

BCIRG 001



# TAC Improves DFS and OS Over FAC in Node Positive Early Breast Cancer Patients, BCIRG001

## 55 Months Follow-up

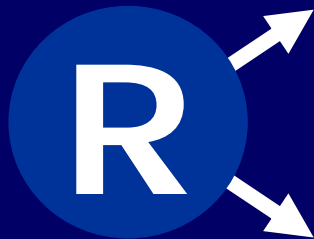
*Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP,  
Weaver CH, Tomiak E, Al-Tweigeri T, Chap L, Juhos E, Guevin R,  
Howell A, Fornander T, Hainsworth J, Coleman R, Vinholes J,  
Modiano M, Pinter T, Hugh J, Nabholz JM, Loret C, Rupin M, Blitz S,  
Riva A, Vogel C. On behalf of the BCIRG 001 Investigators.*

# Study Rationale

- Anthracycline-based regimens are standard adjuvant treatments in node positive breast cancer patients (1998 EBCTCG overview)
- Docetaxel (Taxotere<sup>®</sup>)-containing regimens have shown superior activity over standard regimens in MBC
  - First-line
    - **AT versus AC** (Nabholtz et al, JCO 2003)
    - **TAC versus FAC** (Mackey et al, ASCO 2002)
    - **AT versus FAC** (Bontenbal et al, ECCO 2003)

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# Design



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

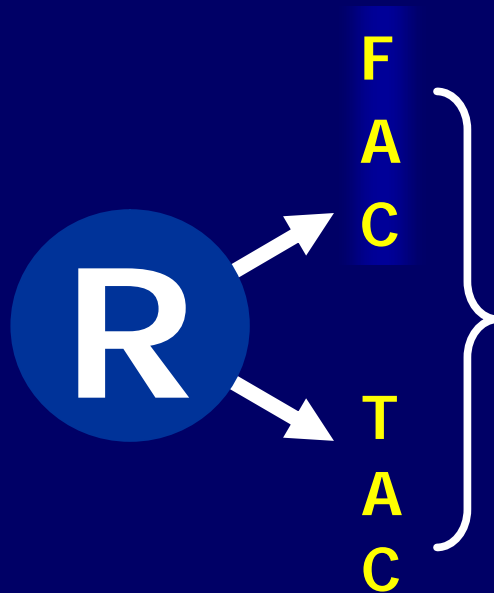
Every 3 weeks x 6 cycles

### Stratification

- Nodes  
1-3  
4+
- Center

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

# 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

# Major Eligibility Criteria

- **Histologically proven node-positive breast cancer**
- **Definitive surgery with axillary LN dissection (<sup>≥</sup> 6 LNs)**
- **Stage T1-3, N1, M0**
- **Normal hematologic, liver, renal, and cardiac function**
- **≤ 60 days between surgery and randomization**
- **Age ≤ 70 years; KPS <sup>≥</sup> 80%**
- **Written informed consent**

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# Endpoints

## Primary

- Disease-free survival

## Secondary

- Overall survival
- Toxicity
- Quality of life (abstract submitted)

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# Efficacy Analyses

- **First planned analysis: 3 year follow-up**
  - ASCO 2002 (abs 141)
- **Second interim analysis: 400 DFS events**
  - IDMC mandated
  - Significance level of 0.001 predefined for primary endpoint DFS
- **Final analysis: 590 DFS event**
  - Significance level 0.048
- **Primary analysis**
  - Log-rank test stratified by nodal status

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# Patient Characteristics

<b>Randomized (n=1,491)</b>	<b>TAC n=745</b>	<b>FAC n=746</b>
<b>Median Age</b>	<b>49(26-70)</b>	<b>49(23-70)</b>
<b>Median KPS</b>	<b>100%</b>	<b>100%</b>
<b>Premenopausal</b>	<b>50%</b>	<b>48%</b>
<b>Mastectomy</b>	<b>60%</b>	<b>59%</b>
<b>Radiotherapy</b>	<b>69%</b>	<b>72%</b>
<b>Tamoxifen</b>	<b>68%</b>	<b>69%</b>

Enrollment: June 1997 to June 1999

Martin et al, SABCS 2003 (abs 43)

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# Tumor Characteristics

	<b>TAC</b> n=745 %	<b>FAC</b> n=746 %
<b>Tumor size, cm*</b>		
≤ 2	40	43
>2 and ≤ 5	53	51
> 5	8	6
<b>Nodal status</b>		
1-3	62	62
4 +	38	38
<b>ER+ and/or PR+*</b>	76	76
<b>HER2+ (FISH)*</b>	21	22

\*Centrally reviewed

Martin et al, SABCS 2003 (abs 43)

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# Exposure to Treatment

	<b>TAC</b> n=744	<b>FAC</b> n=736
<b>Completed 6 cycles</b>	<b>678 (91%)</b>	<b>711 (97%)</b>
<b>Relative dose intensity</b>		
<b>Median</b>	<b>0.99</b>	<b>0.98</b>
<b>&gt; 0.90</b>	<b>90%</b>	<b>85%</b>
<b>Median total dose, mg/m<sup>2</sup></b>		
<b>Docetaxel</b>	<b>449</b>	<b>—</b>
<b>Doxorubicin</b>	<b>299</b>	<b>300</b>
<b>Cyclophosphamide</b>	<b>2,995</b>	<b>2,998</b>
<b>5-FU</b>	<b>—</b>	<b>2,998</b>

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# First Interim Analysis ASCO 2002

Nabholtz et al (abs 141)

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

- Primary Endpoint: Disease-Free Survival

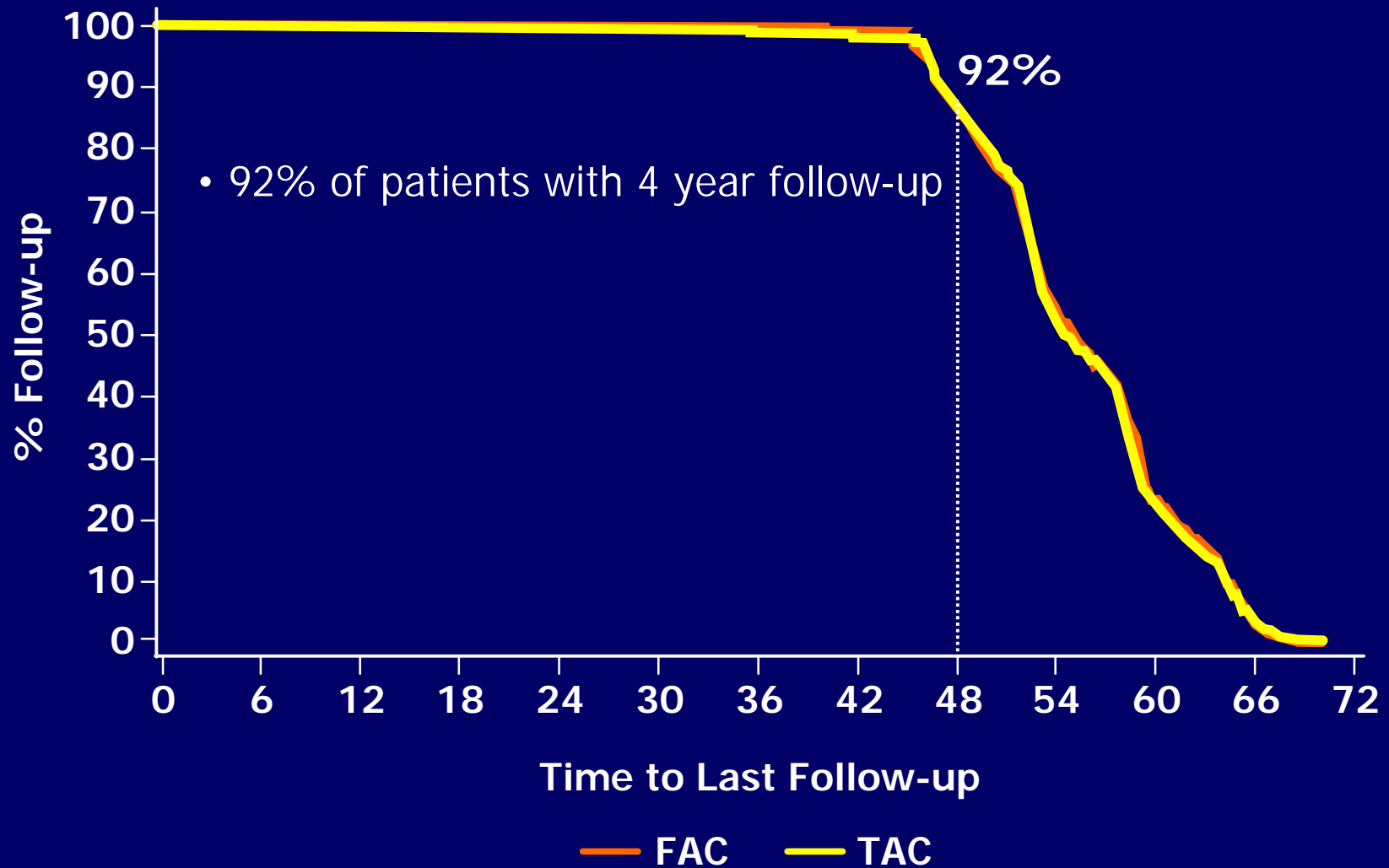
**HR = 0.68 (0.54 – 0.86)      *P* = 0.0011**

- Secondary Endpoint: Overall Survival

**HR = 0.76 (0.54 – 1.07)      *P* = 0.11**

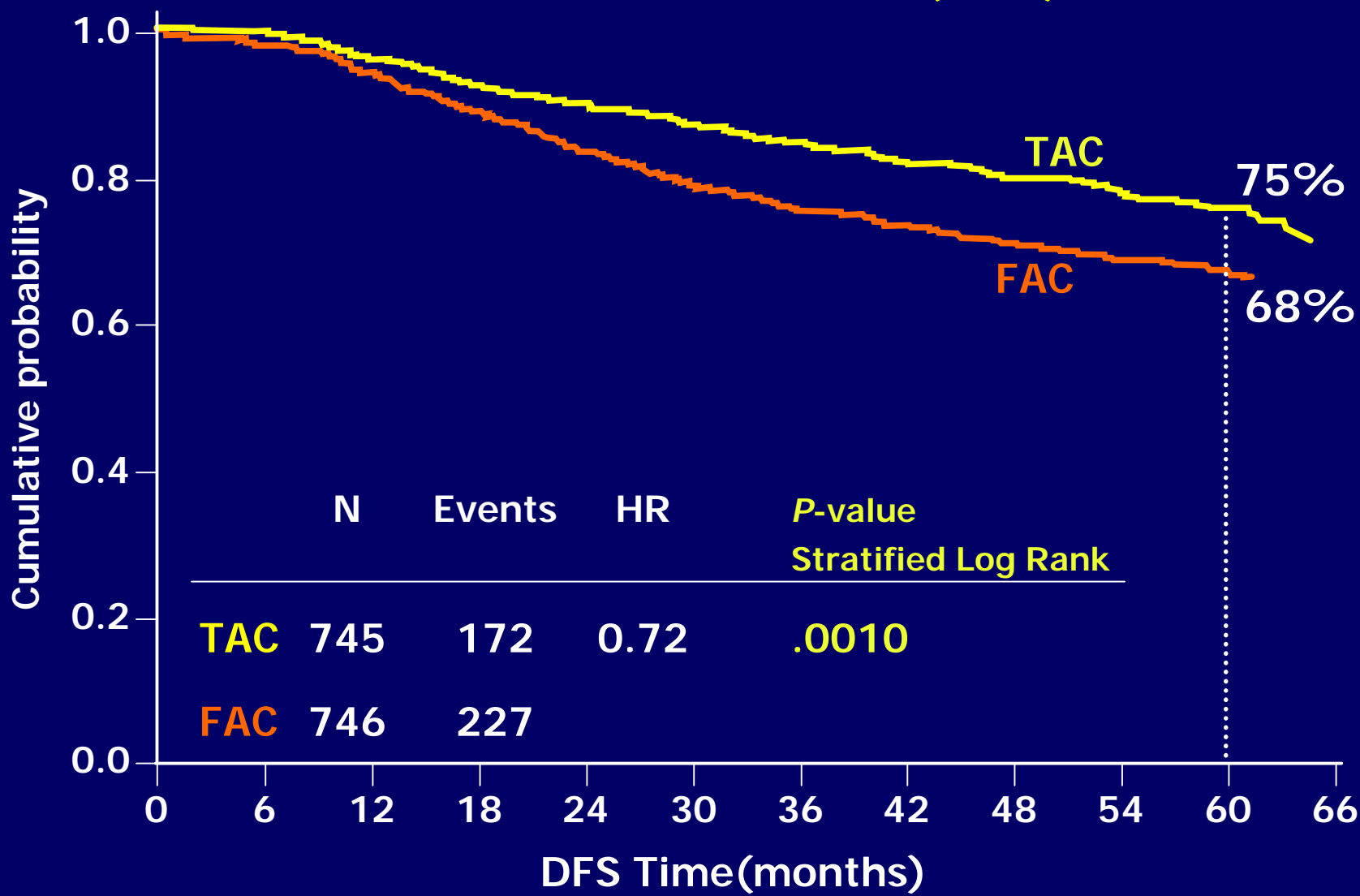
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## Median Follow-up: 55 months



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## Disease-Free Survival (ITT)



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# Disease-Free Survival Secondary Analyses

<b>Analysis</b>	<b>Cohort</b>	<b>HR</b>	<b>P-value</b>
<b>Unadjusted</b>	<b>ITT</b>	<b>0.71</b> <b>(0.59 – 0.87)</b>	<b>0.0008</b>
<b>Cox Model*</b>	<b>ITT</b>	<b>0.70</b> <b>(0.58 – 0.86)</b>	<b>0.0005</b>

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

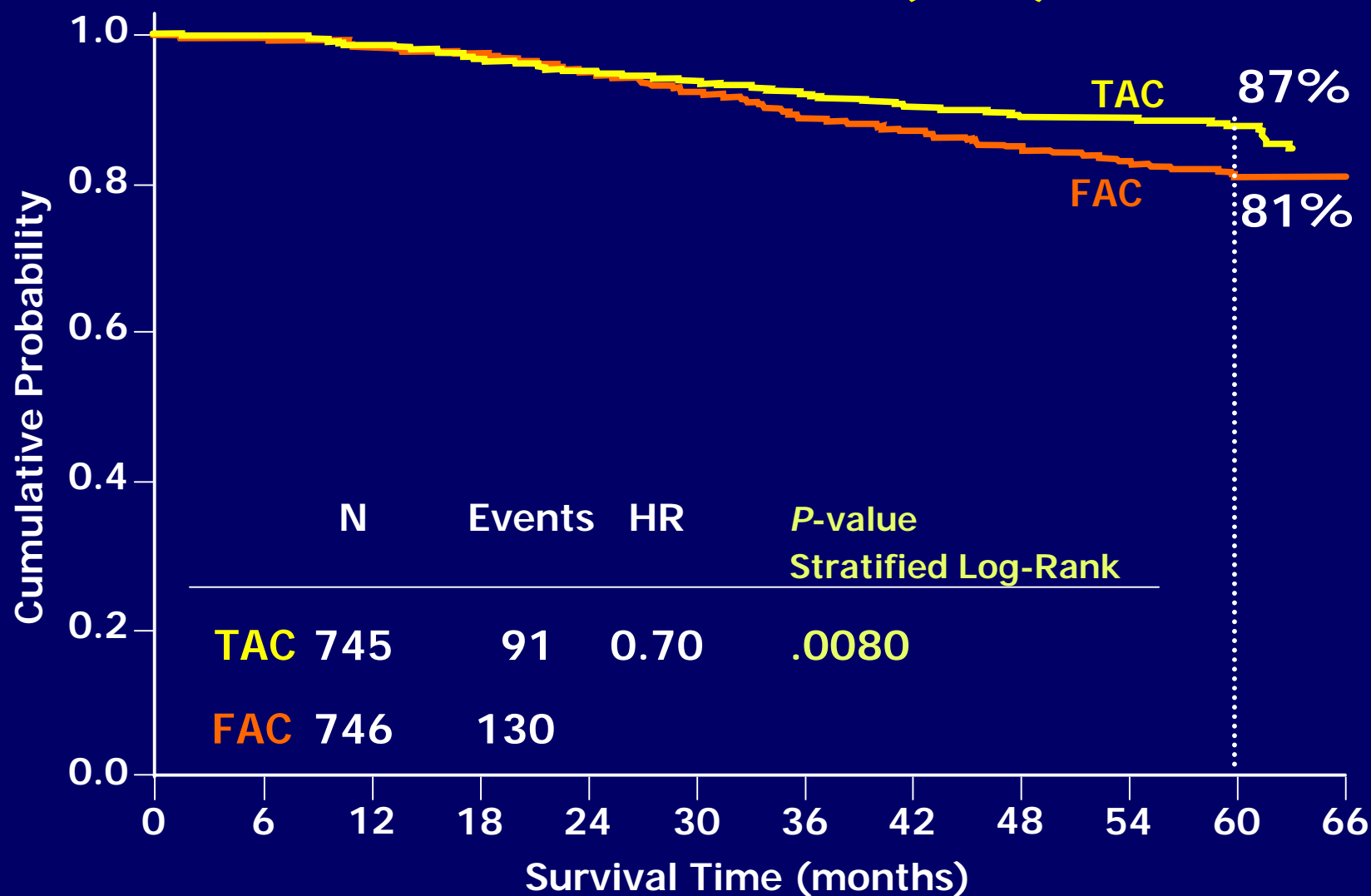
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# Sites of First Events

	<b>TAC</b> n=745	<b>FAC</b> n=746
	<b>No. of Events</b>	
<b>Metastatic</b>	<b>115</b>	<b>158</b>
Local/Regional	29	39
Contralateral	7	8
Other 2 <sup>nd</sup> Primary	13	18
Death NED	8	4
	<b>172</b>	<b>227</b>

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## Overall Survival (ITT)



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# Overall Survival Secondary Analyses

Analysis	Cohort	HR	P-value
Unadjusted	ITT	0.69 (0.52 – 0.90)	<b>0.0053</b>
Cox Model*	ITT	0.68 (0.52 – 0.89)	<b>0.0044</b>

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

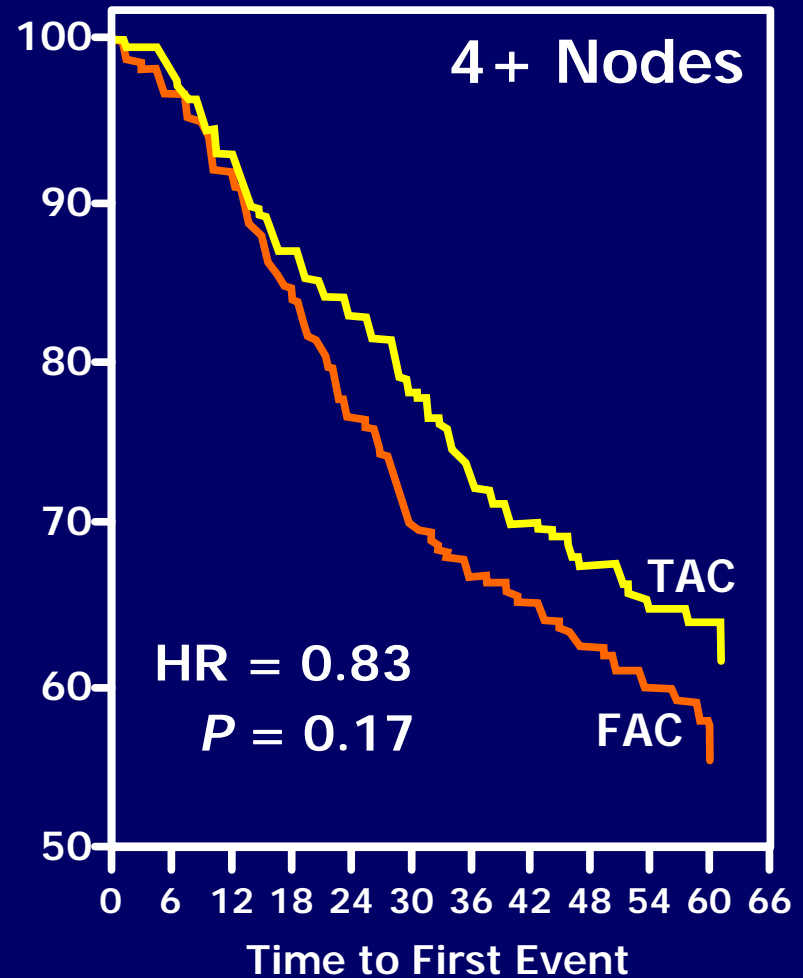
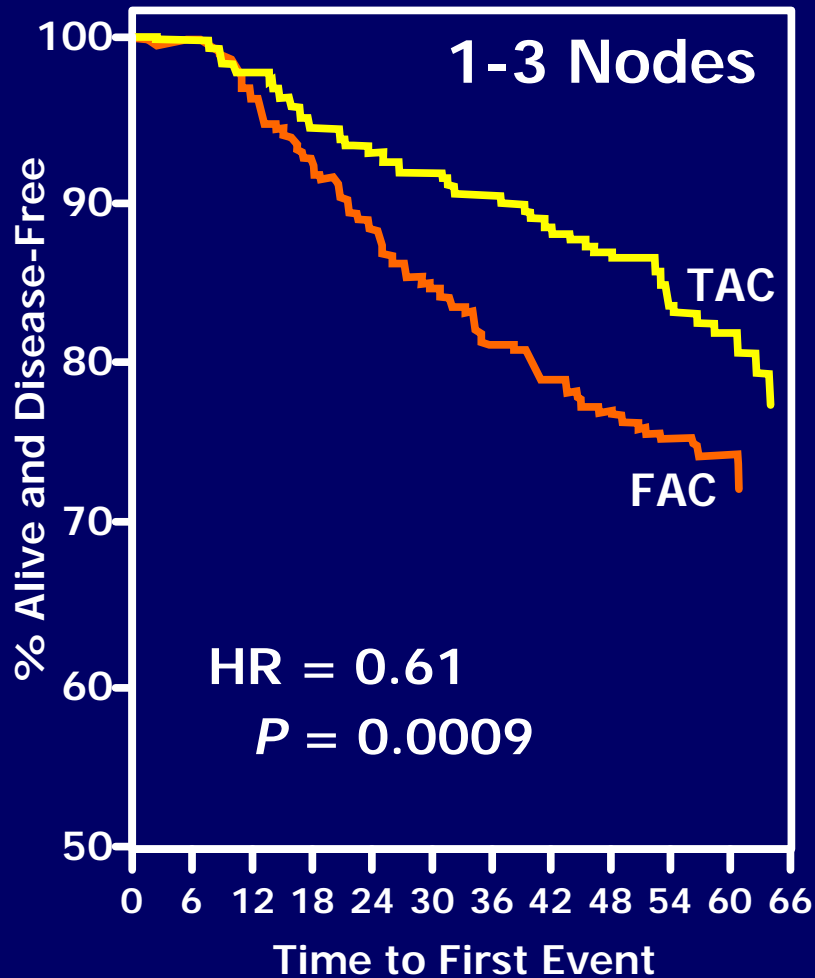
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# Planned Additional Analyses Disease-Free Survival

- **Prospectively defined and powered at 590 events**
  - By nodal status
- **Prospectively defined but not powered**
  - By hormonal receptor status
  - By HER2 status

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# DFS by Nodes

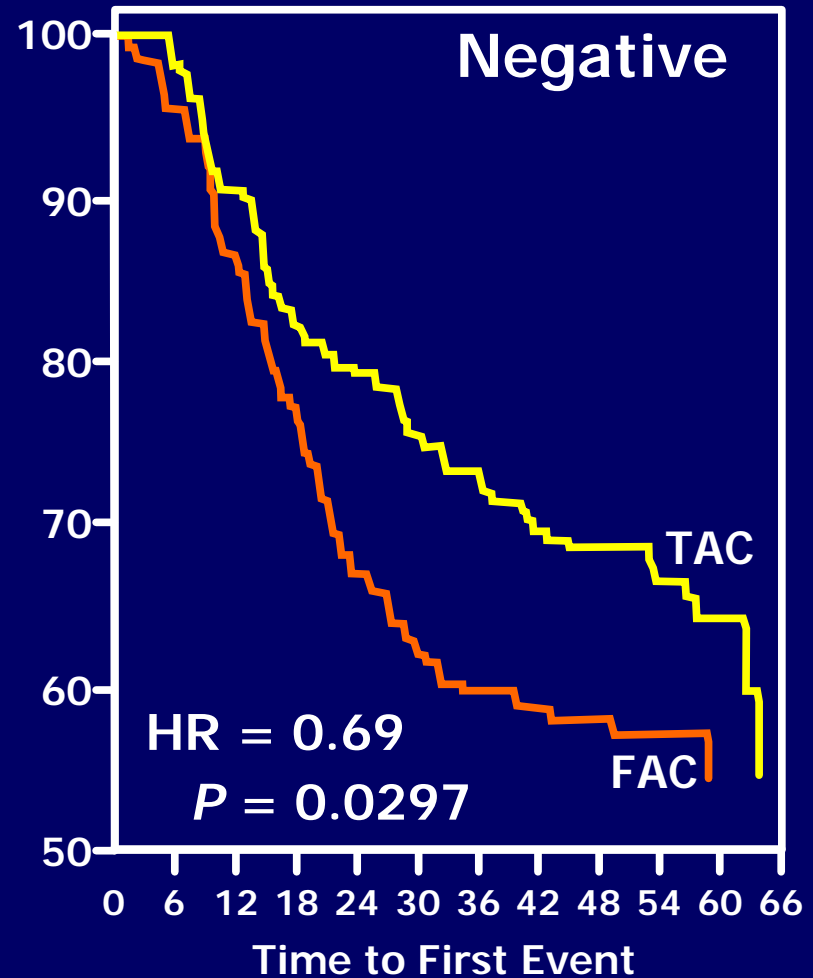
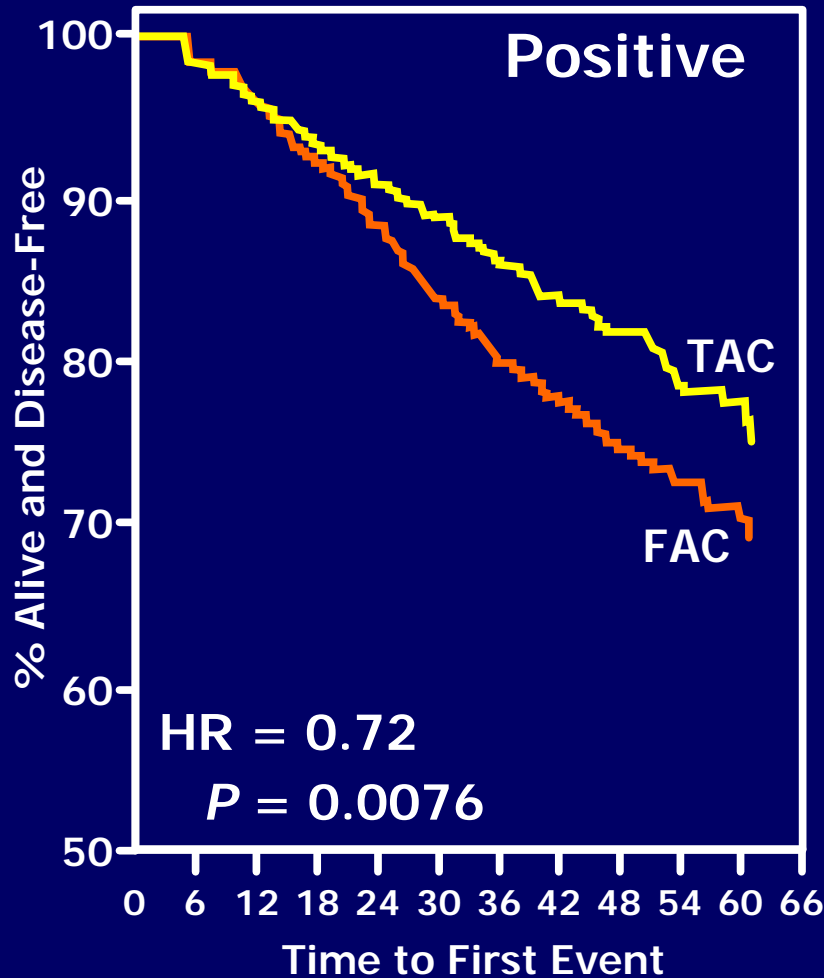


Ratio of HRs 1.34 P = 0.1457

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# DFS by Receptor Status

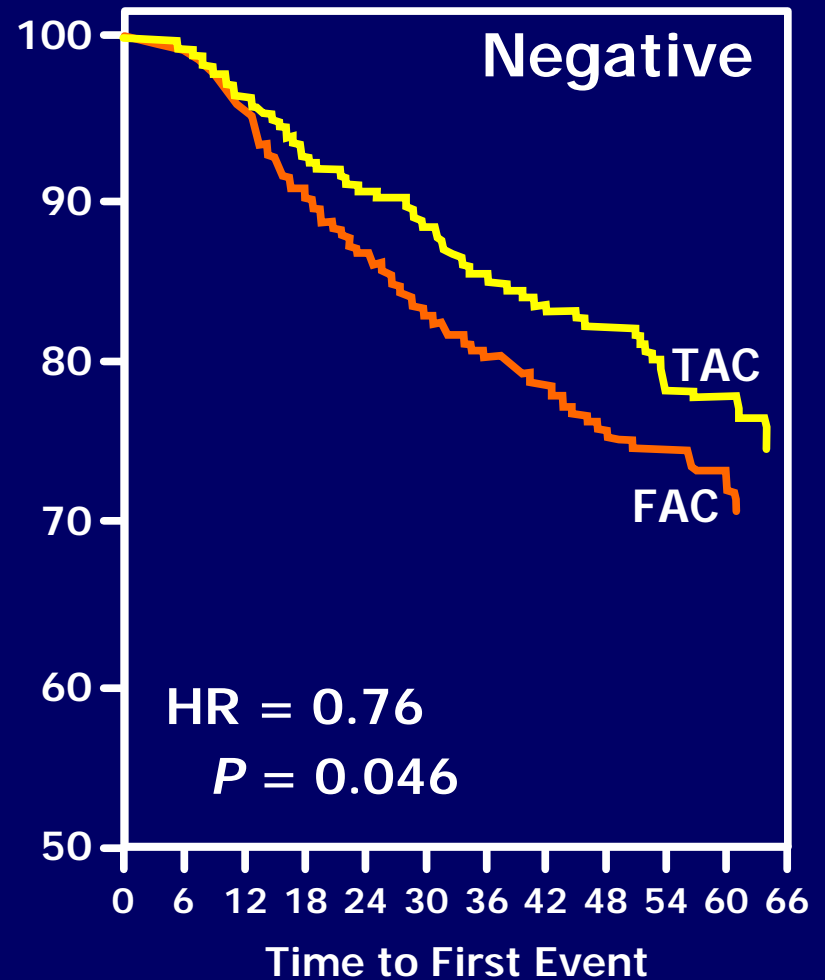
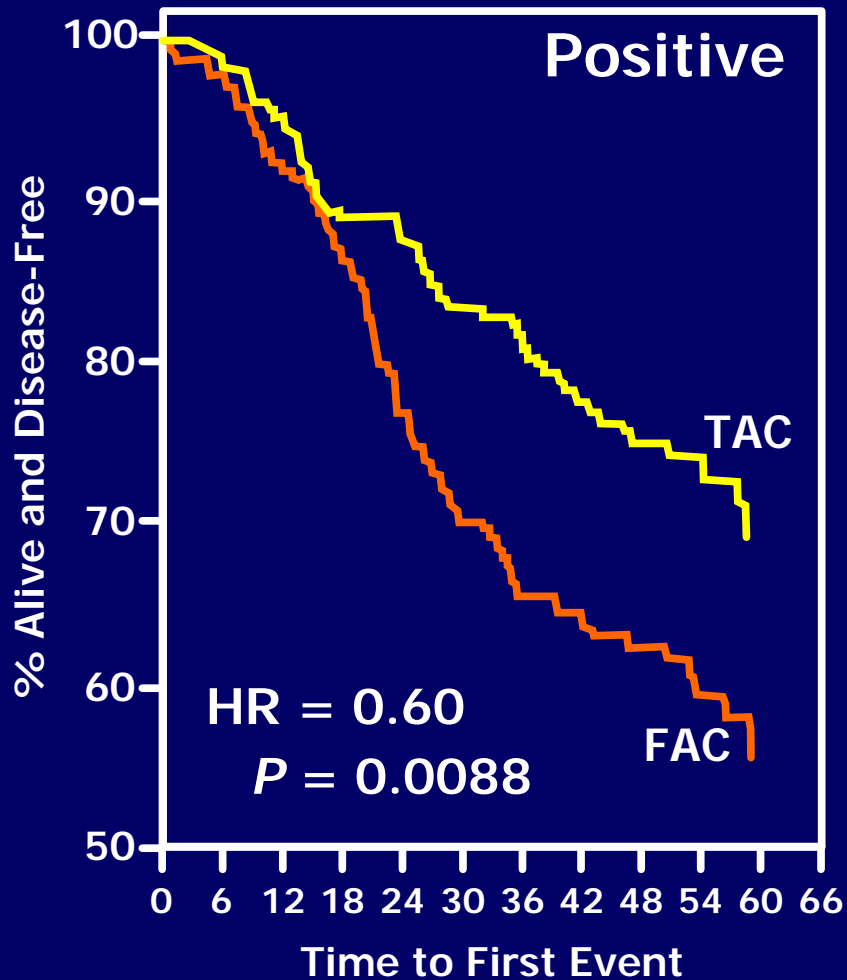
(Centrally reviewed)



Ratio of HRs 1.08 P = 0.7216

# BCIRG 001 DFS by HER2 Status

(FISH performed centrally)



Ratio of HRs 0.85 P = 0.4122

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# Hematologic Toxicity

	<b>TAC</b> n=744	<b>FAC</b> n=736
	%	%
<b>Neutropenia (Gr 3/4)</b>	<b>65.5*</b>	<b>49.3</b>
<b>Febrile Neutropenia</b>	<b>24.7*</b>	<b>2.5</b>
<b>Infection (Gr 3/4)</b>	<b>3.9</b>	<b>2.2</b>
<b>Septic death</b>	<b>0</b>	<b>0</b>
<b>Anemia (Gr 3/4)</b>	<b>4.3*</b>	<b>1.6</b>
<b>Thrombocytopenia (Gr 3/4)</b>	<b>2.0</b>	<b>1.2</b>
<b>Blood transfusions</b>	<b>4.6</b>	<b>1.5</b>

\* $P \leq 0.05$

Martin et al, SABCS 2003 (abs 43)

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# Nonhematologic Toxicity

Grade 3 or 4

	<b>TAC</b> n=744	<b>FAC</b> n=736
	%	%
Nausea	5.1	9.5*
Vomiting	4.3	7.3*
Diarrhea	3.8*	1.8
Stomatitis	7.1*	2.0
Asthenia	11.2*	5.6
CHF	1.6	0.5
<b>Premenopausal</b>	<b>n=372</b>	<b>n=359</b>
Amenorrhea	66%*	54%

\*P ≤ 0.05

Martin et al, SABCS 2003 (abs 43)

## Conclusion (I)

- TAC demonstrated over FAC a significantly improved
  - DFS ( $P = 0.001$ )
    - 28% reduction in risk of relapse
  - OS ( $P = 0.008$ )
    - 30% reduction in mortality risk
- TAC significantly improves DFS irrespective of nodal, hormone receptor or HER 2 status

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## Conclusion (II)

- **Febrile neutropenia was more frequent on TAC**
  - **No septic deaths**
- **Other toxicities were predictable and manageable in both arms**

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## Conclusion (III)

- **This study establishes Taxotere in combination with doxorubicin and cyclophosphamide to have major clinical value in the adjuvant treatment of women with early stage node positive breast cancer**

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# Investigators

<b>Canada</b>	Mackey, Al Tweigeri, 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, Chap, 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		
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<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

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- **The patients who have accepted to participate in the study**
- **The Independent Data Monitoring Committee:**
  - Matti Aapro, MD**
  - John Bryant, PhD**
  - Anna Efremidis, MD**
  - Terry Mamounas, MD**
  - Henning Mouridsen, MD**
  - Edith Perez, MD**
- **Aventis Oncology, sponsor of the study**

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## Conclusion (III)

- **This study establishes Taxotere in combination with doxorubicin and cyclophosphamide to have major clinical value in the adjuvant treatment of women with early stage node positive breast cancer**

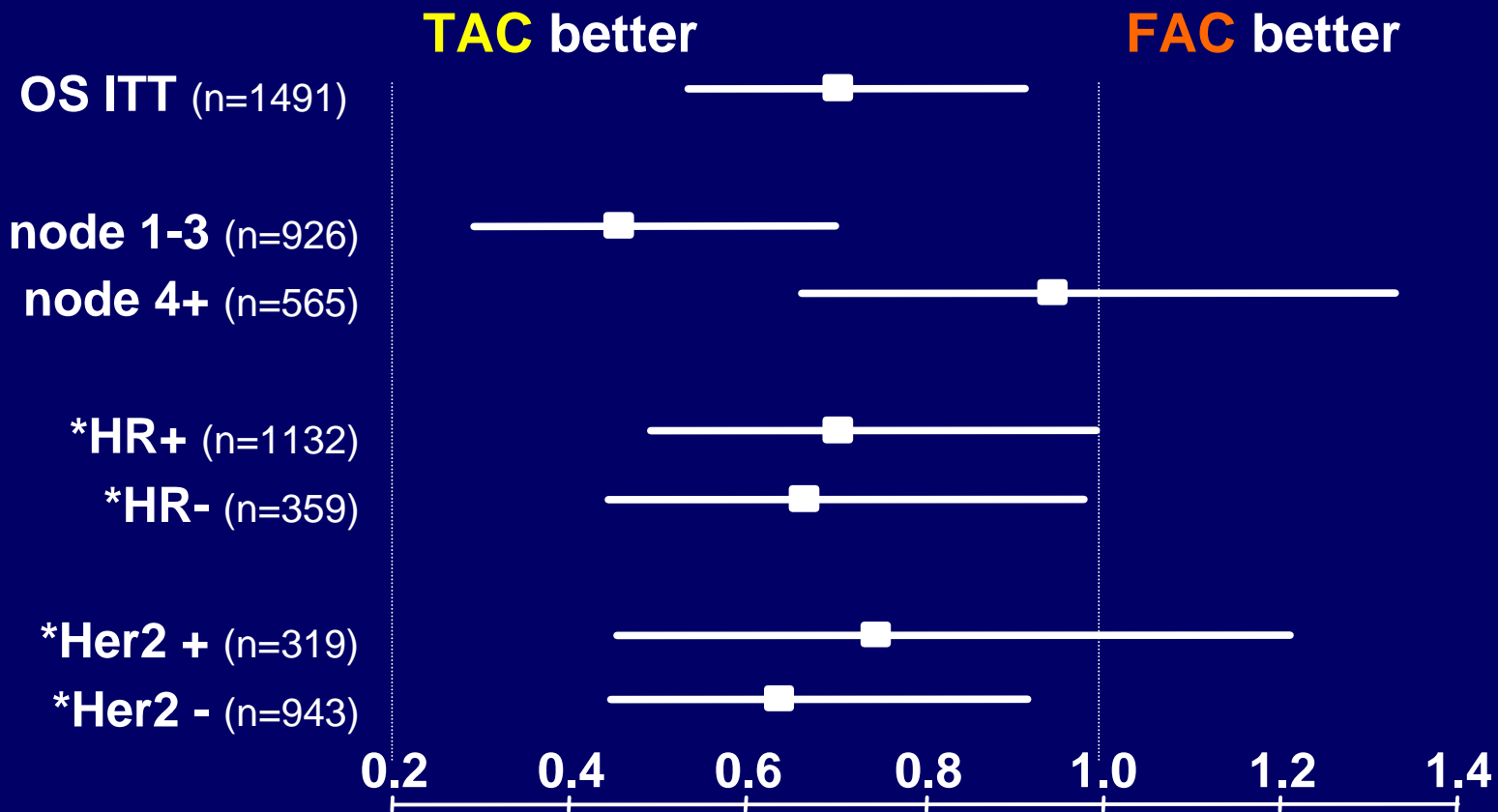
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# Extra Slides

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# Overall Survival

## Hazard Ratio and 95% CI for Subgroups

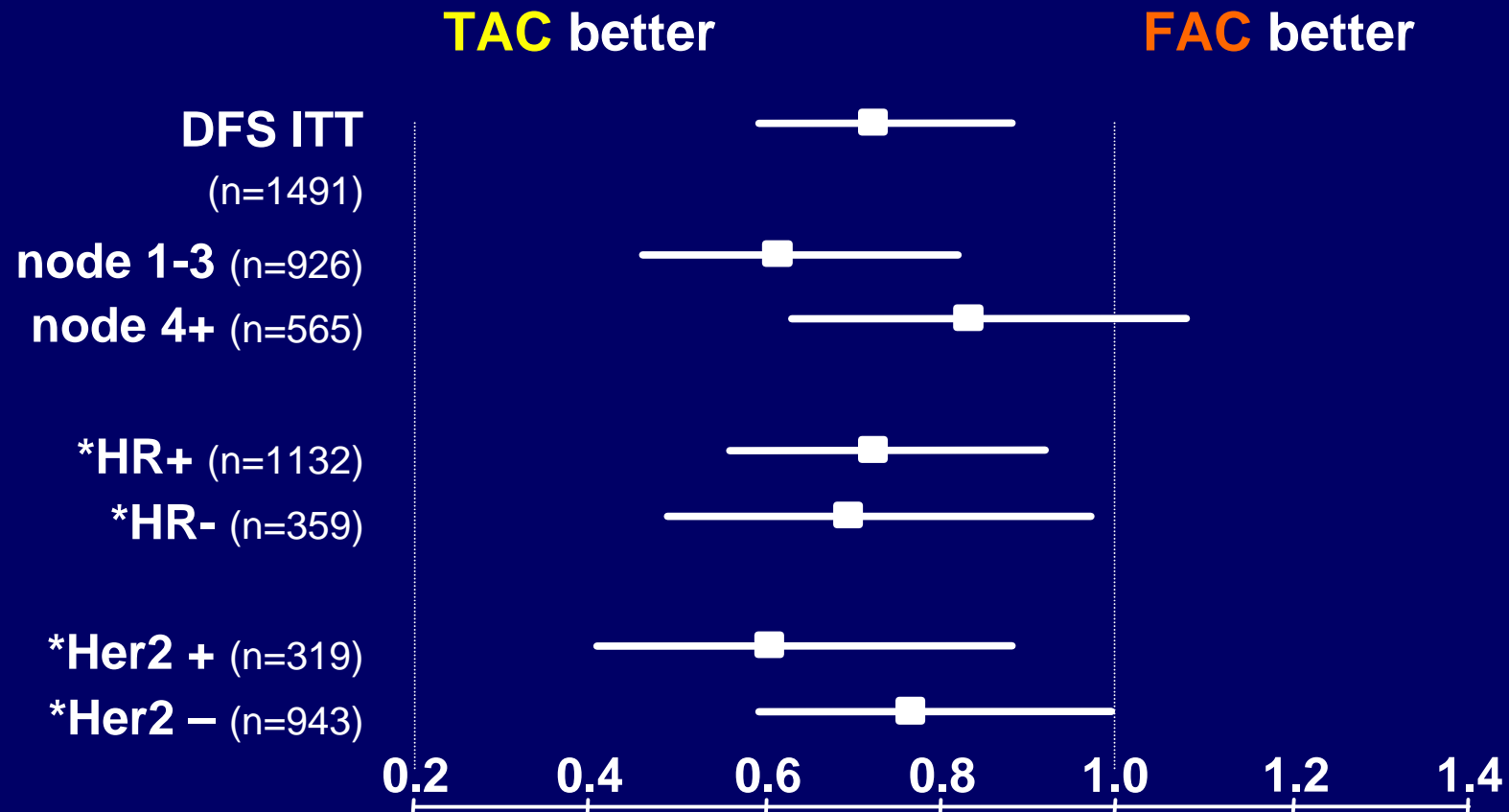


\*centrally reviewed

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# Disease-Free Survival

## Hazard Ratio and 95% CI for Subgroups



\*centrally confirmed

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# ITT Efficacy Analysis

n=1,491

<b>DFS</b>	<b>Hazard Ratio TAC/FAC (95%CI)</b>	<b>P-value</b>
<b>Adjusted nodes</b>	<b>0.72 (0.59-0.88)</b>	<b>0.0010</b>
<b>1-3 nodes</b>	<b>0.61 (0.46-0.82)</b>	<b>0.0009</b>
<b>4+ nodes</b>	<b>0.83 (0.63-1.08)</b>	<b>0.17</b>
<b>ER/PR +</b>	<b>0.72 (0.56-0.92)</b>	<b>0.0076</b>
<b>ER/PR -</b>	<b>0.69 (0.49-0.97)</b>	<b>0.0297</b>
<b>Overall survival</b>		
<b>Adjusted nodes</b>	<b>0.70 (0.53-0.91)</b>	<b>0.0080</b>

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# SPM – Overall

## All events (Other Than CBC)

	<b>TAC</b> n=745	<b>FAC</b> n=746
Endometrium	0	5
Leukemia (AML)	2	1
Ovary	1	1
Colon	1	4
Lung	2	3
Melanoma Skin	1	3
Other	13	7
<b>TOTAL</b>	<b>20</b>	<b>24</b>

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## Death – NED

### Considered as Primary Event for DFS

**TAC**  
n=744

**FAC**  
n=736

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<b>Toxicity due to CTx (non septic)</b>		
<b>On study</b>	<b>1</b>	<b>1</b>
<b>Off study</b>	<b>1</b>	<b>0</b>
<hr/>		
<b>Other: Suicide</b>	<b>2</b>	<b>1</b>
<b>AE not related</b>	<b>3</b>	<b>2</b>
<b>Unknown</b>	<b>1</b>	<b>0</b>
<hr/>		
<b>TOTAL</b>	<b>8</b>	<b>4</b>

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