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

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Support from Genentech

Global Project Coordinator

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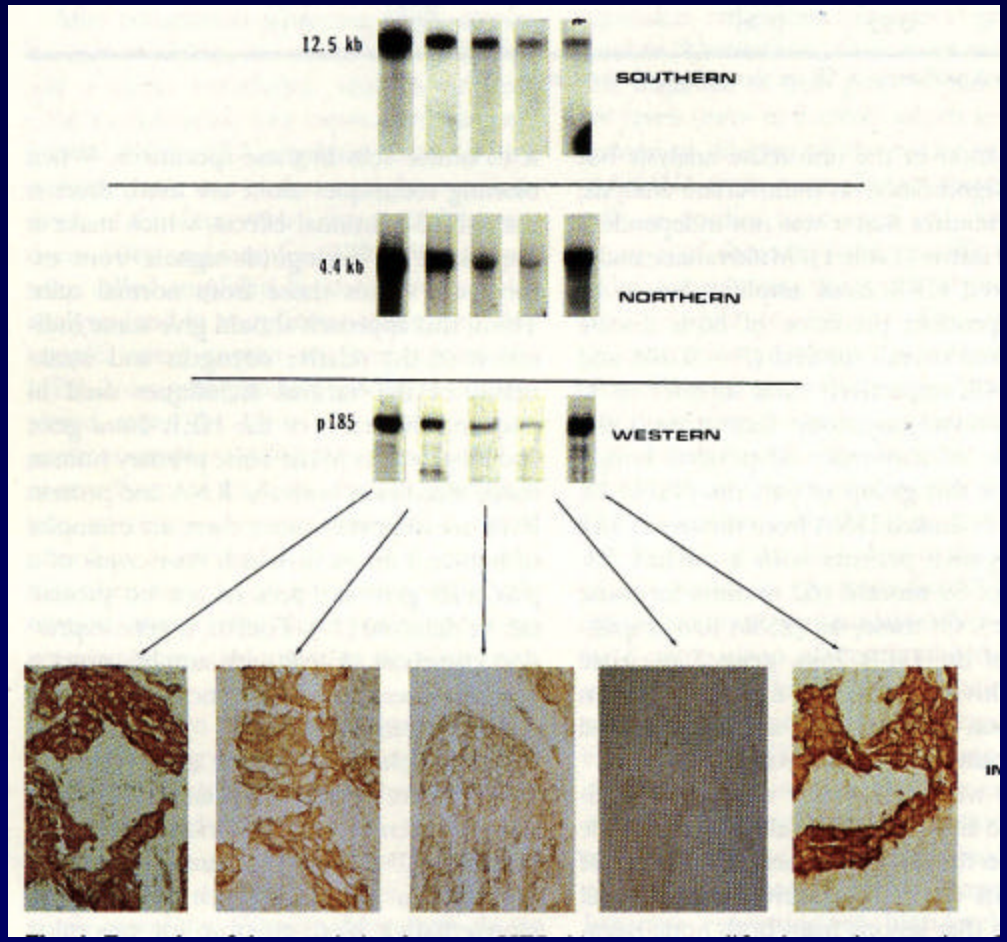
The HER2 Alteration



Southern

Northern

Western

IHC

Slamon et al. *Science* 1987,1989

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Her2+
(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

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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	59	58	60
Hormonotherapy	47	47	49

Enrollment: April 2001 to March 2004

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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	39	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

First Interim Efficacy Analysis (cutoff date June 30, 2005)

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

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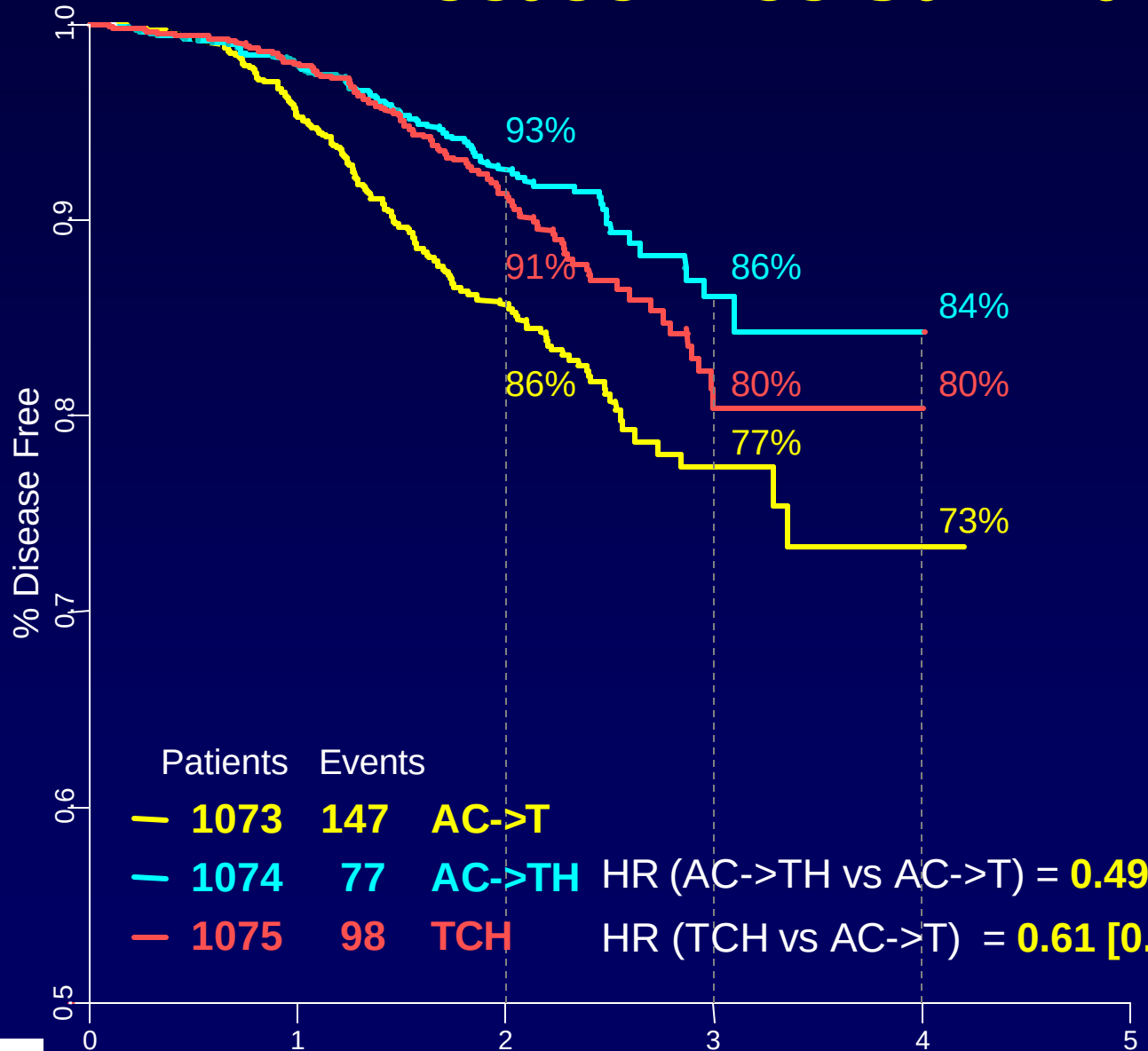
Disease Free Survival



Patients	Events		
1073	147	AC->T	
1074	77	AC->TH	HR (AC->TH vs AC->T) = **0.49 [0.37;0.65]** P<0.0001
1075	98	TCH	HR (TCH vs AC->T) = **0.61 [0.47;0.79]** P=0.0002

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Disease Free Survival

	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
Patients with event	147	77	98

Observed p-values

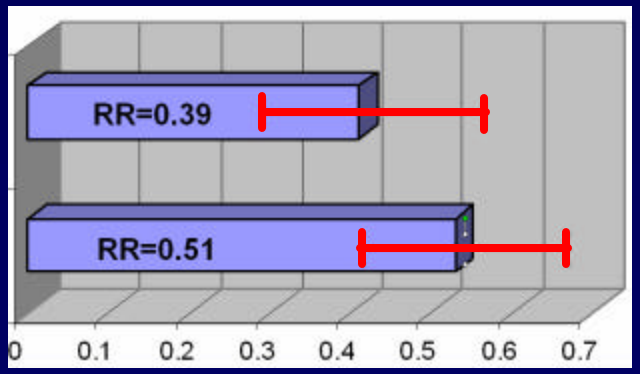
p = 0.0000005

p = 0.000153

p = 0.16

TCH

AC-TH



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Events for DFS

	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
Patients with events	147	77	98
Metastatic	113	52	67

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Deaths

	AC-T n=1,073	AC-TH n=1,074	TCH n=1,075
Total	36	20	28
Within 30 days from last administration	1*	0	2**

*pt died of pneumonia

** 1 pt died of lung infection/hypoglycemic coma/renal failure; 1 pt died of pneumonia

CONCLUSION – EFFICACY RESULTS

- → Both AC-TH and TCH arms statistically significantly improve disease-free survival in comparison to AC-T (hazard ratio of 0.49 with AC-TH and 0.61 with TCH)

- → At this time, there is no statistically significant difference between AC-TH and TCH

- → At this time, there is insufficient information to evaluate the secondary endpoint of the study (overall survival)

Grade 3/4 hematological toxicity

	AC-T n=1,050 %	AC-TH n=1,068 %	TCH n=1,056 %
Neutropenia	63.0	71.2	65.6
Leucopenia	51.4	60.1	48.0
Febrile neutropenia	9.9	11.0	9.4
Neutropenic infection	10.8	11.1	9.8
Anemia	2.9	3.2	6.1
Thrombocytopenia	1.0	1.4	5.3
Leukemia	0.2	0.1	-

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	1.1
Myalgia	5.1	5.2	1.7
Fatigue	6.9	7.1	7.0
Hand-foot syndrome	1.9	1.3	-
Stomatitis	3.7	3.3	1.4
Diarrhea	3.0	5.7	5.6
Nausea	5.8	6.0	4.9
Vomiting	6.1	7.1	3.4
Irregular menses	24.2	20.0	21.6

Specific non-hematological toxicity (all grades)

	AC-T n=1,050 %	AC-TH n=1,068 %	TCH n=1,056 %
Neuropathy-sensory	45.5	46.4	31.2
Neuropathy-motor	4.7	5.9	3.9
Nail changes	47	40	23.3
Myalgia	52.6	54.3	36.8
Renal failure	-	-	0.1
Creatinine	3.7	6.9	9.7
Creatinine Grade 3/4	0.7	0.7	0.6

CARDIAC TOXICITY

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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	34	30
Hypercholesterolemia	54	45	43
Hyperlipidemia	20	10	12
Obesity	27	36	37
Hypertension	172	172	183
Radiotherapy (# of Pts)			
After chemotherapy	638	625	647
To left chest	335	307	323

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Clinically significant cardiac events as per independent review panel

Treatment group: (Number of patients):	AC-T (1,050)	AC-TH (1,068)	TCH (1,056)
Cardiac related death	0	0	0
Cardiac left ventricular function (CHF) Grade 3 / 4	3	17	4
Cardiac ischemia / infarction ++ Grade 3 / 4	0	4	1
Arrhythmias * ++ Grade 3 / 4	7*	4*	9*
Total clinically significant events	**10**	**25**	**14**

*5 arrhythmias out of 20 not yet adjudicated by Panel (2 in AC-T, 1 in AC-TH and 2 in TCH)

++Unique to BCIRG 006

Clinically significant cardiac events as per independent review panel

	AC-T n=1,050	AC-TH n=1,068	TCH n=1,056
Patients	**10**	**25**	**14**
% (95% C.I.)	0.95% (0.46% - 1.74%)	2.34% (1.52% - 3.44%)	1.33% (0.73% - 2.21%)

P = 0.016

P = 0.11

P = 0.54

Patients with >10% relative LVEF decline

	AC-T n = 1012	AC-TH n = 1040	TCH n = 1029
Patients	91	180	82
%	9 %	17.3 %	8 %

P = 0.002

P <0.0001

P = 0.493

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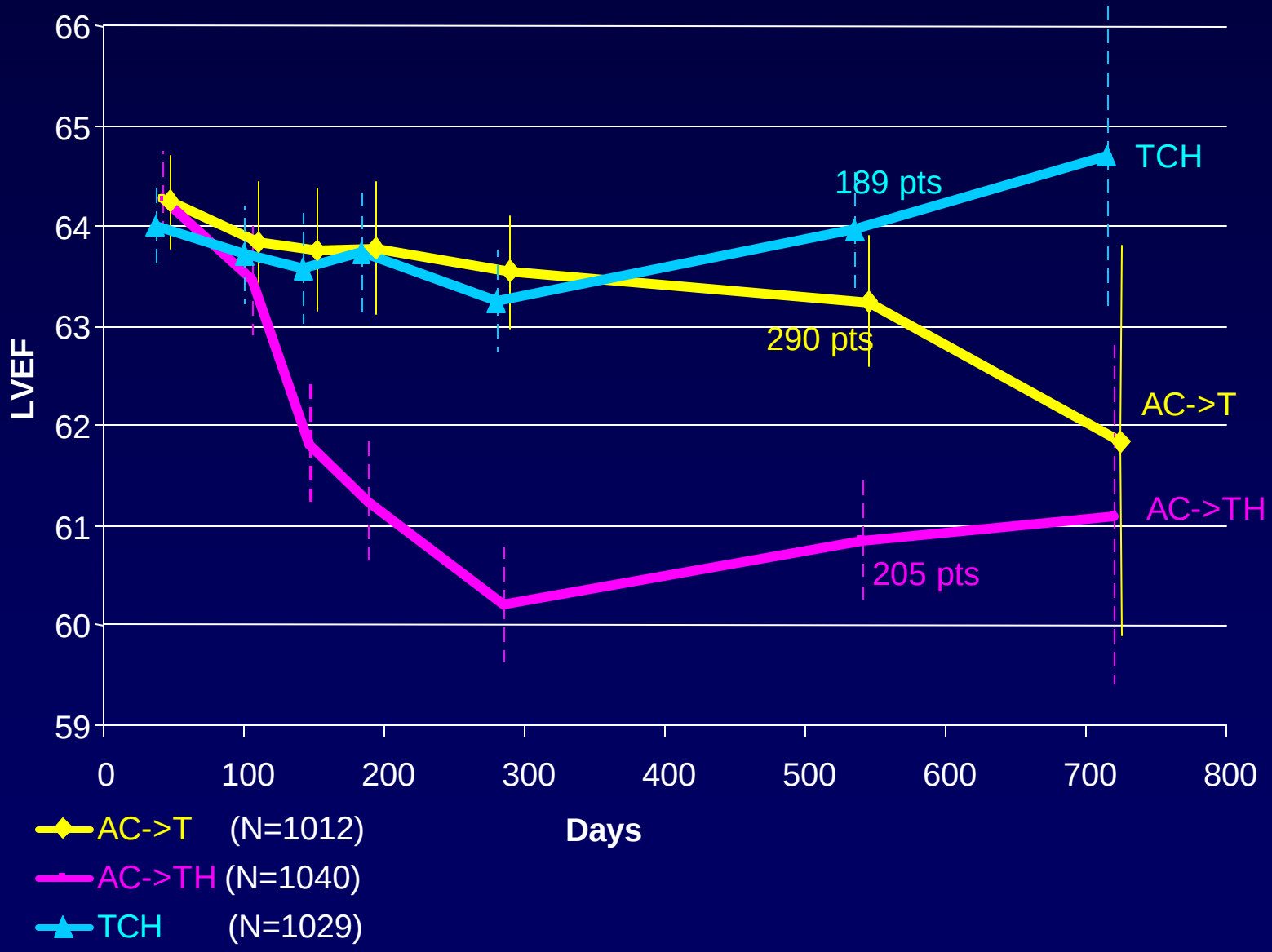
Mean LVEF - All Observations



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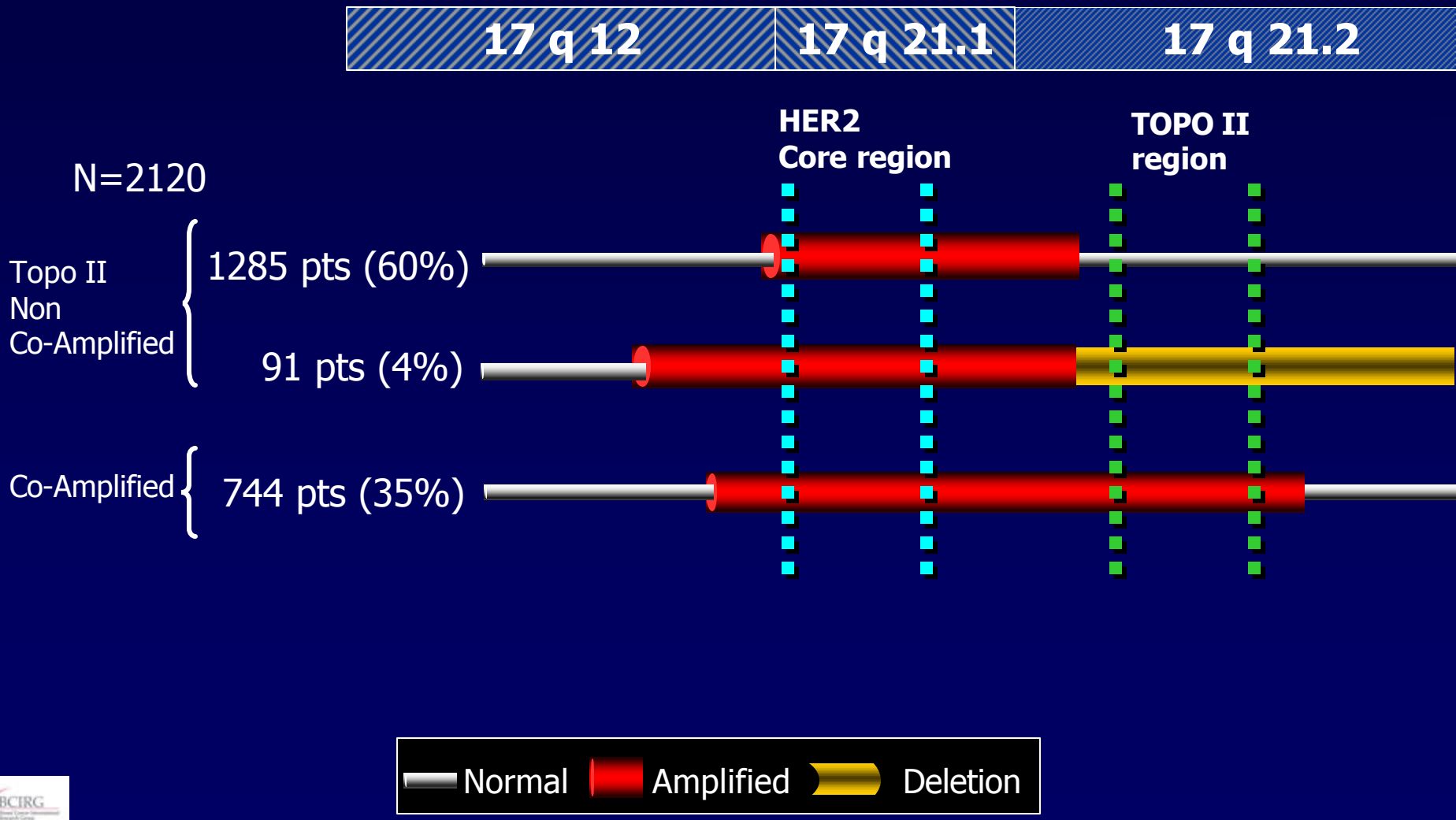
Mapping the HER2 Amplicon

HER2 and TOPO II in BCIRG 006

2120 of 3222 patients analyzed



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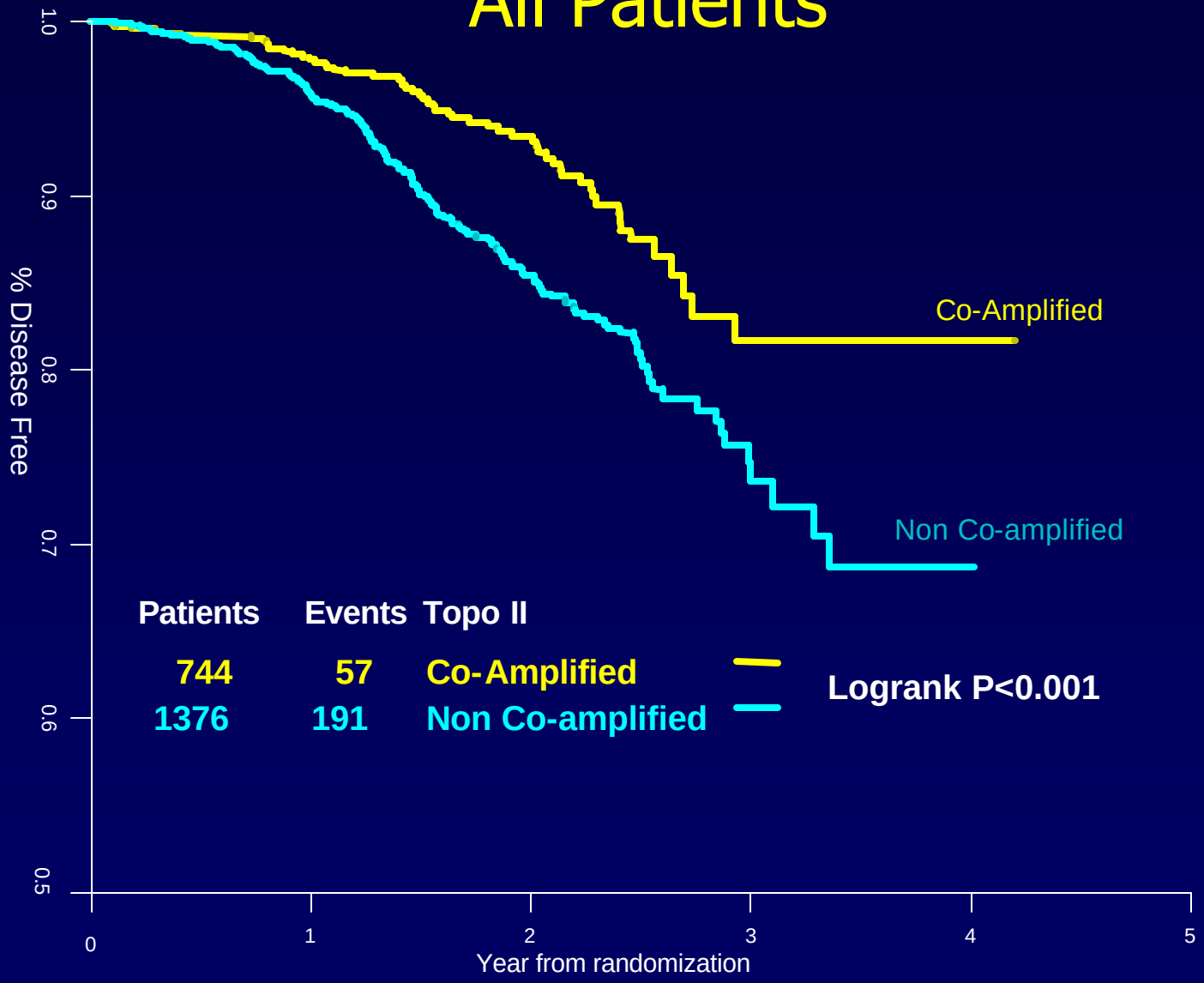
DFS Topo II Co-Amplified vs Non Co-Amplified All Patients



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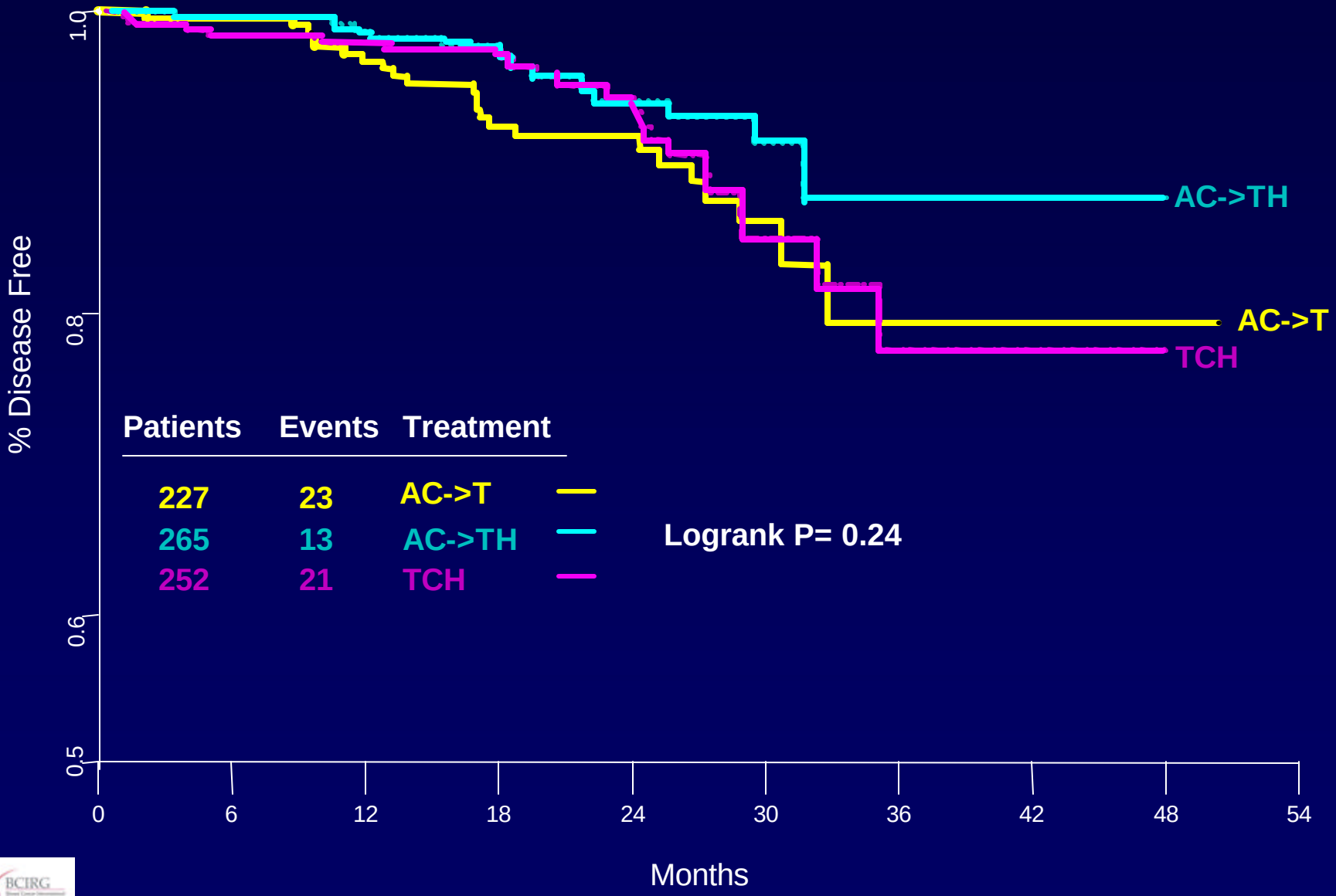
DFS Co-Amplified Topo II by Arm



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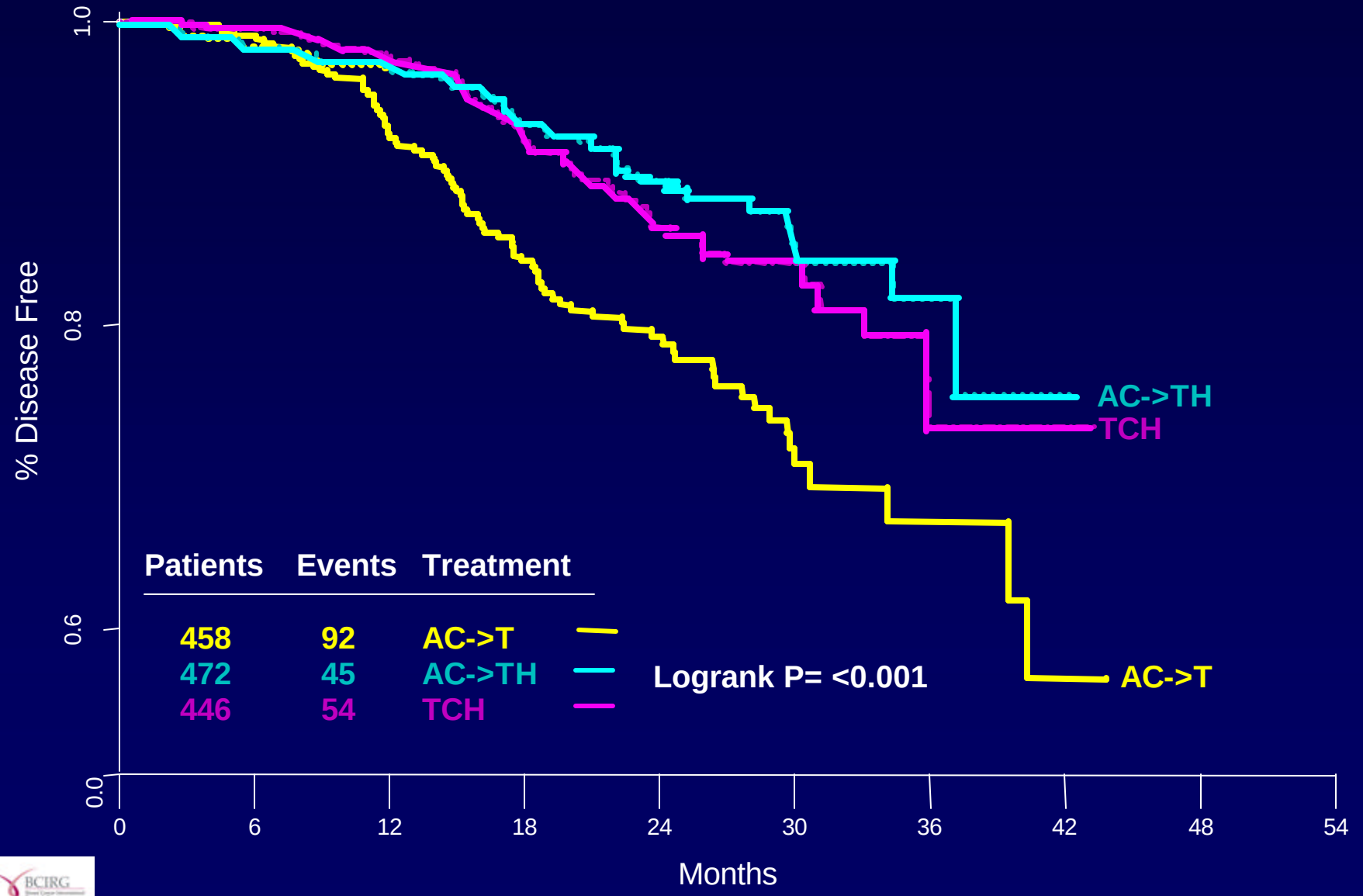
DFS Non Co-Amplified Topo II by Arm



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Summary (I) - Efficacy

At 23 months median follow-up, AC-TH and TCH provide over AC-T:

Primary endpoint: Disease-Free Survival

Statistically significant improvement:

- hazard ratio of 0.49 with AC-TH (p = 0.00000048)
- hazard ratio of 0.61 with TCH (p = 0.00015)

Secondary endpoint: Overall Survival

- data not mature enough at the present time

Summary (II) – Cardiac Safety

- ✓ There is a statistically significant higher incidence of cardiac events in AC-TH in comparison to AC-T but not in TCH in comparison to AC-T

  AC-T: 0.86%

  AC-TH: 2.62% (p = 0.0024)

  TCH: 1.04% (p = 0.82)

- ✓ There is also a statistically significant higher incidence of asymptomatic and persistent LVEF declines in AC-TH in comparison to AC-T and TCH

Summary (III) – Global Safety

- ✓ There was no statistically significant higher incidence of hematological toxicities (febrile neutropenia and neutropenic infection) in any of the 3 treatment arms
- ✓ For non-hematological toxicities, all 3 regimens appear to be safe and with manageable toxicities
- ✓ All 3 regimens were well-tolerated (more than 90% of cycles administered)

Additional Observations

- → LVEF declines are more sustained with AC-T and AC-TH (>550 days at last follow-up) than was previously thought

- → Co-amplification of the topoisomerase II alpha gene occurs in ~35% of HER2 positive patients and may confer a therapeutic advantage to anthracycline-based:Herceptin combination regimens

- → HER2 positive patients that are not co-amplified for topo II alpha (~65%) do not appear to have this same benefit and may be ideal candidates for efficacious, non-anthracycline based regimens thus avoiding potential cardiac toxicity

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- NBCC: Fran Visco and Carolina Hinestrosa
- BCIRG Central Team:
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