

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

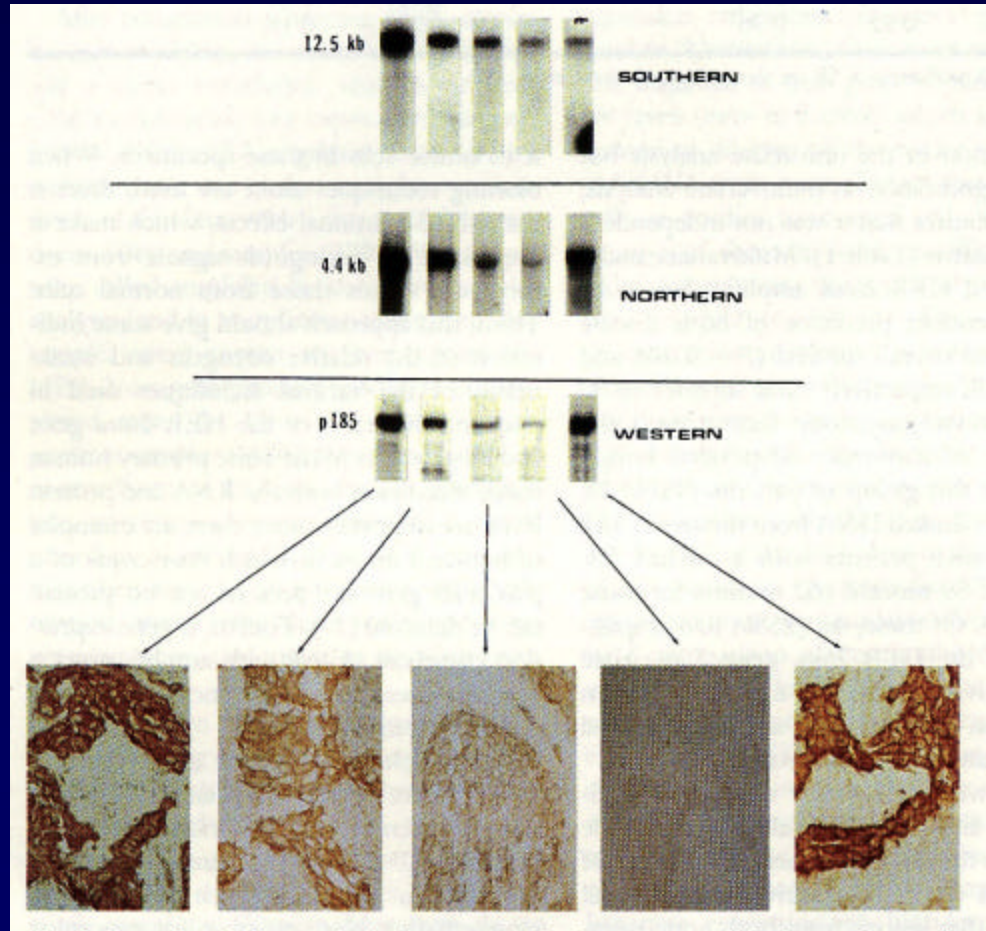
Slamon D, Eiermann W, Robert N, Pienkowski T,
Martin M, Pawlicki M, Chan A, Smylie M, Liu M,
Falkson C, Pinter T, Fornander T, Shiftan T, Valero V,
Von Minckwitz G, Mackey J, Tabah-Fisch I, Buyse M,
Lindsay MA, Riva A, Bee V, Pegram M, Press M,
Crown J, on behalf of the BCIRG 006 Investigators.

Study sponsored by Sanofi-Aventis
Support from Genentech

After the presentation these slides will be
available at:

www.sabcs.org
www.cirg.org

The HER2 Alteration



Southern

Northern

Western

IHC

Global Project Coordinator

Valerie Bee

BCIRG 006

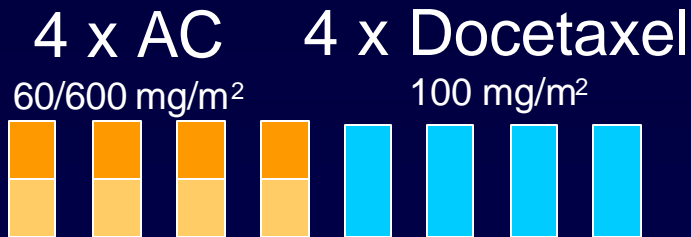
Her 2+
(Central FISH)

N+
or high
risk **N-**

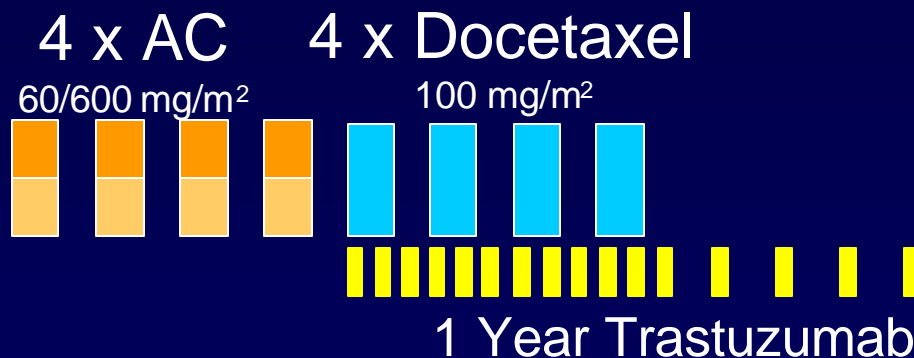
N=3,222

Stratified by Nodes
and Hormonal
Receptor Status

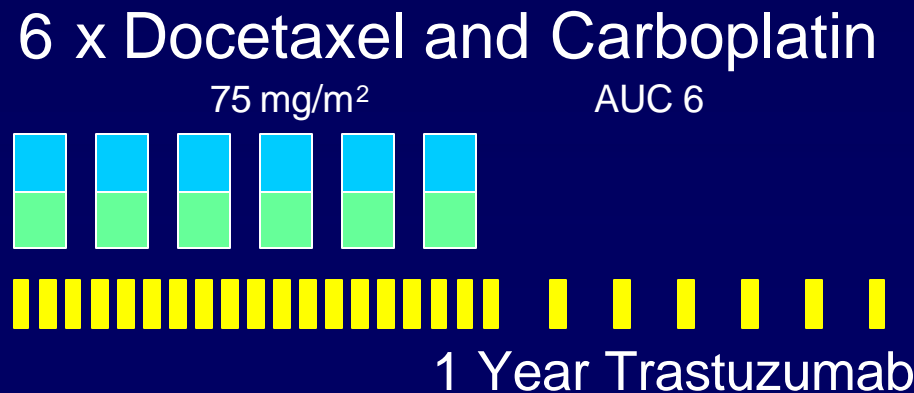
AC→T



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 +	%	%	%
0	29	29	29
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

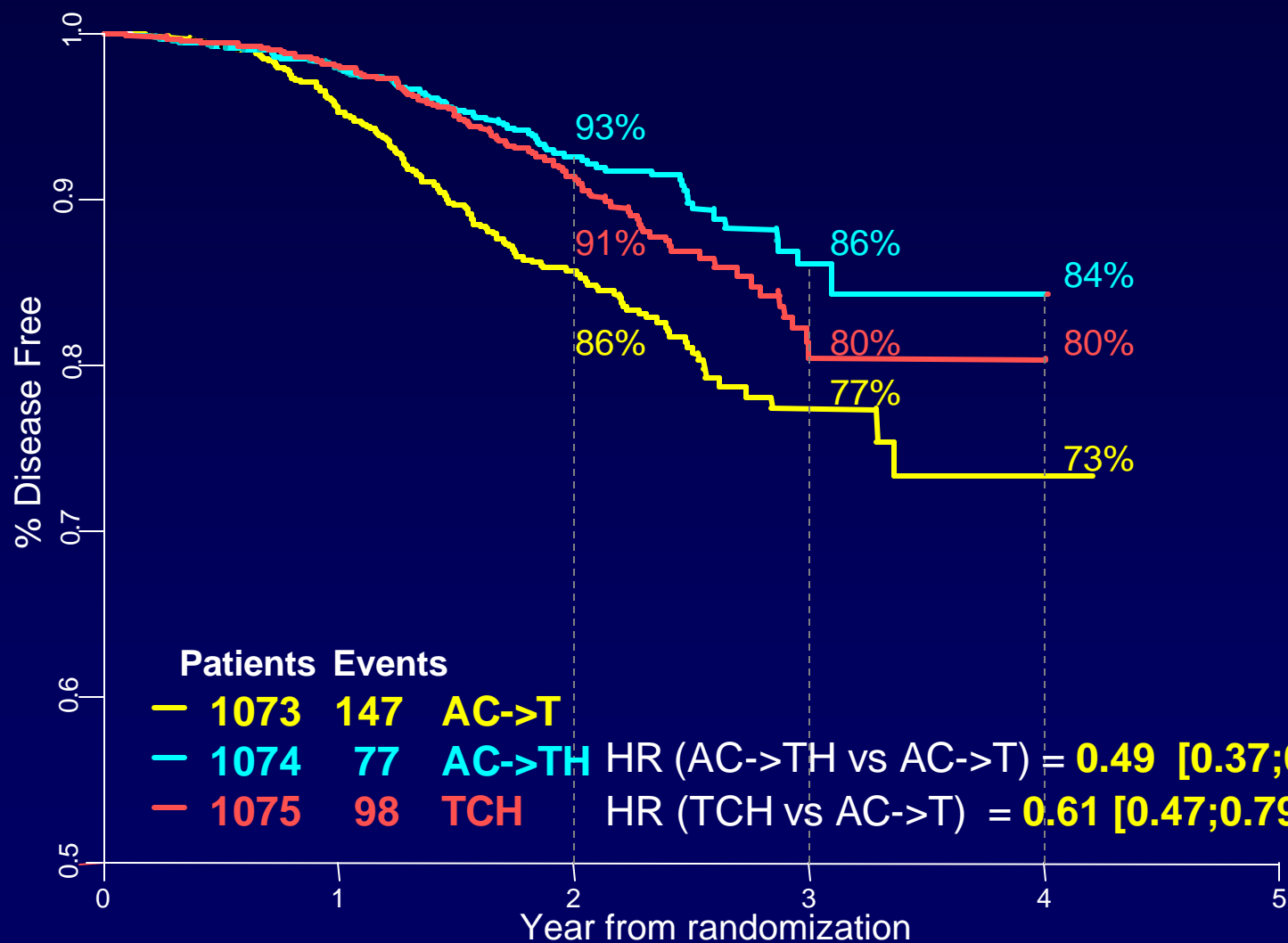
After the trastuzumab efficacy results were announced in April '05, to date:

- ✓ 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)

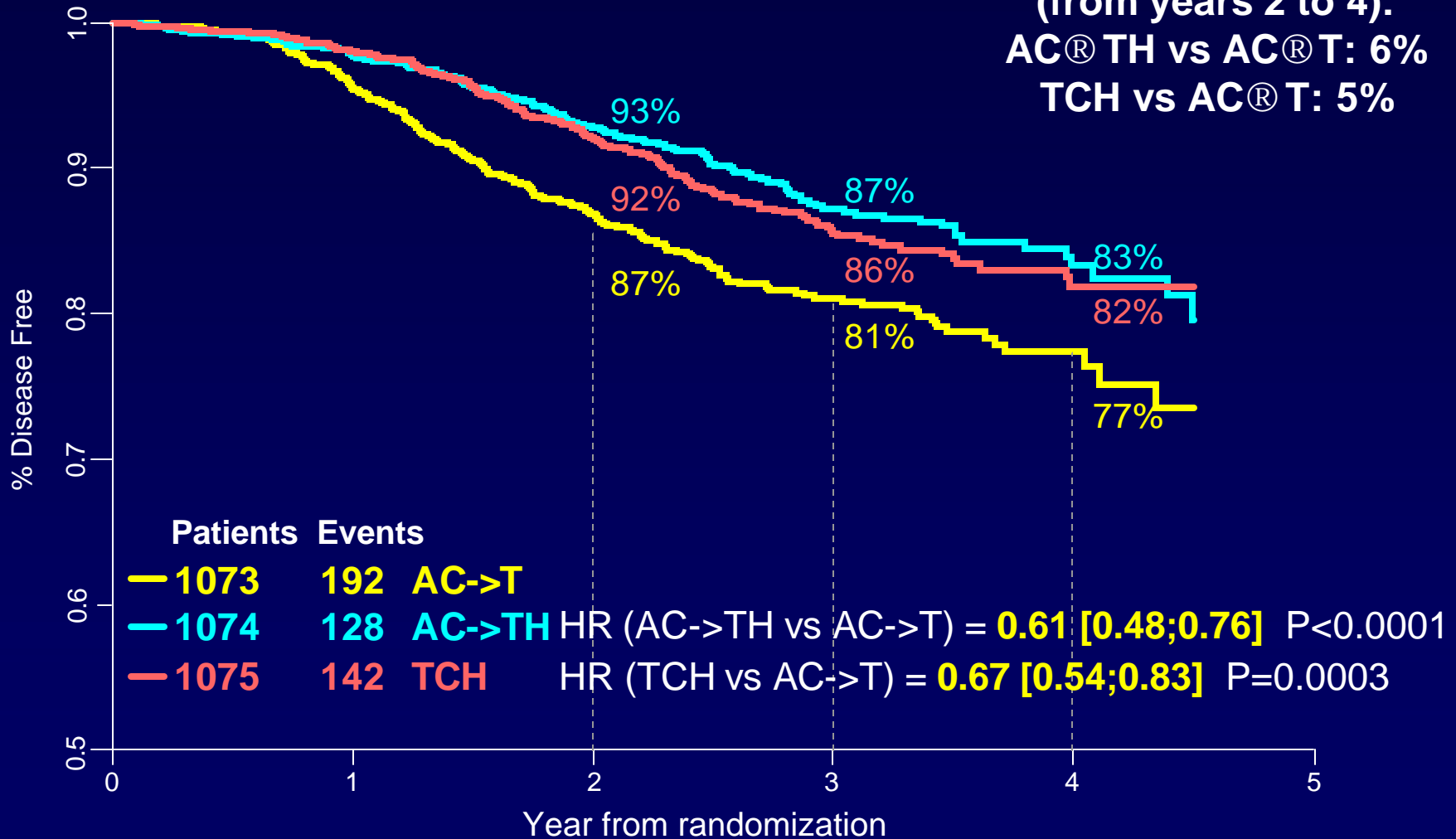
- Median follow-up time = 23 /36 months
- 322 /462 DFS Events
 - ✓ Breast Cancer Relapse
 - ✓ Second Primary Malignancy
 - ✓ Death
- 84 /185 Deaths

Disease Free Survival – 1st interim analysis



Disease Free Survival - 2nd 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
--	-----------------	------------------	----------------

Patients with event	147 / 192	77 / 128	98 / 142
---------------------	------------------	-----------------	-----------------

at 1st interim analysis

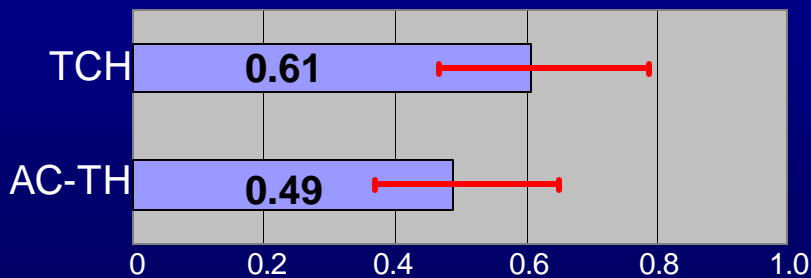
at 2nd interim analysis

p=0.0000005 / **0.000011**

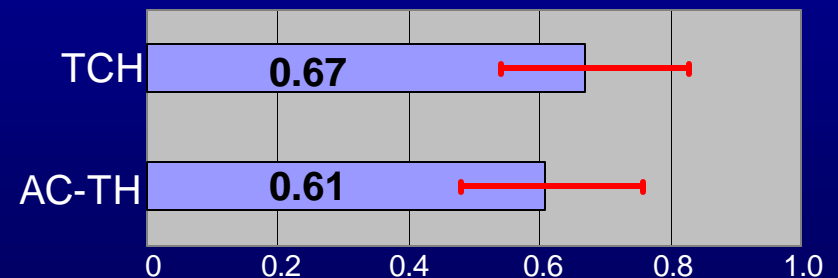
p=0.00015 / **0.00028**

p=0.16 / **0.42**

HR at 1st interim analysis



HR at 2nd interim analysis



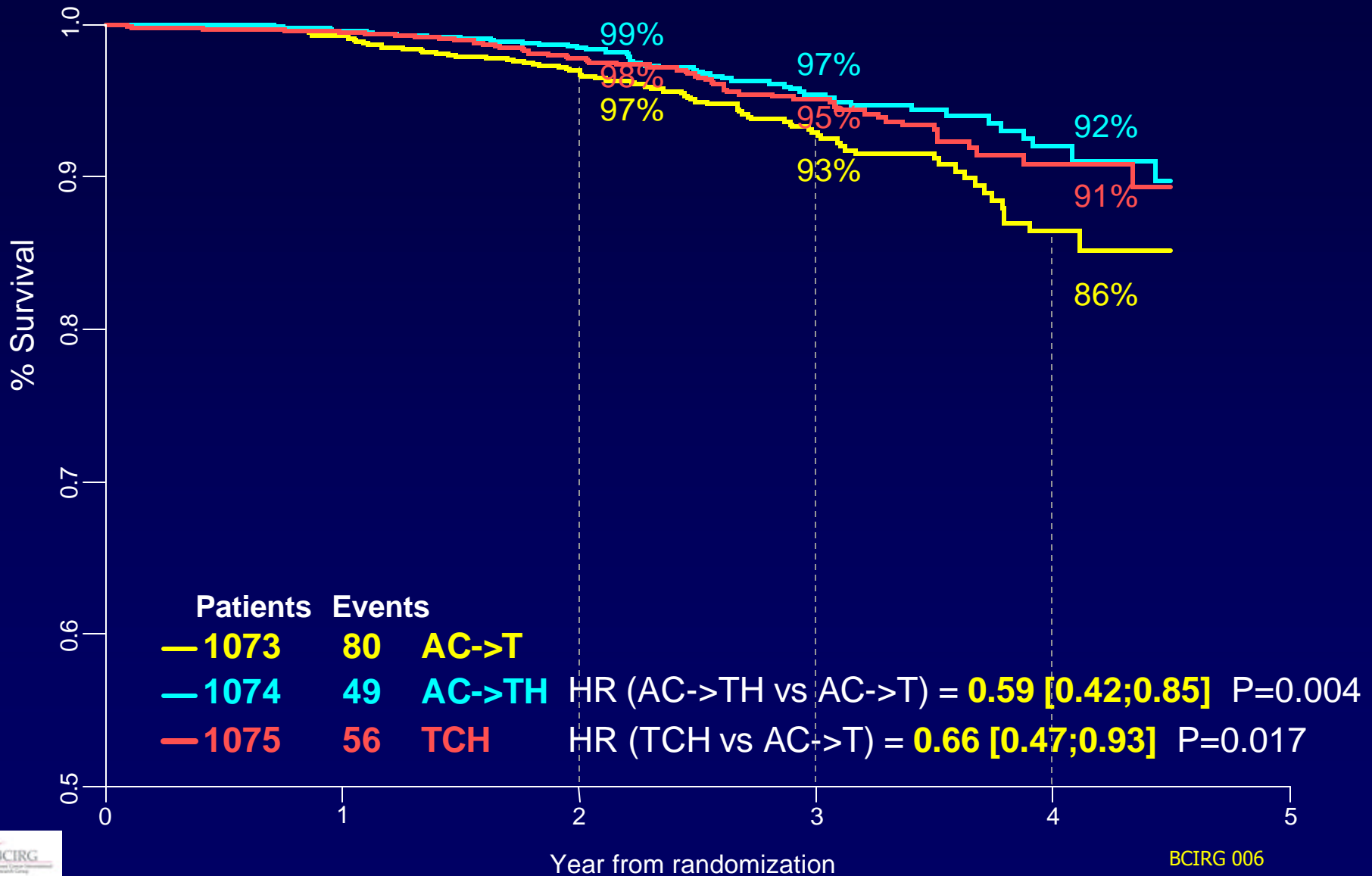
Metastatic events

113 / **143**

52 / **93**

67 / **98**

Overall Survival – 2nd Interim Analysis

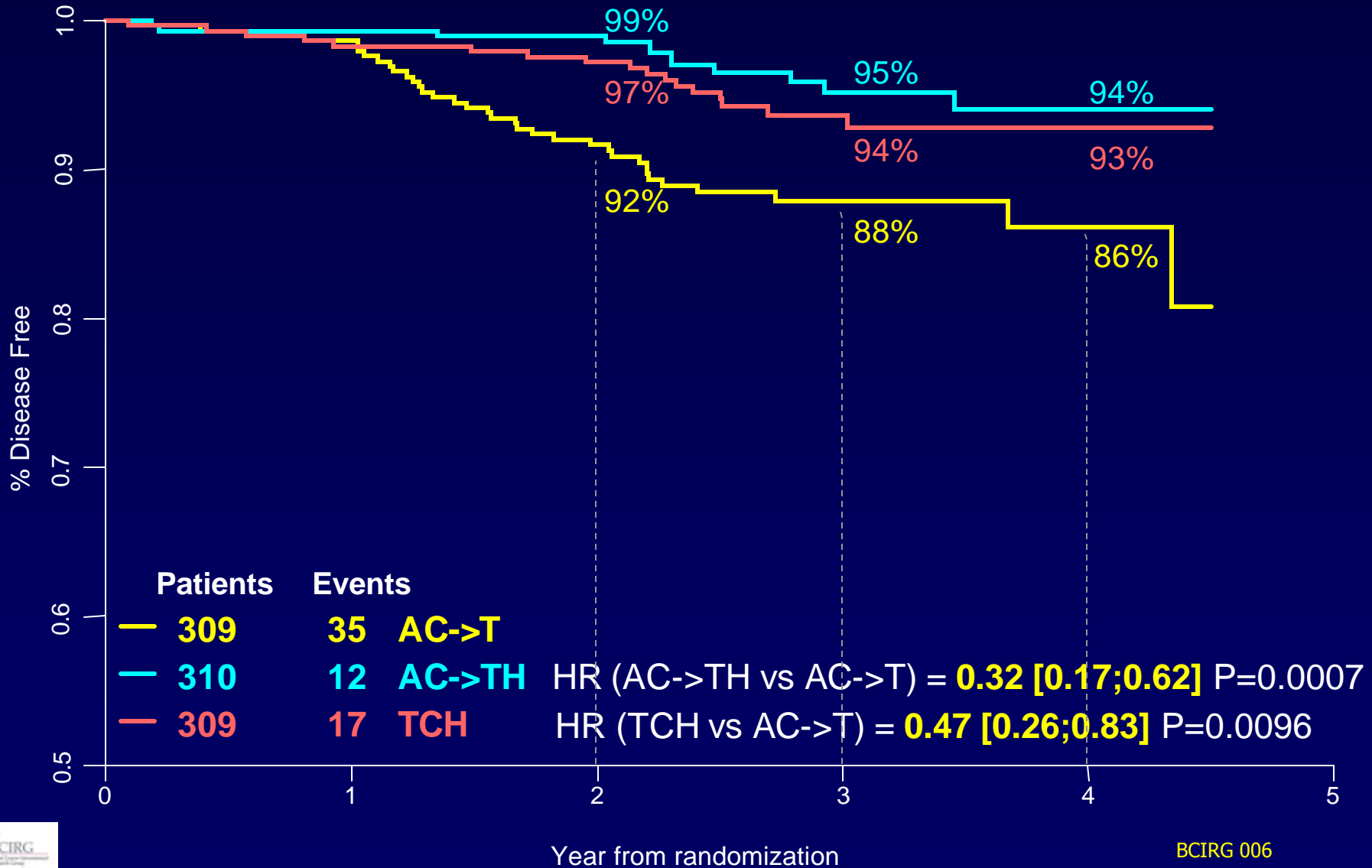


Deaths at Interim Efficacy Analyses

	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 st interim analysis	p=0.004		
at 2 nd interim analysis	p=0.017		p=0.58
Breast Cancer Deaths	33 / 69	19 / 44	21 / 47

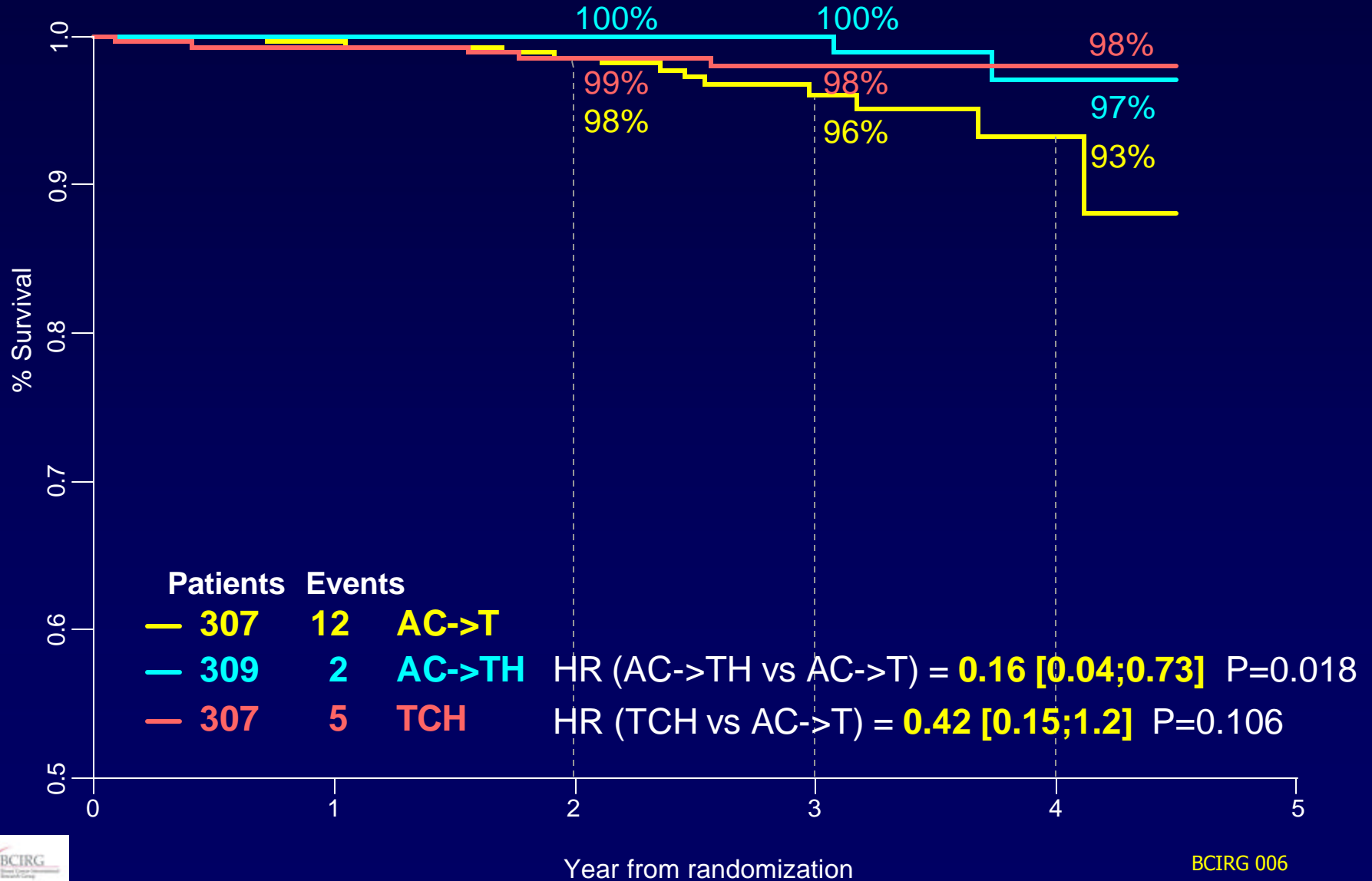
DFS Lymph Node Negative

2nd Interim Analysis



Overall Survival Lymph Node Negative

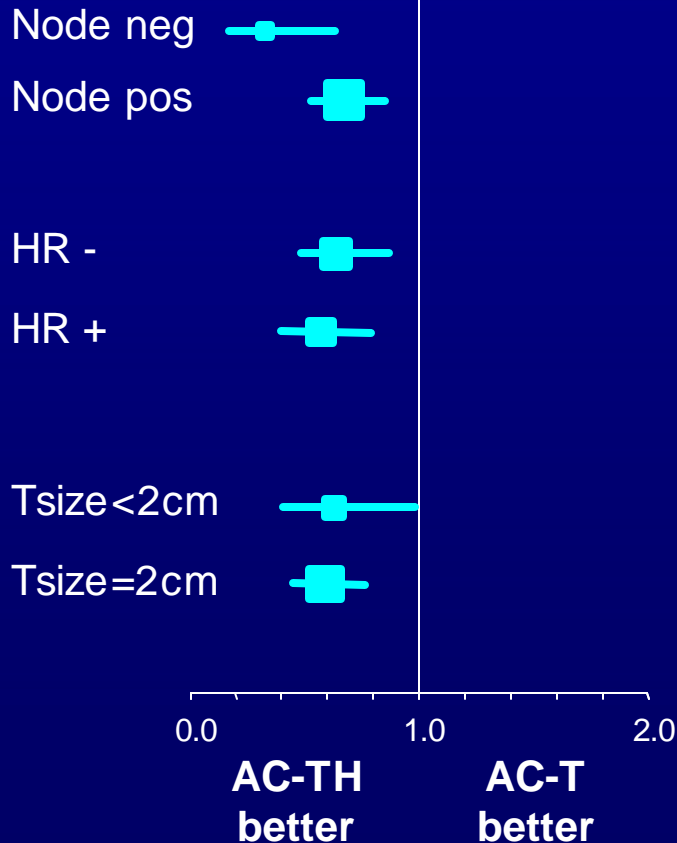
2nd Interim Analysis



DFS Subpopulations

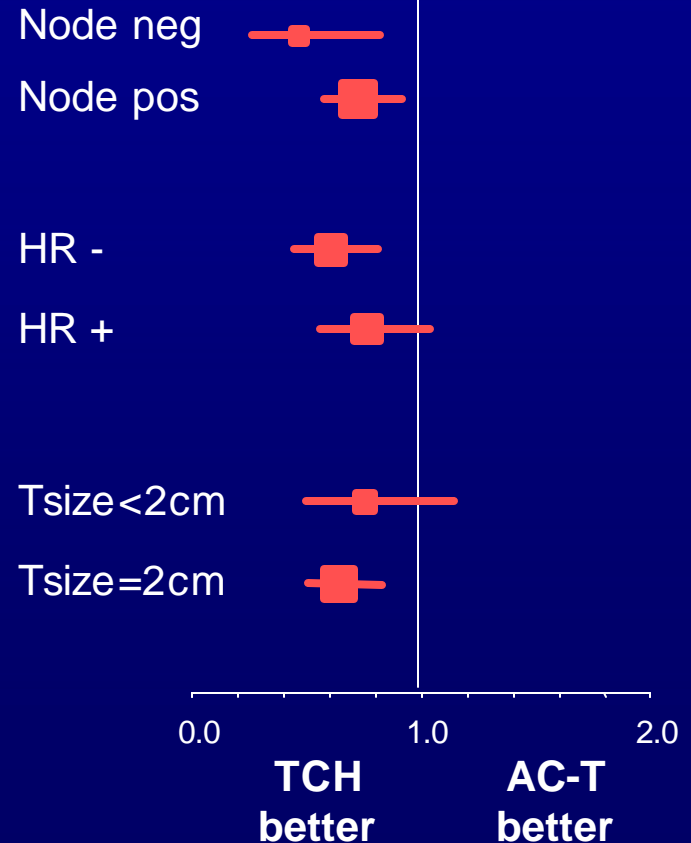
AC-TH vs AC-T

Subgroup



TCH vs AC-T

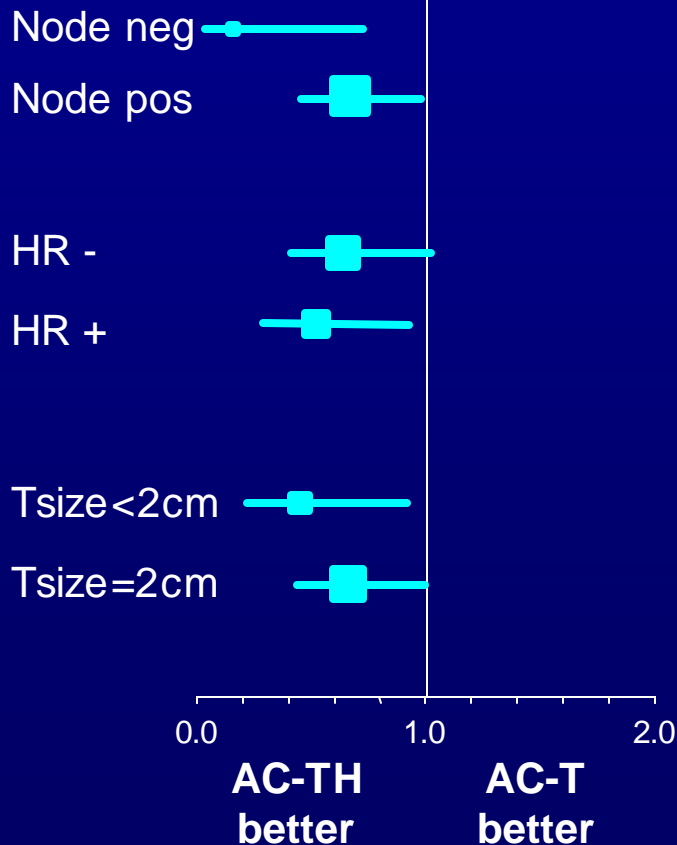
Subgroup



Overall Survival Subpopulations

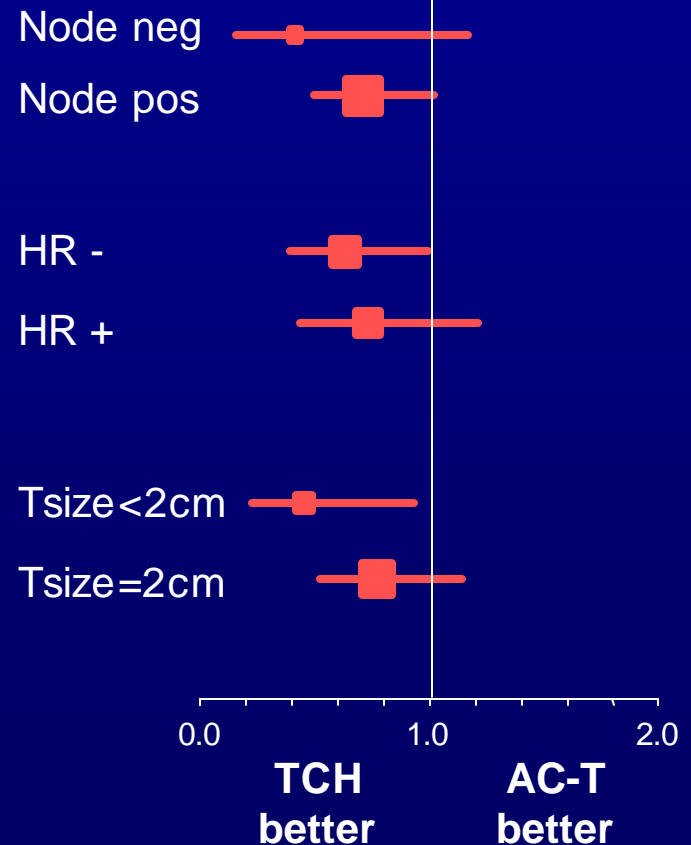
AC-TH vs AC-T

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
Leukemia (%)	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/ 1014	AC-TH n = 1040/ 1042	TCH n = 1029/ 1030
Patients	91 / 102	180 / 189	82 / 89
%	9 / 10	17.3 / 18	8 / 8.6

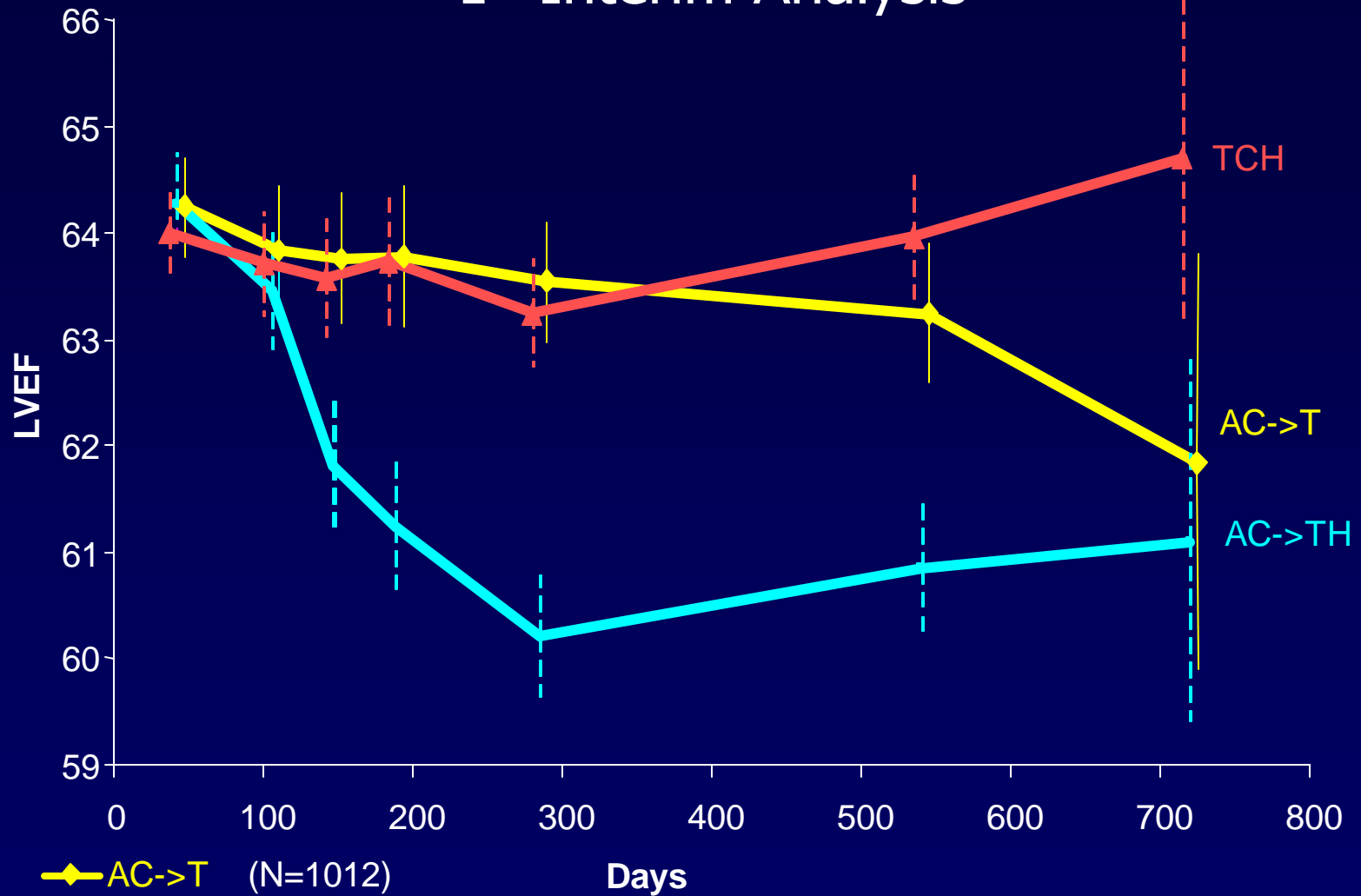
$P = 0.002$ $P < 0.0001$ $P < 0.0001$ $P < 0.0001$
 $P = 0.5$ $P = 0.5$

first interim analysis

second interim analysis

Mean LVEF - All Observations

1st Interim Analysis

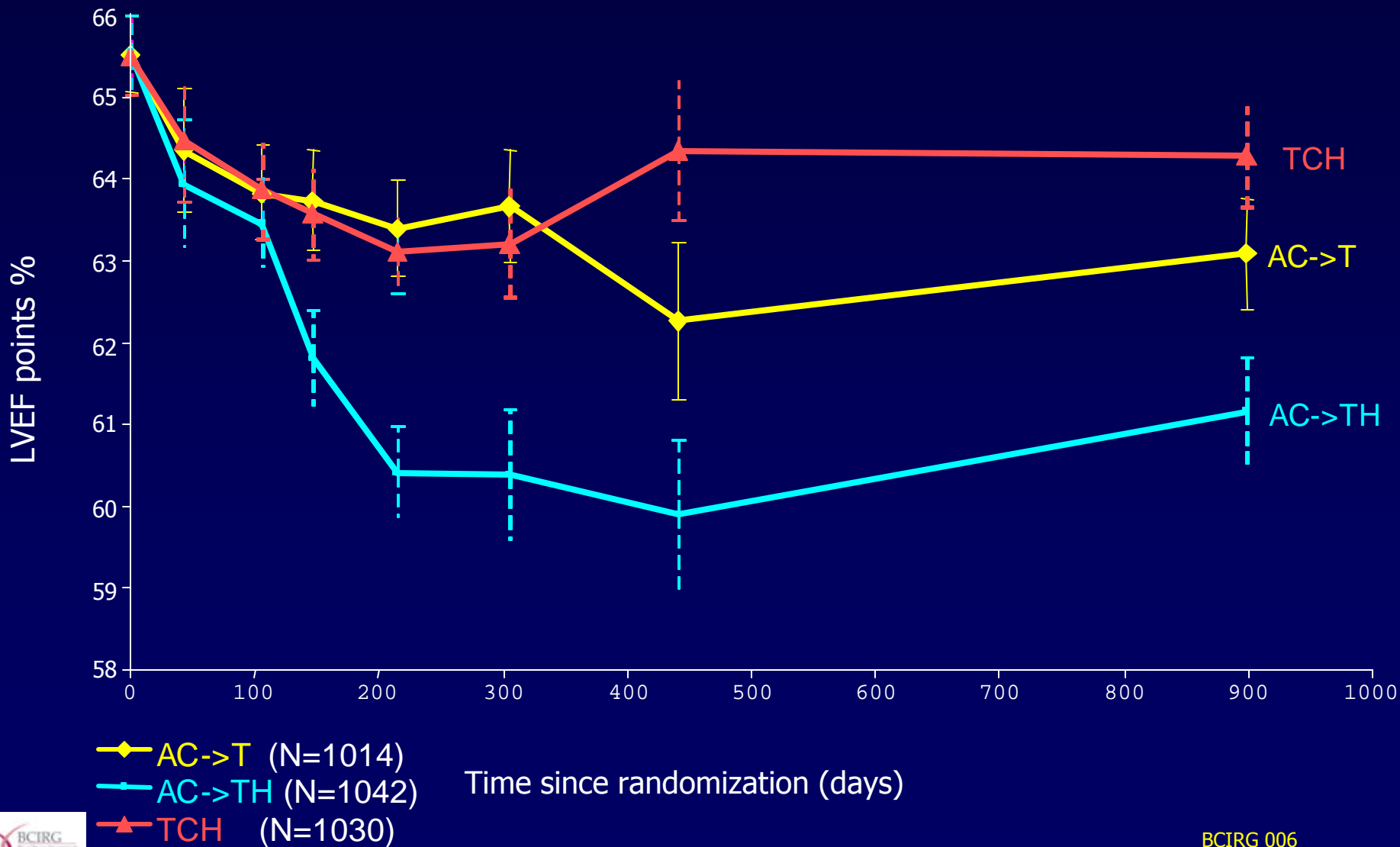


◆ AC->T (N=1012)
■ AC->TH (N=1040)
▲ TCH (N=1029)



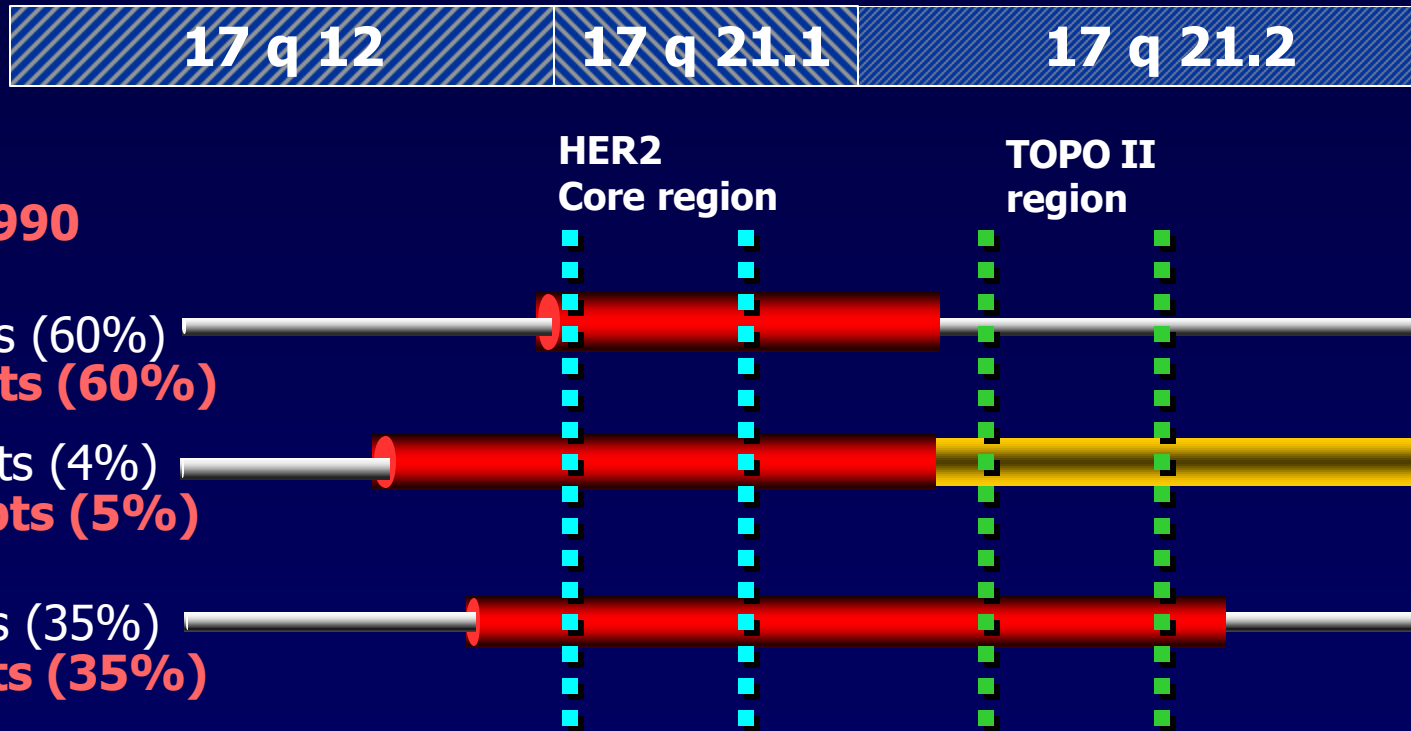
Mean LVEF - All Observations

2nd 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

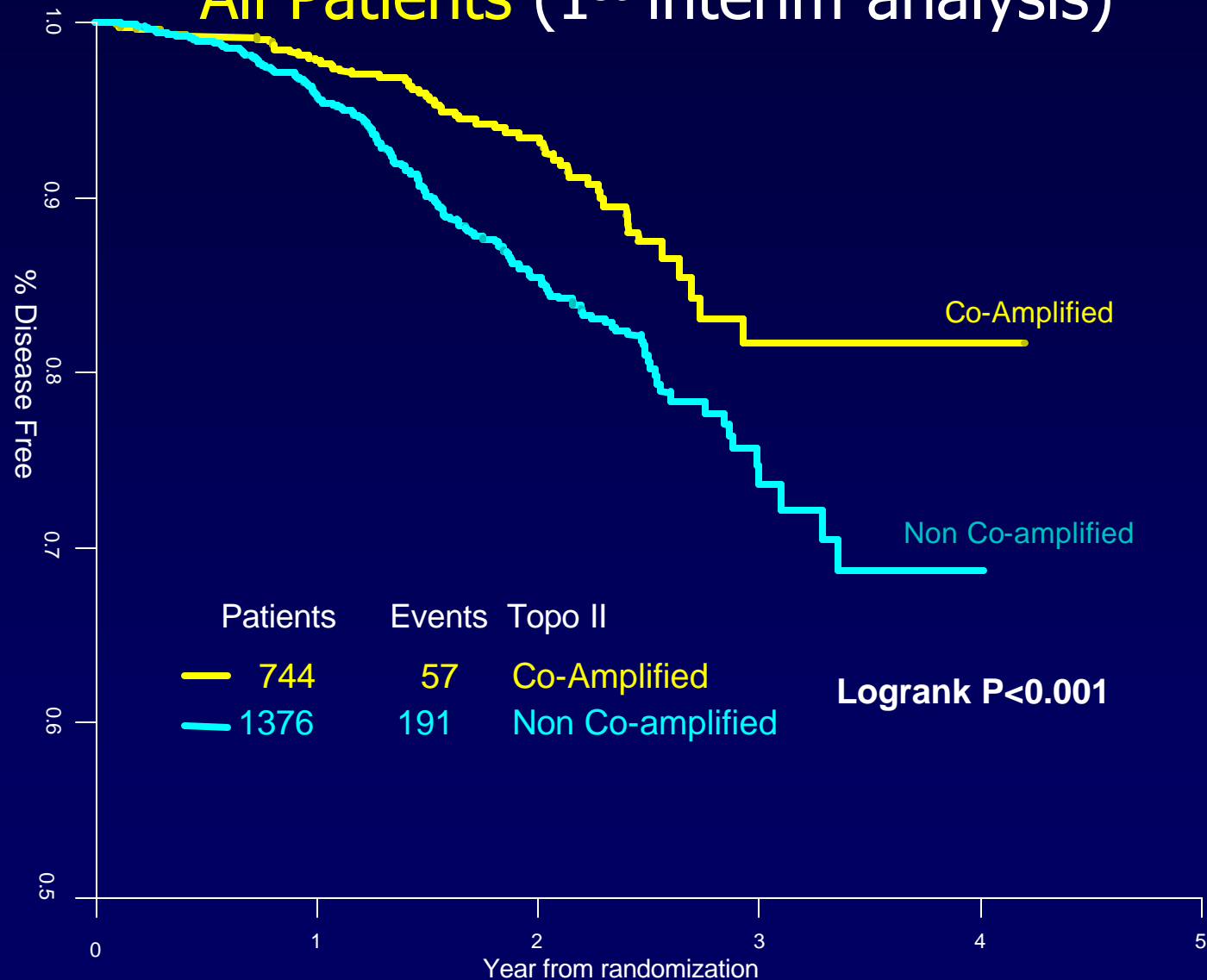


TOPO IIa (not HER2) Amplification as a Predictor of Anthracycline Response in Breast Cancer

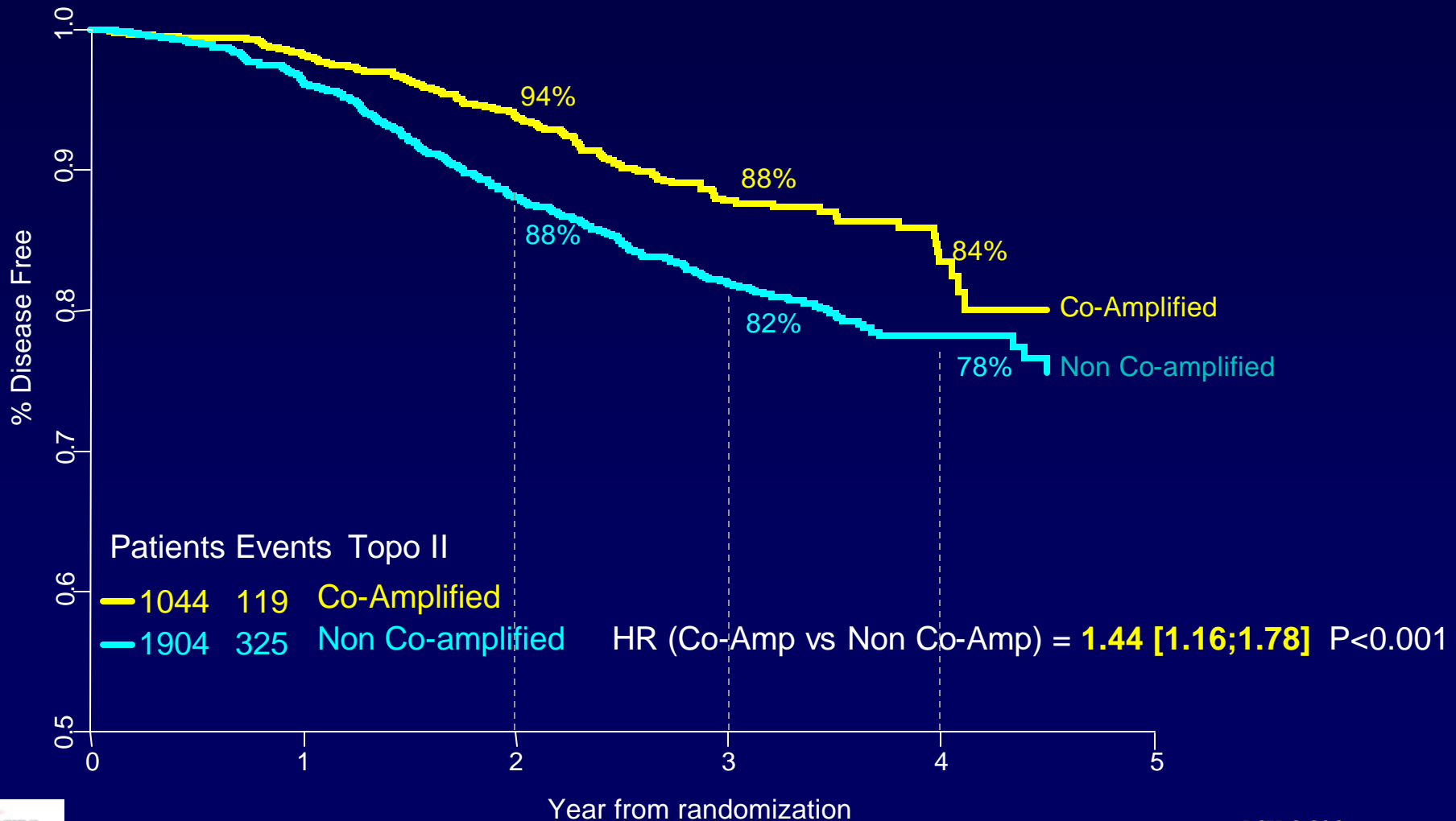
Since 2002, at least 6 studies have been published demonstrating the association between topo II alpha amplification and improved anthracycline response.

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

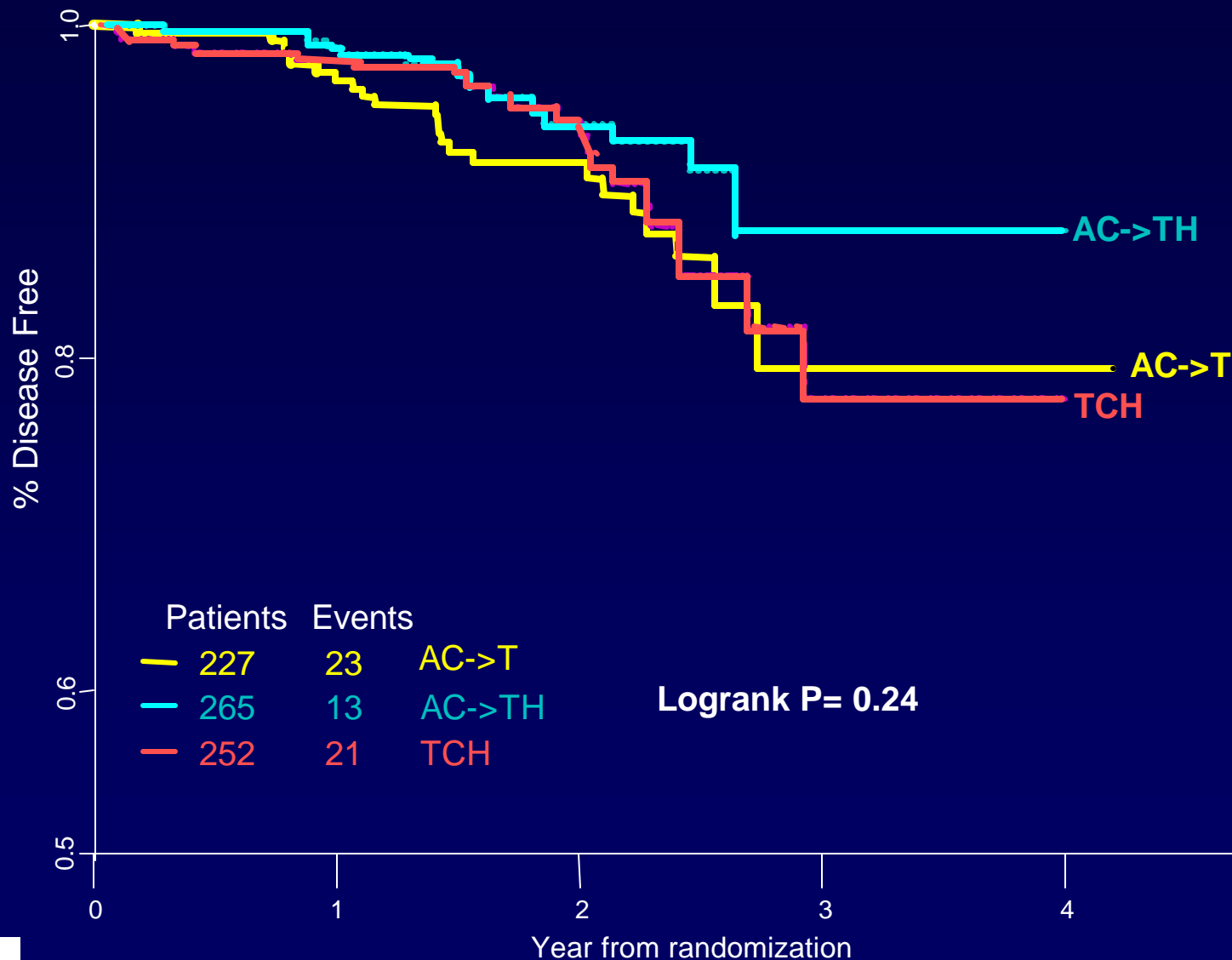
DFS Topo II Co-Amplified vs Non Co-Amplified All Patients (1st interim analysis)



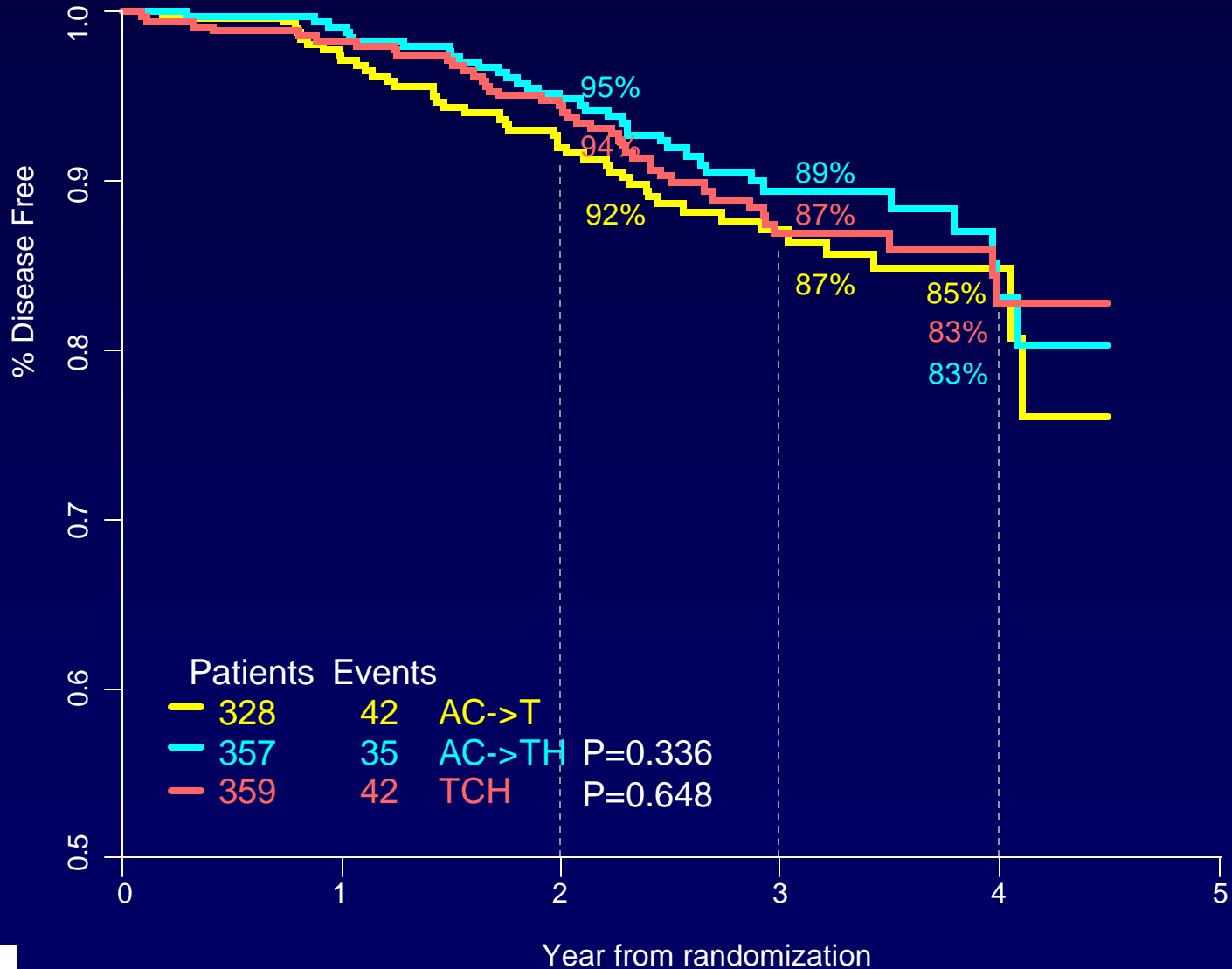
DFS Topo II Co-Amplified vs Non Co-Amplified All Patients (2nd interim analysis)



DFS Co-Amplified Topo II by Arm (1st Interim Analysis)



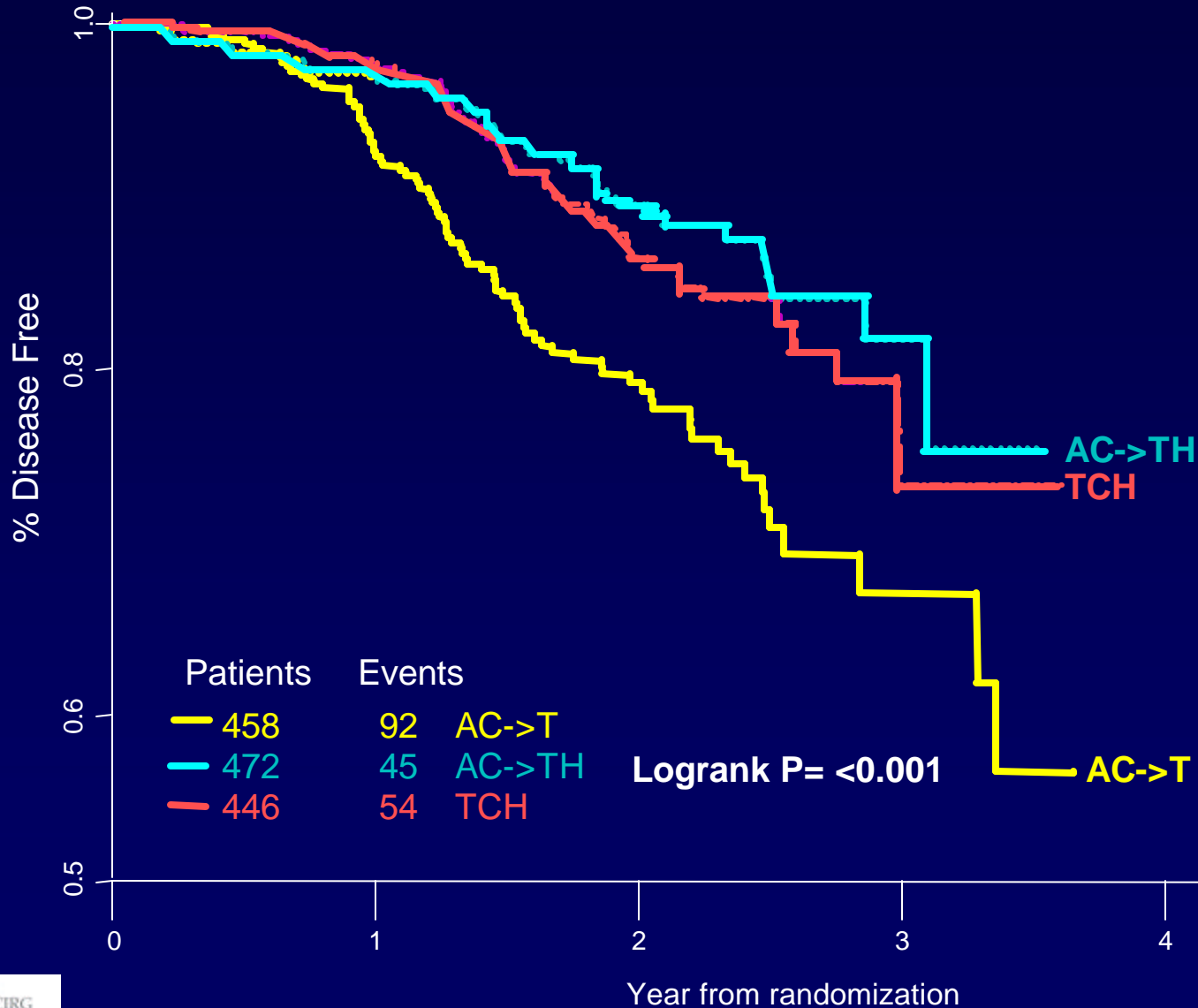
DFS Co-Amplified Topo II by Arm (2nd Interim Analysis)



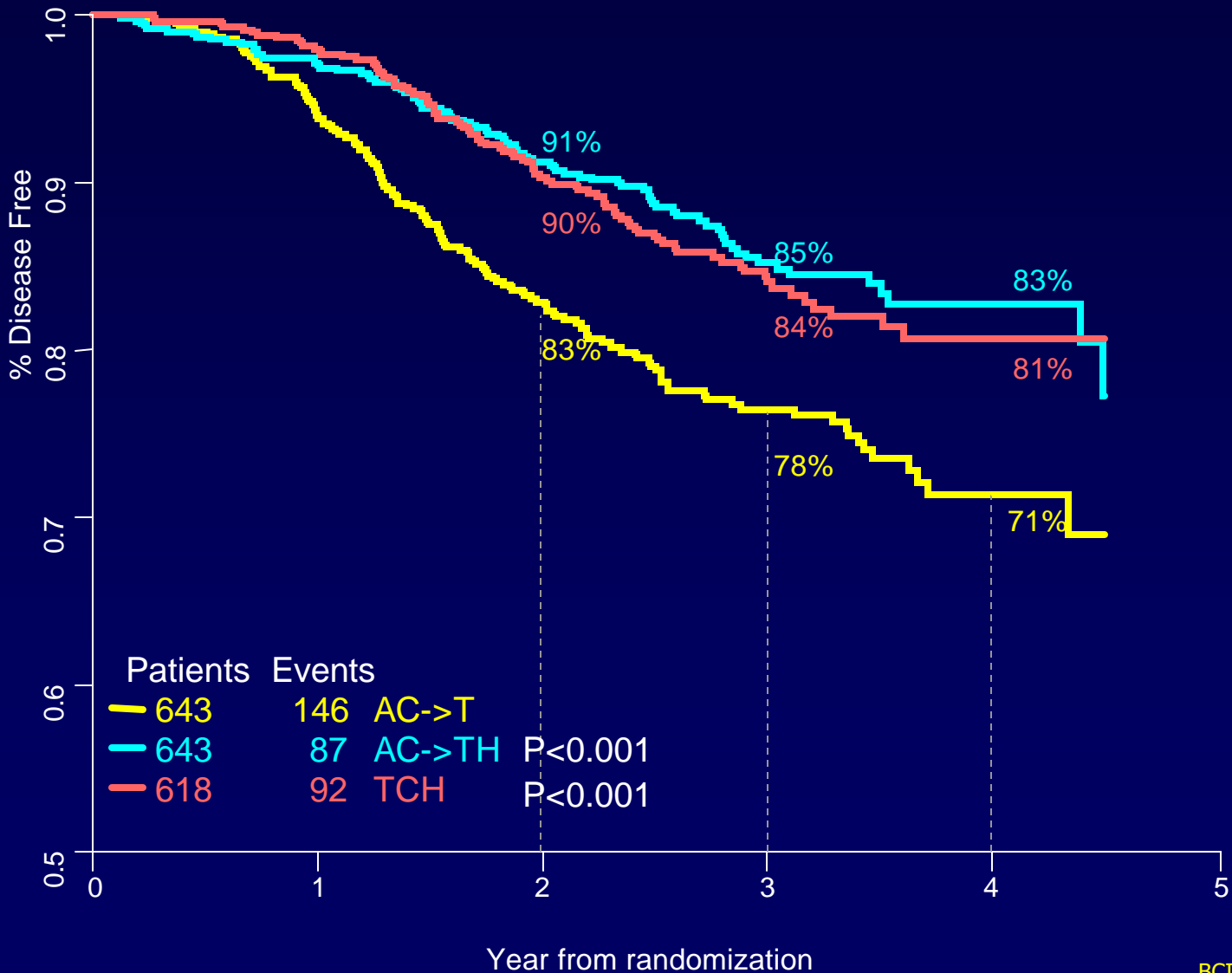
Patients	Events	Arm	P-value
328	42	AC->T	P=0.336
357	35	AC->TH	
359	42	TCH	P=0.648



DFS Non Co-Amplified Topo II by Arm (1st Interim Analysis)



DFS Non Co-Amplified Topo II by Arm (2nd Interim Analysis)



	Patients	Events	
—	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:
V Bee, D Cabaribere, T Kiskartalyi, T Smith,
L Lallaoui, H Taupin, K Afenjar, P Drevot, L Andersen,
H Fung, J Mortimer, A Riva, MA Lindsay

Principal Investigators involved in the study (I)

ARGENTINA

Fein
Giacomi
Martinez
Mickiewicz

AUSTRALIA/NZ

Abdbi
Begbie
Beith
Byard
Chan*

Chirgwin
Clingan
Craft

Dalley

Dewar

Ganju

Green

Grimes

Harvey

Isaacs

Jameson

Kannourakis

Koczwarra

Kotasek

Lewis

Links

Ransom

Richardson

Schwarz

Stewart

Sullivan

Walpole

White

Young

AUSTRIA

Dittrich

Sevelda

BELGIUM

Cocquyt

Demol

Dirix

Verhoeven

Vermorken

BOSNIA

Beslija

BRAZIL

Ferrari

Lago

Schwartzmann

BULGARIA

Beslija

Timcheva

Tzekova

CANADA

Dorreen

Dufresne

Klimo

Latreille

Lopez

Mackey*

Potvin

Provencher

Roy

Sehdev

Smylie*

Wilson

Zibdawi

COLOMBIA

Gomez

Sanchez

Vargas

CROATIA

Grgic

Markulin-Grgic

Mrsic-Krmpotic

Vrdoljak

CYPRUS

Adamou

CZECH REPUBLIC

Petruzelka

Vyzula

EGYPT

Azim

El Khodary

ESTONIA

Padrik

Valvere

FRANCE

Achille

Bonneterre

Bressac

Cals

Carola

Colin

Dalivoust

Dutel

Gligorov

Guastalla

Jaubert

Khayat

Levy

Priou

Tournigand

Valenza

Vannetzel

GERMANY

Breitbach

Brunnert

Carstensen

Christensen

Clemens

Conrad

Dubois

Eiermann*

Feltz-Sussenbach

Hempel

Henschen

Hilfrich

Jonat

Kettner

Klare

Kretzschmar

Kullmer

Lichtenegger

Lürmann

Meerpohl

Meinerz

Prell

Scharl

Schmidt

Schweppe

Souchon

Tessen

Von Minkwitz

Weist

Winzer

Wolf

Zedelius

GREECE

Georgoulas

HONG KONG

Chow

HUNGARY

Baki

Dank

Pinter*

Gupta

Julka

Ranade

Szanto

INDIA

Advani

Doval

IRELAND

Crown*

Grogan

Keane

Kennedy*

McCaffrey

ISRAEL

Barak

Ben Baruch

Geffen

Goldberg

Kaufman

Rizel

Steiner

ITALY

Barone

Bonetti

Gamucci

Gasparini

Geminiani

Iaffaioli

Marangolo

Nardi

Pollera

Ravaioli

LEBANON

Abi Gerges

Chahine

Ghosn

Saghir

* *Highest recruiters*

BCIRG 006

Slamon D., SABCS 2006

Principal Investigators involved in the study (II)

POLAND

Borowska
Karnicka
Pawlicki *
Pienkowski *
Wojtukiewicz
Zaluski

ROMANIA

Badulescu
Ghilezan
Roman

RUSSIA

Garin
Gorbunova
Semiglazov

SLOVAKIA

Koza
Spanik

SLOVENIA

Cufer
Takac

SOUTH AFRICA

Moodley
Pienarr
Rapoport
Slabber

SOUTH KOREA

Bang
Im
Kim
Ro

SPAIN

Adrover
Alba Conejo
Alonso Romero
Alvarez
Ales Martinez
Aranda
Arcusa

Baena Canada
Calvo Martinez
Crespo
Dominguez
Garcia Estevez
Florian Gerico
Jara
Margeli

Martin*

Martin Lorente
Mel Lorenzo
Oltra Ferrando
Pelegri

SWEDEN

Fornander*

SWITZERLAND

Aapro

TAIWAN

Chao

Liu *

TUNISIA

Mezlini
Frikha

TURKEY

Aydiner
Baltali

UK

Chan
sherwin
Wardley

URUGUAY

Rodriguez
Krygier

USA

Abukabr
Adler
Appelbaum
Ansari
Arena
Beall
Berdeaux

Beattie
Bianco

Boros
Brufsky

Burris
Carroll

Chakrabarti
Chitneni

Chowhan
Chuu

Cobb
Dreisbach

Falkson*

Fesen

Goodman
Greenwald

Grosbach
Hajdenberg

Houston
Jhangiani

Jones
Justice

Jutori
Kalman

Kennedy
Kerr

Kincaid
Koneky

Laufman
Lemon

Lewis
Limentani

Link

Lower
Mac Andrew

Malamud
Mc Croskey

McKeen
Mena

Mills
Modiano

Moore
Moroose

Moss

Nair

Neel
Nicholls

Olopade
Orlowski

Osborn
Page

Patel
Patton

Petruska
Philip

Polikoff
Polikoff (network)

Posada
Rahman

Rangineni
Reich

Reiling
Rinaldi

Robert (USO)*
Rodriguez

Rubin
Russell

Schwartzberg
Shaffer

Shiftan*
Silvermann

Slamon *
Sparano

Sylvester
Tang

Tansino
Tchekmedyan

Tezcan

Touroutoglou

Valero*
Vaughn

Vogel
Waintraub

Waisman
Walker

Wallmark
Yost

Young
Yunus

VENEZUELA

De Joghna
Vera