

**BCIRG 005 main efficacy analysis: a Phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (AC-T) in women with HER2 normal and axillary lymph node positive early breast cancer**

Eiermann W, Pienkowski T, Crown J, Chap L, Pawlicki M, Martin M, Chan A, Saleh M, Sehdev S, Provencher L, von Minckwitz G, Semiglazov V, Slamon D, Tabah-Fisch I, Buyse M, Riva A, Taupin H, Sauter G, Mackey J, on behalf of the BCIRG 005 investigators.

Study sponsored by Sanofi-Aventis, TAX GMA 301

# DISCLOSURE

## Advisory board and speaker activity for

Astra Zeneca

Cephalon

Merck Serono

Micromet

Novartis

Roche

Sanofi-Aventis

BCIRG 005

# Global Study Coordinator

Henry Taupin

# BCIRG Adjuvant Program

**Adjuvant Setting**  
Screen by FISH 12000 patients

Her 2 normal  
N+

Her 2 overexpressed  
N+/High risk N-

**BCIRG 005**

**3298 pts**

enrollment

Aug/2000 – Feb/2003

BCIRG 006  
3222 pts

Pilot Phase  
II (TCH)

BCIRG 101

BCIRG 102

# Study Rationale

- **The first generation** of taxane trials established the role of taxanes in adjuvant treatment of breast cancer  
**(BCIRG 001 : TAC vs. FAC 1997-99)**
- **The Second Generation** of trials were designed to establish optimal scheduling of taxanes
  - **BCIRG 005 : TAC (6) vs. AC (4)→T(4) (2000 – 03)**
  - NSABP B-30: TAC (4) vs. AT (4) vs. AC (4) →T(4) (1999 -04)
  - CALGB 9741
  - BIG 2-98
  - ECOG 1199
  - NSABP B-38

# Design



**HER2 normal  
(FISH)  
N= 3298**

**Stratification:**

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

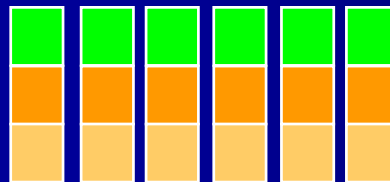
**4 x AC 4 x Docetaxel**

60/600 mg/m<sup>2</sup> 100 mg/m<sup>2</sup>



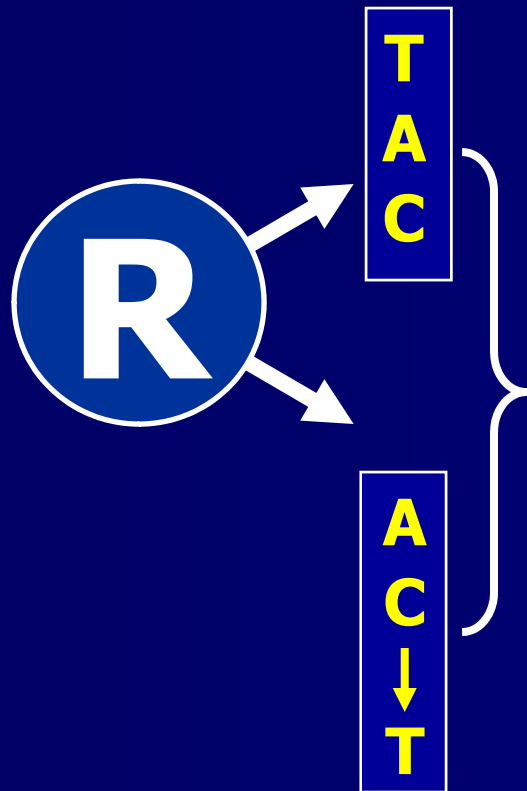
**6 x TAC**

75 / 50 / 500 mg/m<sup>2</sup>



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

# Post Chemotherapy Treatment



## Tamoxifen 20 mg/day for 5 years

- Patients with ER and/or PR positive tumors
- Switch to aromatase inhibitors allowed

## Radiation Therapy

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

# Major Eligibility Criteria

- **HER2 normal by central FISH**
- **Histologically proven node-positive breast cancer**
- **Stage T1-3, N1, M0**
- **Age  $\leq$  70 years, KPS  $\geq$  80%**
- Definitive surgery with axillary LN dissection ( $\geq$  6 LNs)
- $\leq$  60 days between surgery and randomization
- Normal hematologic, liver, renal and cardiac function
- Informed consent

# Endpoints

## Primary

- Disease-free Survival

## Secondary

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

# Patient Characteristics

	<b>TAC</b> <b>n= 1649</b>	<b>AC-T</b> <b>n= 1649</b>
Median Age	50	50
Median KPS	100	100
	<b>%</b>	<b>%</b>
Premenopausal	47	47
Mastectomy	59	58
Radiotherapy	66	65
Endocrine therapy	78	78

# Tumor Characteristics

	<b>TAC</b> <b>n= 1649</b>	<b>AC-T</b> <b>n= 1649</b>
	<b>%</b>	<b>%</b>
<b>Nodal Status</b>		
1-3	61	61
4-10	28	28
>10	11	11
<b>Tumor Size (cm)</b>		
≤2	41	42
>2 and ≤5	51	50
>5	8	8
<b>ER+ and/or PR+</b>	<b>82</b>	<b>82</b>

# Exposure to Treatment

**TAC**  
**n= 1635**

**AC-T**  
**n= 1634**

	<b>TAC</b> <b>n= 1635</b>	<b>AC-T</b> <b>n= 1634</b>
Treatment duration (wk)	18	12-12
Planned Dose intensity mg/m <sup>2</sup> /week		
Docetaxel	25	33
Doxorubicin	17	20
Cyclophosphamide	167	200
Completed all cycles	1528 (94%)	1478 (91%)
Relative dose intensity		
Median	0.99	0.99
>0.90	89%	86%

# **First Planned Analysis**

**(cut-off date August 11, 2005)**

**Median follow-up 30 months**

**Number of events:**

**392 DFS events**

**175 deaths**

**Efficacy data not released by IDMC**  
**Safety data presented at SABCS 2005**

# **Protocol Defined Statistical Analysis Disease Free Survival**

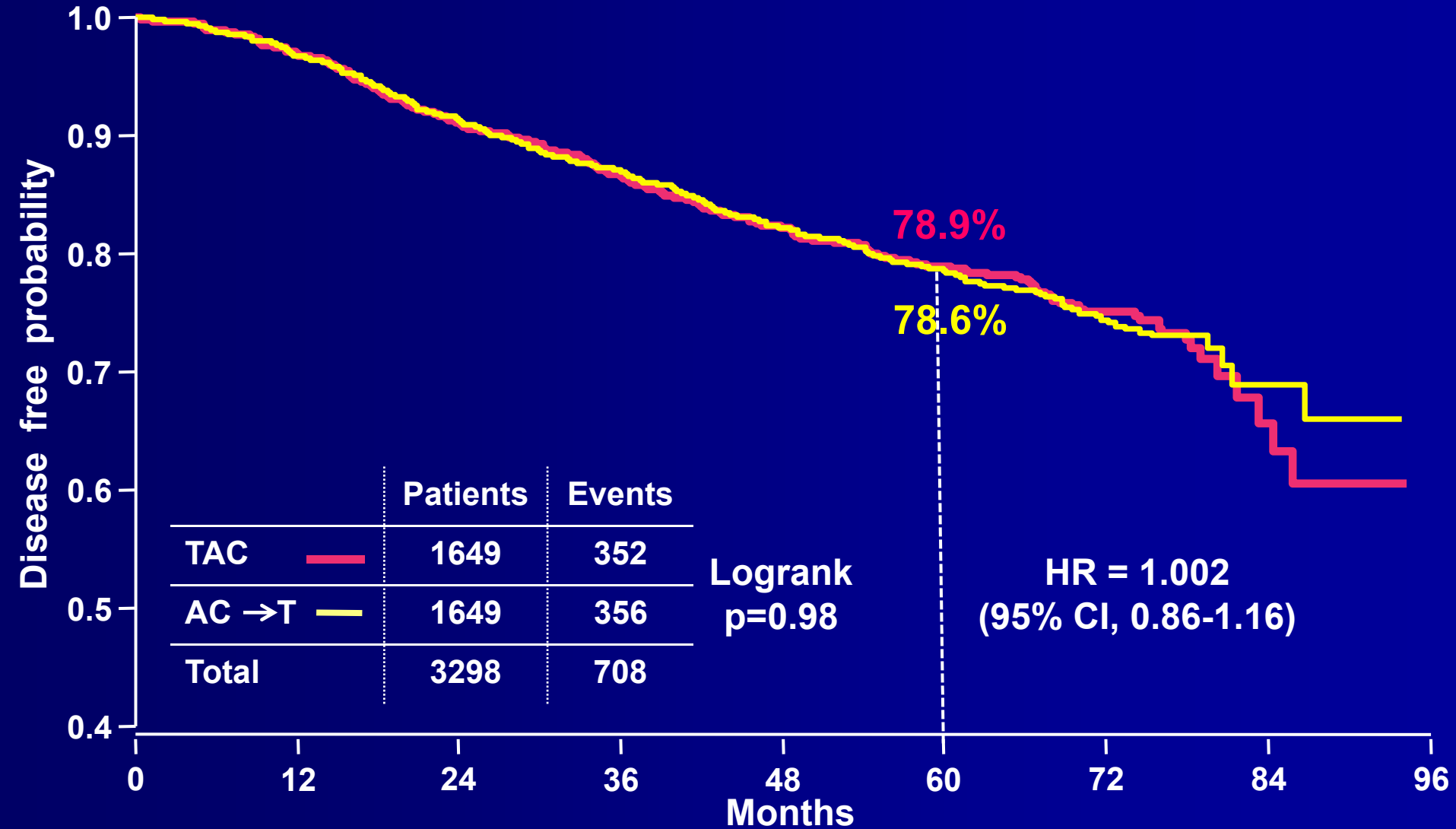
**Cohort: Intent to treat**

**Primary analysis: 688 events for 80% power to detect a HR of 0.81 (5% absolute benefit in DFS at 5yrs)**

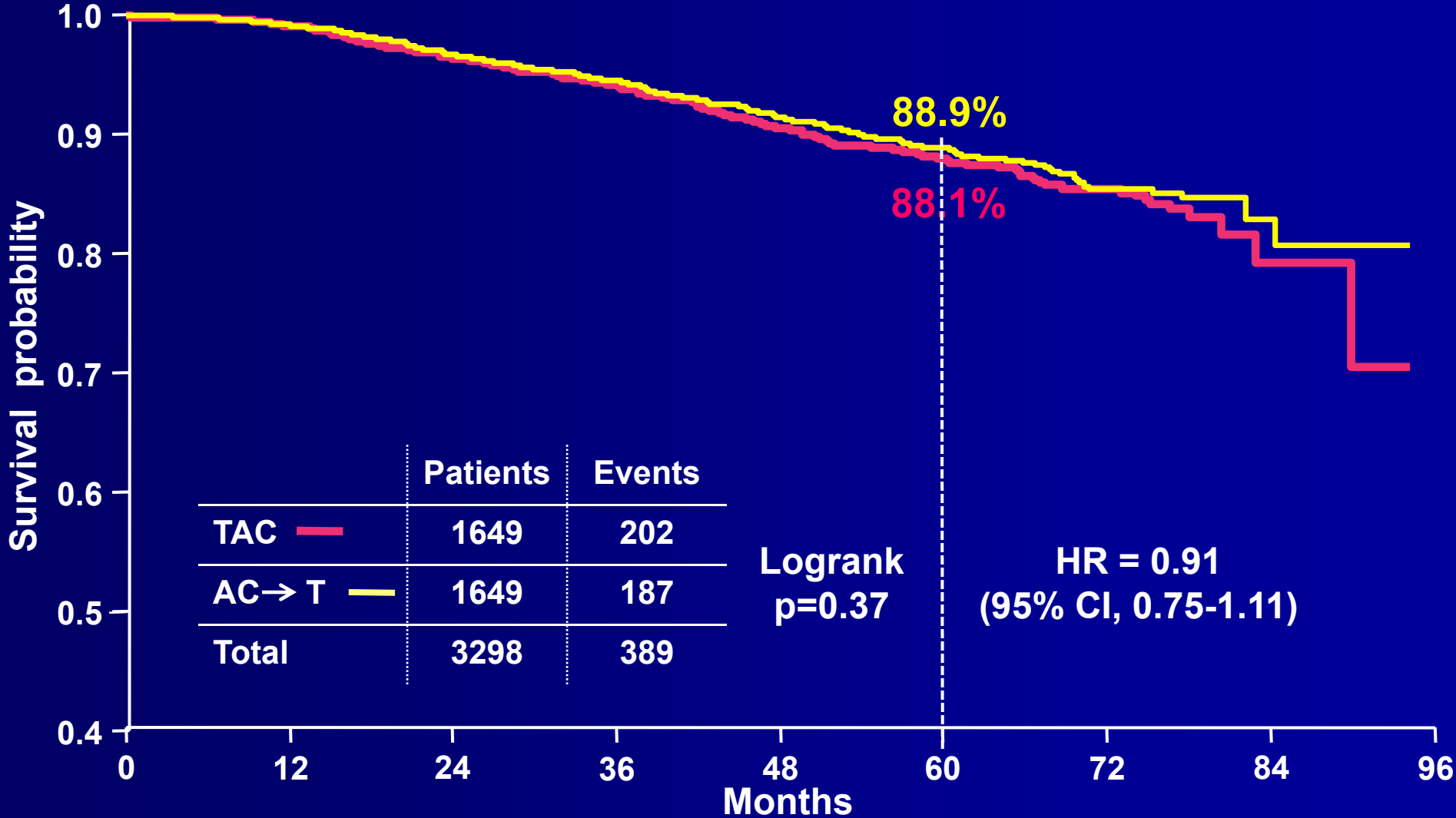
**Event = Breast Cancer Relapse  
Second Primary Malignancy  
Death**

**Median follow-up: 65 months, 708 events**

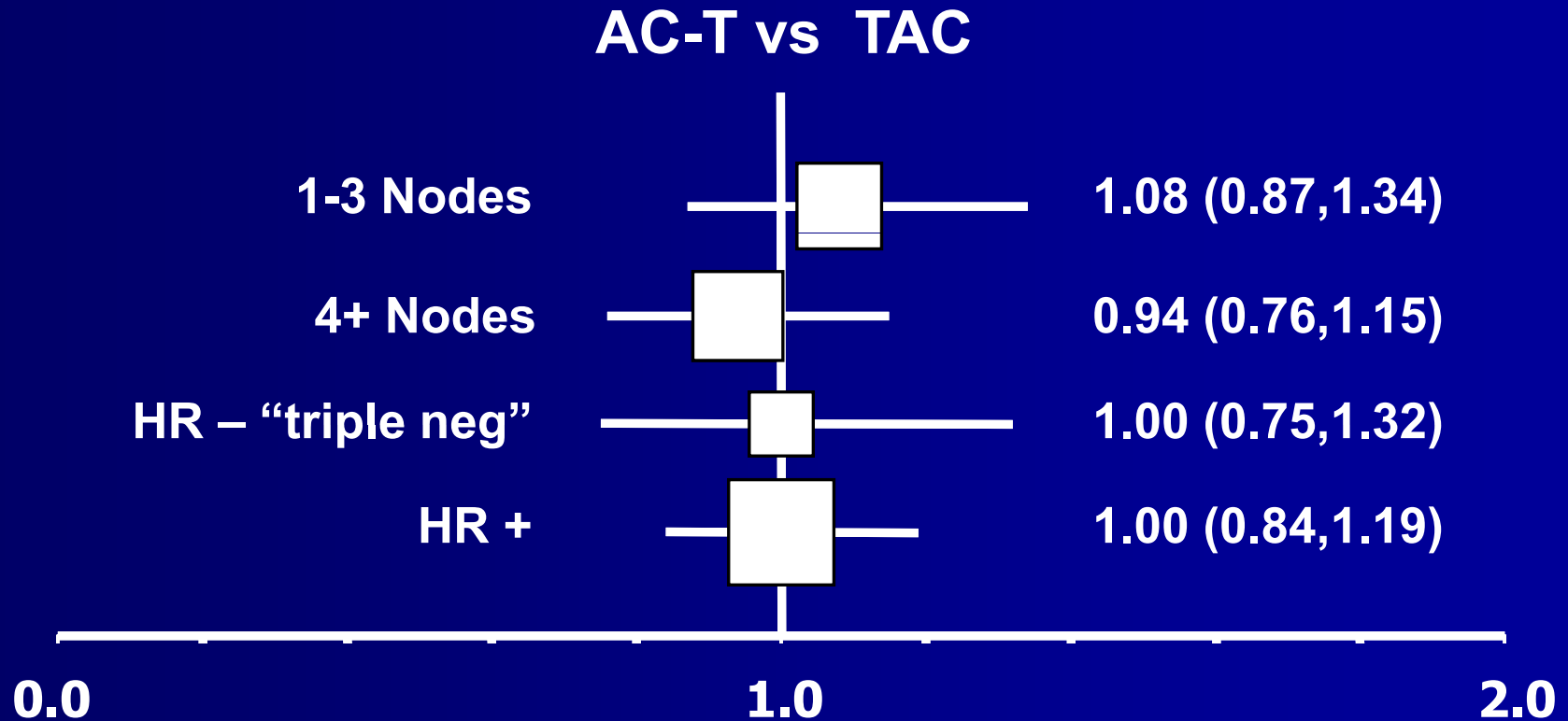
# Disease-free Survival – Primary Analysis



# Overall Survival – Primary Analysis



# DFS Subpopulations



# G-CSF Support

- Curative treatment for febrile neutropenia or infection
- Prophylactic treatment following an episode of febrile neutropenia
- Treatment for delayed recovery of neutropenia
- Primary prophylaxis was permitted

# Hematological Adverse Events

	<b>TAC</b> <b>n=1635</b>	<b>AC-T</b> <b>n=1634</b>	
	%	%	p-value
<b>Febrile Neutropenia</b>	<b>17.9</b>	<b>8.3</b>	<b>&lt;0.0001</b>
Neutropenic Infection (Gr 3/4)	9.7	8.5	0.25
Septic Death	0.06	0	>0.99
Anemia (Gr 3/4)	2.9	2.0	0.07
<b>Thrombocytopenia (Gr 3/4)</b>	<b>2.5</b>	<b>1.3</b>	<b>0.01</b>
Leukemia / Myelodysplastic Syndrome	0.24	0.18	>0.99

# Specific Non-Hematological Adverse Events (All Grades)

	<b>TAC</b> <b>n=1635</b>	<b>AC-T</b> <b>n=1634</b>	
	%	%	p-value
<b>Neuropathy-Sensory</b>	<b>27.5</b>	<b>42.8</b>	<b>&lt;0.0001</b>
Neuropathy-Motor	5.3	6.1	0.32
<b>Nail Changes</b>	<b>22.1</b>	<b>44.5</b>	<b>&lt;0.0001</b>
<b>Myalgia</b>	<b>35.8</b>	<b>50.9</b>	<b>&lt;0.0001</b>
Stomatitis	62.7	63.3	0.73
CHF (Gr 3/4)	0.1	0.4	0.06

# Non-Hematological Adverse Events (Grade 3 or 4 with Incidence >1%)

	<b>TAC n=1635</b>	<b>AC-T n=1634</b>	
	%	%	p-value
Nausea	4.4	3.9	0.49
Vomiting	4.1	5.2	0.13
Diarrhea	2.9	3.1	0.76
Stomatitis	2.6	2.9	0.59
Asthenia	5.1	6.3	0.15
Allergic reaction	1.8	1.1	0.11
<b>Arthralgia</b>	<b>0.9</b>	<b>2.4</b>	<b>0.001</b>
<b>Neuropathy-Sensory</b>	<b>0.3</b>	<b>1.5</b>	<b>0.0004</b>
<b>Fluid Retention</b>	<b>1.3</b>	<b>2.8</b>	<b>0.011</b>

# Non-Hematological Adverse Events (Grade 3 or 4 with Incidence >1%)

	<b>TAC</b> <b>n=1635</b>	<b>AC-T</b> <b>n=1634</b>	
	%	%	p-value
Dyspnea	1.3	1.5	0.65
<b>Hand Foot Syndrome</b>	<b>0</b>	<b>1.8</b>	<b>&lt;0.0001</b>
Hyperglycemia	1.3	1.4	0.88
<b>Myalgia</b>	<b>0.9</b>	<b>4.9</b>	<b>&lt;0.0001</b>
Syncope	2.9	1.9	0.07
Thrombosis/Embolism	1.3	1.3	0.88

# Conclusions

1. For the primary endpoint, DFS, adjuvant TAC is equivalent to AC-T in patients with HER2 normal, node + breast cancer
2. Despite AC-T delivering higher dose intensity for each of the three agents and requiring 8 cycles, AC-T was not more effective than TAC
3. Compared to AC-T, TAC is associated with:
  - ✓ more febrile neutropenia and GCSF use but no increased incidence of infections
  - ✓ less sensory neuropathy, nail change, myalgia and shorter duration of therapy

# ACKNOWLEDGEMENTS

→ **3298 women participants**

→ **259 independent centers**

→ **Cooperative groups**

- ✓ ICORG
- ✓ GBG
- ✓ Geicam
- ✓ Gercor

→ **Top recruiters**

- ✓ Pienkowski
- ✓ Chap
- ✓ Pawlicki
- ✓ Mackey
- ✓ Crown

→ **Central Laboratories**

- ✓ M. Press
- ✓ G. Sauter

→ **Medical Supervision**

- ✓ J. Mackey
- ✓ A. Riva

→ **Statistics**

- ✓ M. Buyse, IDDI
- ✓ H. Fung, CIRG
- ✓ E. Quinaux, IDDI

→ **IDMC Members**

→ **Data Management**

- ✓ V. Wilson
- ✓ D. Tlapanco
- ✓ M. Johnson
- ✓ D. Goodburn

→ **Clinical Operations**

- ✓ H. Taupin      MA. Lindsay
- ✓ P. Drevot      A. Schindele
- ✓ D. Fabry      F. Thireau
- ✓ M. Vlachou    P. Bandet
- ✓ S. De Ducla

# Principal Investigators Involved In The Study (I)

<b>ARGENTINA</b>	Koczwarra	Schwartzmann	<b>CROATIA</b>	Khayat	Kullmer	<b>HUNGARY</b>
Blajman	Kotasek	Skare	Grgic	Levy	Kunz/Kristen	Baki/Boer
Campos	Lewis	<b>BULGARIA</b>	Mrsic-Krmpotic	Rotarski	Künzig/V.Müller	Dank
Coppola	Links	Timcheva	Vrdoljak	Tournigand	Lichtenegger	Pinter
Fein	McCarthy	Tzekova	<b>CYPRUS</b>	Vanlemmens	Lürmann	Szanto
Giacomi	Oliver/Selva-Nayagam	<b>CANADA</b>	Adamou/Kakouri	Vannetzel	Meerpohl	<b>IRELAND</b>
Martinez/Korbenfeld	Ransom	Cantin/Potvin	<b>CZECH REPUBLIC</b>	<b>GERMANY</b>	Meinerz	Breathnach/O'Reilly
Mickiewicz	Richardson	Dufresne	Abrahamova	Aga/Christl	Morack/Keil	Crown
Orti	Schwarz	Guevin	Petruzelka	Bastert/Schneeweiss	Noschel/Camara	Grogan
Viniegra/O'Connor	Sullivan	Klimo	Vodvarka/Kysela	Bischoff/Bastert	Scharl	Keane
<b>AUSTRALIA</b>	Walpole/Woodward	Lopez	Vyzula	Brunnert	Schlotter	Kennedy
Abdi	White	Mackey	<b>EGYPT</b>	Carstensen	Schmidt	McCaffrey
Begbie	Young	Prady/Whitlock	Azim	Christensen	Schweppe	Mullins/Janku
Beith	<b>BELGIUM</b>	Provencher	El-Khodary	Clemens	Sillem	<b>ISRAEL</b>
Bell	Bastin	Rahim	<b>ESTONIA</b>	Conrad	Souchon/Kurzeja	Barak
Bonaventura	Bols	Roy	Valvere	Costa/Gauwerky	T. Müller	Ben Baruch
Byard	Cocquyt	Rubin	<b>FRANCE</b>	Deichert	Von Minckwitz	Geffen
Byrne/Dewar	Demol	Sehdev	Achille/Schaeffer	Du Bois	Watermann	Goldberg/Fried
Chan	Dirix	Wilson	Bennamoun	Eiermann	Weist	Merimski
Chirgwin	Vanstraelen/Mebis	Zibdawi	Boaziz	Feltz-Sussenbach	Winzer	Rizel
Clingan	Verhoeven	<b>CHINA</b>	Cals	Gerber/Reimer	Wolf	Safra/Isacson
Craft	Vermorken	Chu	Carola	Henschen	Zedelius	Siegelmann-Danieli/Sella
Dalley	<b>BOSNIA</b>	Li	Colin	Hilfrich	<b>GREECE</b>	Steiner
Davidson/Claringbold	Musanovic	Shen	Dalivoust	Jackisch/Kiesel	Efremidis	Uziely
Ganju	<b>BRAZIL</b>	Song	Dutel	Jonat	Georgoulis	Weitzen/Kaufman
Green	Ferrari	<b>COLOMBIA</b>	Ganem	Kettner	<b>HONG KONG</b>	
Green/De Boer	Lago	Gomez	Gligorov	Koelbl/Thomssen	Chow/Kwong	
Kannourakis	Sanches	Sanchez	Guastalla	Kretzschmar	Yeo	

# Principal Investigators Involved In The Study (II)

## LEBANON

Abbas/Saghir  
Abi Gerges  
Chahine  
Ghosn

## MEXICO

Cervantes Sanchez  
Silva

## NEW ZEALAND

Harvey

Isaacs

Jameson  
Jeffery  
McLaren

Simpson

## POLAND

Karnicka-Mlodkowska  
Pawlicki/Rolski  
Pienkowski

Wojtukiewicz

Zaluski

## PORTUGAL

Gervasio

## ROMANIA

Badulescu  
Ghilezan  
Gutulescu/Stanculeanu  
Roman

## RUSSIA

Garin  
Gorbunova  
Semiglazov

## SAUDIA ARABIA

Ibrahim

## SLOVENIA

Cufer  
Takac

## SOUTH AFRICA

Callaghan/De Bruyne  
Eek/Cohen  
Jacobs/Maart  
Moodley

Pienaar

Slabber/Beltchev

## SOUTH KOREA

Bang  
Im

Kim/Ahn

Lim/Choi

Ro

## SPAIN

Adrover  
Ales Martinez  
Arizcun  
Calvo Martinez  
Del Mar Munoz  
Sanchez

Franquesa Grane

Jara-Sanchez  
Llorca Ferrandiz  
Martin

Mayordomo

Mel Lorenzo

Munarriz Gandia

Munoz Mateu

Oltra Ferrando

Pelegri

Ramos Vazquez

Rodriguez Sanchez

Ruiz Simon

Sanchez Rovira

Segui Palmer/Fernandez-  
Morales

## TAIWAN

Chao

Liu

## URUGUAY

Rodriguez

Viola Alles/Krygier

## USA

Adler  
Allen  
Arena  
Bank  
Barstis  
Beall

Beck

Berdeaux

Berkowitz

Boros/Solky

Bryan

Carroll

Chap

Chitneni

Chlebowski

Chowhan

Desch/Trent

Dookeran/Zaren

Fesen

Forsthoff

Foulke/Reiling

Hajdenberg

Hargis

Heim

Holt

Hotchner/Diaz-

Lacayo

Houston

Hurvitz

Kalman

Kaplan

Kennedy

Kerr/Fain

Kruger

Lafollette

Laufman

Lewis/Perez

Limentani

Lower

McAndrew

McKeen

Moore

Moroose

Moss

Overmoyer/Silverman

Page

Patel

Patton

Pendergrass

Perkins

Pluard/Beattie

Priebat

Rinaldi

Riseberg

Russell

Saleh

Sanal

Shiftan

Slamon

Smith/Lemon

Strickland

Sylvester/Naot

Tai/Koneru

Tansino

Teczan

Tkaczuk

Touroutoglou/Wierman

Vaughn

Venkatraj

Vogel

Weisberg

Wiznitzer/Philip

Yunus

## VENEZUELA

De Jongh

Vera-Gimon

# Resources

- These slides will be available from December 15, 2008 at

[www.cirg.org](http://www.cirg.org)