Faculty Disclosures

BCIRG 006 Phase III Trial Comparing AC→T with AC→TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients: Third Planned Efficacy Analysis

- Dr. Buyse has no relevant financial relationships to disclose.
- Dr. Chan has no relevant financial relationships to disclose.
- Dr. Crown has disclosed that he is the recipient of research grants from sanofi-aventis, GSK and Roche. He has also disclosed that he is on the speaker's bureau for sanofi-aventis, GSK, BMS and Roche.
- Dr. Eiermann has disclosed that he is on the speaker's bureau for Novartis, Roche, AZ and Sanofi-Aventis. He has also disclosed that he is a consultant for AZ and Sanofi.
- Dr. Falkson has no relevant financial relationships to disclose.
- Dr. Fornander has no relevant financial relationships to disclose.
- Dr. Kiskartalyi has no relevant financial relationships to disclose.
- Dr. Landreau has no relevant financial relationships to disclose.
- Dr. Liu has no relevant financial relationships to disclose.
- Dr. Mackey has disclosed that he is on the speaker's bureau for Amgen and Roche.
- Dr. Martin has disclosed that he is on the speaker's bureau for BMS, Sanofi-Aventis, Roche, Pharmamar, Pfizer and Novartis. He has also disclosed that he is a consultant for Sanofi, Lilly, Glaxo and Pfizer.

Faculty Disclosures

BCIRG 006 Phase III Trial Comparing AC→T with AC→TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients: Third Planned Efficacy Analysis

- Dr. Olsen has disclosed that he is an employee of sanofi-aventis.
- Dr. on Behalf of BCIRG006 Investigators has no relevant financial relationships to disclose.
- Dr. Pienkowski has disclosed that he is the recipient of a research grant from Roche. He has also disclosed that he is on the speaker's bureau for Roche and Sanofi. He has also disclosed that he is a consultant for Roche.
- Dr. Pinter has no relevant financial relationships to disclose.
- Dr. Press has no relevant financial relationships to disclose.
- Dr. Robert has no relevant financial relationships to disclose.
- Dr. Rolski has no relevant financial relationships to disclose.
- Dr. Shiftan has no relevant financial relationships to disclose.
- Dr. Slamon has disclosed that he is the recipient of a research grant from Amgen. He has also disclosed that he is on the speaker's bureau for Genentech and Sanofi-Aventis. He has also disclosed that he is a consultant for Pfizer.
- Dr. Valero has no relevant financial relationships to disclose.
- Dr. Wilson has no relevant financial relationships to disclose.

BCIRG 006
Phase III Trial Comparing AC→T with AC→TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients:

Third Planned Efficacy Analysis

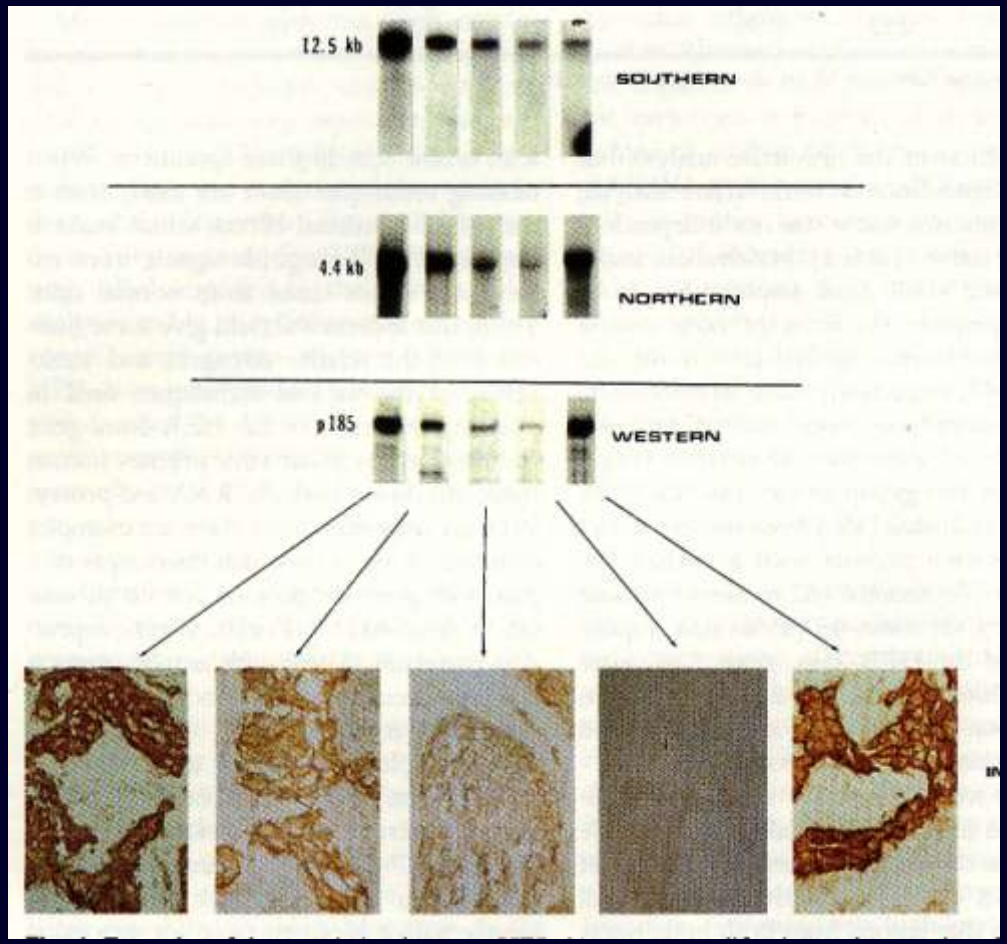
Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Rolski J, Chan A, Mackey J, Liu M, , Pinter T, Valero V, Falkson C, Fornander T, Shiftan T, Olsen S, Buyse M, Kiskartalyi T, Landreau V, Wilson V, Press M, Crown J, on behalf of the BCIRG 006 Investigators.

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

Slamon et al. *Science* 1987,1989

BCIRG 006 Trial Design

Her 2+
(Central FISH)

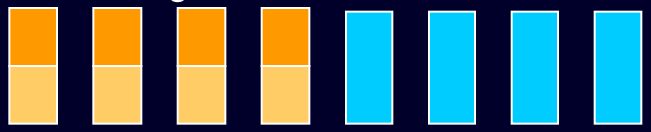
N+
or high
risk N-

N=3,222

Stratified by Nodes and Hormonal Receptor Status

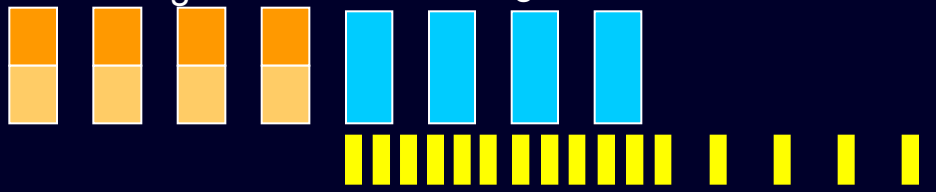
AC→T

4 x AC 60/600 mg/m²
4 x Docetaxel 100 mg/m²



AC→TH

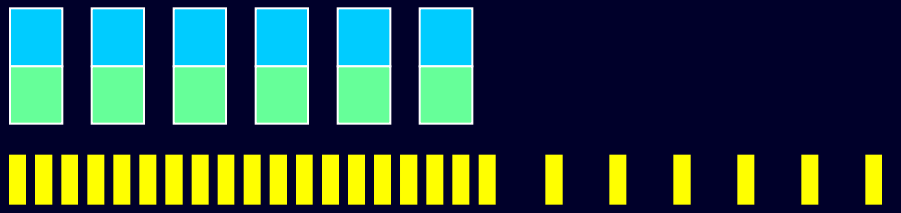
4 x AC 60/600 mg/m²
4 x Docetaxel 100 mg/m²



1 Year Trastuzumab

TCH

6 x Docetaxel and Carboplatin
75 mg/m² AUC 6



1 Year Trastuzumab

Global Project Coordinator

Valerie Bee

BCIRG 006 Endpoints

Primary

- Disease-free Survival

Secondary

- Overall Survival
- Toxicity
- Pathologic & Molecular Markers

BCIRG 006 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	68	67	69
Hormonotherapy	51	51	51

Enrollment: April 2001 to March 2004

BCIRG 006 Tumor Characteristics

	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

BCIRG 006 Crossover

After the trastuzumab efficacy results were announced in April 2005, to date:

- 23 patients (2.1%) of 1,073 randomized to the control arm (AC→T) crossed-over to receive trastuzumab
- leaving 97.9 % of the control arm enrollment intact for subsequent DFS, OS and safety comparisons

Efficacy

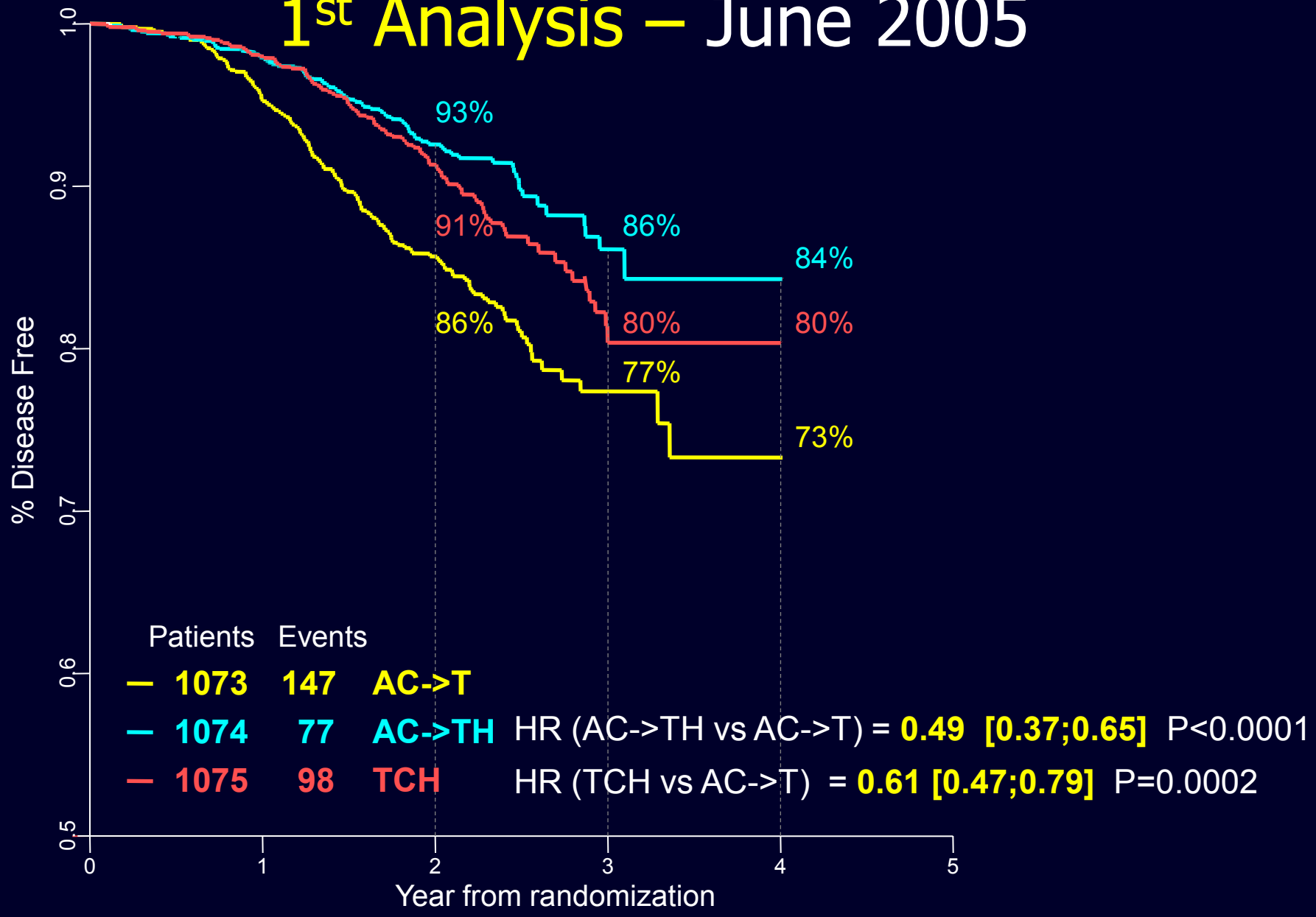
BCIRG 006 DFS Events

First/Second/**Third** Planned Efficacy Analyses

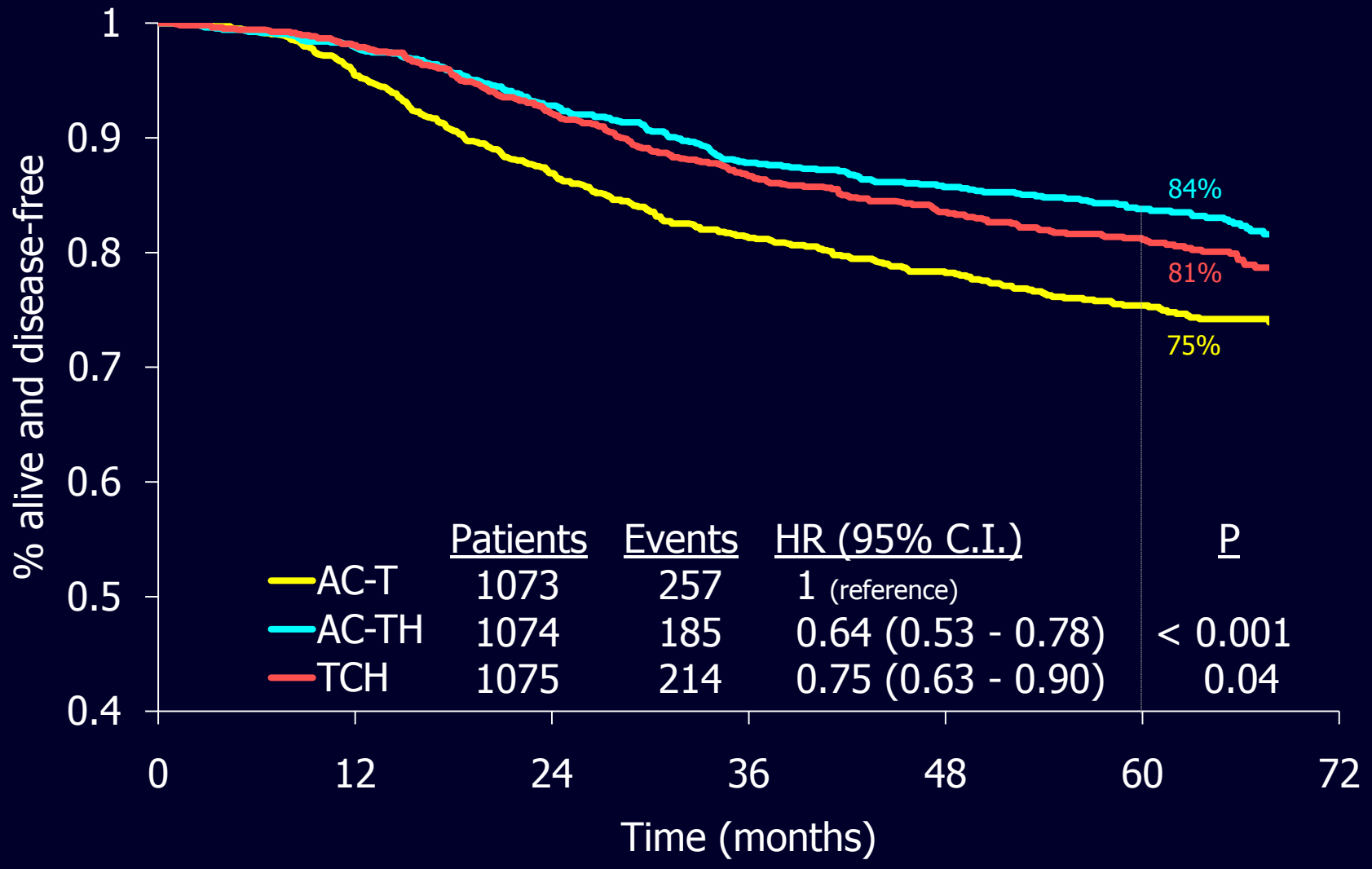
(cutoff dates 30Jun2005 / 01Nov2006 / **16Oct2009**)

- Median follow-up time = 23/36/**65** mths
- 322/462/**656** DFS Events
  (42% additional events)
  - Breast Cancer Relapse
  - Second Primary Malignancy
  - Death
- 84/185/**348** Deaths
  (88% additional deaths)

Initial Disease Free Survival from 1st Analysis – June 2005



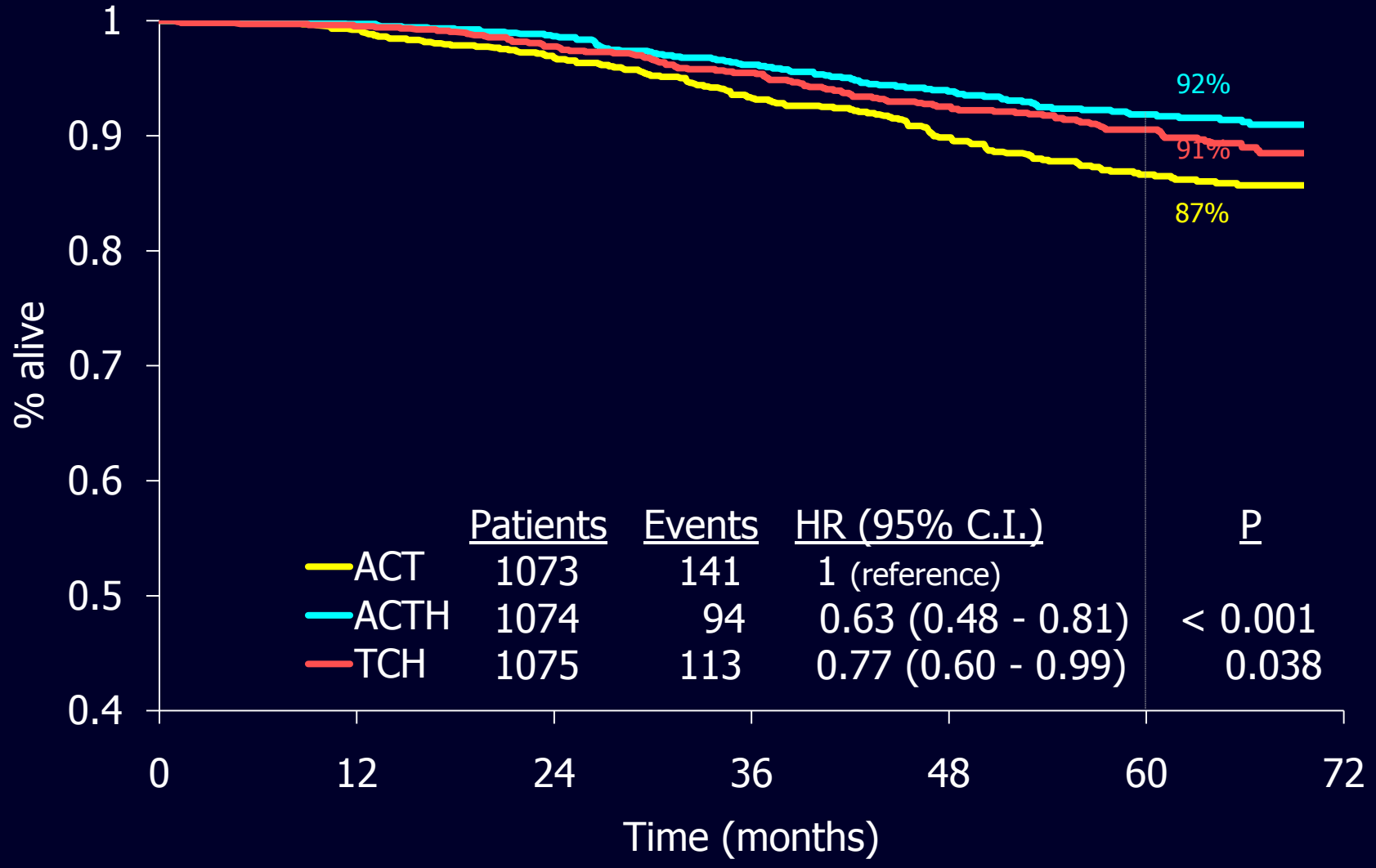
Current BCIRG 006
Disease Free Survival – 3rd Planned Analysis



BCIRG 006 Events by Arm

	AC→T n=1,073	AC→TH n=1,074	TCH n=1,075
Total number of DFS events	147/192/**257**	77/128/**185**	98/142/**214**
at 1st planned analysis		P **<0.001**	
at 2nd analysis			
at 3rd analysis		P=**0.002**	P=**0.21**
Metastatic events	113/143/**188**	52/93/**124**	67/98/**144**

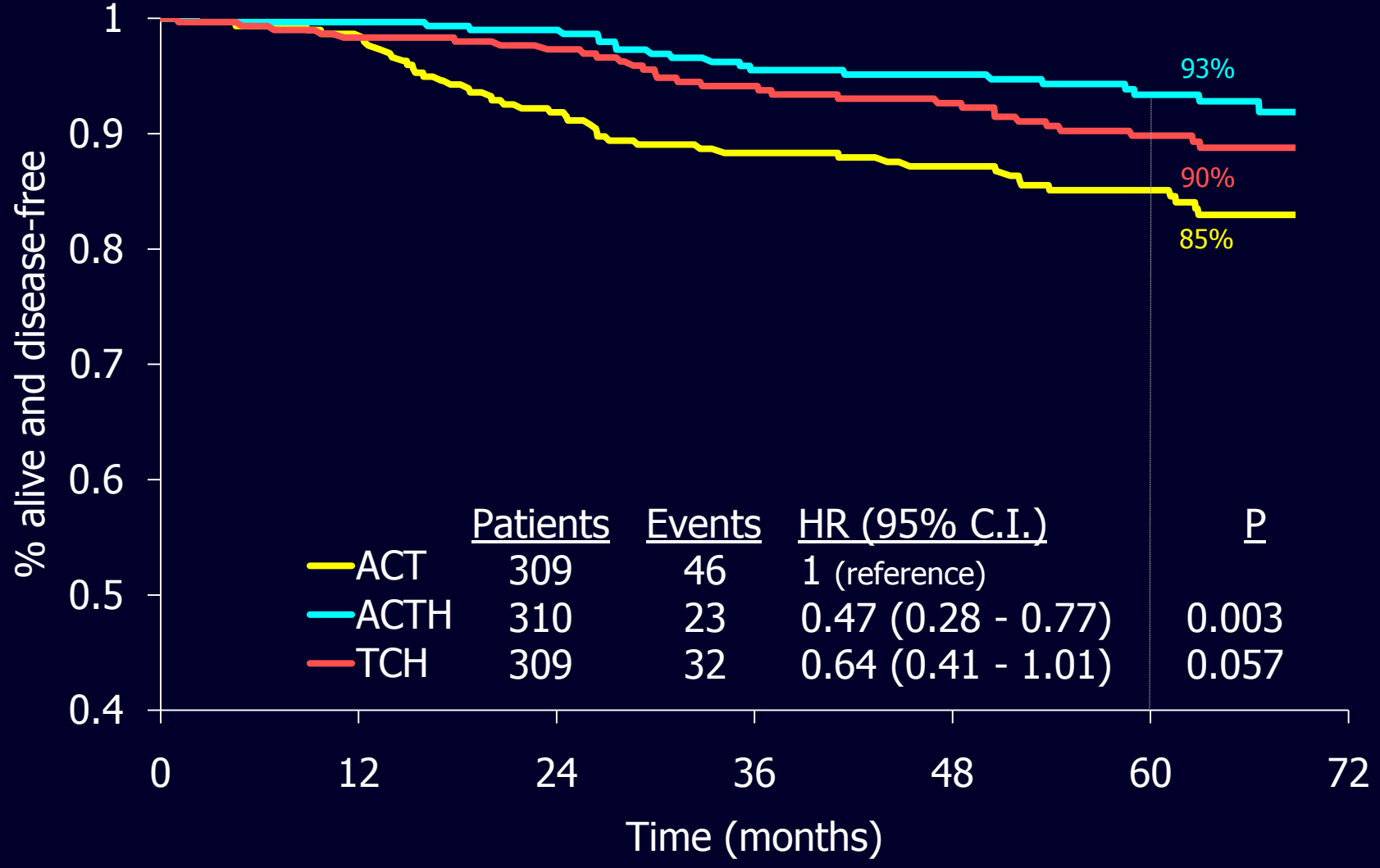
BCIRG 006
Overall Survival – 3rd Planned Analysis



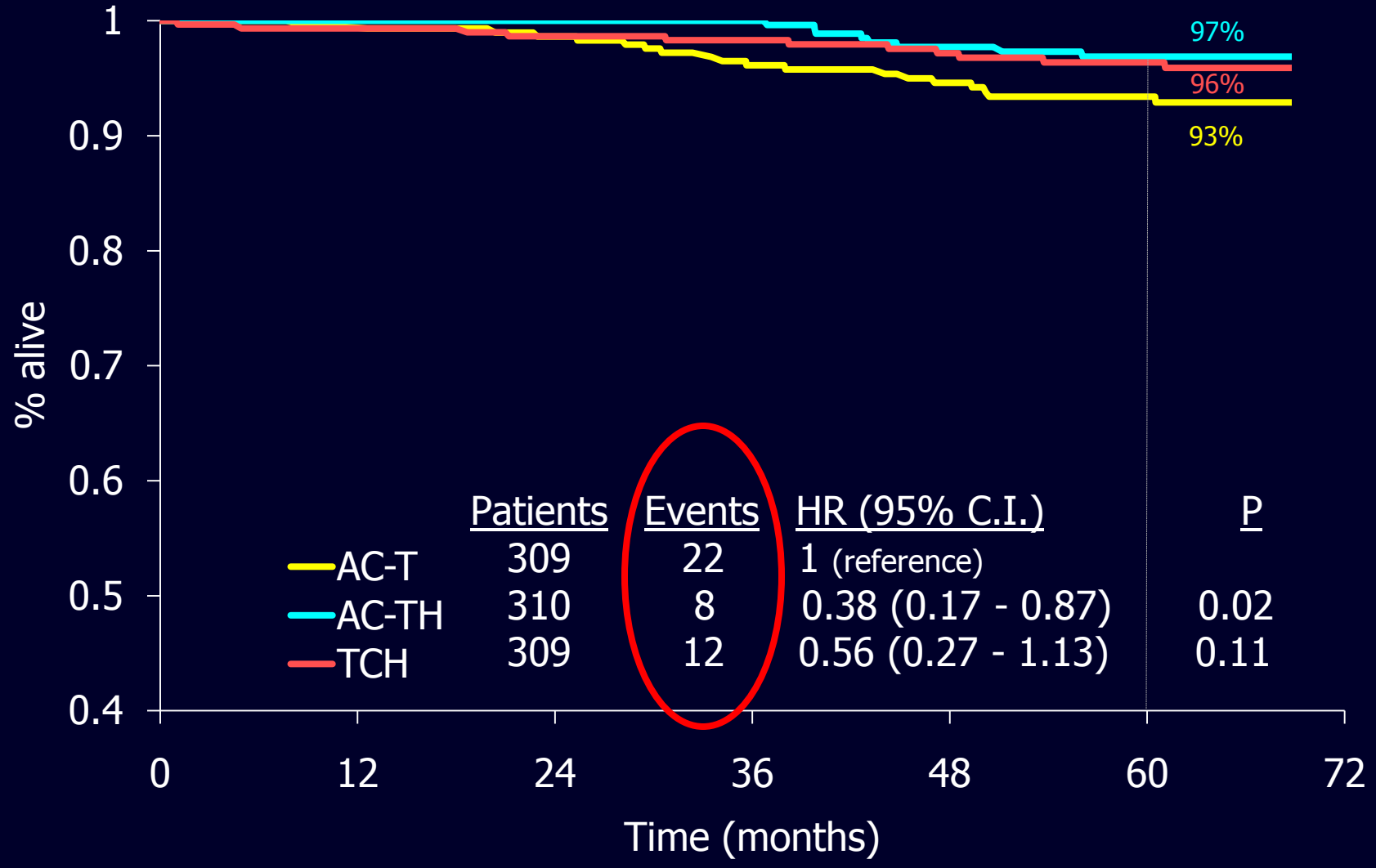
BCIRG 006 Deaths

	AC→T n=1,073	AC→TH n=1,074	TCH n=1,075
Total number of deaths from any cause	36/80/**141**	20/49/**94**	28/56/**113**
at 1st planned analysis		P **<0.001**	
at 2nd analysis			
at 3rd analysis		P=**0.038**	P=**0.14**
Breast cancer deaths	33/69/**122**	19/44/**83**	21/47/**97**

BCIRG 006
DFS Lymph Node Negative



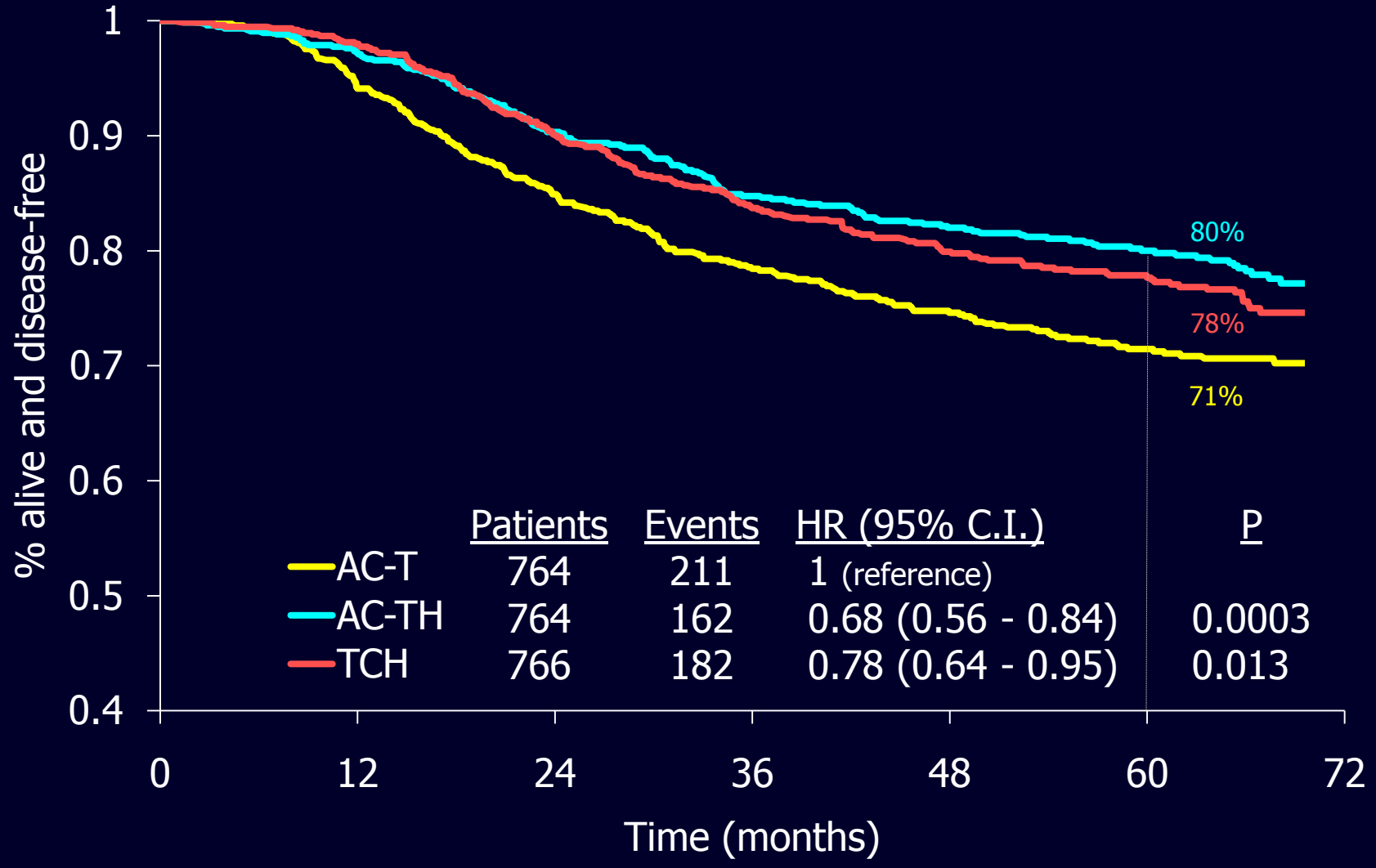
BCIRG 006
OS Lymph Node Negative



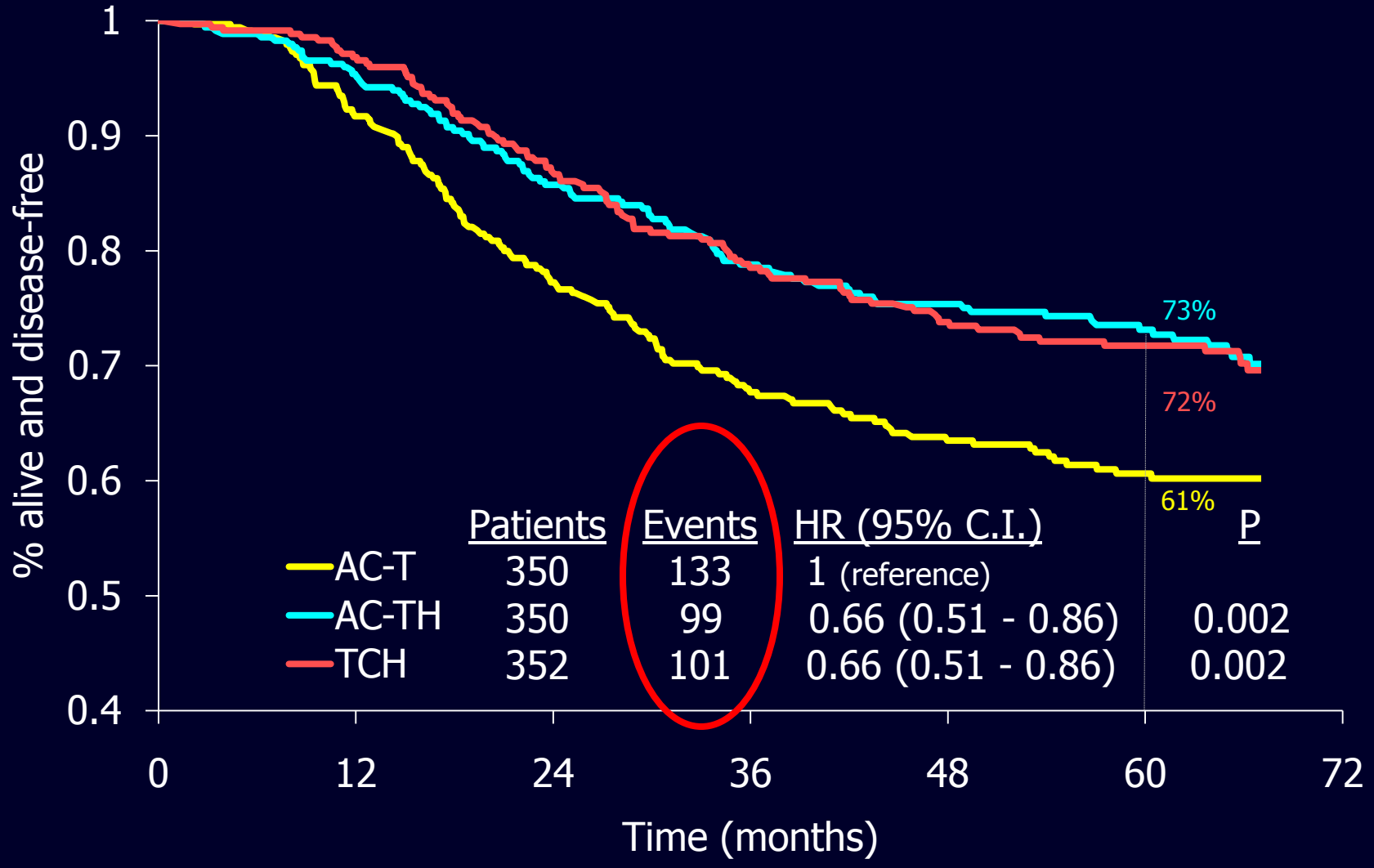
Do Higher Risk HER2-positive Breast Cancers Require Anthracycline-based Rx ????

BCIRG 006
Slamon D., SABCS 2009

BCIRG 006
DFS Lymph Node Positive



BCIRG 006
DFS Lymph Node ≥4



General Safety

BCIRG 006
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	7.2	7.2
Hand-foot syndrome	1.9	1.4	0.0*
Stomatitis	3.5	2.9	1.4*
Diarrhea	3.0	5.6	5.4
Nausea	5.9	5.7	4.8
Vomiting	6.1	6.7	3.5*
Irregular menses	27	24.3	26.5

Yellow=*Statistically significant less events

BCIRG 006
Specific non-hematological toxicity (all grades)

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
	%	%	%
Neuropathy-sensory	48.6	49.7	36.1*
Neuropathy-motor	5.2	6.3	4.2*
Nail changes	49.3	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	0.1

Yellow=*Statistically significant less events

BCIRG 006
Grade 3/4 Hematological Toxicity

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
	(%)	(%)	(%)
Neutropenia	63.5	71.6	66.2*
Leucopenia	51.9	60.4	48.4*
Febrile neutropenia	9.3	10.9	9.6
Neutropenic infection	11.5	12.1	11.2
Anemia	2.4	3.1*	5.8
Thrombocytopenia	1.6	2.1*	6.1
Acute Leukemias: #(%)	6 (0.6)	1 (0.1)	1 (0.1**)

Yellow=*Statistically significant less events

**B-cell lymphoma developed 24 months after TCH in this pt and represented her ITT DFS event. This acute leukemia occurred 20 months after rx with CHOP for the B cell lymphoma.

Cardiac Safety

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 patients)			
Diabetes	38	36	28
Hypercholesterolemia	54	47	43
Hyperlipidemia	20	10	12
Obesity (BMI $\geq$ 30)	214	242	234
Hypertension	178	178	190
Radiotherapy (# of patients)			
After chemotherapy	718	723	729
To left chest	378	349	364

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**	0 / 0 / **0**
Cardiac left ventricular function (CHF)			
Grade 3 / 4	3 / 4 / **7**	17/ 20 / **21**	4 / 4 / **4**

First planned analysis

Second analysis

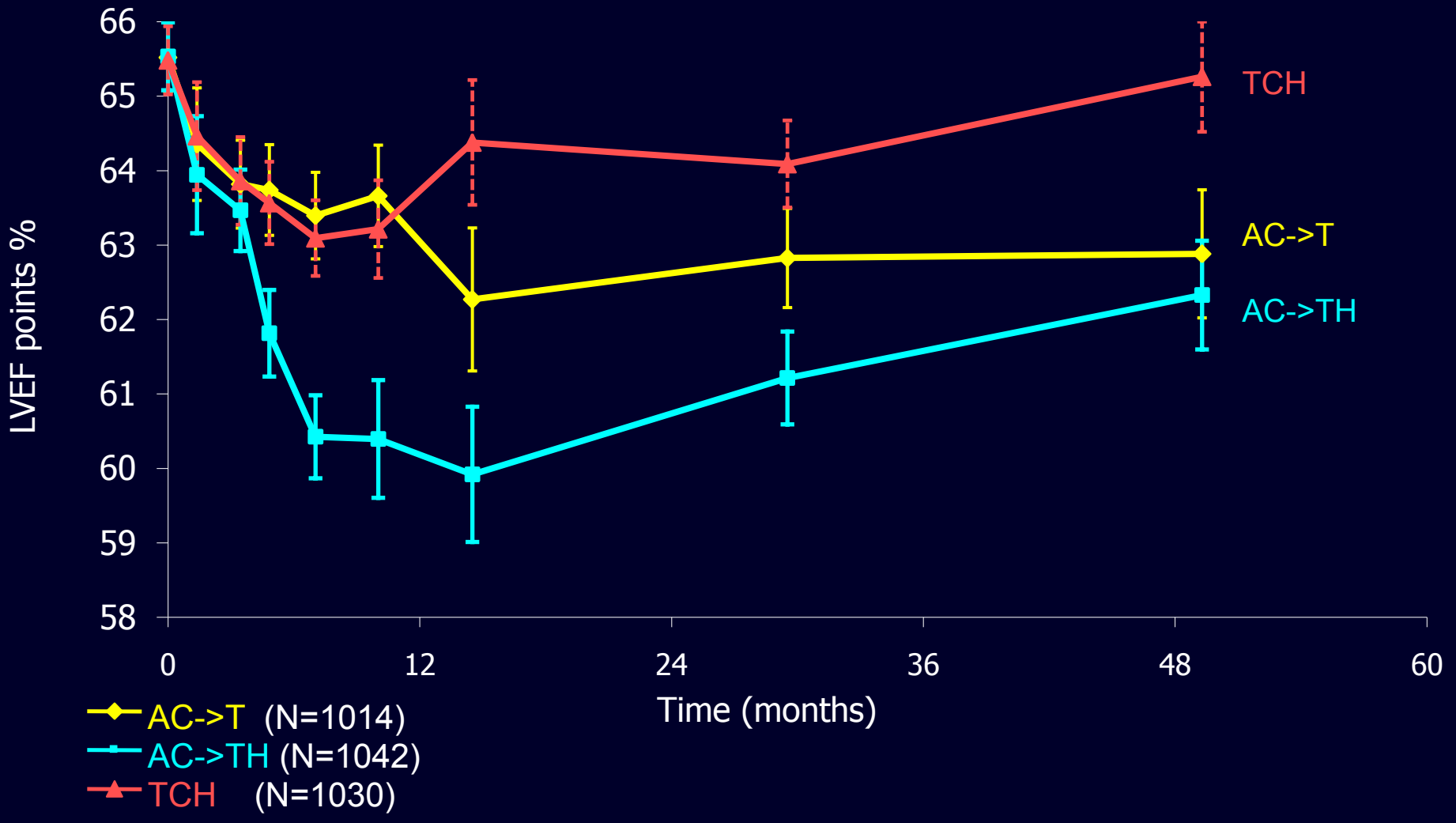
Third analysis

P = **0.0121**

P < 0.001

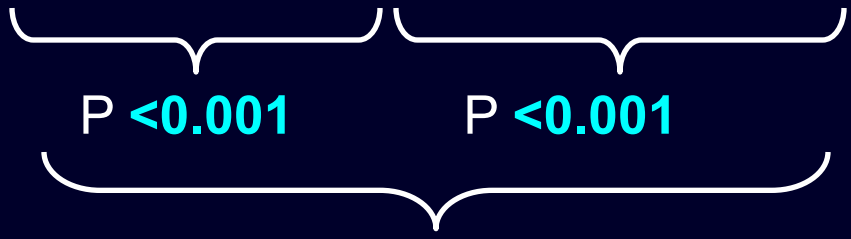
P=**0.3852**

BCIRG 006
Mean LVEF - All Observations
3rd Planned Analysis



Patients with >10% relative LVEF decline

	AC→T n = 1,018	AC→TH n = 1,042	TCH n = 1,031
Patients	91/102/**114**	180/189/**194**	82/ 89/**97**
% of Pts	9/10 /**11**	17/18/**19**	8/9/**9**



First interim analysis

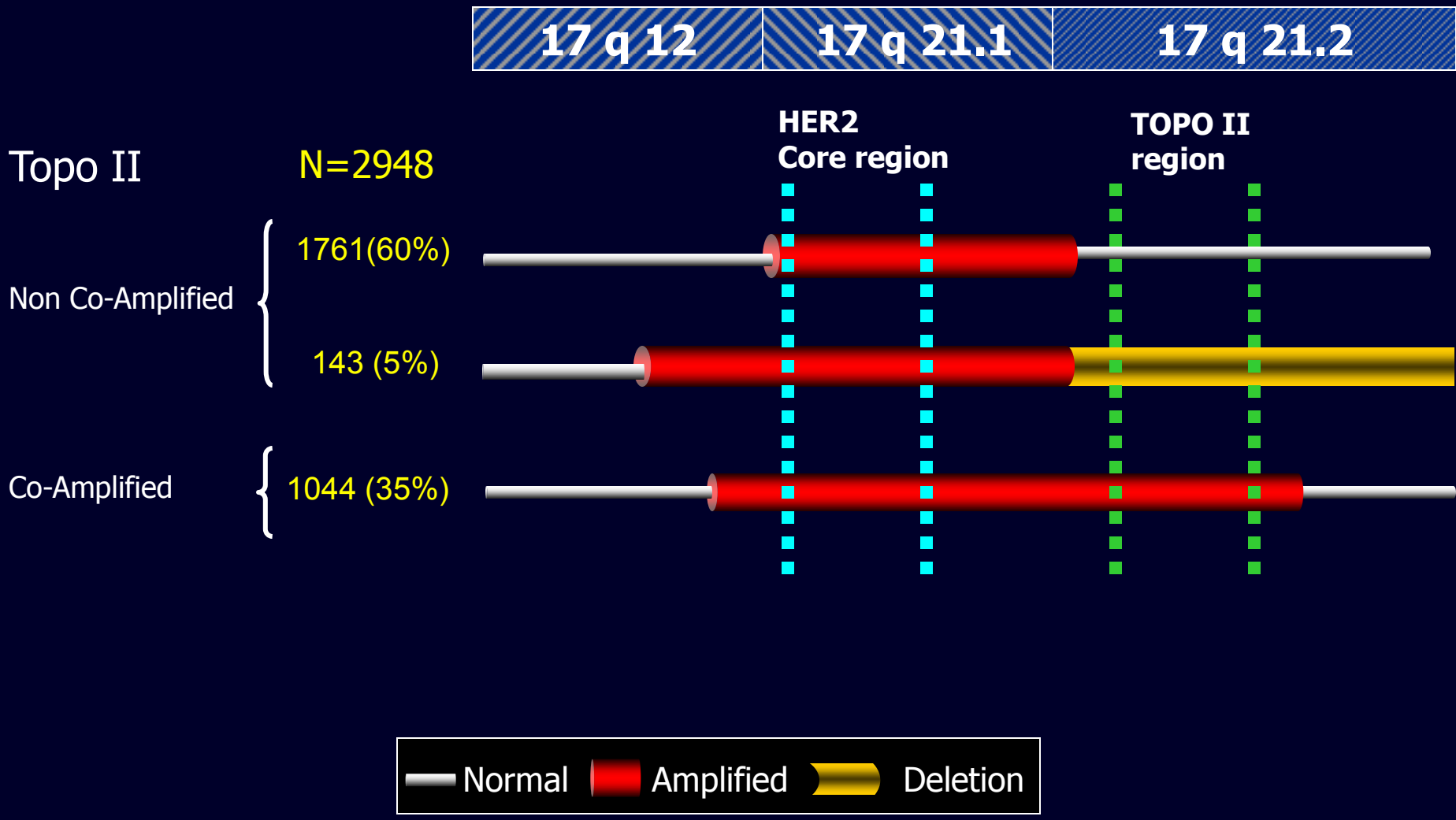
Second analysis

Third analysis

Topo IIa Amplification

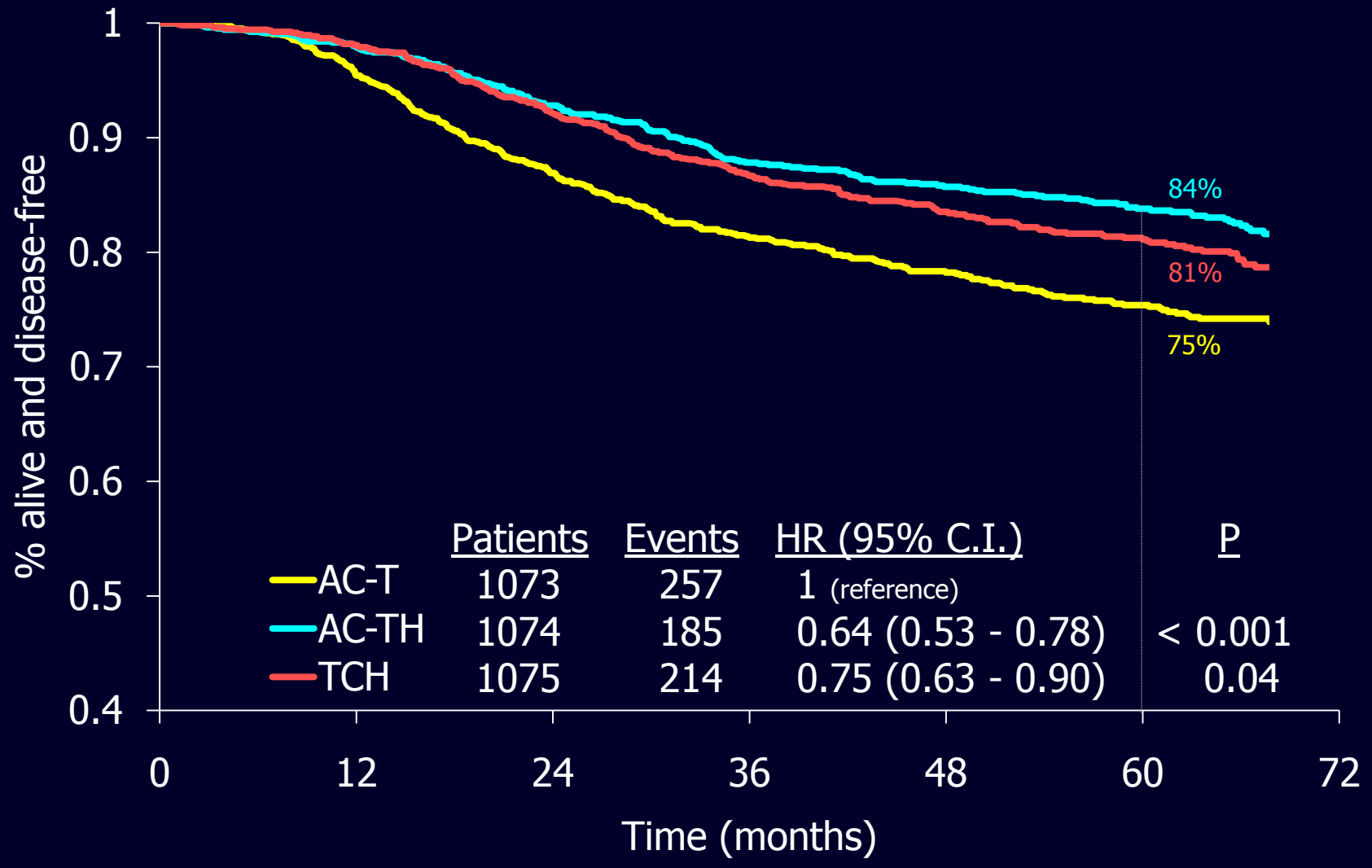
HER2 and TOPO IIa in BCIRG 006

2990 of 3222 patients tested

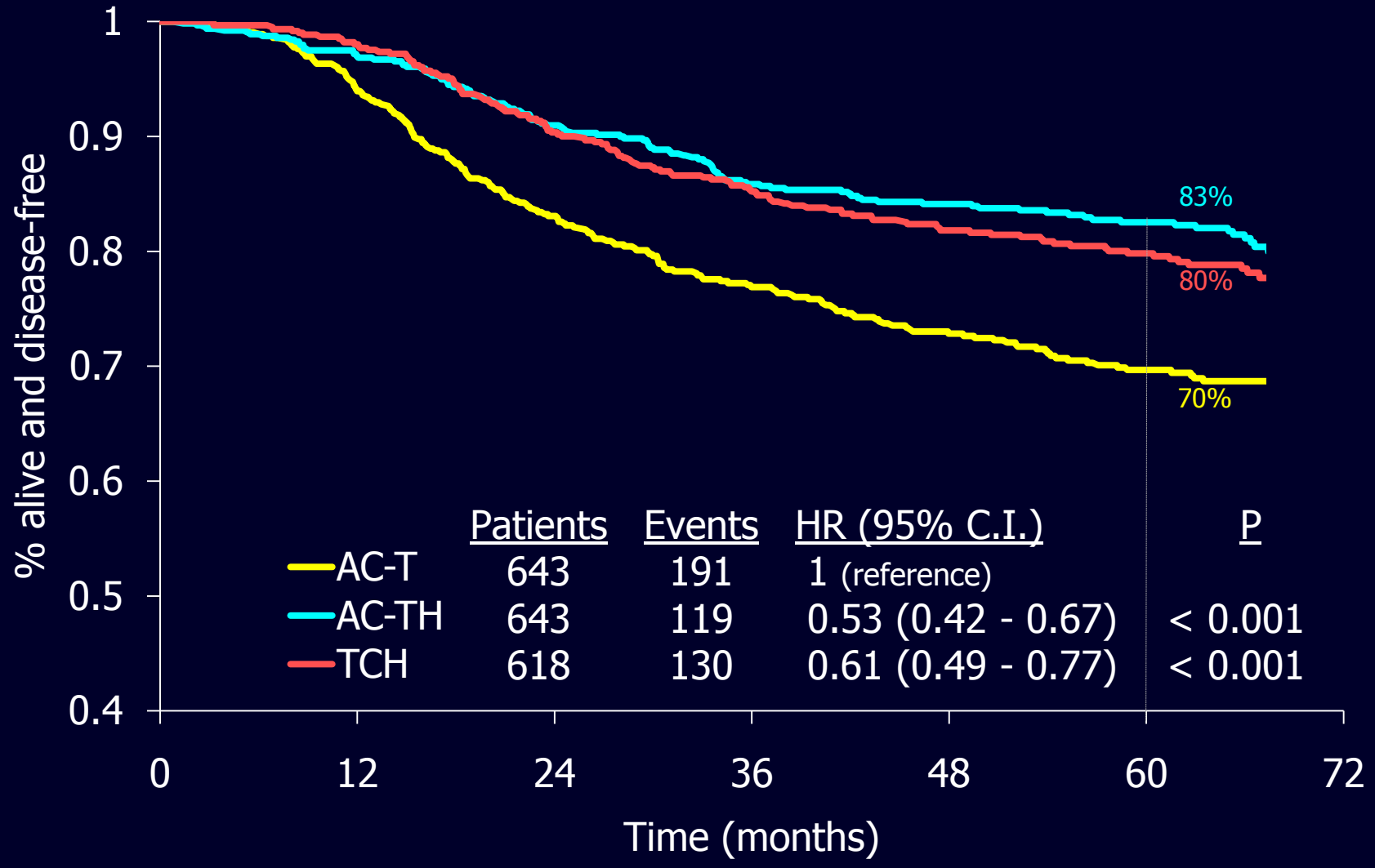


Slamon D., SABCS 2009

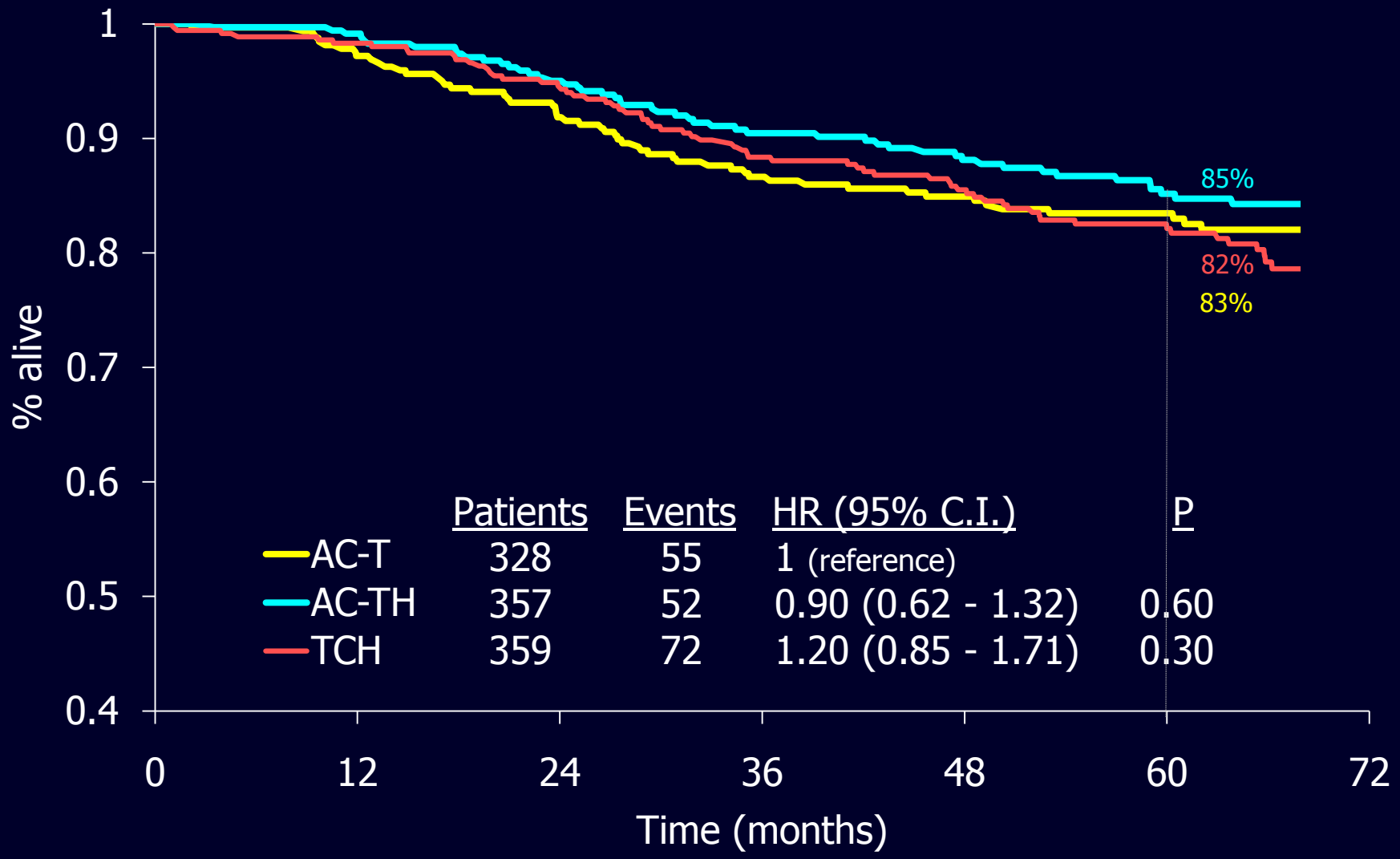
BCIRG 006
Disease Free Survival – 3rd Planned Analysis



DFS by Arm: Topo IIa Non Co-Amplified



DFS by Arm: Co-Amplified for Topo IIa



Therapeutic Index – Most Recent 006 Data

	AC-TH	TCH
DFS Events	185	214
Grade 3 / 4 CHF	21	4
Totals	**206**	**218**

Rx-Related Leukemias	*7(8)** **Only in AC-Rx patients*	*0(1)*** ***Leukemia developed after CHOP Rx*
Sustained LVEF Loss >10%	194	97

Conclusions:BCIRG-006

- → Trastuzumab provides a similar and significant advantage for both DFS and OS when used with either anthracycline-based (ACTH) or non-anthracycline (TCH) chemotherapy. This advantage is seen in both low and high-risk patients
- → The acute and chronic toxicity profiles of TCH are better than those seen with the ACTH regimen in almost all parameters measured
- → There is no statistical advantage of ACTH over TCH but there is a 29 event numerical advantage in DFS events in the ACTH treatment arm
- → This numeric advantage comes at the cost of 21 CHFs (5X more than in TCH) and to date, there are 8 acute leukemias in BCIRG-006…..all occurring in patients receiving AC as part of their treatment
- → BCIRG-006 demonstrates that the incremental benefit conferred by AC that is known for HER2-positive breast cancers is restricted to TOP2A co-amplified malignancies which constitute a subset (35%) of these cancers
- → This same incremental benefit (found in the TOP2A subset) can also be achieved by trastuzumab used in a non-anthracycline regimen, avoiding the long-term and life-altering toxicities (CHF or acute leukemia) seen with the anthracycline-based regimens

Acknowledgements

- All participating Patients and Investigators
- IDMC (Chair, S Swain) and Independent Cardiac Panel
- Central laboratories:
  M Press (USC), G Sauter (Basel)
- IDDI: M Buyse, F Piette
- NBCC: Fran Visco and Carolina Hinestrosa
- CIRG Central Team:
  L Andersen, V Bee, D Cabaribere, P Drevot, H Fung, T Kiskartalyi, V Landreau, M Lindsay, T Manella, E Mekercke, T Smith, V Wilson

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McKeen
Mena
Mills
Modiano
Moore
Moroose
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Nael
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