

# **Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients: Second Interim Efficacy Analysis**

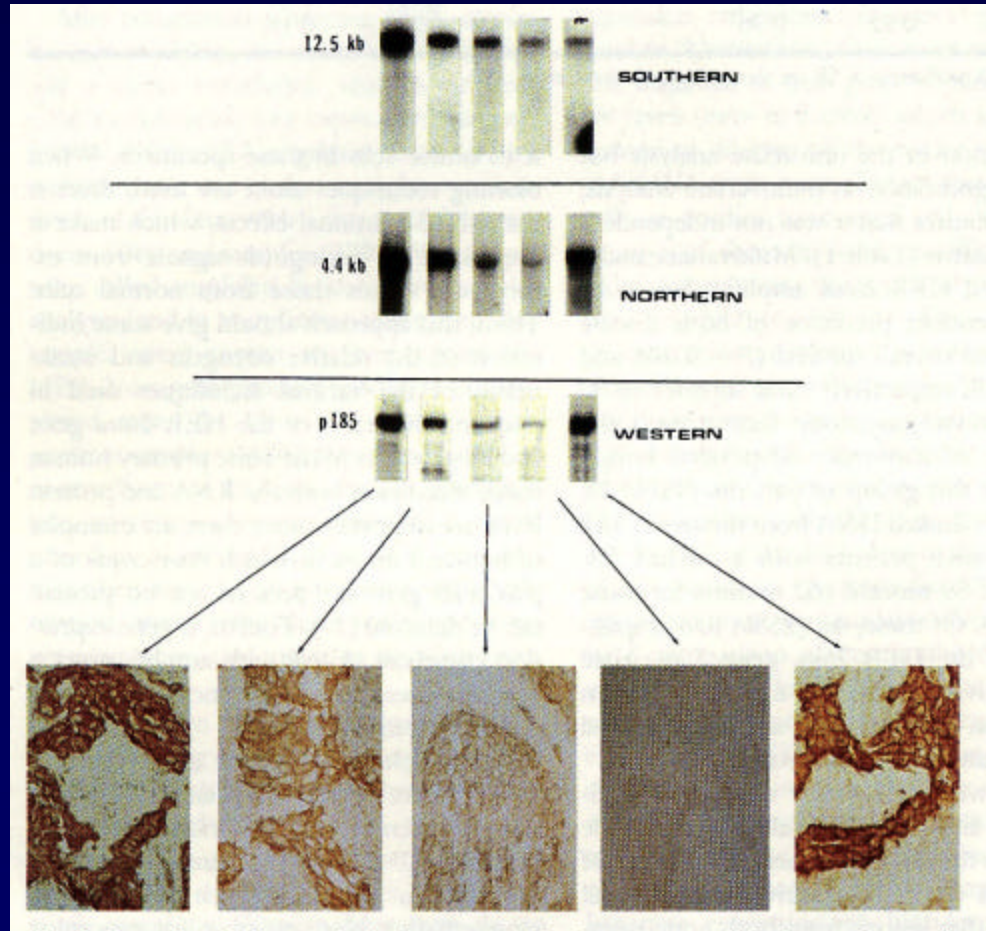
Slamon D, Eiermann W, Robert N, Pienkowski T,  
Martin M, Pawlicki M, Chan A, Smylie M, Liu M,  
Falkson C, Pinter T, Fornander T, Shiftan T, Valero V,  
Von Minckwitz G, Mackey J, Tabah-Fisch I, Buyse M,  
Lindsay MA, Riva A, Bee V, Pegram M, Press M,  
Crown J, on behalf of the BCIRG 006 Investigators.

Study sponsored by Sanofi-Aventis  
Support from Genentech

After the presentation these slides will be  
available at:

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

# The HER2 Alteration



**Southern**

**Northern**

**Western**

**IHC**

# Global Project Coordinator

Valerie Bee

# BCIRG 006

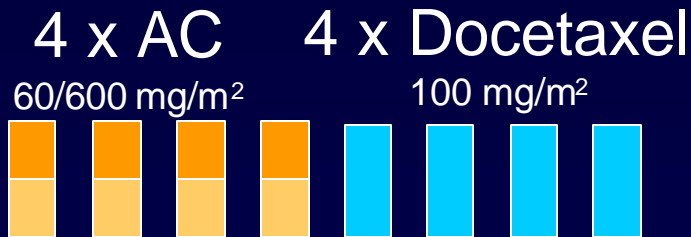
**Her 2+**  
(Central FISH)

**N+**  
or high  
risk **N-**

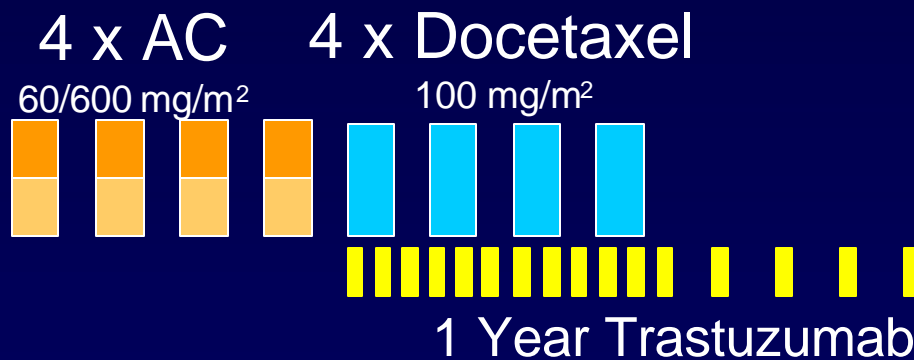
**N=3,222**

Stratified by Nodes  
and Hormonal  
Receptor Status

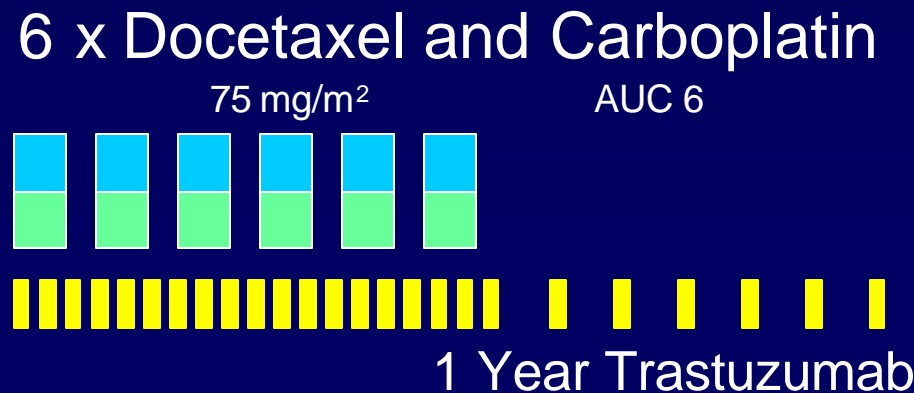
AC→T



AC→TH



TCH



# Endpoints

## Primary

→ Disease-free Survival

## Secondary

→ Overall Survival

→ Toxicity

→ Pathologic & Molecular Markers

# Patient characteristics

Randomized (n=3,222)	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
	%	%	%
Age < 50 years	52	52	54
KPS = 100	80	79	80
Mastectomy	60	63	60
Radiotherapy	63	61	63
Hormonotherapy	50	51	51

Enrollment: April 2001 to March 2004

# Tumor Characteristics

Randomized (n=3,222)	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
Number of nodes +	%	%	%
<b>0</b>	<b>29</b>	<b>29</b>	<b>29</b>
1 – 3	38	38	39
4 – 10	22	24	23
> 10	11	9	10
Tumor Size (cm)	%	%	%
≤ 2	41	38	40
> 2 and ≤ 5	53	55	54
> 5	6	7	6
ER and/or PR +	54	54	54



# Crossover

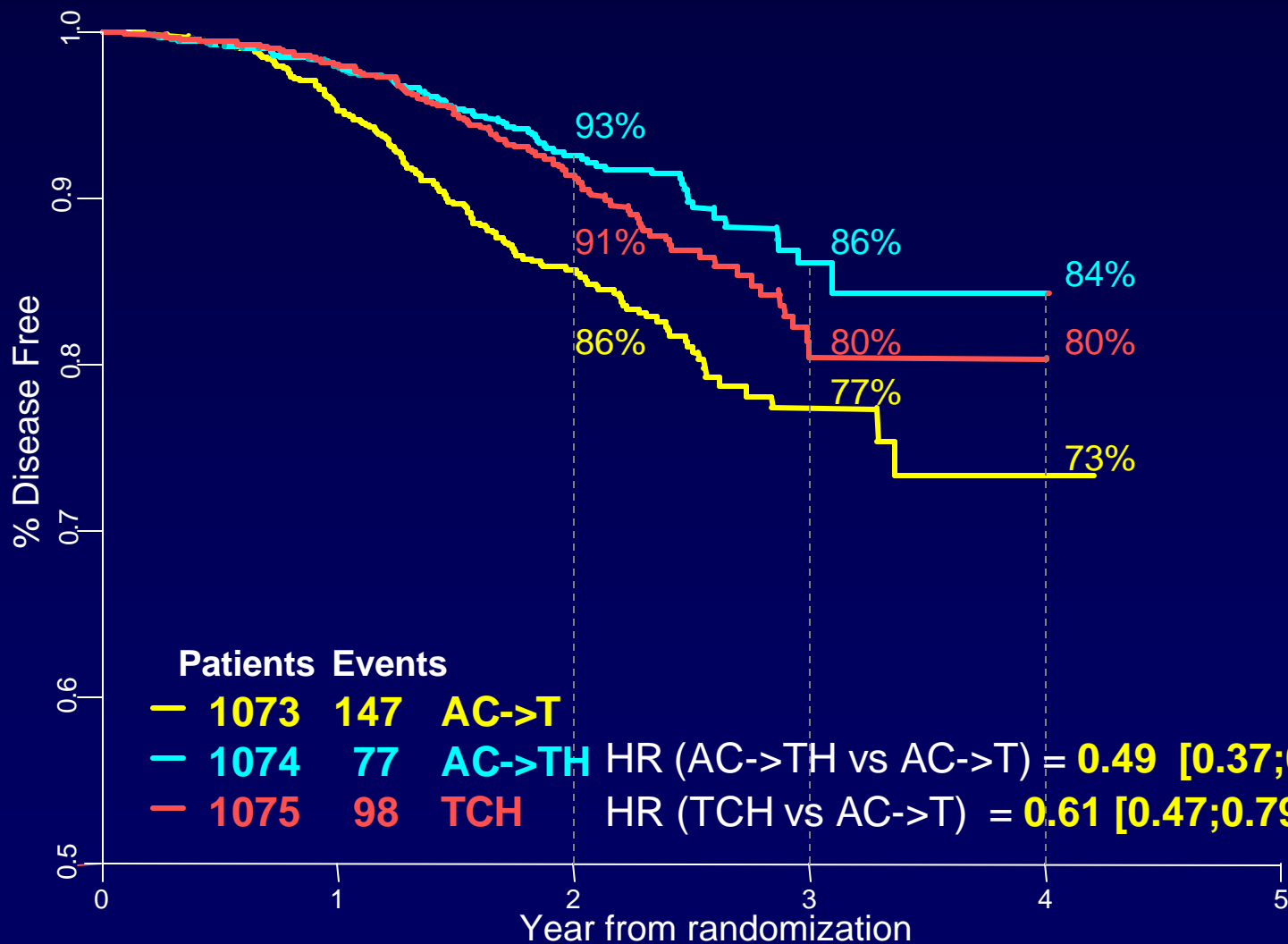
After the trastuzumab efficacy results were announced in April '05, to date:

- ✓ A total of **17 patients (1.6%)** of 1,073 randomized to the the ITT control arm (AC-T) crossed-over to receive trastuzumab
- ✓ Leaving **98.4%** of the control arm enrollment intact for subsequent DFS, OS and safety comparison analyses

# First/Second Interim Efficacy Analysis (cutoff date June 30, 2005/November 01, 2006)

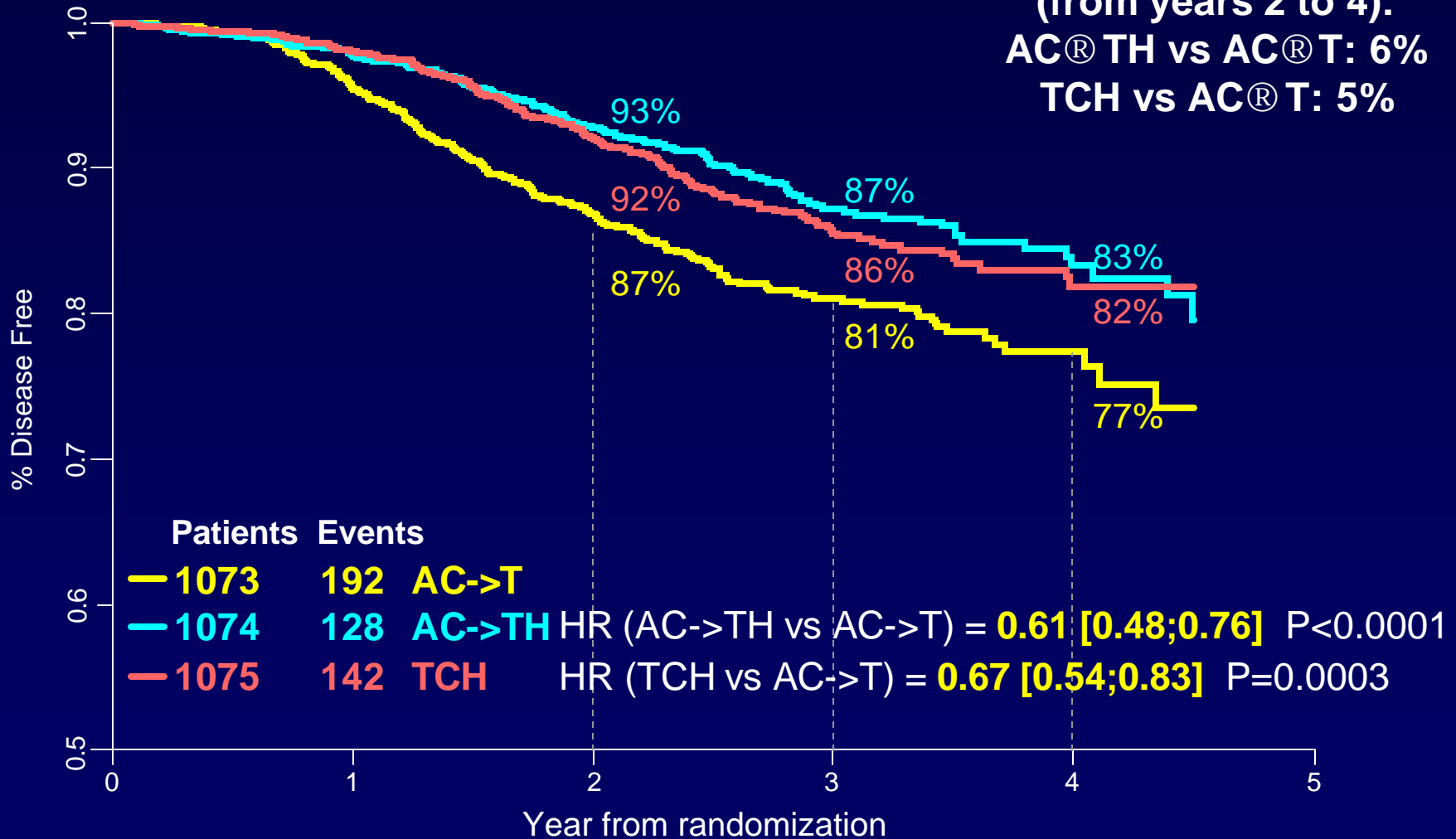
- Median follow-up time = 23 /36 months
- 322 /462 DFS Events
  - ✓ Breast Cancer Relapse
  - ✓ Second Primary Malignancy
  - ✓ Death
- 84 /185 Deaths

# Disease Free Survival – 1<sup>st</sup> interim analysis



# Disease Free Survival - 2<sup>nd</sup> Interim Analysis

**Absolute DFS benefits  
(from years 2 to 4):  
AC® TH vs AC® T: 6%  
TCH vs AC® T: 5%**



# p-values at Interim Efficacy Analyses

	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
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Patients with event	147 / <b>192</b>	77 / <b>128</b>	98 / <b>142</b>
---------------------	------------------	-----------------	-----------------

at 1<sup>st</sup> interim analysis

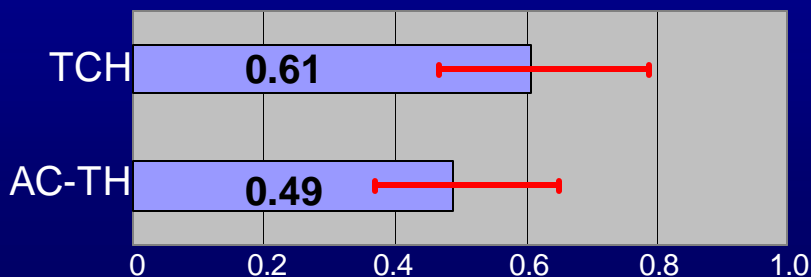
at 2<sup>nd</sup> interim analysis

p=0.0000005 / **0.000011**

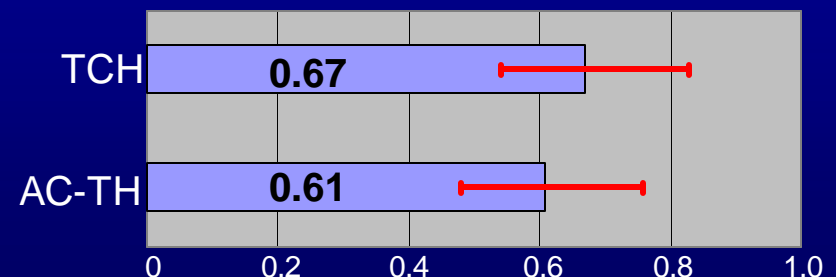
p=0.00015 / **0.00028**

p=0.16 / **0.42**

## HR at 1<sup>st</sup> interim analysis



## HR at 2<sup>nd</sup> interim analysis



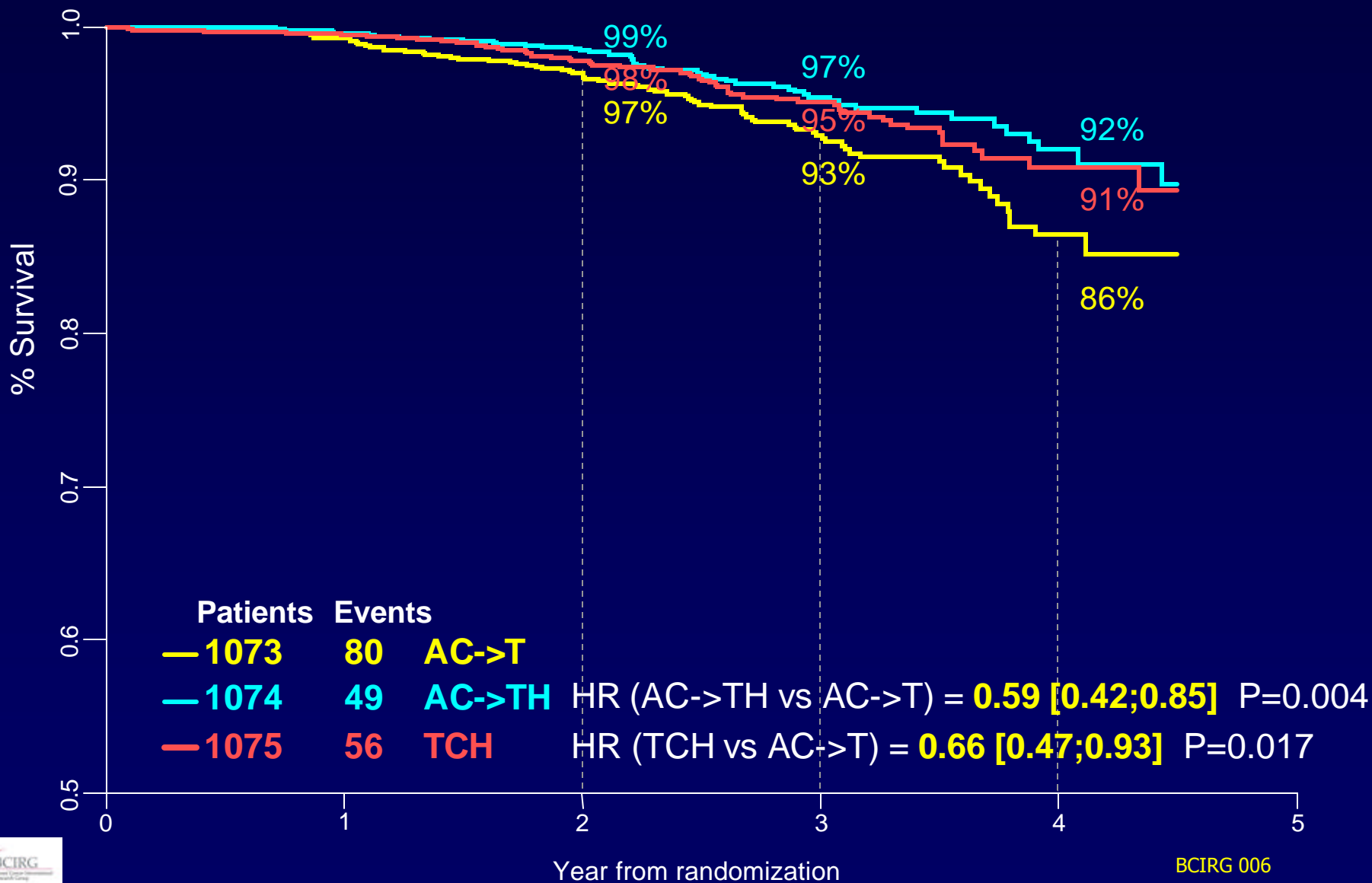
Metastatic events

113 / **143**

52 / **93**

67 / **98**

# Overall Survival – 2<sup>nd</sup> Interim Analysis

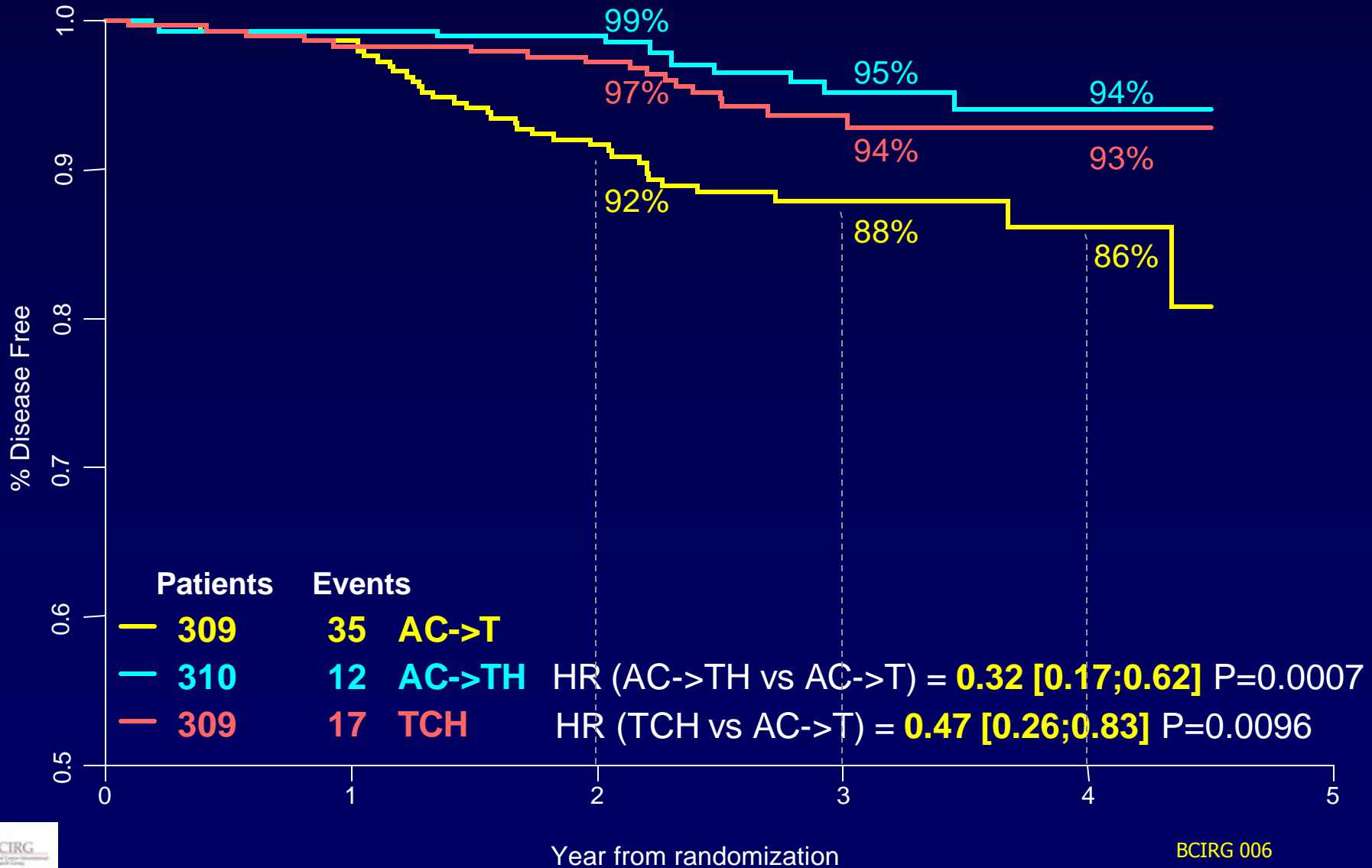


# Deaths at Interim Efficacy Analyses

	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
Total number of deaths from any cause	36 / 80	20 / 49	28 / 56
at 1 <sup>st</sup> interim analysis	p=0.004		
at 2 <sup>nd</sup> interim analysis	p=0.017		p=0.58
Breast Cancer Deaths	33 / 69	19 / 44	21 / 47

# DFS Lymph Node Negative

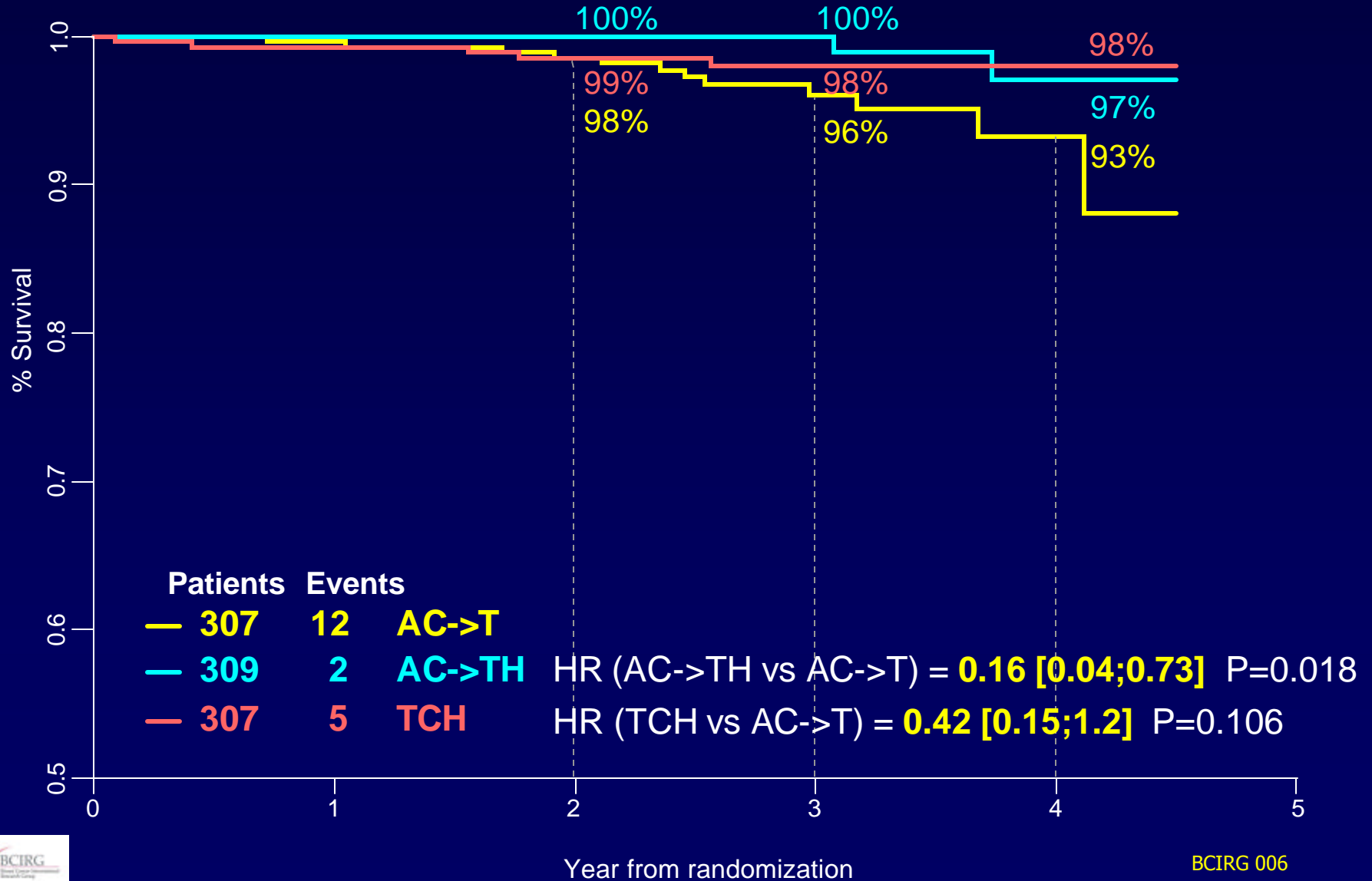
## 2<sup>nd</sup> Interim Analysis





# Overall Survival Lymph Node Negative

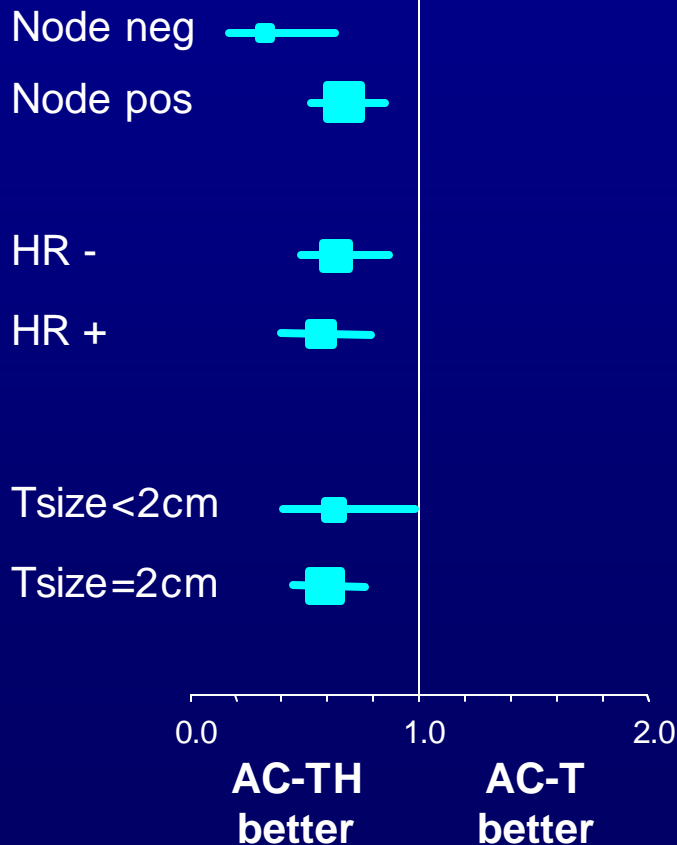
## 2<sup>nd</sup> Interim Analysis



# DFS Subpopulations

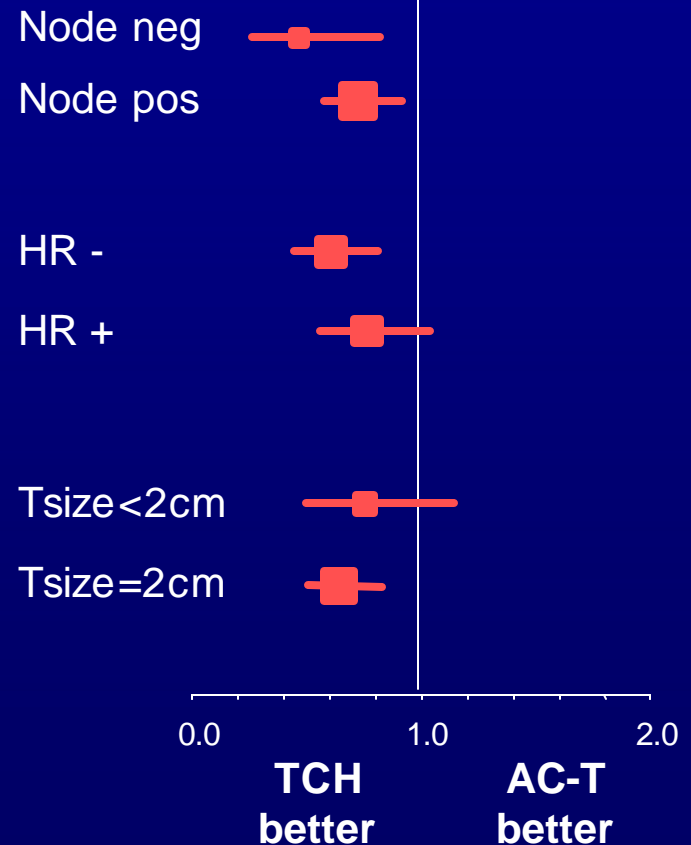
## AC-TH vs AC-T

Subgroup



## TCH vs AC-T

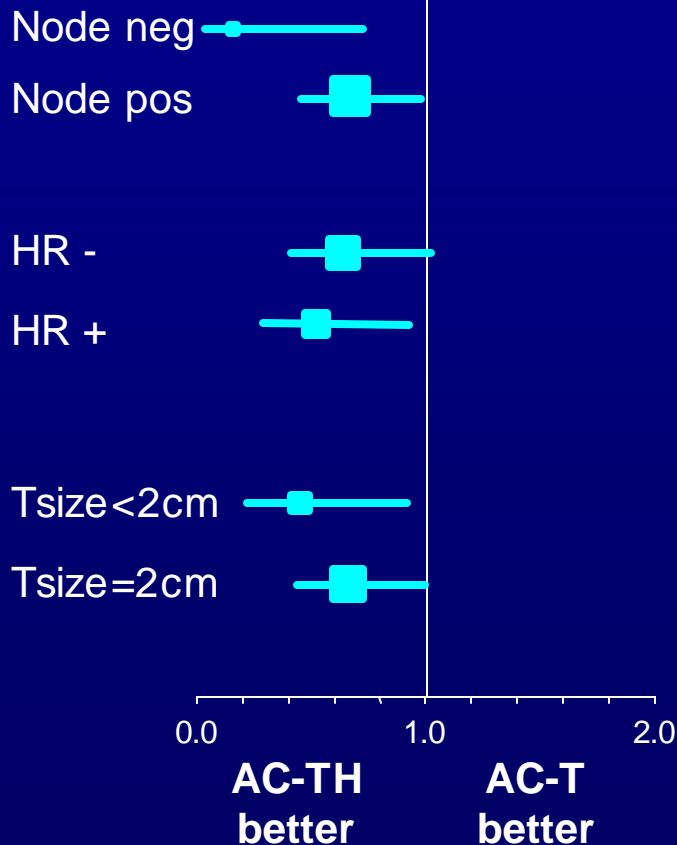
Subgroup



# Overall Survival Subpopulations

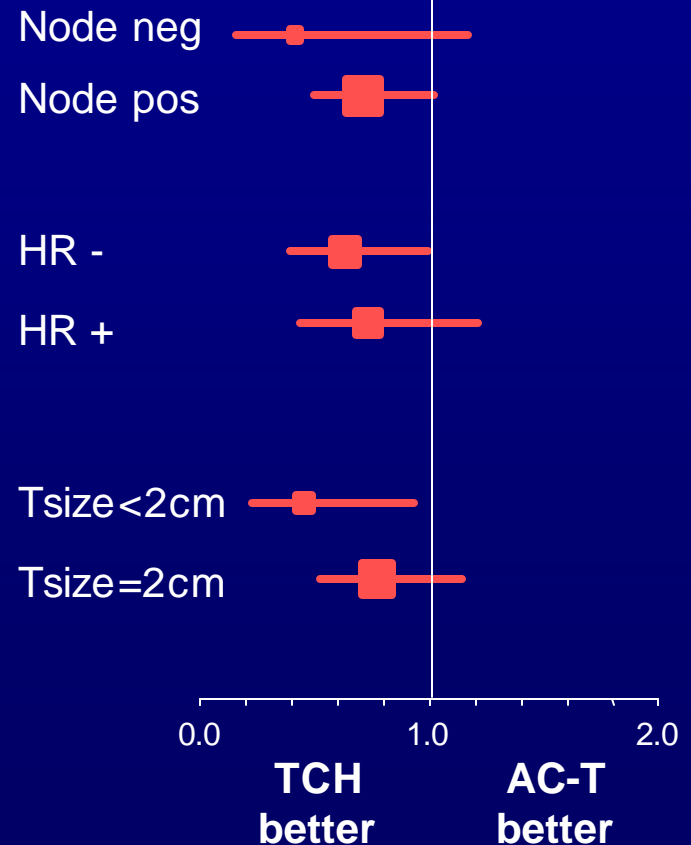
## AC-TH vs AC-T

Subgroup



## TCH vs AC-T

Subgroup



# Safety Results

# Grade 3/4 Non-Hematological toxicity

	AC-T n=1,050 %	AC-TH n=1,068 %	TCH n=1,056 %
Arthralgia	3.2	3.3	1.4*
Myalgia	5.2	5.2	1.8*
Fatigue	7.0	7.3	7.2
Hand-foot syndrome	1.9	1.4	0.0*
Stomatitis	3.6	3.1	1.4*
Diarrhea	3.0	5.7	5.5
Nausea	6.0	5.7	4.8
Vomiting	6.1	6.8	3.4*
Irregular menses	27.1	24.2	26.4

Yellow = numerically less events AC-TH or TCH

\*Statistically significant AC-TH or TCH

# Specific non-hematological toxicity (all grades)

	AC-T n=1,050 %	AC-TH n=1,068 %	TCH n=1,056 %
Neuropathy-sensory	48.3	49.7	36.1 *
Neuropathy-motor	5.2	6.3	4.2 *
Nail changes	49.2	43.6	28.7 *
Myalgia	52.8	55.5	38.6 *
Renal failure	0.0	0.0	0.1
Creatinine Grade 3/4	0.6	0.3	0.2

Yellow = numerically less events AC-TH or TCH

\*Statistically significant AC-TH or TCH

# Grade 3/4 Hematological Toxicity

	AC-T n=1,050 %	AC-TH n=1,068 %	TCH n=1,056 %
Neutropenia	63.3	71.3	66.2*
Leucopenia	51.5	60.2	48.2*
Febrile neutropenia	9.1	11.0	9.8
Neutropenic infection	11.3	12.0	11.0
Anemia	2.5	3.1*	5.8
Thrombocytopenia	1.0	1.2*	5.4
<b>Leukemia (%)</b>	3 pts (0.3)	1 pt (0.1)	0 pts

Yellow = numerically less events AC-TH or TCH

\*Statistically significant AC-TH or TCH

# CARDIAC TOXICITY



## Cardiovascular risk factors

Randomized (n=3,222)	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
Age			
Median	49 yrs	49 yrs	49 yrs
Range	(23 - 74 yrs)	(22 - 74 yrs)	(23 - 73 yrs)
Risk factors (# of Pts)			
Diabetes	38	36	28
Hypercholesterolemia	54	47	43
Hyperlipidemia	20	10	12
Obesity (BMI $\geq$ 30)	214	242	234
Hypertension	177	177	190
Radiotherapy (# of Pts)			
After chemotherapy	662	656	671
To left chest	346	320	333

# Cardiac Deaths and CHF as per Independent Review Panel

	AC-T n=1,050	AC-TH n=1,068	TCH n=1,056
Cardiac related death	0 / 0	0 / 0	0 / 0
Cardiac left ventricular function (CHF) Grade 3 / 4	3 / 4	17 / 20	4 / 4

**P = 0.0015**

first interim analysis

**second interim analysis**

# Patients with >10% relative LVEF decline

	AC-T n = 1012/ <b>1014</b>	AC-TH n = 1040/ <b>1042</b>	TCH n = 1029/ <b>1030</b>
Patients	91 / <b>102</b>	180 / <b>189</b>	82 / <b>89</b>
%	9 / <b>10</b>	17.3 / <b>18</b>	8 / <b>8.6</b>

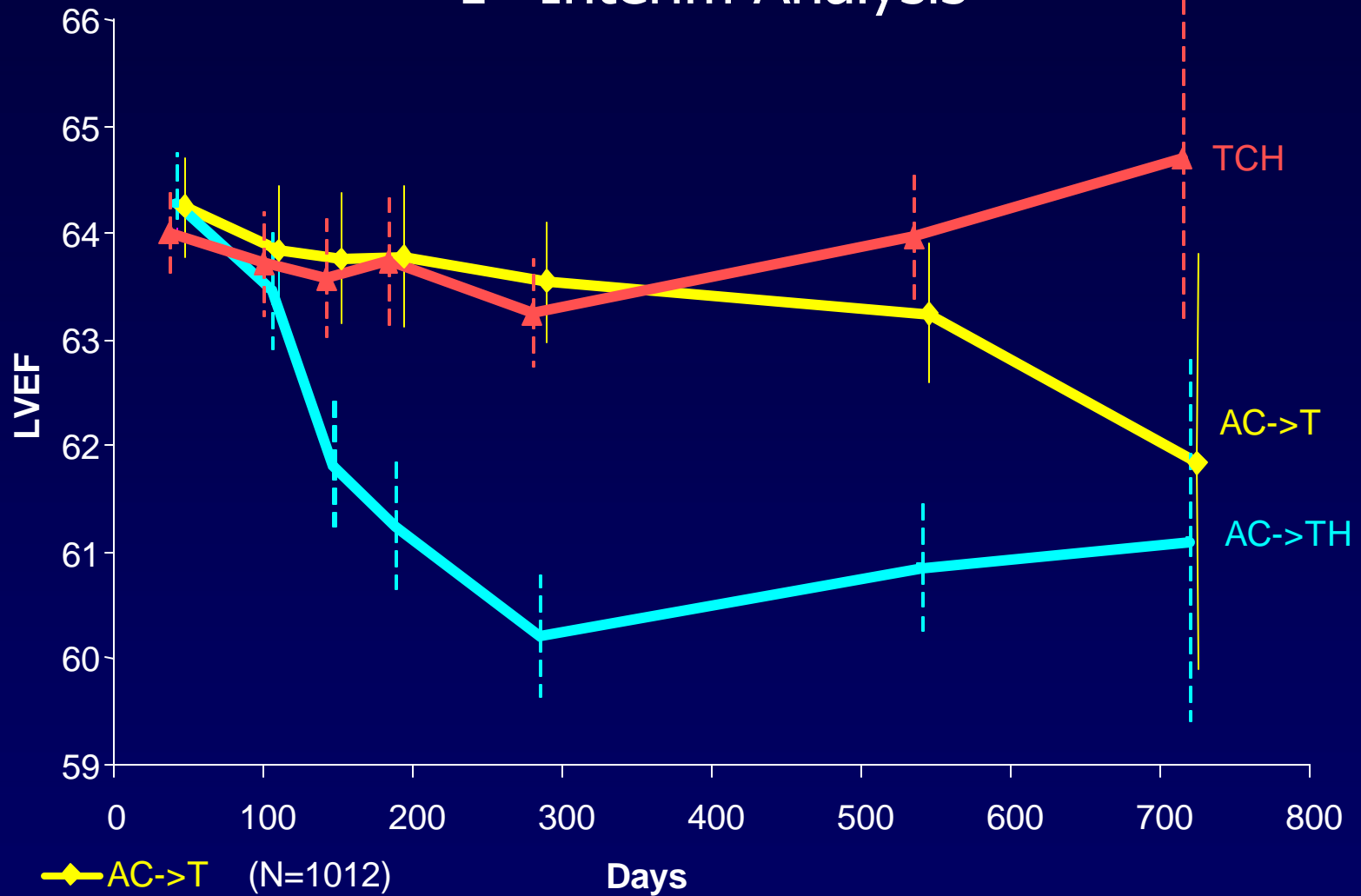
$P = 0.002$     $P < 0.0001$     $P < 0.0001$     $P < 0.0001$   
 $P = 0.5$     $P = 0.5$

first interim analysis

**second interim analysis**

# Mean LVEF - All Observations

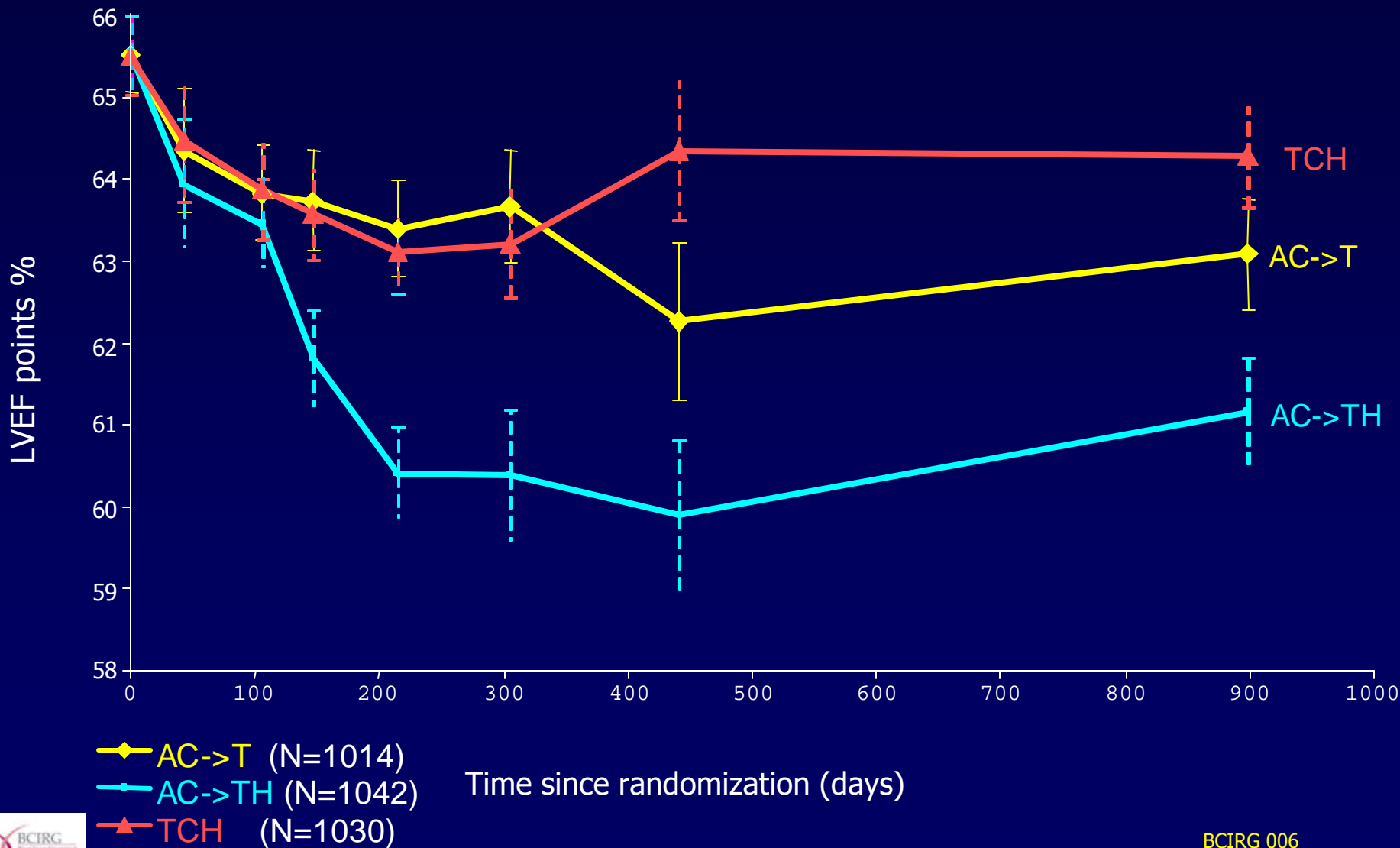
## 1<sup>st</sup> Interim Analysis



◆ AC->T (N=1012)  
■ AC->TH (N=1040)  
▲ TCH (N=1029)

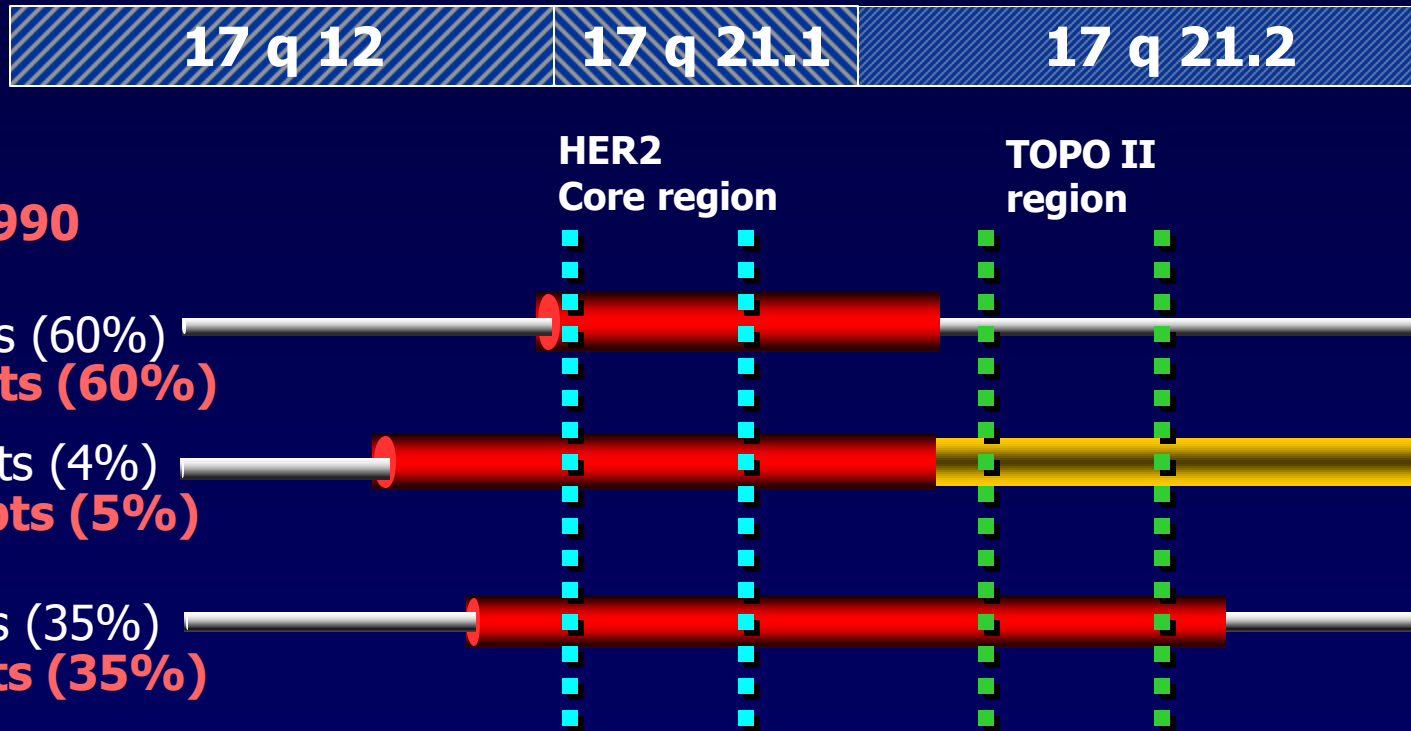
# Mean LVEF - All Observations

## 2<sup>nd</sup> Interim Analysis



# HER2 and TOPO II in BCIRG 006

2120 of 3222 patients analyzed  
**2990 of 3222 patients analyzed**



first interim analysis  
**second interim analysis**

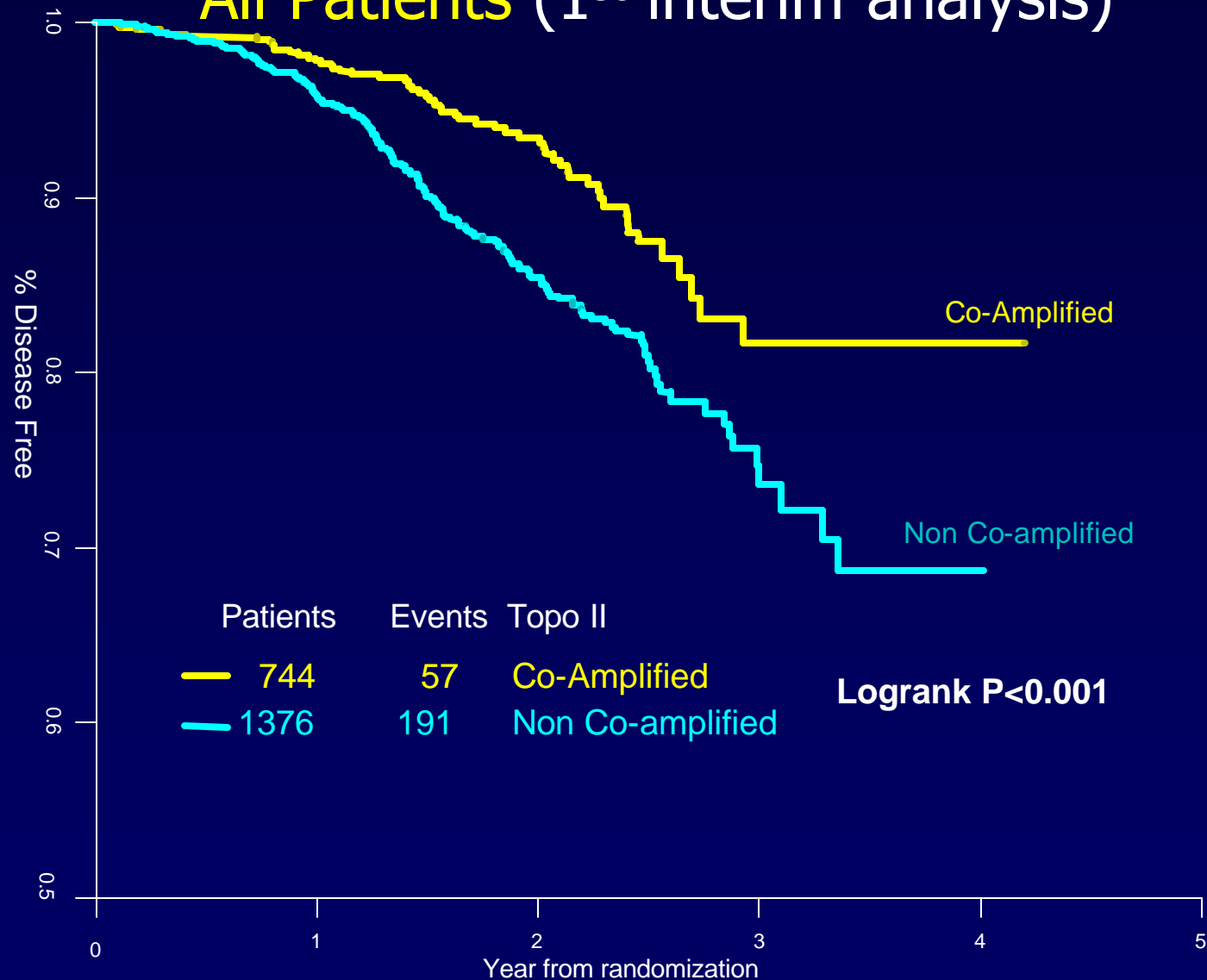


# TOPO IIa (not HER2) Amplification as a Predictor of Anthracycline Response in Breast Cancer

Since 2002, at least 6 studies have been published demonstrating the association between topo II alpha amplification and improved anthracycline response.

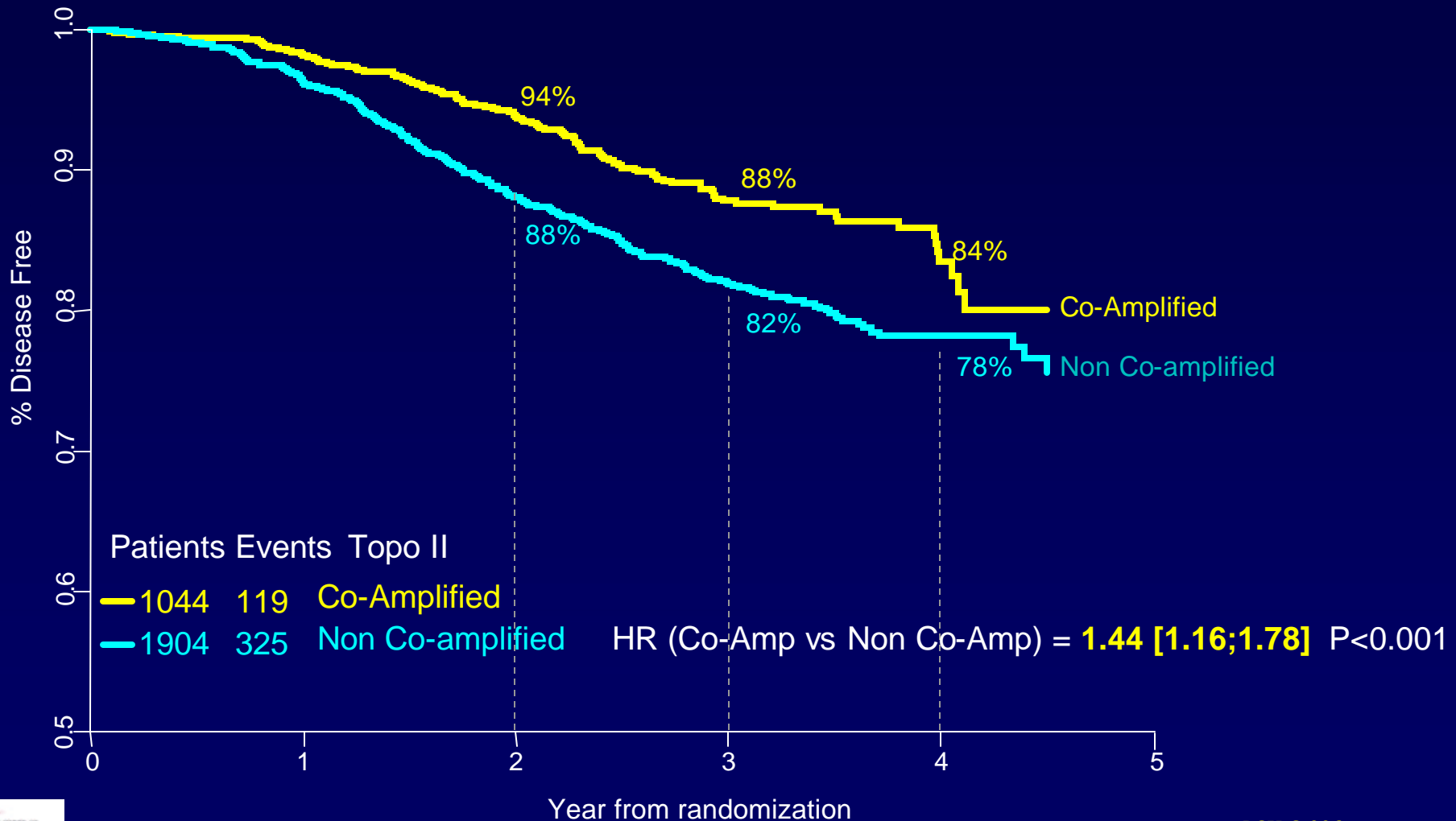
Study	Yr	N
Park et al.	2006	284
Tanner et al.	2006	525
Knoop at al.	2005	805
Park et al.	2003	188
Coon et al.	2002	35
Di Leo et al.	2002	354

# DFS Topo II Co-Amplified vs Non Co-Amplified All Patients (1<sup>st</sup> interim analysis)

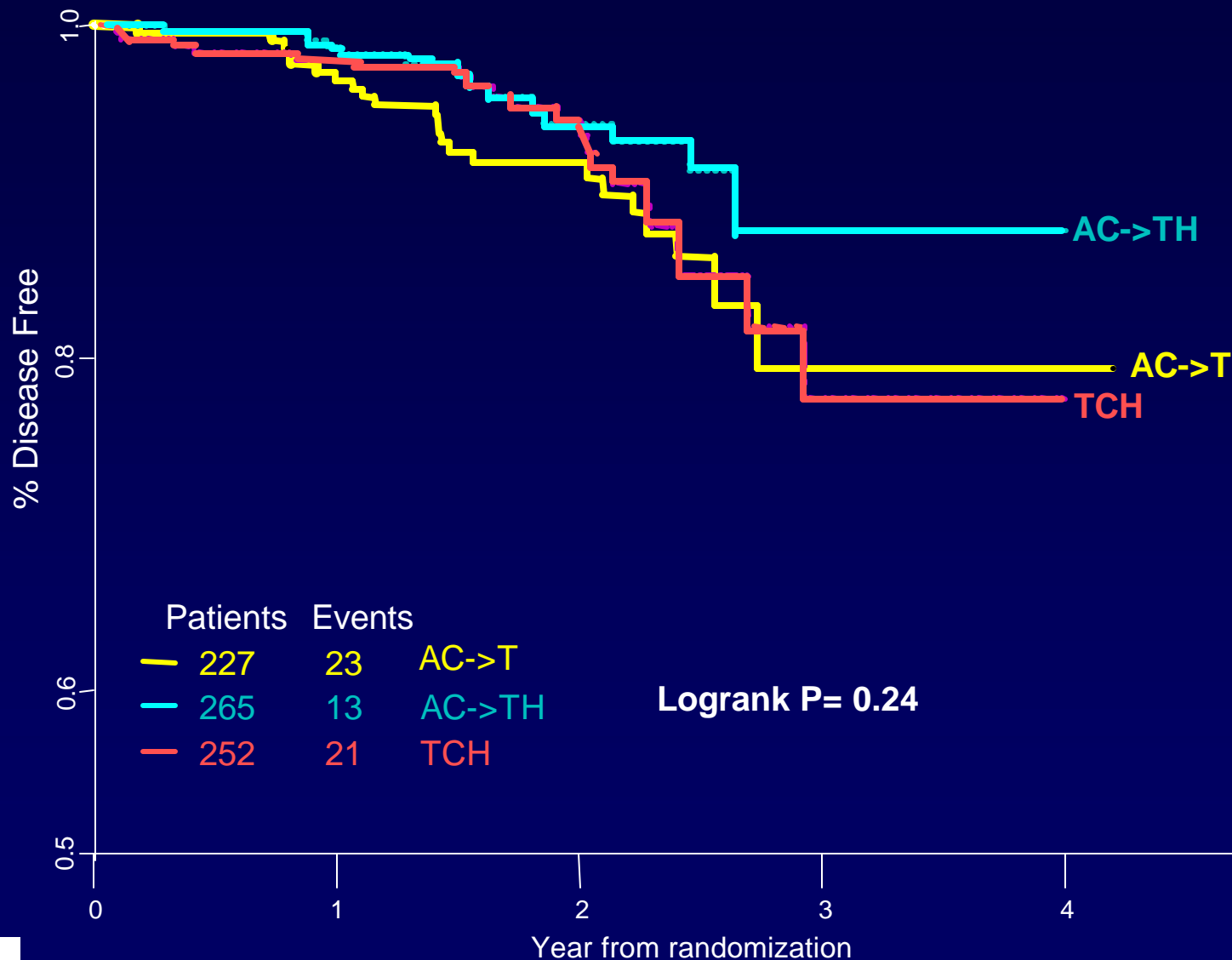




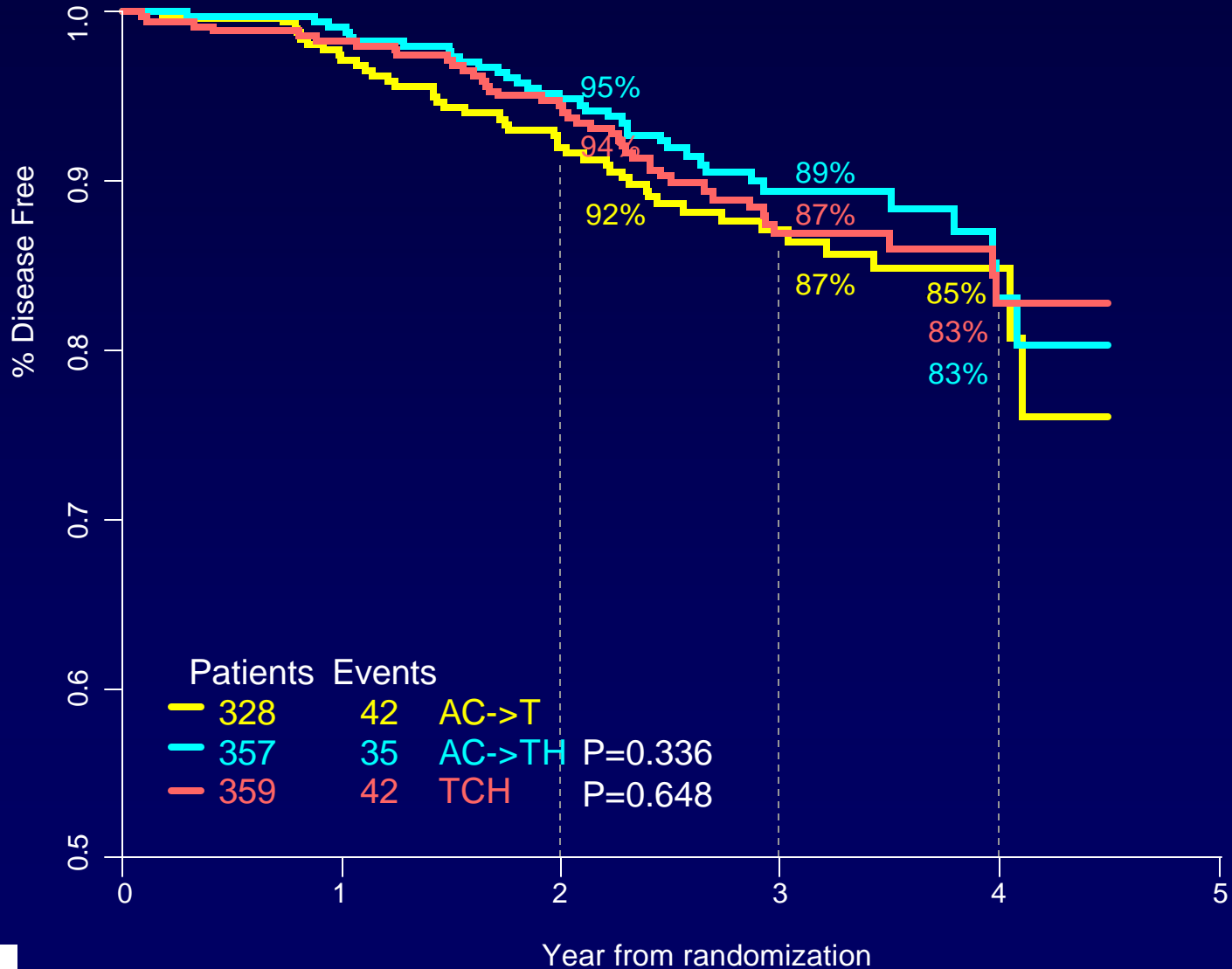
# DFS Topo II Co-Amplified vs Non Co-Amplified All Patients (2<sup>nd</sup> interim analysis)



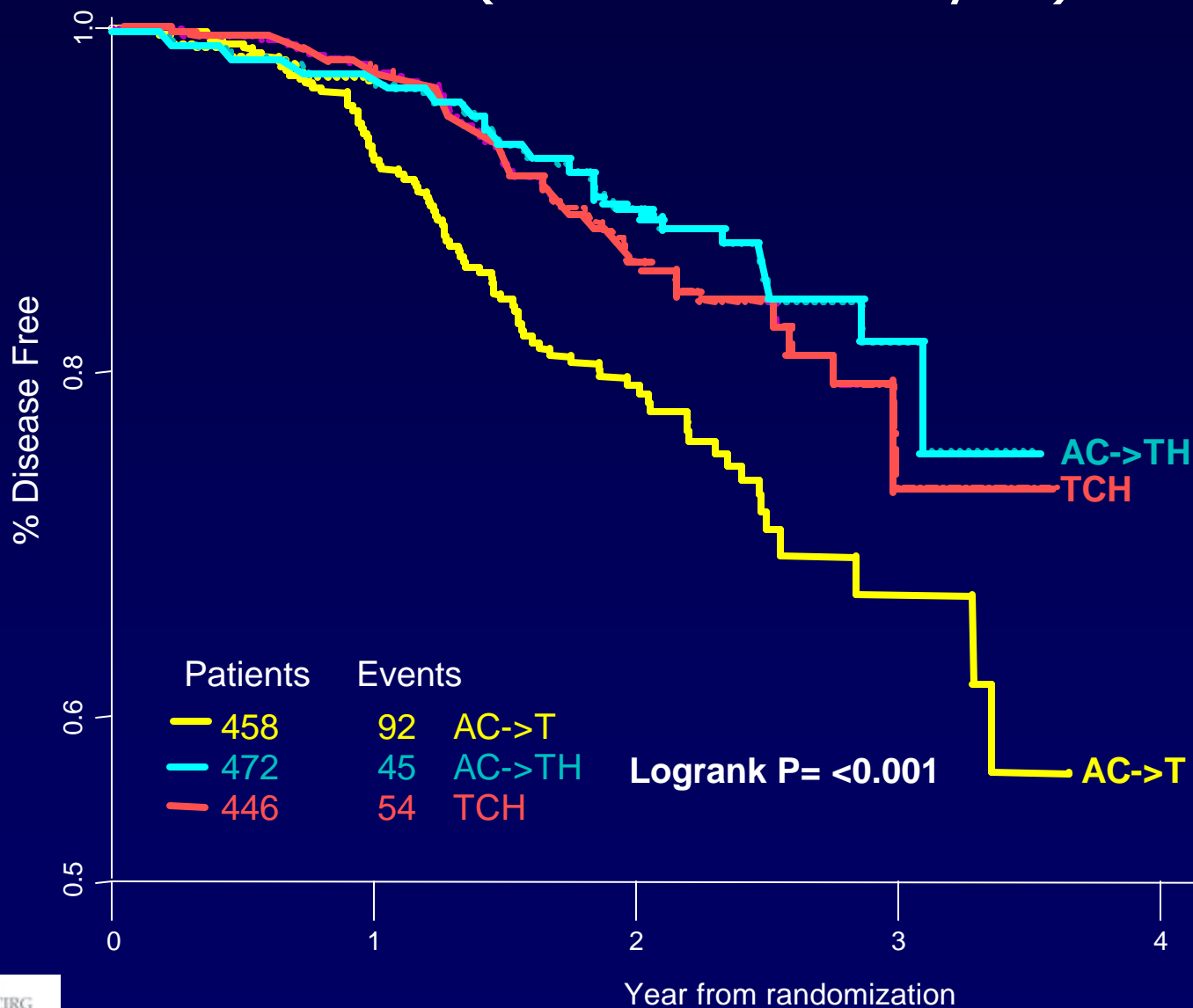
# DFS Co-Amplified Topo II by Arm (1<sup>st</sup> Interim Analysis)



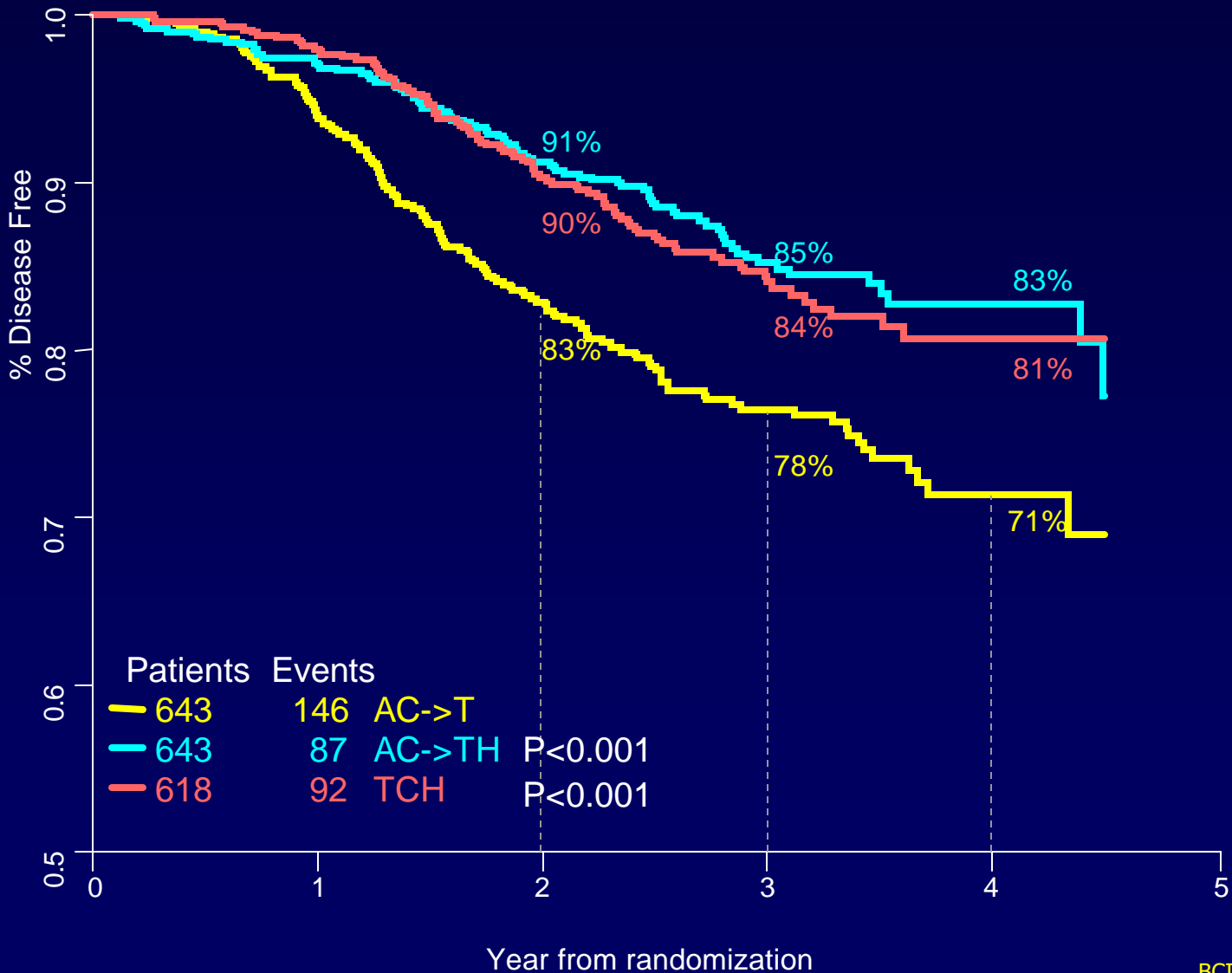
# DFS Co-Amplified Topo II by Arm (2<sup>nd</sup> Interim Analysis)



# DFS Non Co-Amplified Topo II by Arm (1<sup>st</sup> Interim Analysis)



# DFS Non Co-Amplified Topo II by Arm (2<sup>nd</sup> Interim Analysis)



	<b>Patients</b>	<b>Events</b>	
—	643	146	AC->T
—	643	87	AC->TH
—	618	92	TCH
			P<0.001
			P<0.001



# Therapeutic Index – Most Recent Data

- Difference in DFS, OS and BC death events (ITT) between the 2 Herceptin-containing arms
  - ✓ DFS AC-TH - 128 TCH – 142
  - ✓ OS AC-TH - 49 TCH – 56
  - ✓ Br Ca Deaths AC-TH - 44 TCH – 47
  
- Difference in critical adverse events between anthracycline and non-anthracycline containing arms
  - ✓ Grade 3/4 CHF
    - AC-T - 5 AC-TH - 20 TCH - 4
  - ✓ Leukemia
    - Anthracycline-Based Arms - 4 TCH – 0
  
- Global safety TCH > AC-TH
  
- In addition, 23 pts with bona fide HER2 amplification who were randomized to the AC-TH arm never got trastuzumab due to unacceptable declines in LVEF before receiving the antibody

# Critical Question

## ✓ Considering:

- ✓ The recently published data from US Oncology showing a highly statistically significant superiority of docetaxel-cyclophosphamide (TC) over adriamycin-cyclophosphamide (AC) in terms of breast cancer efficacy (Jones, S. JCO 24:5381, 2006).
- ✓ The 006 update for HER2 positive malignancies shows the difference in number of DFS events and breast cancer deaths in favor of AC-TH, neither of which are statistically significant, is now exceeded by the number of critical adverse events. These include grade III/IV CHF and AC- related leukemia as well as a small AND sustained loss of LVEF for 18% (189 pts) both of which are highly statistically significant...

**What is the role of anthracyclines  
in the adjuvant treatment of breast cancer?**

# Acknowledgements

- All participating **Investigators** and **Patients**
- IDMC (Chair, S Swain) and Independent Cardiac Panel
- Central laboratories:  
M Press (USC), G Sauter (Basel)
- IDDI: M. Buyse
- NBCC: Fran Visco and Carolina Hinestroza
- BCIRG Central Team:  
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## BELGIUM

Cocquyt

Demol

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Verhoeven

Vermorken

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## BRAZIL

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Mrsic-Krmpotic

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Goldberg

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Chahine

Ghosn

Saghir

\* *Highest recruiters*

BCIRG 006

Slamon D., SABCS 2006

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Carroll  
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Chitneni  
Chowhan

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Grosbach  
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Justice

Jutori  
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Kennedy  
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Laufman  
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Mc Croskey

McKeen  
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Modiano

Moore  
Moroose

Moss

Nair

Neel  
Nicholls

Olopade  
Orlowski

Osborn  
Page

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Petruska  
Philip

Polikoff  
Polikoff (network)

Posada  
Rahman

Rangineni  
Reich

Reiling  
Rinaldi

**Robert (USO)\***  
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Rubin  
Russell

Schwartzberg  
Shaffer

**Shiftan\***  
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**Slamon \***  
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Tansino  
Tchekmedyan

Tezcan

Touroutoglou

**Valero\***  
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Waintraub

Waisman  
Walker

Wallmark  
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Yunus

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