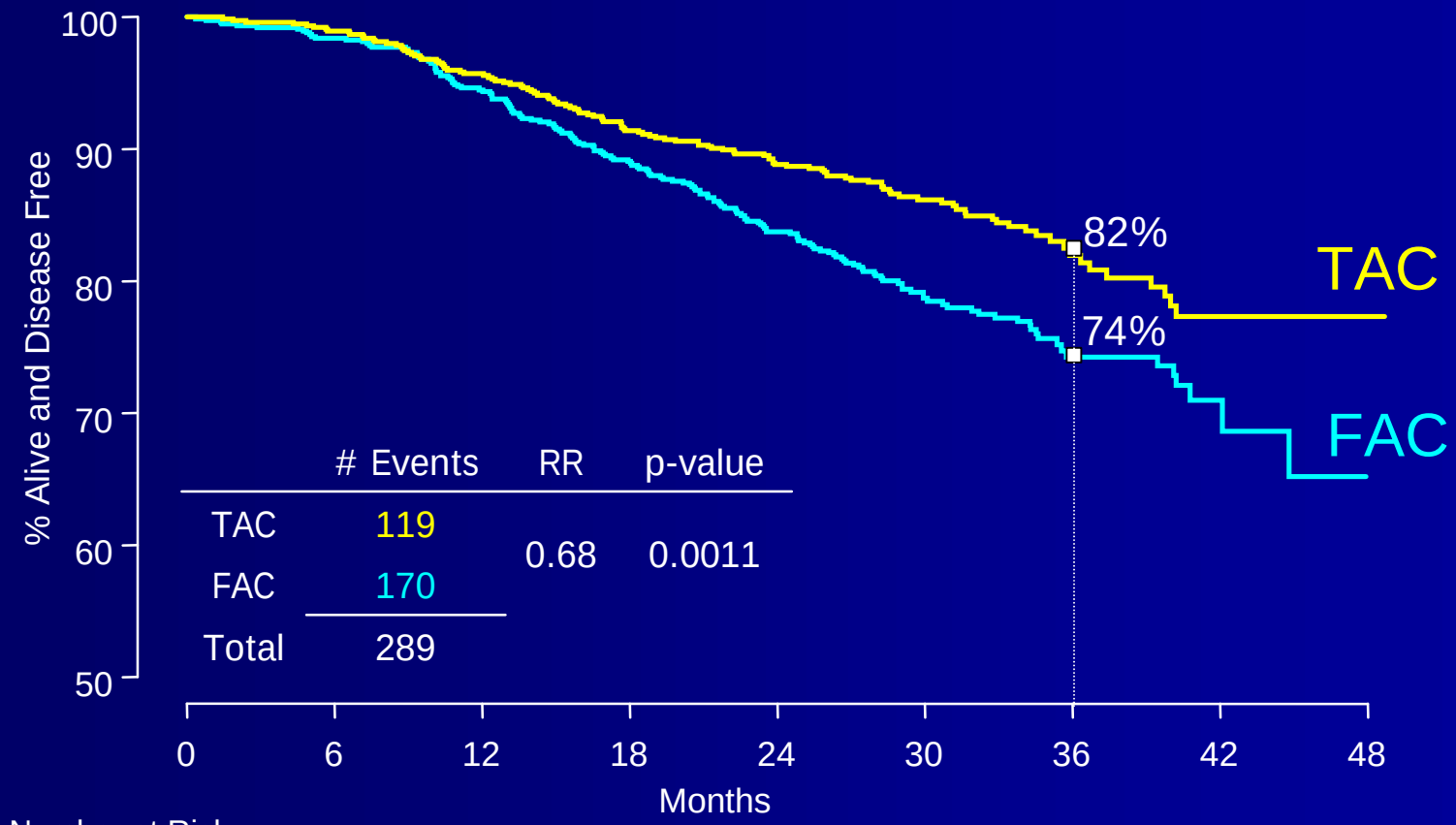
# Disease Free Survival (ITT)

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 |

Nabholtz et. al, ASCO 2002 (abs 141)

# 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 2nd Primary | 6 | 10 |
| Death NED | 7 | 4 |
| | 119 | 170 |

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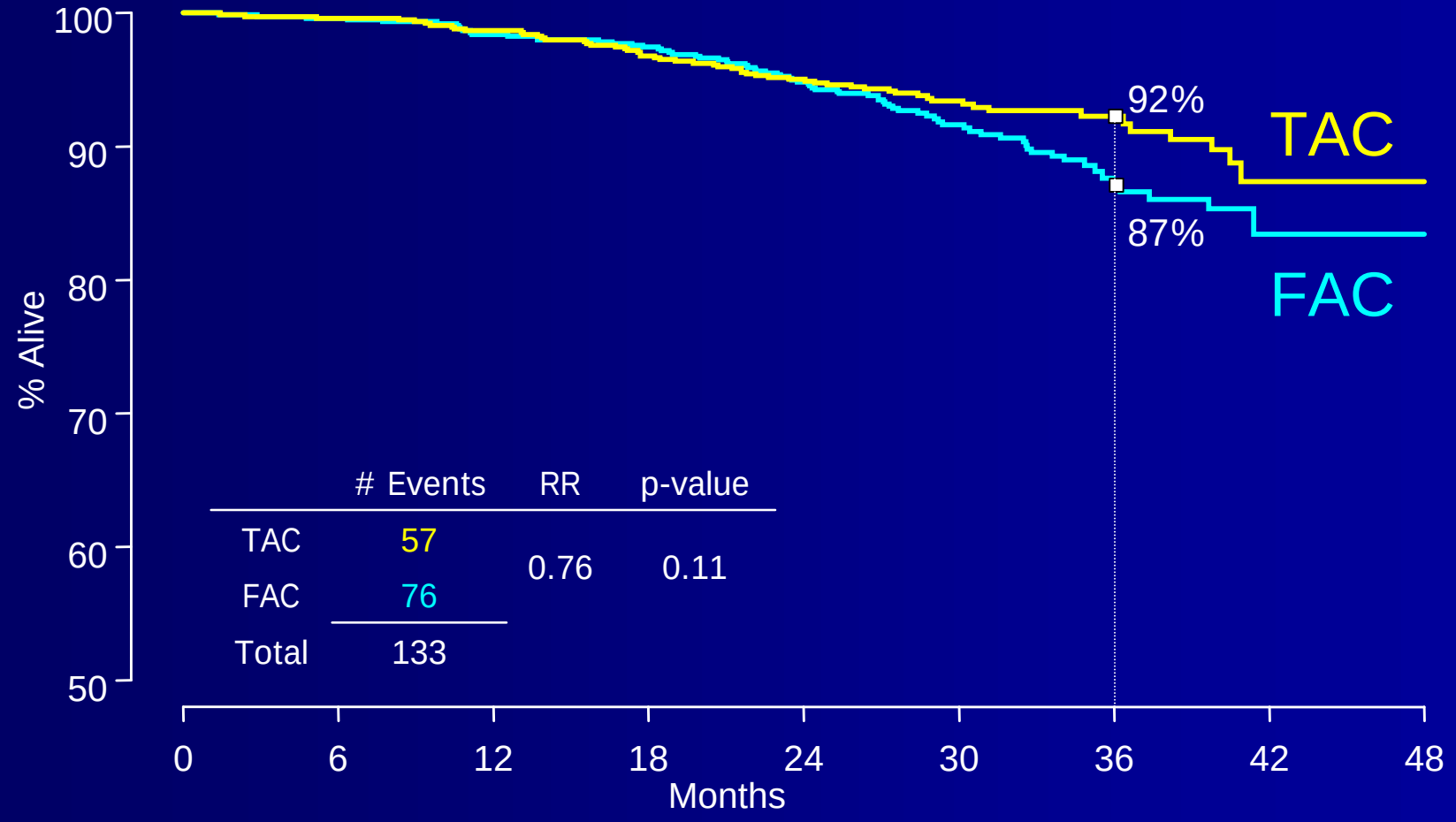
# Overall Survival (ITT)

## 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 |

Nabholtz et. al, ASCO 2002 (abs 141)

# 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

Nabholtz et. al, ASCO 2002 (abs 141)

# 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)

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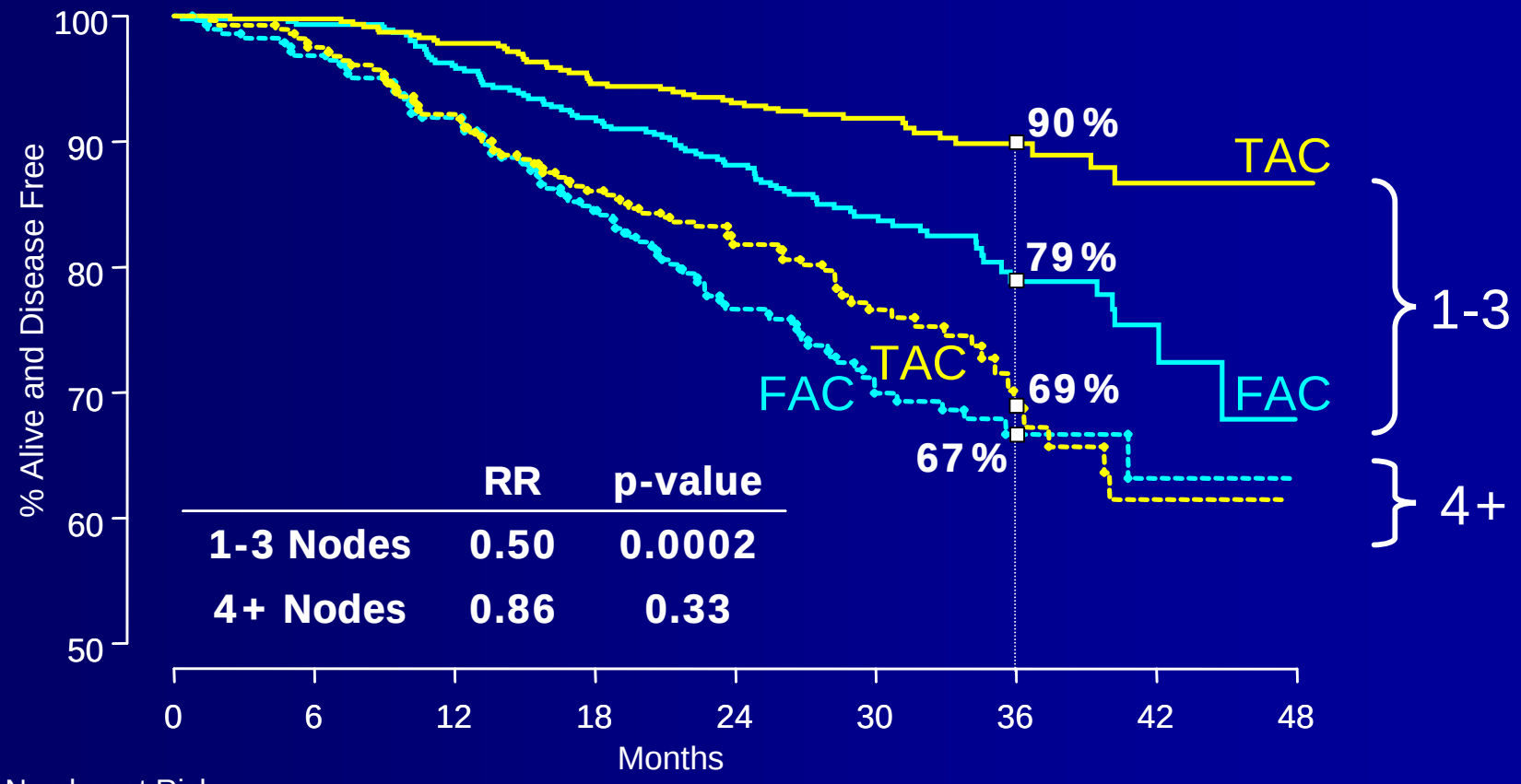
# Disease Free Survival by Nodal Status




Number at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 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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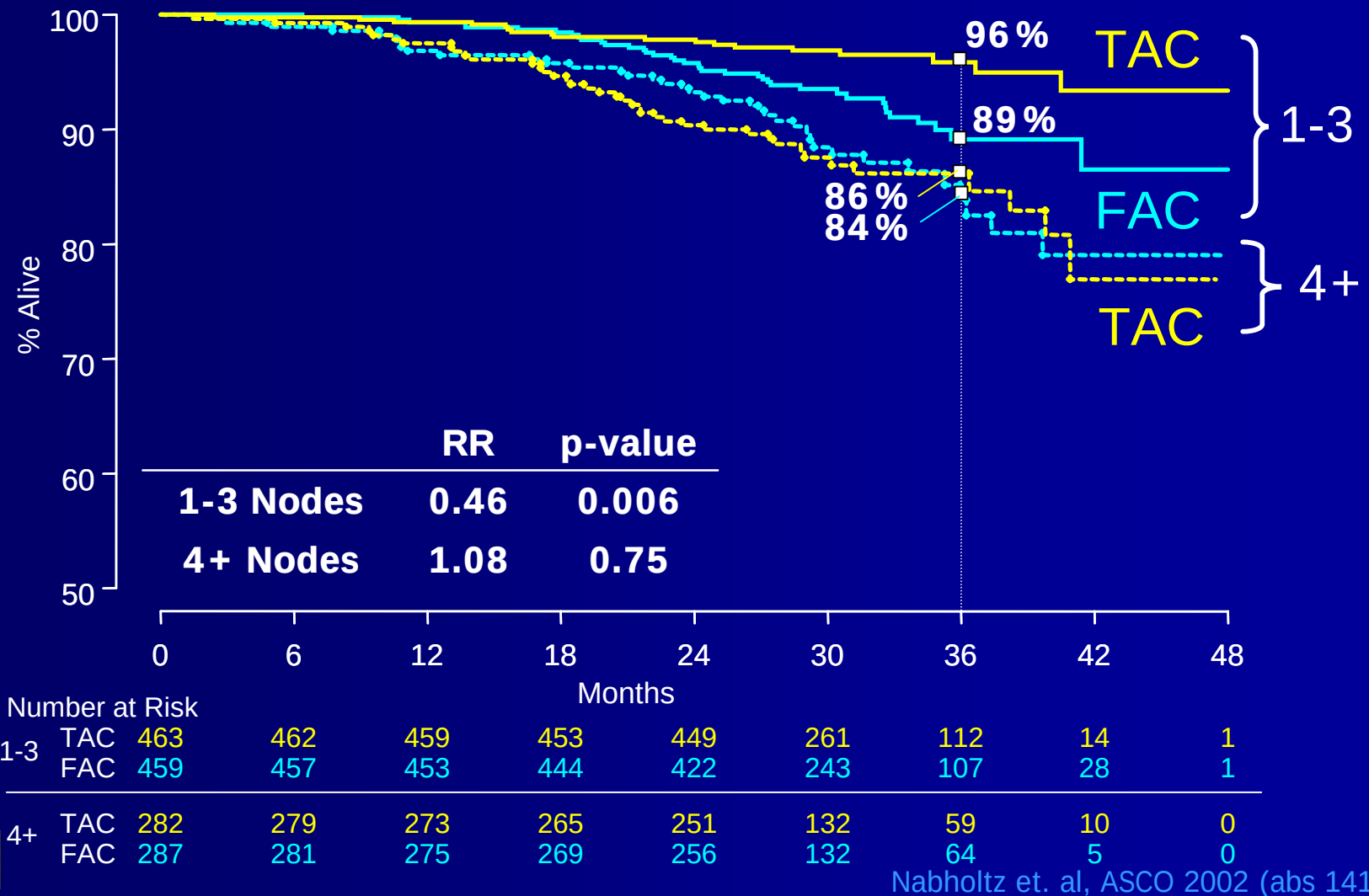
# Overall Survival by Nodal Status

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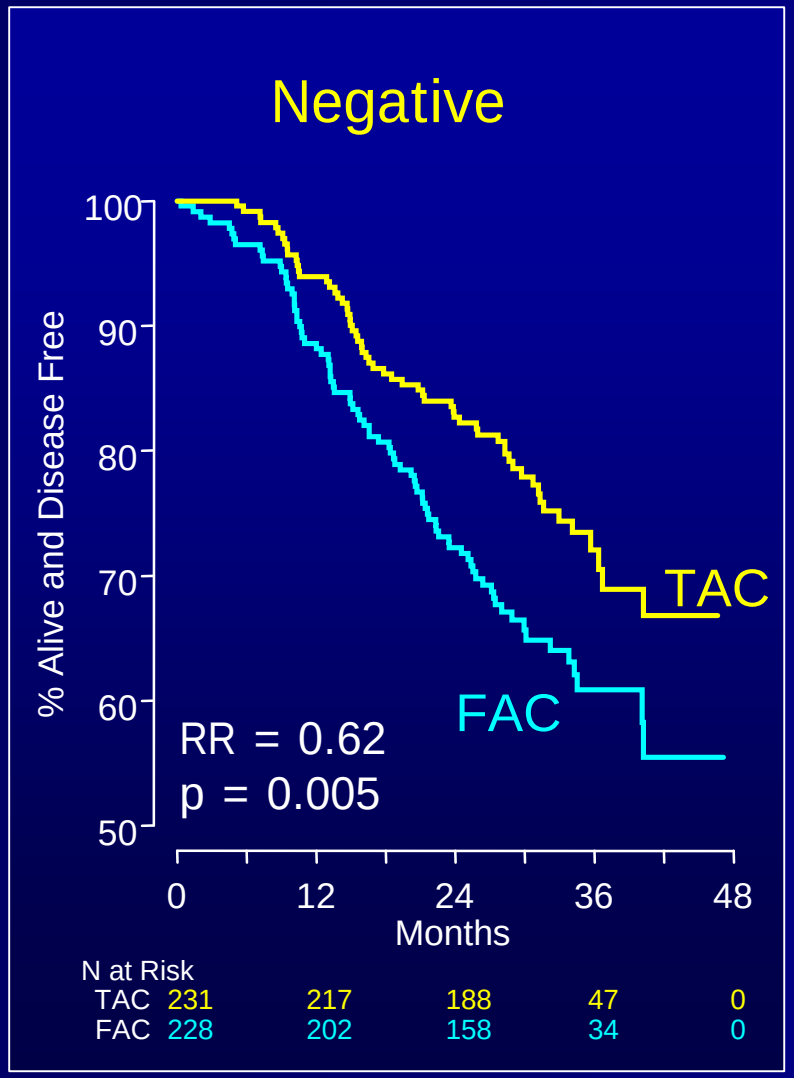
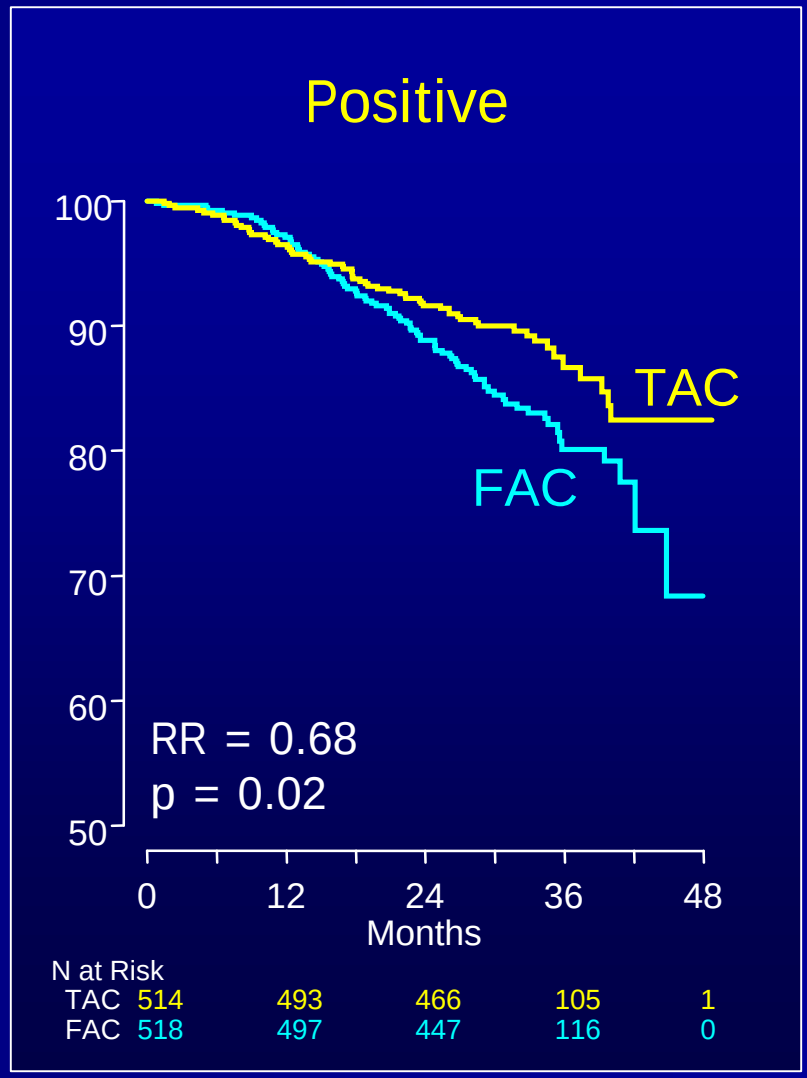
# Disease Free Survival by Hormonal Status

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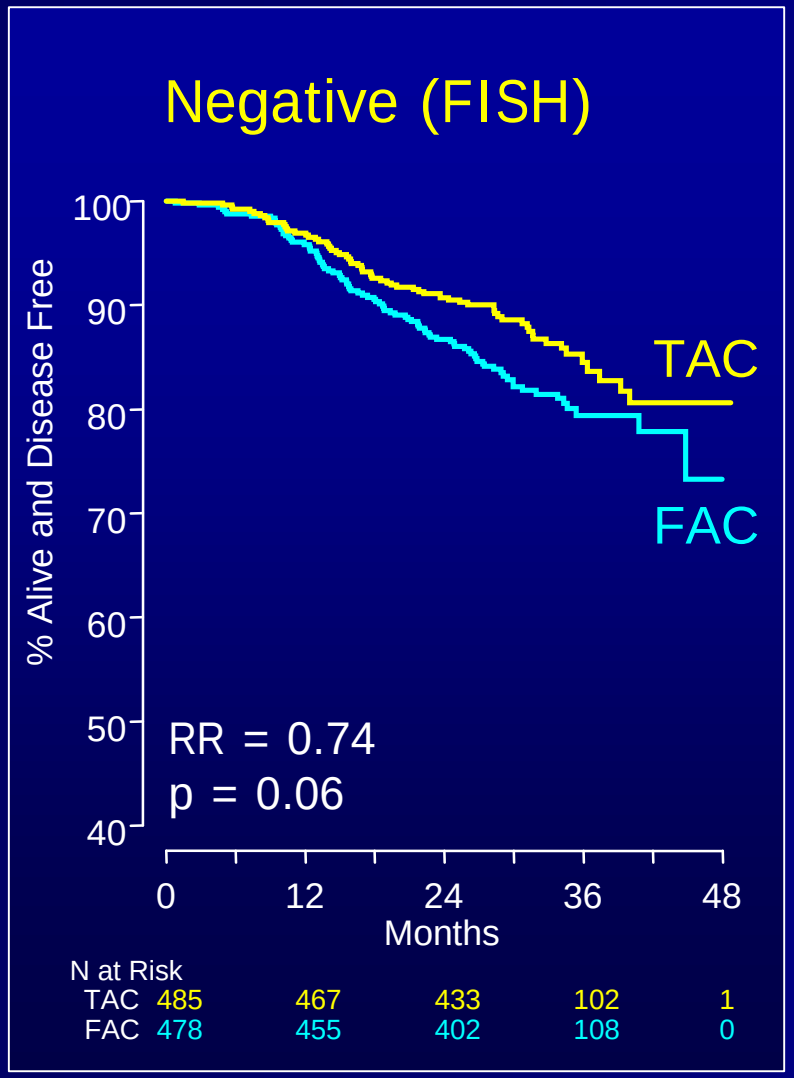
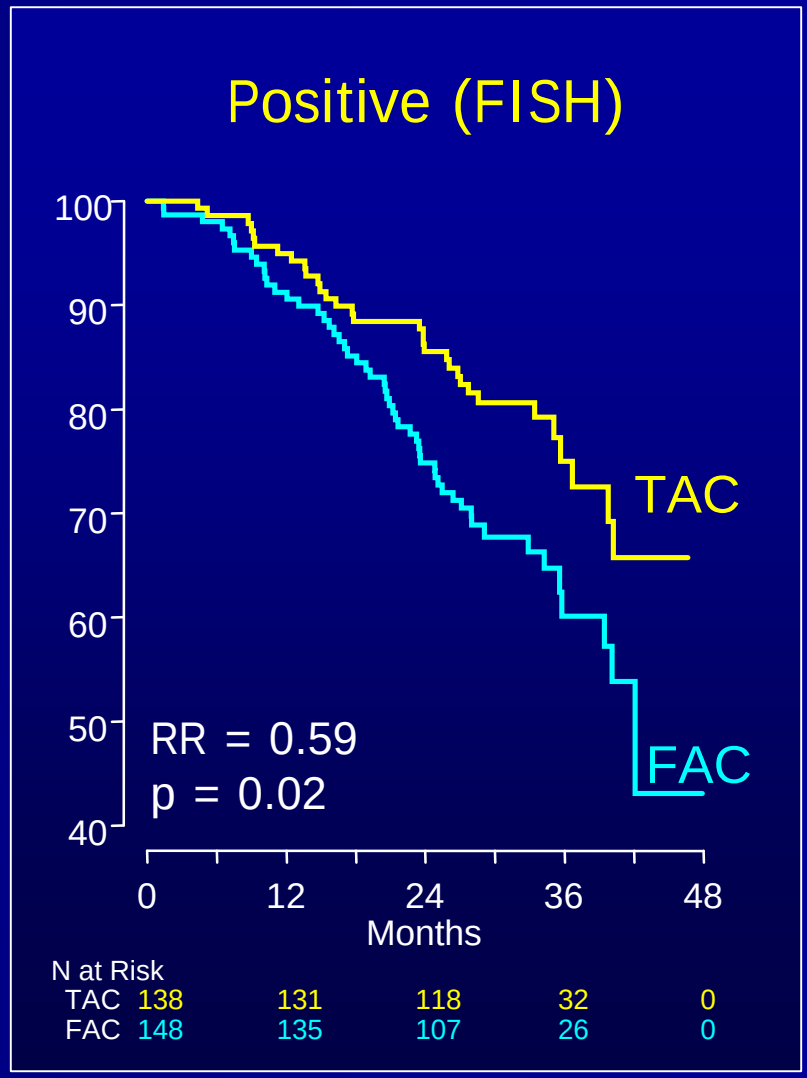
# Disease Free Survival by HER2 status

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# 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

* $p \leq 0.05$

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# 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

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# 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

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# 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

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# 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

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# 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** | Georgoulias |
| **Hungary** | Juhos, Pinter, Szanto | **Germany** | Oberhoff |
| **France** | Guastalla | **So. Africa** | Ruff |
| **Brazil** | Vinholes , Teixeira | **Egypt** | Abd-El-Azim, Gad-El-Mawla |
| **Sweden** | Fornander, Nylen | **Austria** | Schuller |
| **Israel** | Lurie, Merimsky, Steiner | **Czech Rep** | Abrahamova, Finek |
| **Argentina** | Guixa, Mickiewicz, Martinez | **Portugal** | Goncalves, Chumbo |
| **Uruguay** | Viola, Garbino | **Slovak Rep** | Koza |

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# Development of Adjuvant Chemotherapy Breast Cancer

**1970s**

→ **Before anthracyclines**

- ✓ CMF, CMFVP

**1980s**

→ **With anthracyclines**

- ✓ Combinations: AC, FAC, AVCMF, FEC, CEF
- ✓ Sequence and Alternating

**1990s**

- ✓ Dose intensity, dose density

→ **Taxanes (Paclitaxel/Docetaxel)**

**2000s**

- ✓ Sequential: A⇒ T⇒ C or AC⇒ T
- ✓ Combinations: TA, TAC

# 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 |