The Georgia Society of Clinical Oncology's

San Antonio Breast Cancer Symposium Review
HER2-positive Breast Cancer

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Atlanta Cancer Care

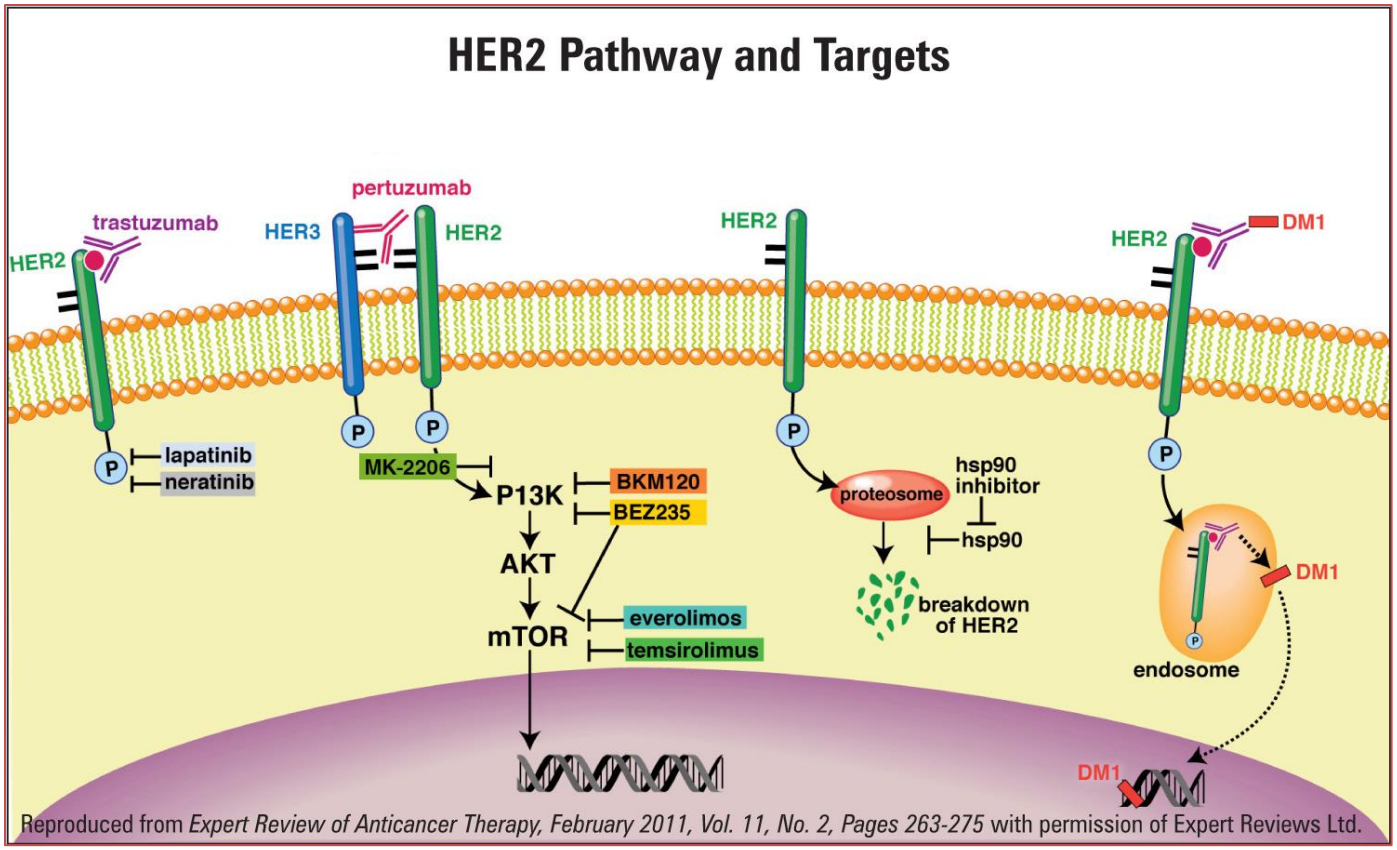
Northside Hospital Cancer Institute

January 9, 2016

Outline

- Neoadjuvant Abstracts
  - S5-03: ADAPT trial
  - S5-01: Predictors of response in neoALTTO trial
- Adjuvant Abstracts
  - S5-04: BCIRG 006
  - S5-02: ExteNET
  - S6-06: Netherlands Cohort Study
  - S1-05: MANTICORE
- Metastatic Abstracts
  - S5-05: TH3RESA

Targeted Therapies for HER2+ Breast Cancer: Trastuzumab, Lapatinib, Pertuzumab, and T-DM1



Available at: http://am.asco.org/her2-pathway-breast-cancer.

San Antonio Breast Cancer Symposium, December 8-12, 2015

Final analysis of the WSG-ADAPT HER2+/HR+ phase II trial: Efficacy, safety, and predictive markers for 12-weeks of neoadjuvant T-DM1 with or without endocrine therapy vs. trastuzumab+endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer

WSG

WOMEN'S HEALTHCARE STUDY GROUP

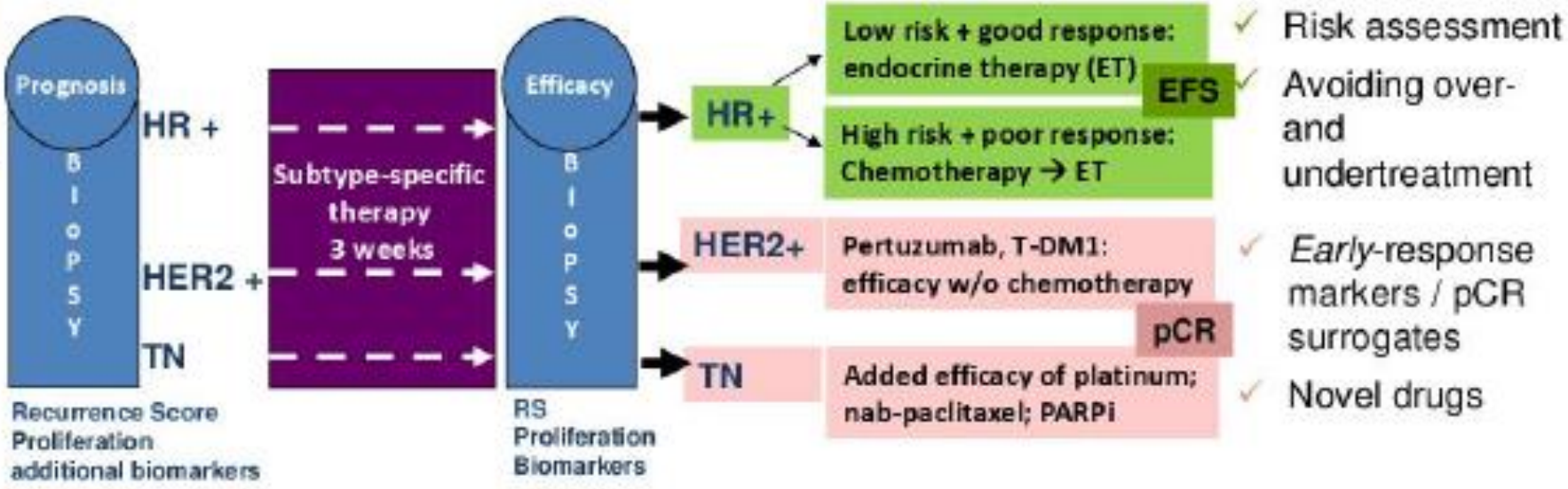
N. Harbeck, O. Gluz, M. Christgen, M. Braun, S. Kuemmel, C. Schumacher, A. Potenberg, S. Kraemer, A. Kleine-Tebbe, D. Augustin, B. Aktas, H. Forstbauer, Tio, C. Liedtke, RE Kates, R. Wuerstlein, S. de Haas, A. Kiermaier, HH Kreipe, Nitz, on behalf of the West-German Study Group (WSG)-ADAPT investigato

Adjuvant Dynamic marker-Adjusted Personalized Therapy trial (ADAPT)

WSG
WOMEN'S HEALTHCARE STUDY GROUP

ADAPT

umbrella trial, n ~ 5,000

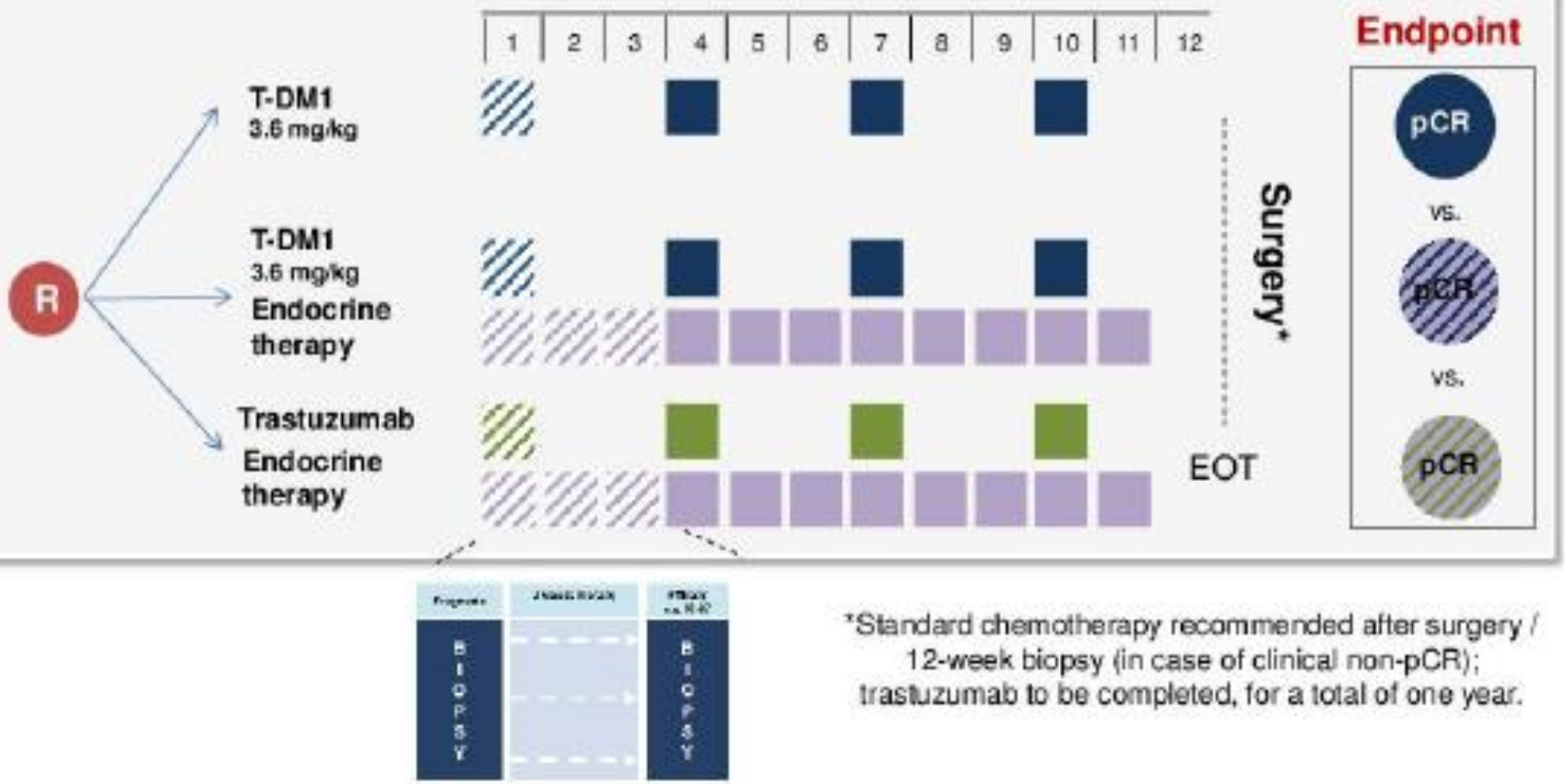


WSG AM06 Principal Investigators: Nadia Harbeck (LKP), Munich; Ulrike Nitz, Mönchengladbach, Germany.

Hofmann et al, Trials 2013

ADAPT HER2+/HR+: Trial design

WSG
WOMEN'S HEALTHCARE STUDY GROUP
ADAPT



*Standard chemotherapy recommended after surgery / 12-week biopsy (in case of clinical non-pCR); trastuzumab to be completed, for a total of one year.

Hofmann et al, Trials 2013

ADAPT HER2+/HR+: Baseline patient and tumor characteristics

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WOMEN'S HEALTHCARE STUDY GROUP

		T-DM1		T-DM1 + ET		Trast. + ET	
	n	119		127		129	
age	median (range)	50.0	(21 – 78)	51.0	(27 – 76)	51.5	(23 – 77)
cT	1	60	(50.4%)	62	(48.8%)	60	(46.5%)
	≥2	59	(49.6%)	65	(51.2%)	69	(53.5%)
cN	0	85	(71.4%)	96	(75.6%)	91	(70.5%)
	≥1	34	(28.5%)	31	(24.4%)	38	(29.5%)
PR	negative	21	(17.6%)	20	(15.7%)	21	(16.3%)
	positive	98	(82.4%)	106	(83.5%)	108	(83.7%)
ER	negative	3	(2.5%)	1	(0.8%)	5	(3.9%)
	positive	116	(97.5%)	125	(98.4%)	124	(96.1%)
central grading	3	97	(81.5%)	103	(81.1%)	98	(76.0%)
Ki67	median (range)	40.0	(10 – 90)	40.0	(15 – 80)	35.0	(10 – 85)

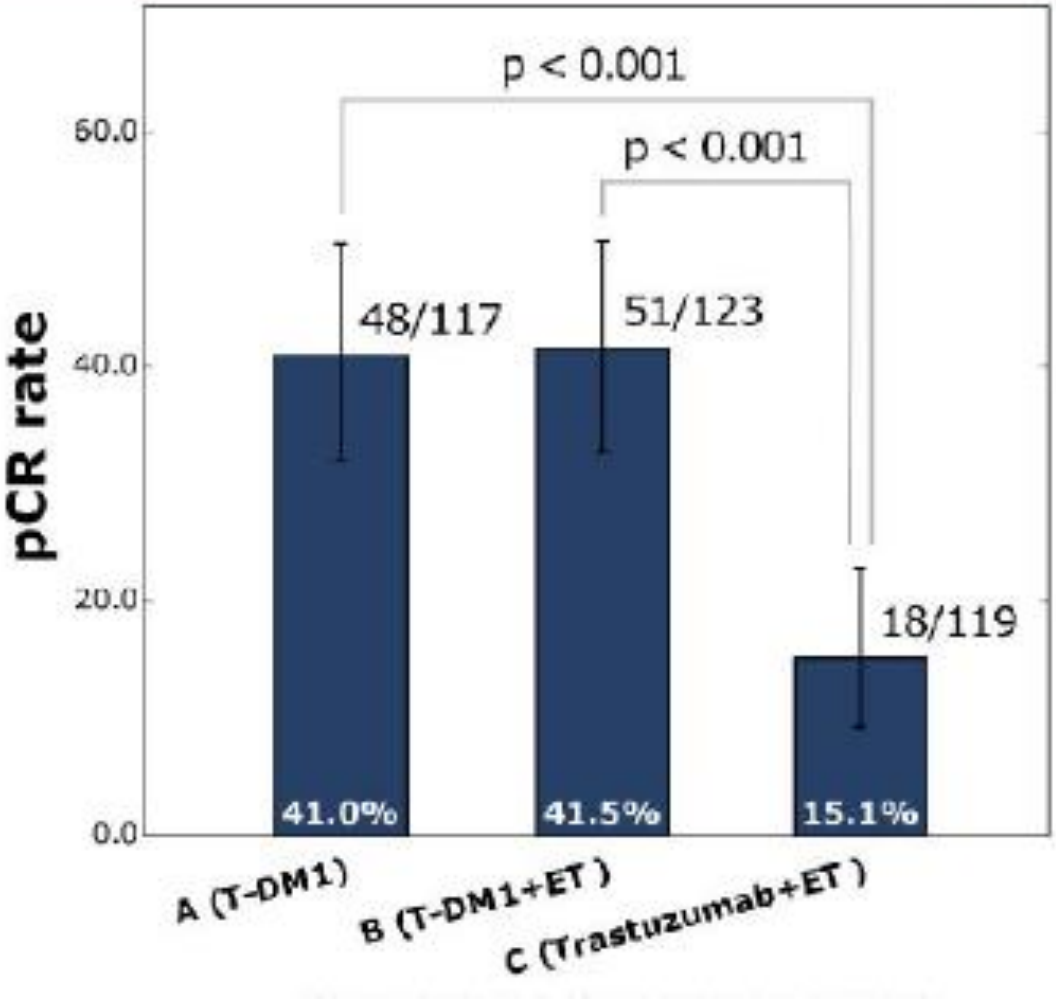
ADAPT HER2+/HR+: all AEs
pooled T-DM1 vs. T+ET with significance

WSG
WOMEN'S HEALTHCARE STUDY GROUP

AE	T-DM1 arms (n)	%	Trastuzumab + ET (n)	%	p-value
Thrombocytopenia	25	10.4	0	0.0	< 0.01
Constipation	25	10.4	5	4.1	0.04
Dry mouth	15	6.2	1	0.8	0.02
Nausea	50	20.7	6	4.9	< 0.01
Fatigue	55	22.8	14	11.5	0.01
Mucosal inflammation	18	7.5	2	1.6	0.03
Nasophaaryngitis	19	7.9	2	1.6	0.02
Investigations (total)	56	23.2	11	9.0	< 0.01
ALT	45	18.7	7	5.7	< 0.01
AST	41	17.0	4	3.3	< 0.01
Arthralgia	20	8.3	3	2.5	0.04
Dysgeusia	11	4.6	0	0	0.02
Headache	39	16.2	3	2.5	< 0.01
Hot flush	9	3.7	14	11.5	0.01

ADAPT HER2+/HR+: pCR (no invasive tumor in breast and nodes)

WSG
WOMEN'S HEALTHCARE STUDY GROUP



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ADAPT HER2+/HR+: pCR according to menopausal status*

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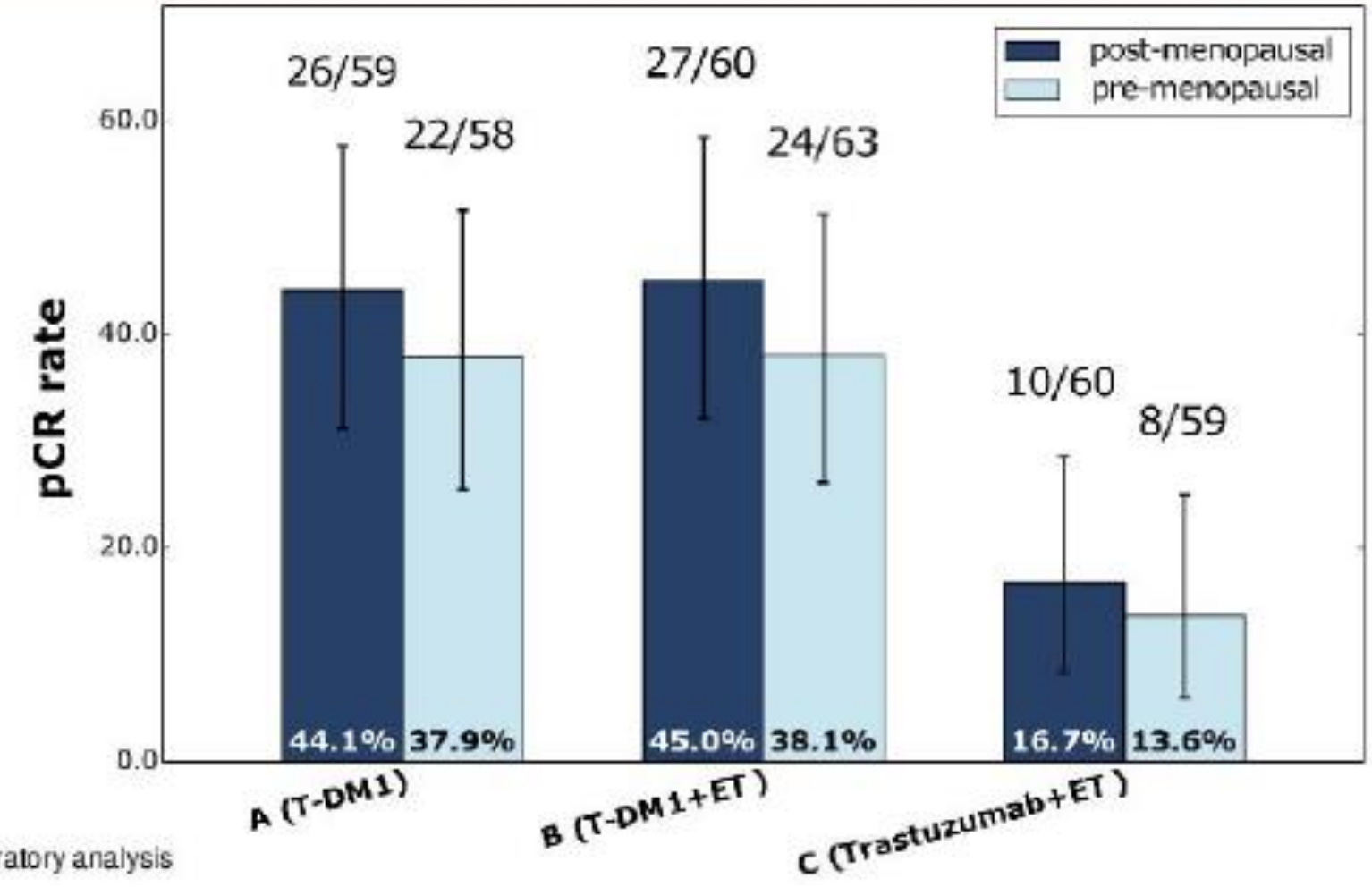
WOMEN'S HEALTHCARE STUDY GROUP

ADAPT



*exploratory analysis

Conclusions

- The addition of endocrine therapy to T-DM1 resulted in similar pCR rates
- pCR rate with neoadjuvant T-DM1 of 45%
  - Patients received standard chemotherapy in the adjuvant setting and completed 1 year of trastuzumab
  - Do patients who achieve pCR with T-DM1 benefit from additional chemotherapy?

Whole exome sequencing of pre-treatment biopsies from the neoALTTO trial to identify DNA aberrations associated with response to HER2-targeted therapies

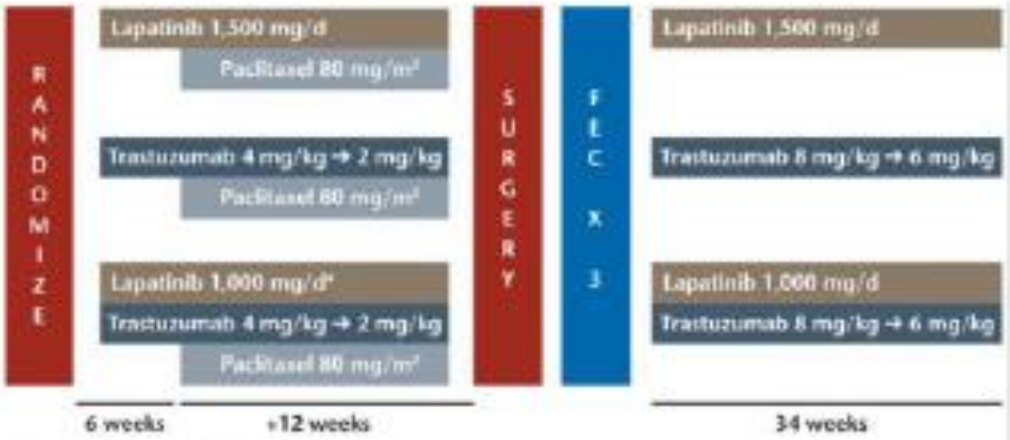
Weiwei Shi, Tingting Jiang, Paolo Nuciforo, Eileen Holmes, Nadia Harbeck, Christos Sotiriou, David Rimm, Christos Hatzis, Lorena de la Peña, Alison Armour, Martine Piccart-Gebhart, Jose Baselga, Lajos Pusztai

On Behalf of the NeoALTTO/TransALTTO investigators

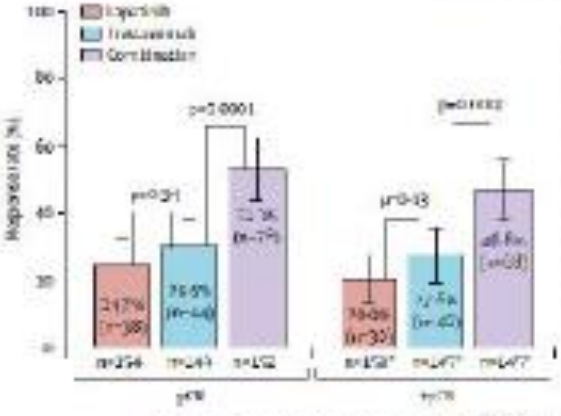
contact: lajos.pusztai@yale.edu

NeoALTTO Study

Trial Schema



Pathologic Complete Response (pCR) rates by treatment arm



(Baselga J *et al*, Lancet , 2012)

Pre-treatment core needle biopsies for biomarker analysis

- **PIK3CA mutation analysis** (Majewski IJ *et al, JCO 2015)*
- **TIL count** (Salgado R *et al, JAMA Onc 2015)*
- **PTEN** (Nuciforo et al *Annals Onc*, 2015)
- **HER2 / p95 quantification** (Scaltriti et al *Clin Cancer Res* 2015)
- **Whole Exome Sequencing**
- **Ongoing: RNA Seq, Immune profiling, HER2 ICD/ECD expression**

contact: lajos.pusztai@yale.edu

Specimens included in the whole exome sequencing (WES) study

N=455 Randomized

↓

N=423 Baseline biopsy

↓

N=357 adequate tumor cellularity

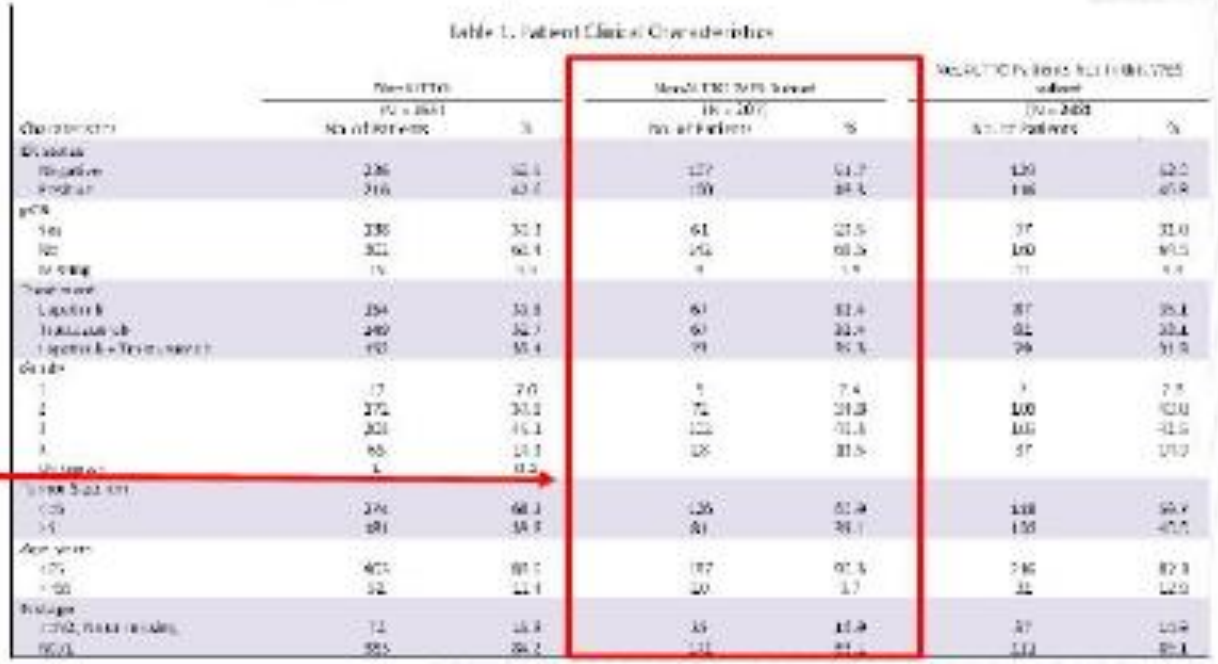
↓

N=227 >1 μg DNA left

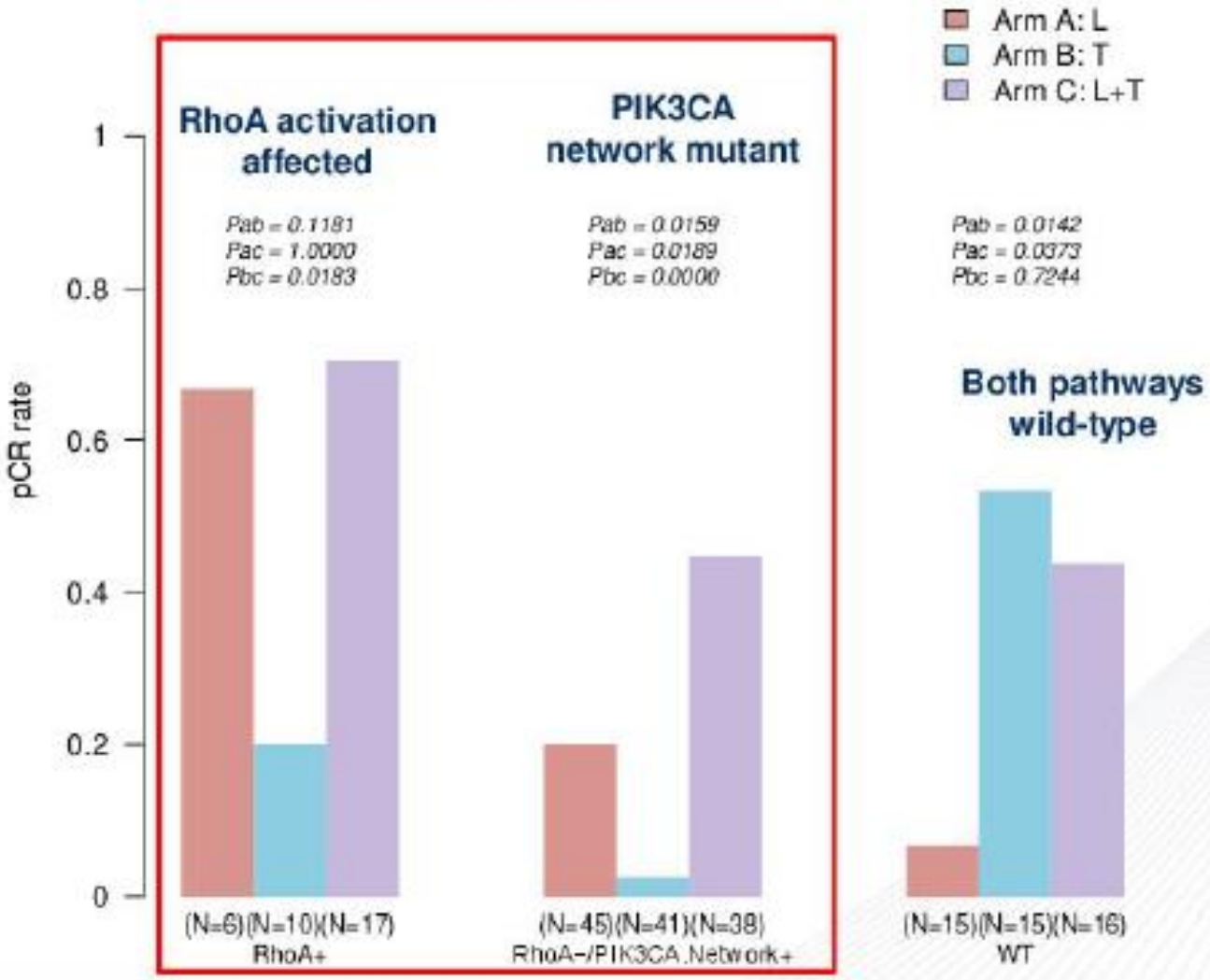
↓

N=207 (45%) Successful WES

ER and PR distribution, pCR rates similar to main trial



Combined mutation status of the "PIK3CA network" and the "Regulation of RhoA activity" pathway defines a population who benefits the most from inclusion of Lapatinib

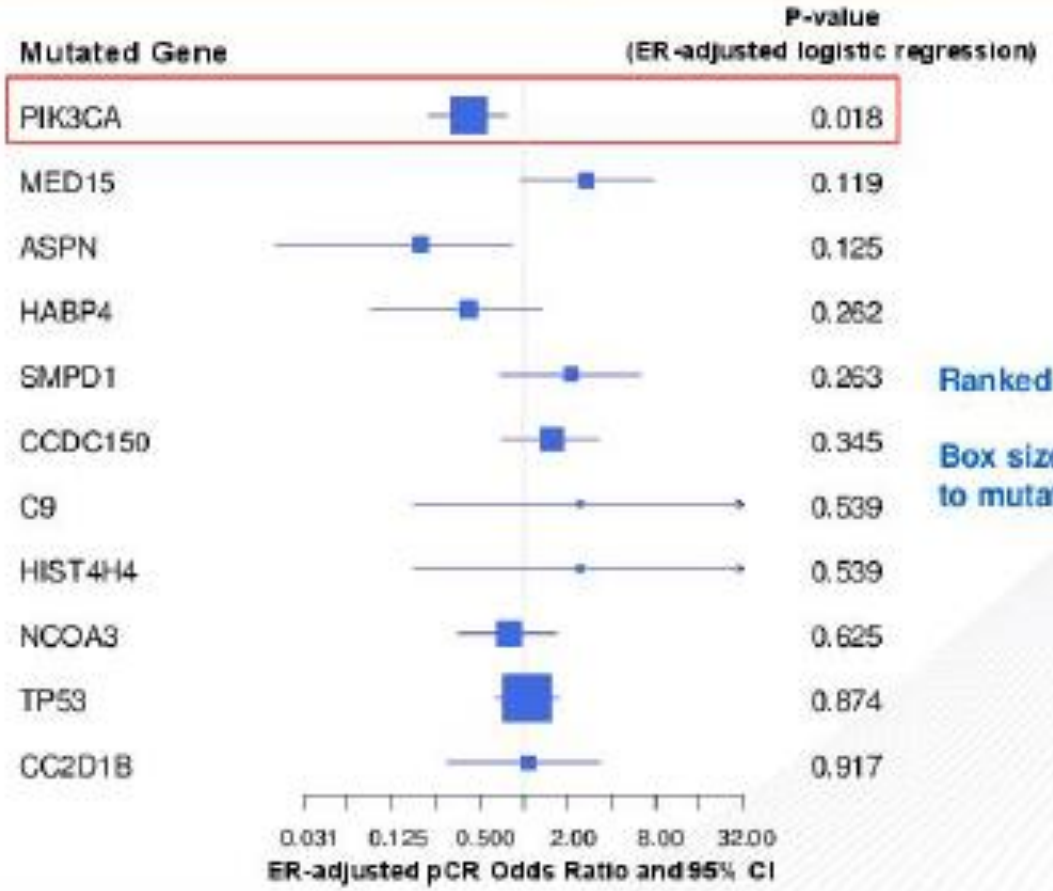


contact: lajos.pusztai@yale.edu

Results

Mean coverage = 150x
90% of target bases had >30x coverage in 99% of samples
Median number of somatic variants = 65 /sample
Median number of HFI variants = 34 / sample

At gene level, only PIK3CA mutations showed significant (negative) association with pCR

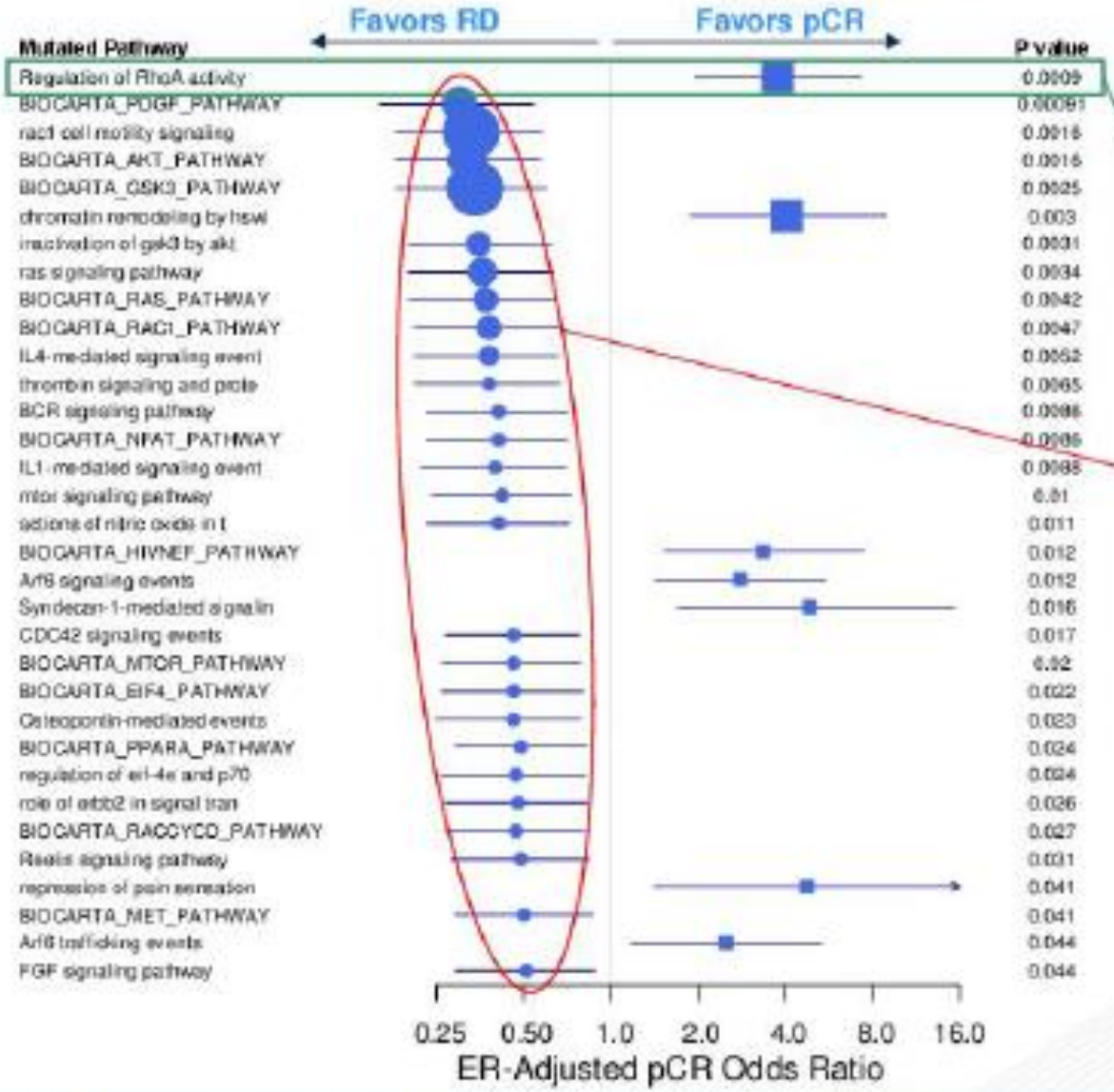


Ranked by p-value

Box size proportional to mutation frequency

contact: lajos.pusztai@yale.edu

Mutations in 33 of 713 biological pathways were associated with pCR in all arms combined



Few pathway mutations are associated with pCR.

The most significant is "Regulation of RhoA Activity" including 48 genes (NCI Pathway Interaction DB).

All pathway mutations associated with RD included the PIK3CA gene.

These pathways were combined into a "PIK3CA-network" of 459 unique genes.

● Includes PIK3CA gene

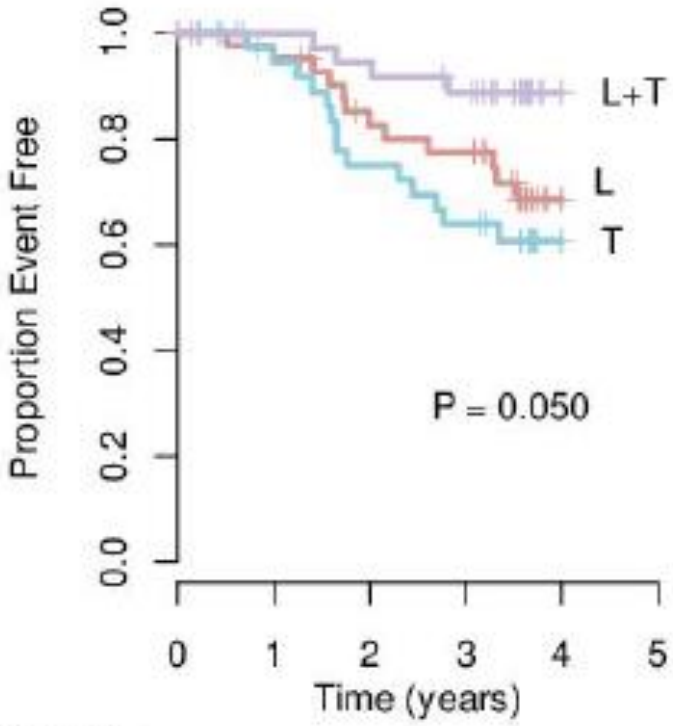
■ No PIK3CA gene in pathway

Size of circles and squares is inversely proportional to FDR

contact: lajos.pusztai@yale.edu

RhoA pathway wild-type and PIK3CA network mutant cancers (60%) have better outcome with L+T compared to T alone

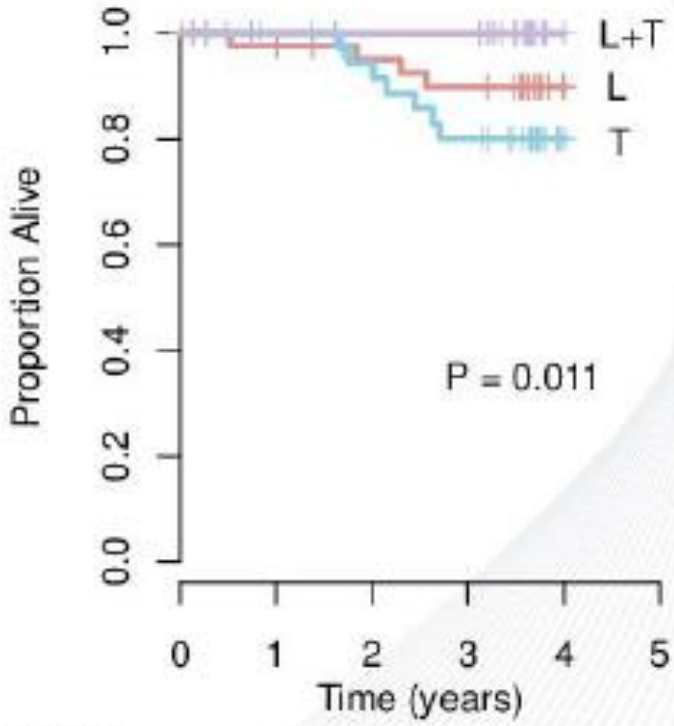
Event Free Survival



No. At Risk

L	45	40	32	30	12	0
T	41	34	27	23	11	0
L+T	38	36	34	31	14	0

Overall Survival



No. At Risk

L	45	41	37	35	16	0
T	41	38	33	28	14	0
L+T	38	36	36	36	14	0

Conclusions

- PIK3CA single gene and pathway mutations were associated with lower pCR rate
  - Adding lapatinib to trastuzumab increased pCR rate
- Pathway mutations involving regulation of RhoA activity associated with higher pCR rate to lapatinib-containing arms
- Combined mutation status of PIK3CA and RhoA could define group of patients with low pCR rate to trastuzumab alone where addition of lapatinib may have greater benefit

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:

10-year Follow-up analysis

Slamon D, Eiermann W, Robert N, Giermerk J, Martin M, Jasiowka M, Mackey J, Chan A, Liu M, , Pinter T, Valero V, Falkson C, Fornander T, Shiftan T, Bensfia S, Hitier S, Xu N, Bee-Munteanu V, Drevot P, Press M, Crown J, on behalf of the BCIRG 006 Investigators.

Study sponsored by sanofi
Support from Genentech

San Antonio Breast Cancer Symposium, December 8-12, 2015

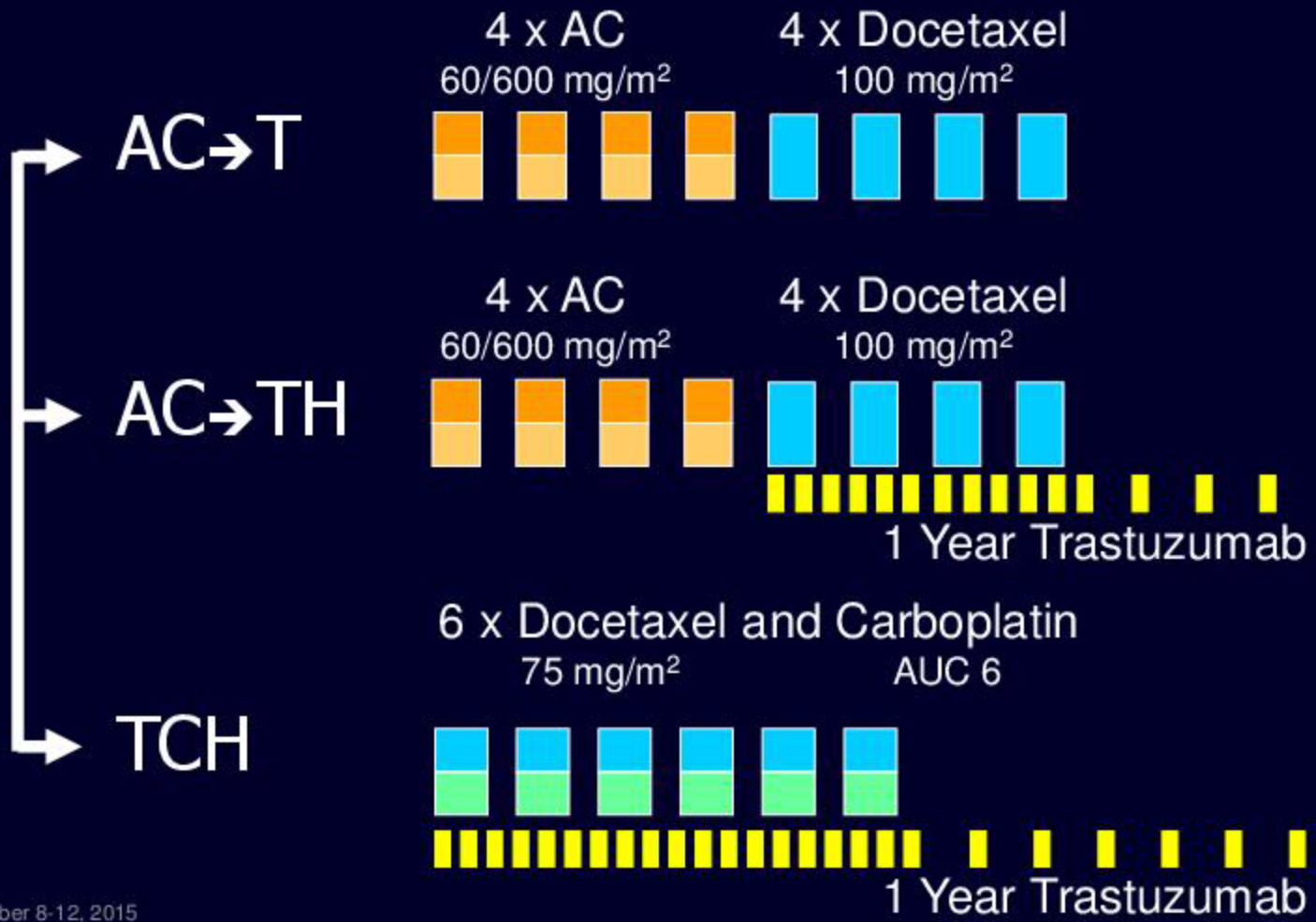
BCIRG 006 Trial Design

Her 2+
(Central FISH)

N+
or high
risk N-

N=3,222

Stratified by Nodes and Hormonal Receptor Status



BCIRG 006 Patient Characteristics

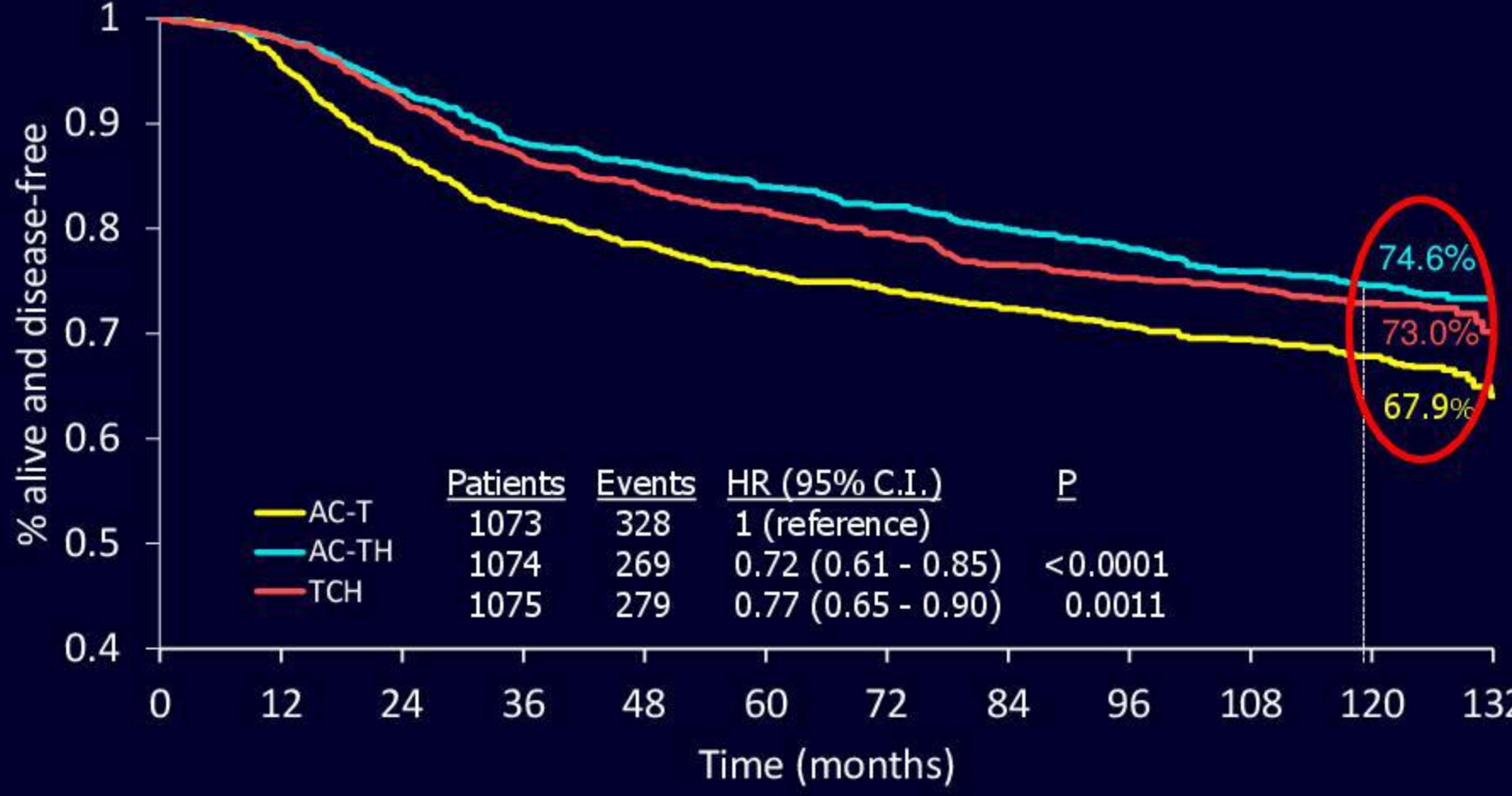
Randomized (n=3,222)	AC→T n=1,073	AC→TH n=1,074	TCH n=1,075
	%	%	%
Age < 50 years	52	52	54
KPS = 100	80	79	80
Mastectomy	60	63	60
Radiotherapy	68	67	69
Hormonotherapy	51	51	51

Enrollment: April 2001 to March 2004

BCIRG 006 Tumor Characteristics

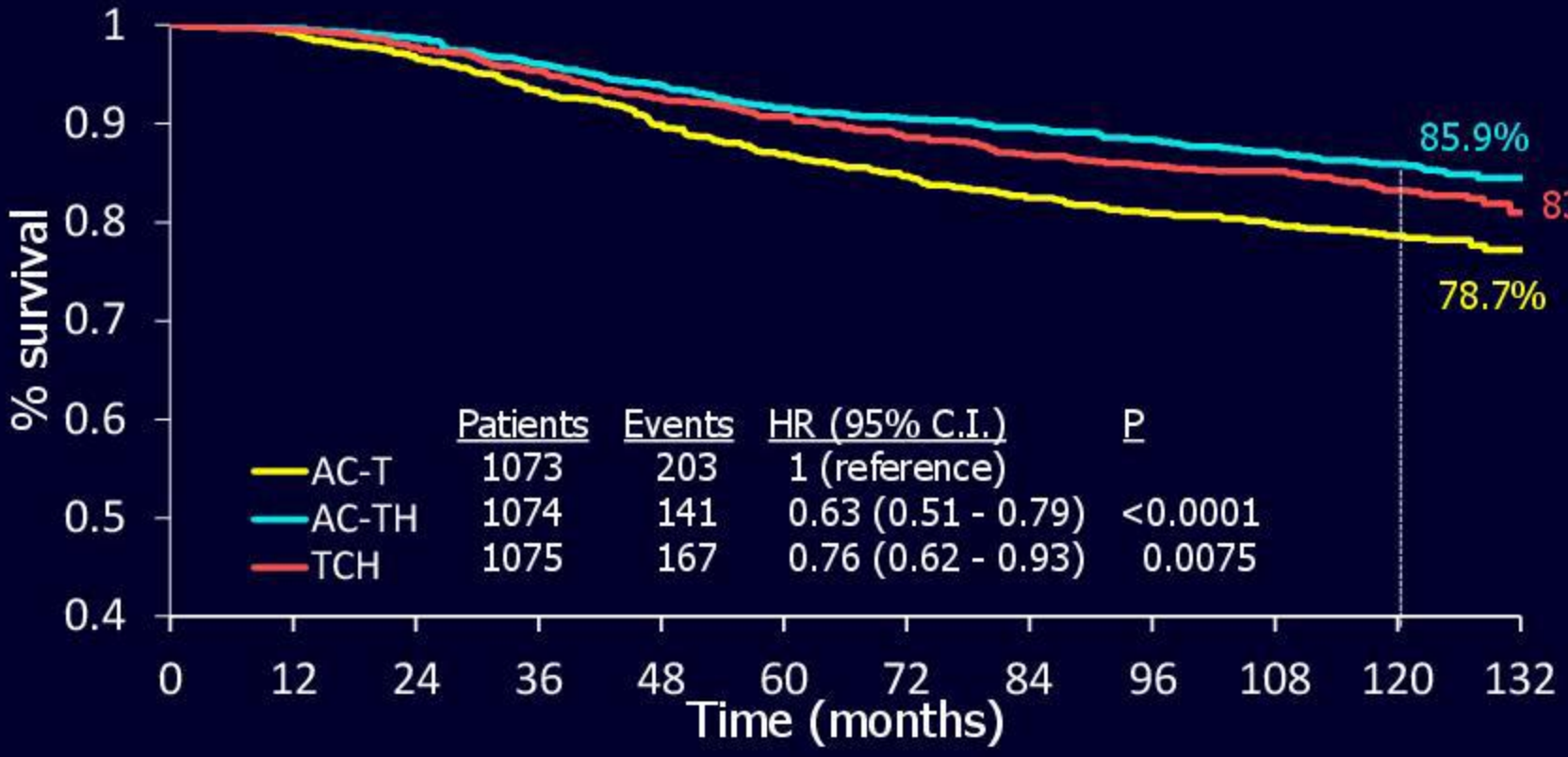
	AC→T n=1,073	AC→TH n=1,074	TCH n=1,075
	%	%	%
Number of nodes +			
0	29	29	29
1 – 3	38	38	39
4 – 10	22	24	23
> 10	11	9	10
Tumor Size (cm)			
≤ 2	41	38	40
> 2 and ≤ 5	53	55	54
> 5	6	7	6
ER and/or PR +	54	54	54

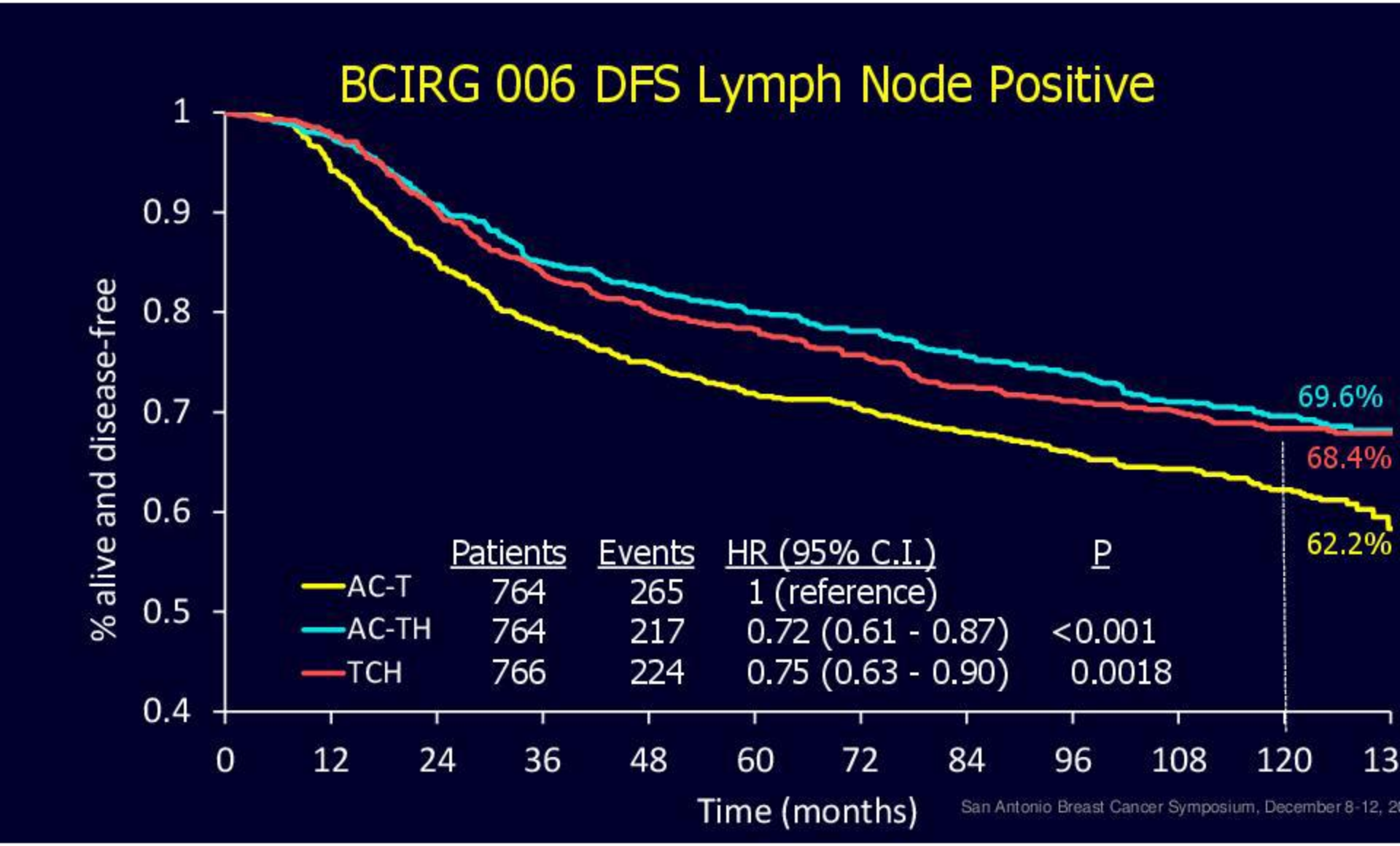
BCIRG-006 Disease Free Survival Final Analysis(10.3y

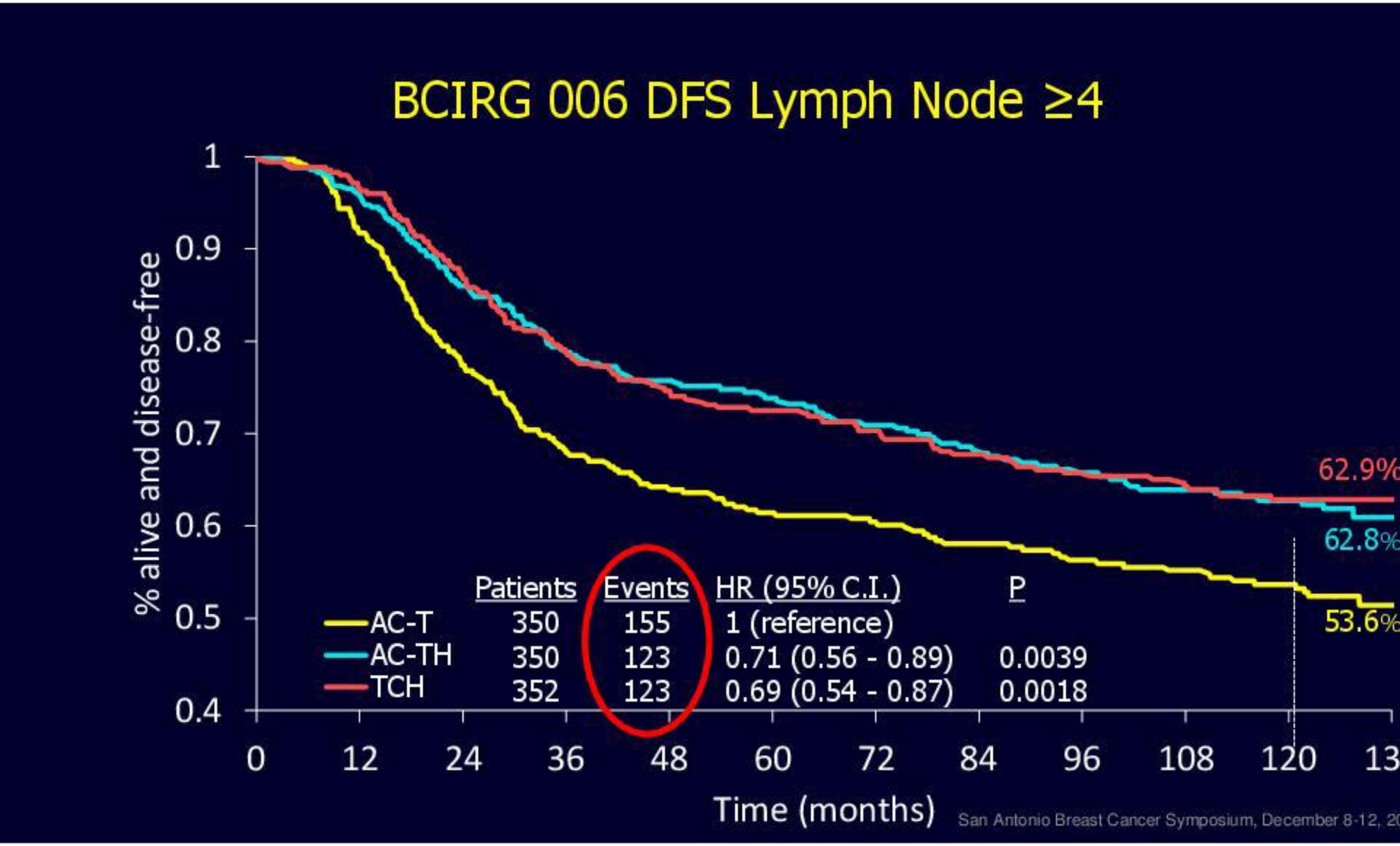


San Antonio Breast Cancer Symposium, December 8

BCIRG 006 Overall Survival (10.3 yrs)




BCIRG 006 DFS Lymph Node Positive
% alive and disease-free
1
0.9
0.8
0.7
0.6
0.5
0.4
0
12
24
36
48
60
72
84
96
108
120
Time (months)
69.6%
68.4%
62.2%
Patients
Events
HR (95% C.I.)
P
AC-T 764 265 1 (reference)
AC-TH 764 217 0.72 (0.61 - 0.87) <0.001
TCH 766 224 0.75 (0.63 - 0.90) 0.0018
San Antonio Breast Cancer Symposium, December 8-12,


BCIRG 006 DFS Lymph Node ≥4
% alive and disease-free
1
0.9
0.8
0.7
0.6
0.5
0.4
0
12
24
36
48
60
72
84
96
108
120
Time (months)
62.9%
62.8%
53.6%
Patients
Events
HR (95% C.I.)
P
AC-T 350 155 1 (reference)
AC-TH 350 123 0.71 (0.56 - 0.89) 0.0039
TCH 352 123 0.69 (0.54 - 0.87) 0.0018
San Antonio Breast Cancer Symposium, December 8-12, 20

BCIRG 006 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

BCIRG 006 Cardiac Deaths and CHF

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,0
Cardiac related death	**0**	**0**	**0**
Cardiac left ventricular function (CHF) Grade 3 / 4	**8**	**21**	**4**

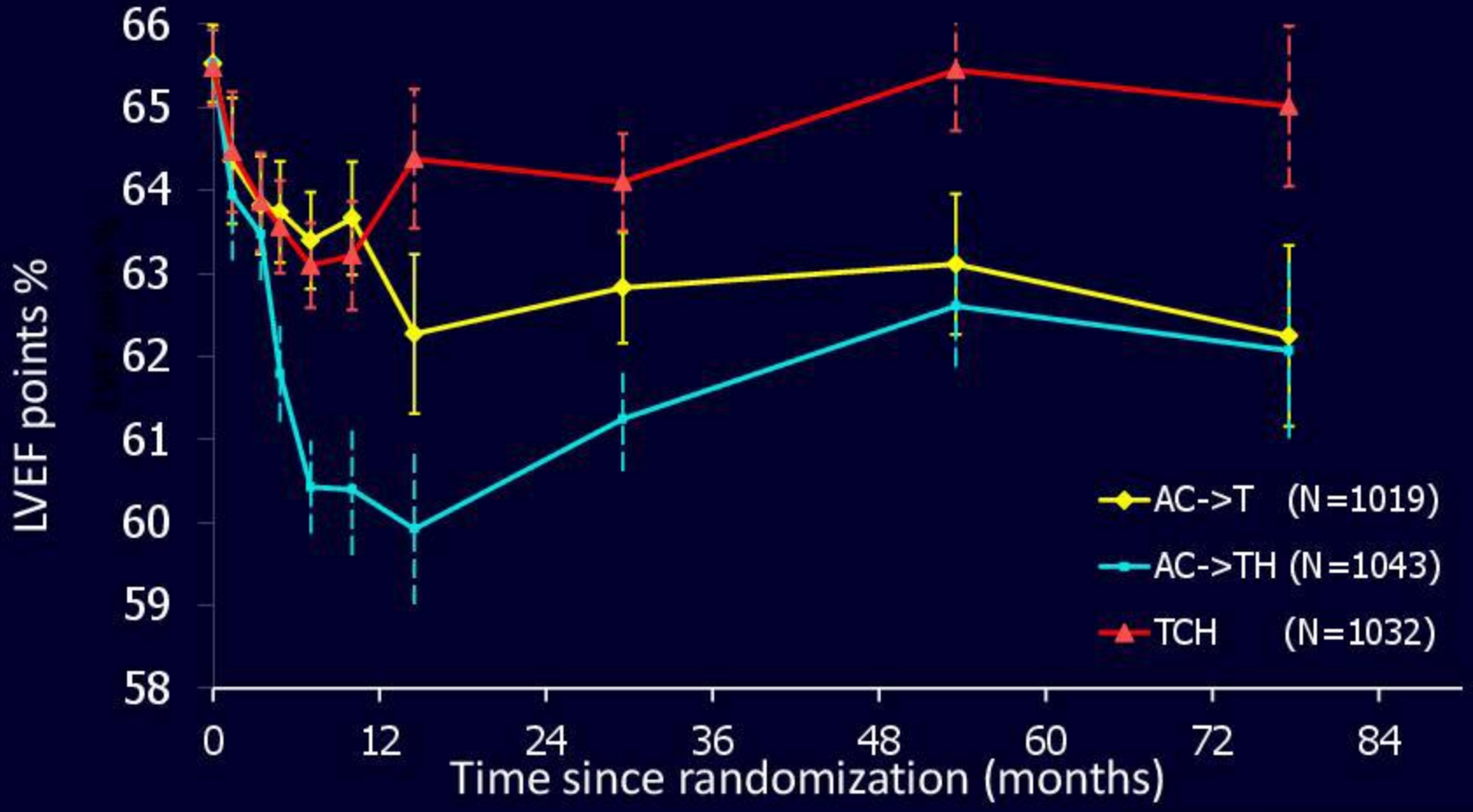
p=0.0005

BCIRG 006
Patients with >10% relative LVEF decline

	AC→T n = 1,018	AC→TH n = 1,042	TCH n = 1,031
Number of Patients	120	200	97

p<0.0001

BCIRG-006 Mean LVEF - All Observations (Final Analysis)



Therapeutic Index – Most Recent 006 Data

	AC→TH	TCH
DFS Events	269	279
Grade 3 / 4 CHF	21	4
Totals	**290**	**283**
Rx-Related Leukemias	*7(8)** **Only in AC-Rx patients*	*0(1)*** ***Leukemia developed after CHOP Rx*
Sustained LVEF Loss >10%	200	97

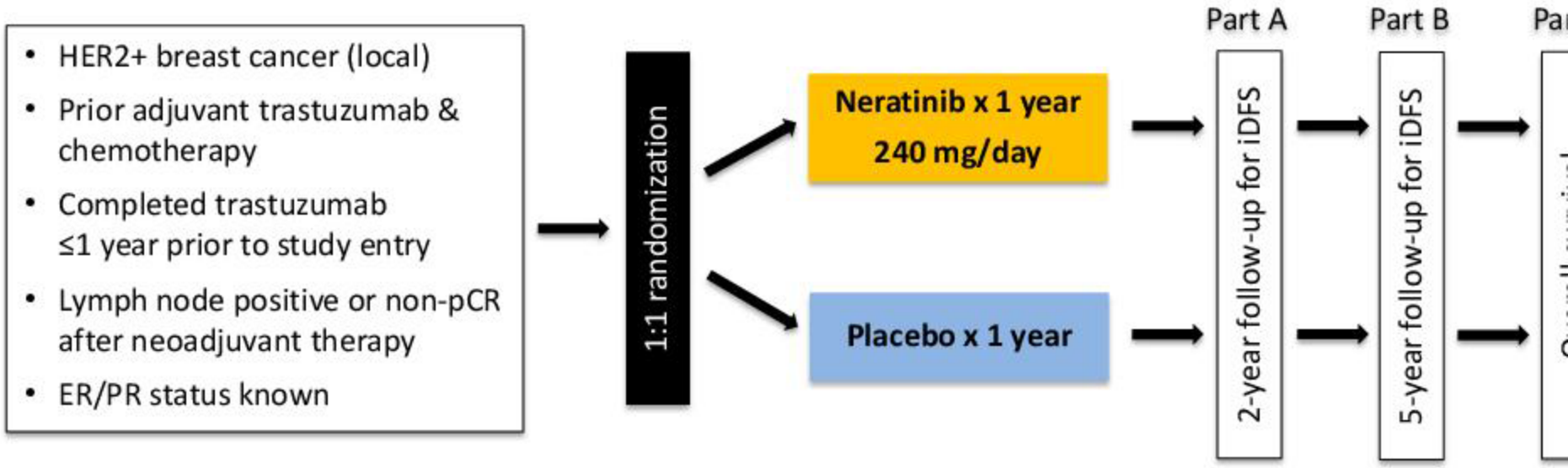
Conclusions

- 10 year follow-up show significant advantage of trastuzumab-containing arms over AC-T
- No statistical advantage in DFS and OS of AC-TH over TCH
  - 10 additional recurrences in TCH arm
- Long-term toxicity greater with AC-TH vs. TCH
  - Congestive Heart Failure: 21 vs. 4
  - Higher rate of sustained LVEF loss
  - Leukemia higher with anthracycline

Neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ breast cancer: 3-year analysis from a phase 3 randomized, placebo-controlled double-blind trial (ExteNET)

Arlene Chan, Suzette Delaloge, Frankie Ann Holmes, Beverly Moy, Hiroji Iwata, Graydon Harker, Norikazu Masuda, Zora Neskovic Konstantinovic, Katerina Petrakova, Angel Guerrero Zotano, Nicholas Iannotti, Gladys Rodriguez, Pierfrancesco Tassone, Gunter von Minckwitz, Bent Ejlertsen, Stephen Chia, Janine Mansi, Carlos Barrios, Marc Buyse, Alvin Wong, Richard Bryce, Yining Ye, Feng Xu, Michael Gnant, Miguel Martin

ExteNET: final study design

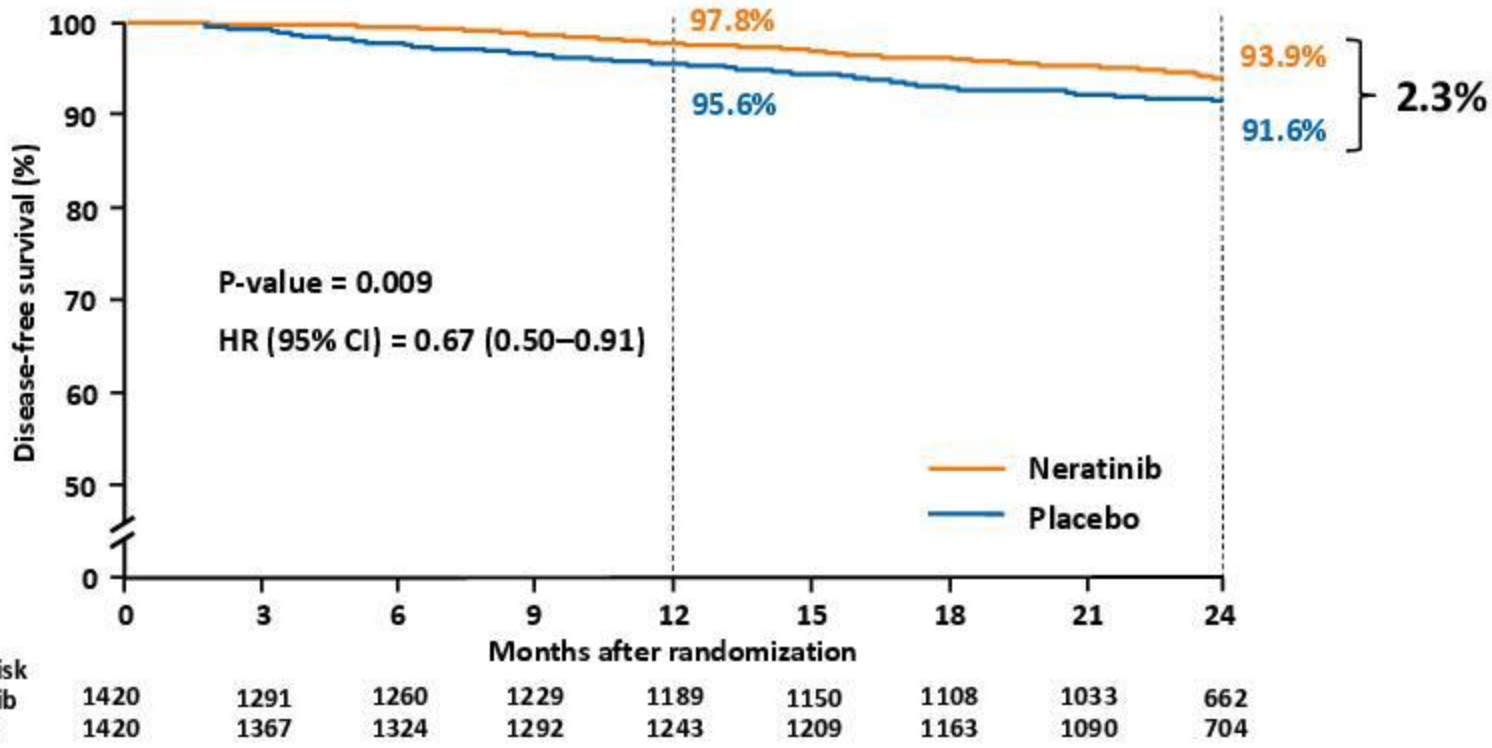


Primary analysis: invasive DFS (iDFS) in ITT population (n=2840)

- iDFS at 2 years: HR=0.67 (0.50–0.91); p=0.009
  - Hormone receptor-positive (n=1631; 57.4%); HR=0.51; p=0.001
  - Centrally-confirmed HER2-positive 60% (n=1463; 51%); HR=0.51; p=0.002

Chan A et al. Lancet Oncol 2015

ExteNET: primary analysis at 2 years



P-value and HR adjusted for hormone receptor statu
trastuzumab (concurrent vs > sequential) and lymph node
Chan A et al. Lancet Oncol 2015

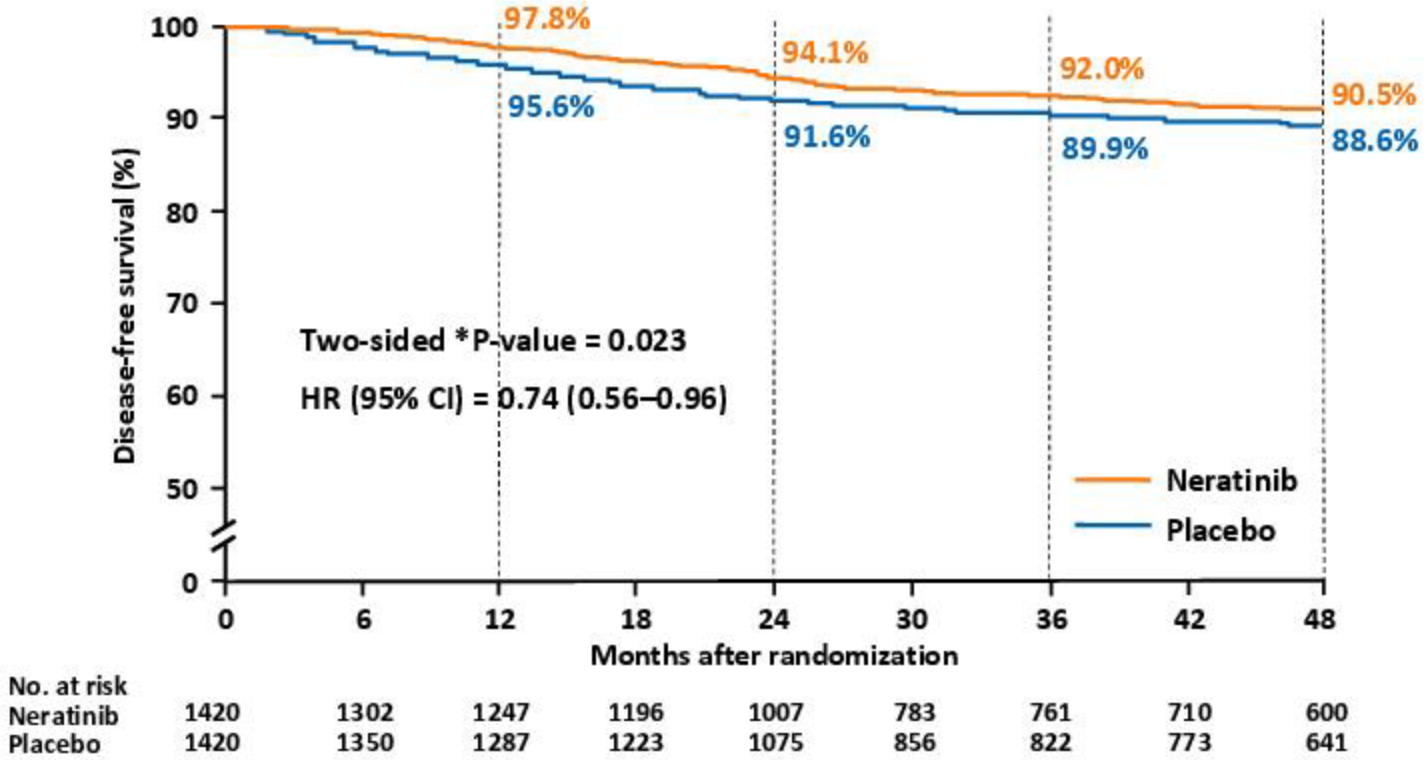
3-year exploratory iDFS analysis

- SAP pre-defines 2-year iDFS as the primary analysis (all alpha spent on primar
  - 5-year iDFS as supportive analysis, OS not mature
- 3-year iDFS analysis is exploratory
  - Data cut-off 30 November 2015
  - HRs based on 3-year data with p-values unadjusted for multiplicity
  - KM curves drawn to 4 years
- Central HER2 testing performed in 2041 patients
  - 1709 HER2-positive (84%)*
  - 332 HER2-negative (16%)

*Similar to TEACH[1] study where 80%
patients were centrally-confirmed as HER2-

[1]Goss P et al. Lancet On

3-year iDFS analysis (ITT: n=2840)

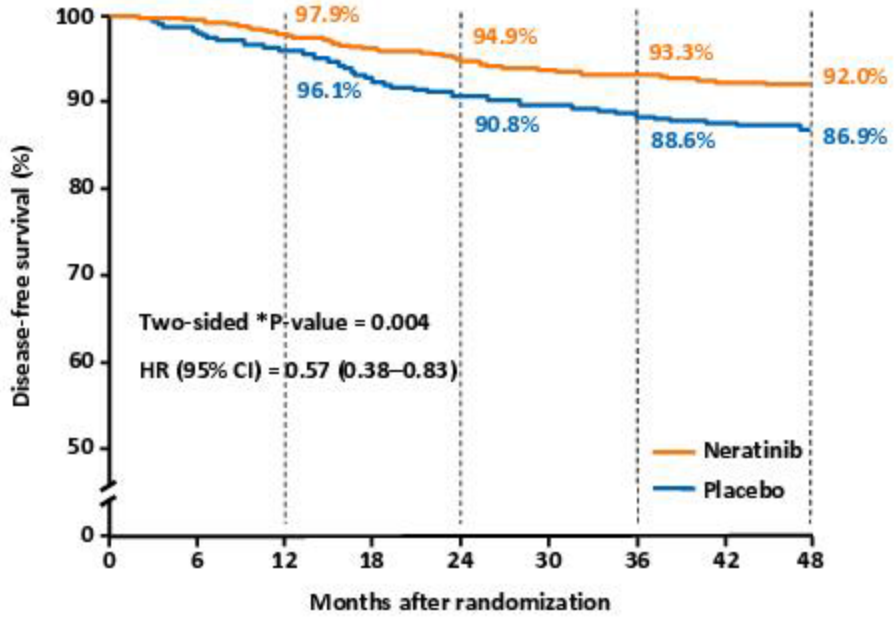


* p value descriptive

3-year iDFS analysis:

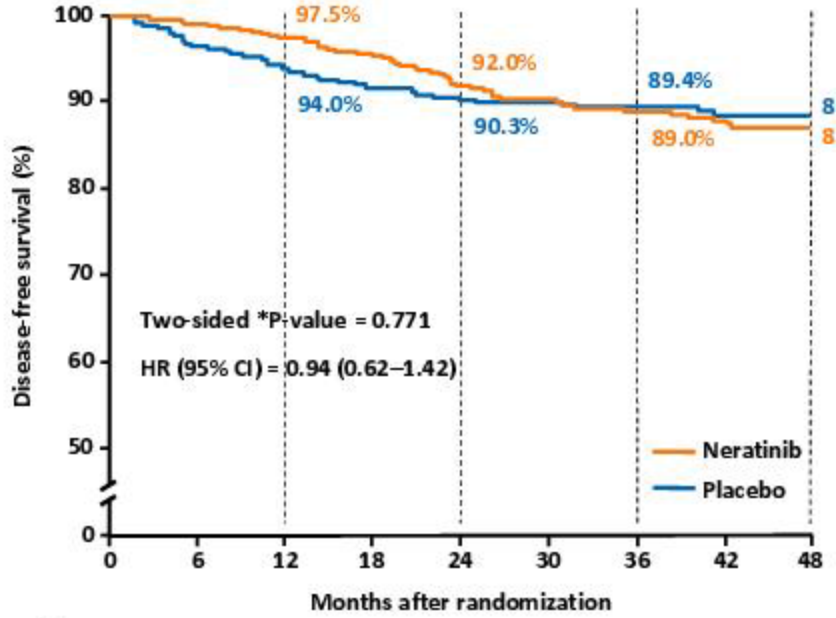
Hormone receptor status & trastuzumab completed ≤1 year prior to study en

Hormone receptor-positive



No. at risk									
Neratinib	670	614	585	562	481	384	377	352	289
Placebo	664	632	603	573	508	407	391	365	291

Hormone receptor-negative



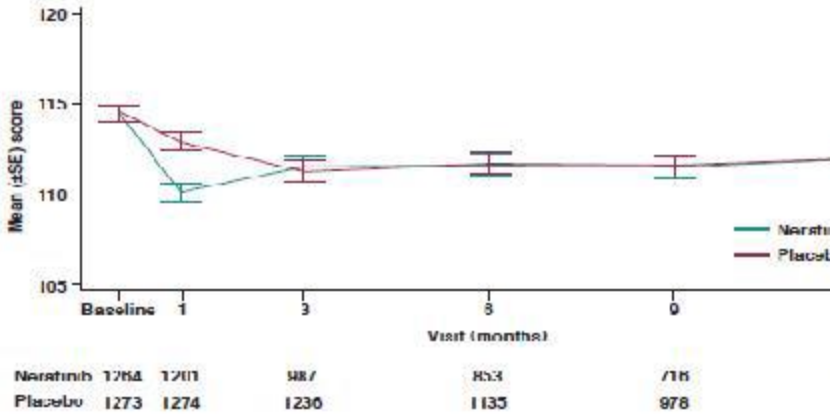
No. at risk									
Neratinib	482	441	428	408	338	260	250	229	187
Placebo	481	450	426	402	358	288	279	263	213

* p value descriptive

Safety & quality of life

Main adverse event was diarrhea

- Grade 3: 39.9% with median duration 5 days (1–139); most occurred <30 days; 1.4% patients hospitalized
- No loperamide prophylaxis given
- Quality of life (FACT-B) difference observed at month 1 and no differences afterwards



Chan A et al. Lancet Oncol 2015

Conclusions

- Primary analysis at 2 years showed 2.3% improvement in DFS with 1 year of neratinib after completing 1 year of trastuzumab
  - Contrast with HERA trial which showed no benefit to 2 years of trastuzumab compared to 1
- Exploratory analysis showed greater benefit among hormone-receptor, HER2-positive patients
  - Bidirectional cross-talk between HR and HER2 associated with endocrine resistance
- Diarrhea improved with imodium prophylaxis, but still a limiting factor in the clinic
  - 16.8% discontinuation; greatest incidence in first 30 days

San Antonio Breast Cancer Symposium, December 8-12

The effect of trastuzumab-based therapy on overall survival in small, node-negative HER2-positive breast cancer: to treat or not to treat?

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Margriet van der Heijden-van der Loo
Gwen M Dackus
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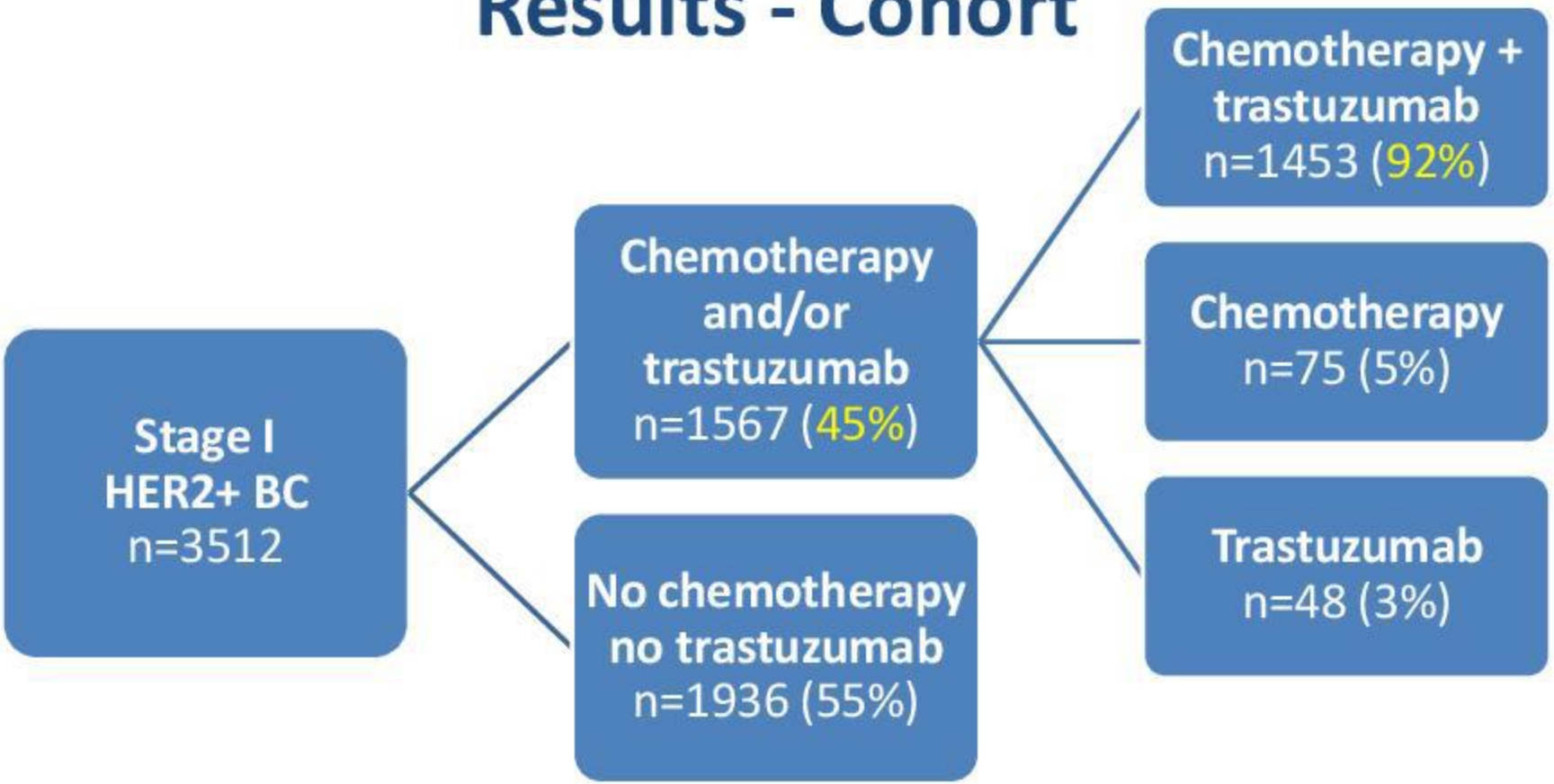
Methods – Data Collection

- Population-based cohort study
- Netherlands Cancer Registry (NCR)[1-2]
- Stage I HER2+ BC diagnosed between 2006-2012
- Linkage with Statistics Netherlands[3]

[1] Schouten et al. *Int J Epidemiol* 1993;22:369
[2] www.iknl.nl
[3] www.cbs.nl

Results - Cohort



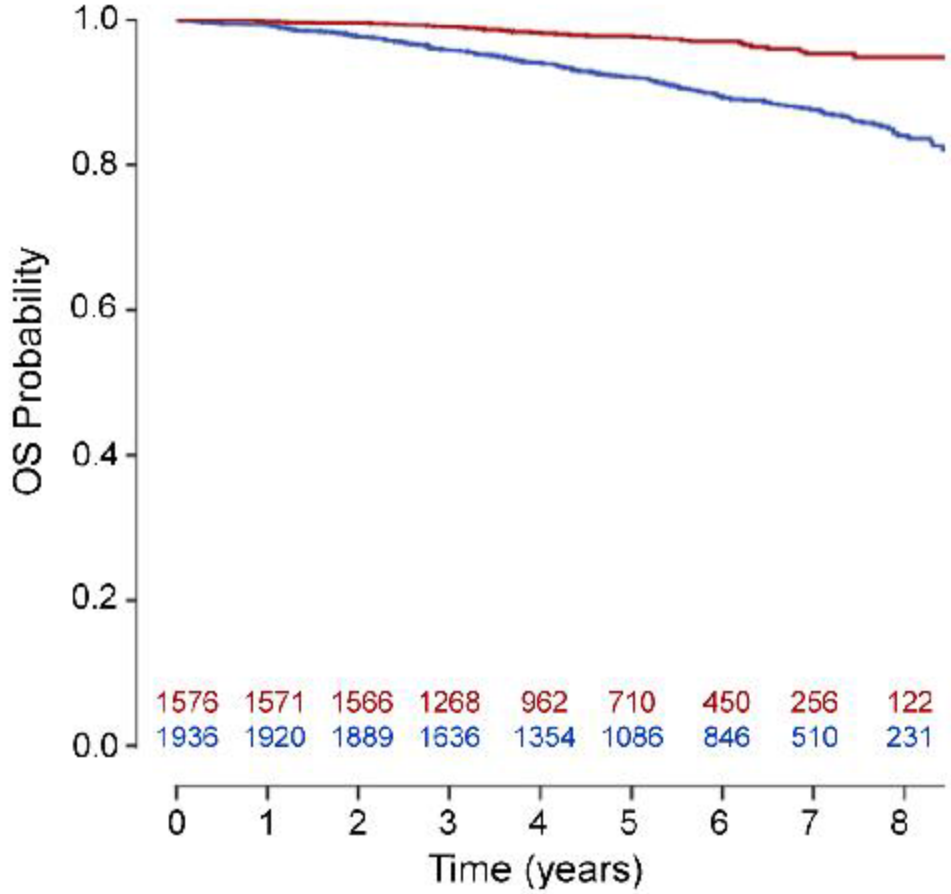
Results - Cohort

	No chemo no Tzt n=1936		Chemo and/or Tzt n=1576		
	n	(%)	n	(%)	*p-value*
Age (years)					*<0.001*
Median (range)	62	(26-90)	52	(19-75)	
Pathologic tumor stage					*<0.001*
T1a	357	(19%)	28	(1%)	
T1b	650	(34%)	150	(10%)	
T1c	929	(48%)	1398	(89%)	
Pathologic nodal stage					*0.003*
Negative	1833	(95%)	1453	(92%)	
Isolated tumor cells	103	(5%)	123	(8%)	
Grade					*<0.001*
I	267	(14%)	28	(2%)	
II	954	(49%)	472	(30%)	
III	599	(31%)	1033	(66%)	
Unknown	116	(6%)	43	(3%)	

Results - Cohort

	No chemo no Tzt n=1936		Chemo and/or Tzt n=1576		
	n	**(%)**	**n**	**(%)**	***p-value***
Hormone receptor status					*<0.001*
ER- and PR-	529	(27%)	554	(35%)	
ER+ and/or PR+	1394	(72%)	1013	(64%)	
Unknown	13	(1%)	9	(1%)	
Endocrine therapy					*<0.001*
No	1475	(76%)	713	(45%)	
Yes	461	(24%)	863	(55%)	

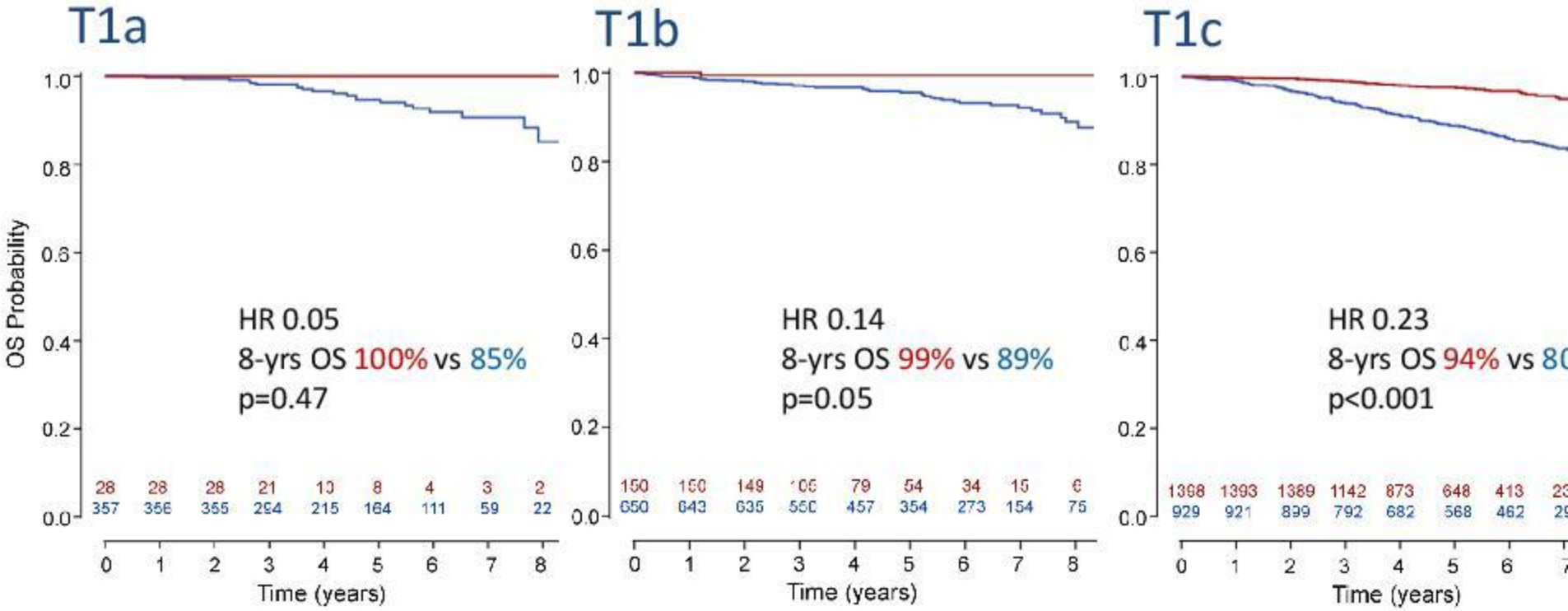
Results - Overall Survival



HR 0.29 (95%CI 0.21-0.41)
8-yrs OS 95% vs 84%
p<0.001

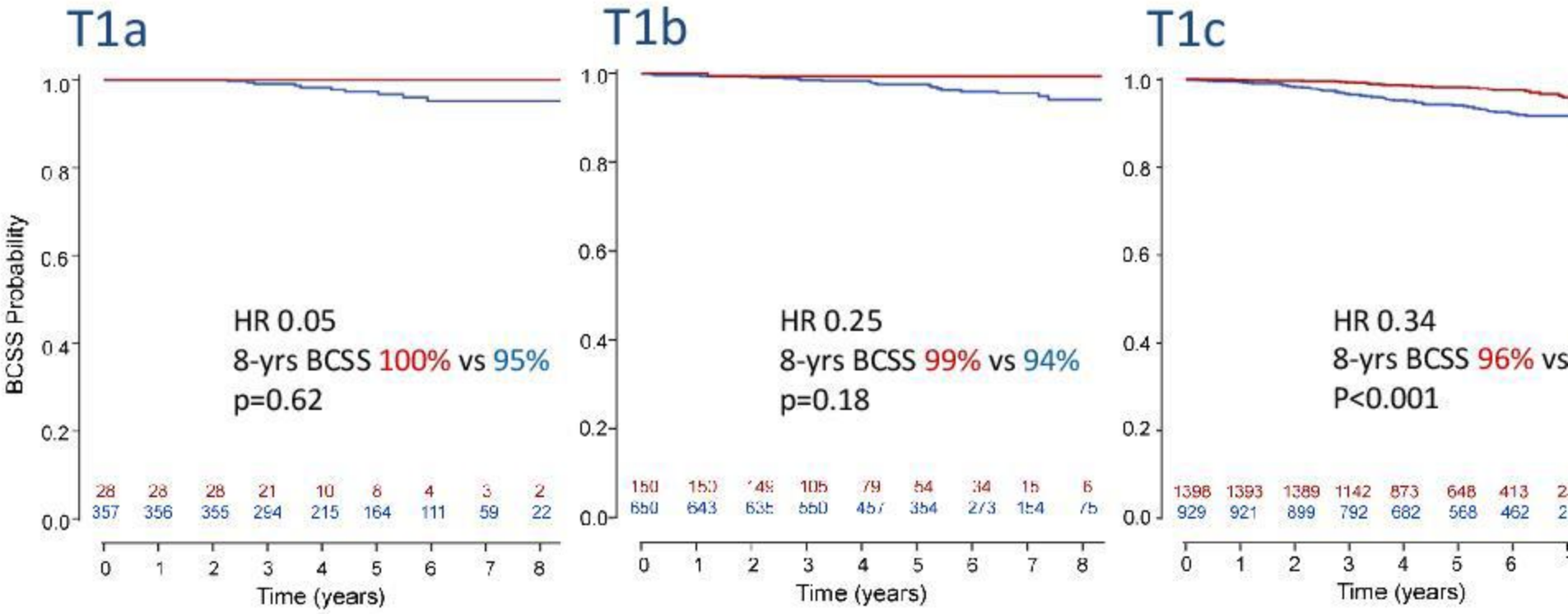
HR_{adj} 0.35 (95%CI 0.23-0.52)
p<0.001

Results - Overall Survival



Treated - Untreated

Results – Breast Cancer Specific Survival



Treated - Untreated

Conclusions

- Cohort study shows benefit in breast-cancer specific survival and OS with chemo + trastuzumab among T1a, T1b, T1c tumors
  - Selection bias in cohort has potential to impact OS
- Results support NCCN guidelines which currently recommend consideration of adjuvant chemo + trastuzumab for T1a-T1b tumors

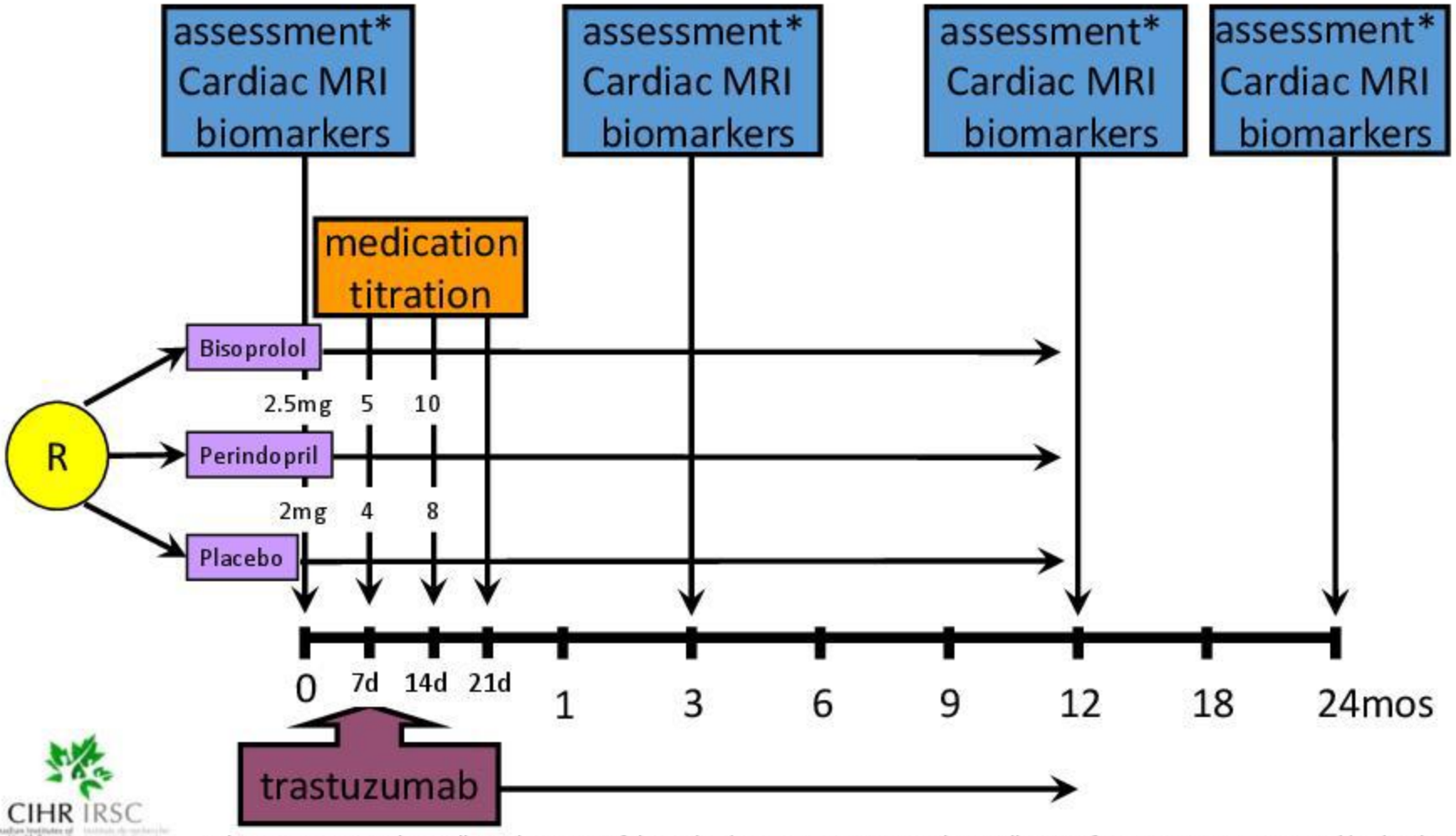
MANTICORE 101:
Multidisciplinary Approach to Novel Therapies In Cardio-Oncology REsearch

Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, Thompson R, Oudit G, Ezekowitz J, Paterson I.

University of Alberta, Edmonton, AB, Canada; Cross Cancer Institute, Edmonton, AB, Canada; Mazankowski Alberta Heart Institute, Edmonton, AB, Canada; University of Manitoba, Winnipeg, MB, Canada; University of Texas, Arlington, TX.

San Antonio Breast Cancer Symposium, December 8-12, 2015

MANTICORE Design Overview



Safety

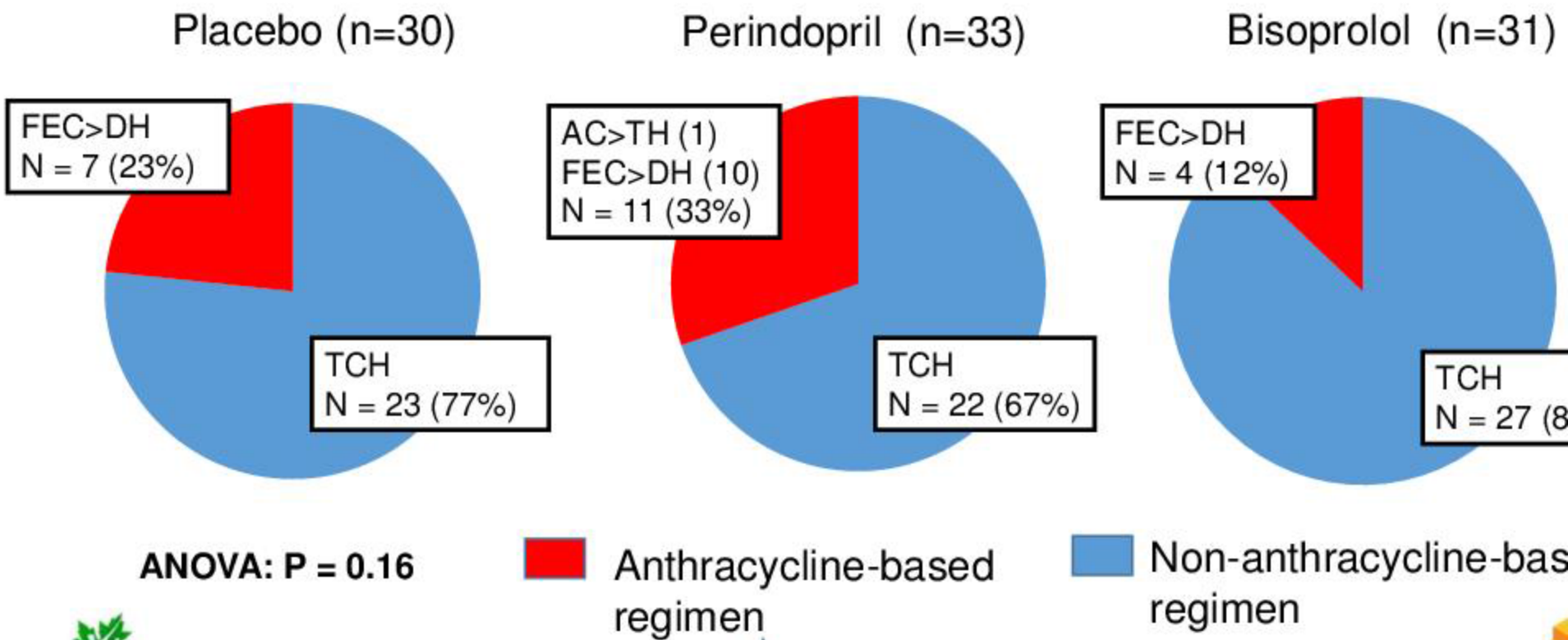
	Placebo (N=30)	Perindopril (N=33)	Bisoprolol (N=31)	ANOVA P value
Max dose level achieved, number (%)				0.02
(perindopril 2mg, bisoprolol 2.5mg)	0	3 (10%)	6 (19%)	
(perindopril 4mg, bisoprolol 5mg)	3 (10%)	5 (15%)	5 (16%)	
(perindopril 8mg, bisoprolol 10mg)	27 (90%)*	25 (75%)	20 (65%)	
Pre-cycle #1 trastuzumab				
Systolic blood pressure	124 ± 13	126 ± 13	121 ± 12	0.32
Diastolic blood pressure	75 ± 10	78 ± 11	74 ± 6	0.13
Heart rate	76 ± 11	82 ± 14*	72 ± 9	< 0.01
Post-cycle #17 trastuzumab				
Systolic blood pressure	122 ± 16	117± 11†	118 ± 18	0.50
Diastolic blood pressure	75 ± 13	70 ± 19†	72 ± 12	0.20
Heart rate	72 ± 14	74 ± 12	62 ± 10*†	0.001

* $P < 0.05$ compared to other groups, † $P < 0.05$ from baseline

Safety

	Placebo (N=30)	Perindopril (N=33)	Bisoprolol (N=31)
Premature study drug termination	0	0	0
Dose reductions explanations			
- hyperkalemia/renal	1 (3%)	6 (18%)	6 (19%)
- bradycardia	1 (3%)	0	1 (3%)
- dizziness	0	0	2 (6%)
- hypotension	1 (3%)	0	1 (3%)
- patient preference	0	2 (6%)	1 (3%)

Patient Characteristics – Anthracyclines



Patient Characteristics - Cardiovascular

	Placebo (n=30)	Perindopril (n = 33)	Bisoprolol (n=31)	Total (n=94)	ANOVA P value
Dyslipidemia	0	1	1	2	0.62
Hypertension	2	2	0	4	0.36
Type 2 diabetes	0	1	3	4	0.16
Smoking history					0.49
- never	14	17	21	52	
- past	12	14	7	33	
- current	3	2	3	8	
- not stated	1	0	0	1	
Alcohol use					0.20
- none	5	7	8	20	
- < 1 drink/day	23	26	20	69	
- 1 – 2 drinks/day	0	0	2	2	
- 3 + drinks/day	2	0	1	3	

Results – Cardiac MRI

	Placebo (N=30)	Perindopril (N=33)	Bisoprolol (N=31)	ANOVA P value
Pre LVEDVi (ml/m^2)	76 ± 13*	67 ± 14	69 ± 10	**< 0.01**
Post LVEDVi (ml/m^2)	79 ± 12	74 ± 16†	76 ± 14†	**0.27**
Δ LVEDVi from baseline	+4 ± 11	+7 ± 14	+8 ± 9	**0.36**
Pre LVEF (%)	61 ± 5	62 ± 5	62 ± 4	**0.55**
Post LVEF (%)	56 ± 4*†	59 ± 6†	61 ± 4	**0.0001**
Δ LVEF from baseline	-5 ± 5	-3 ± 4	-1 ± 5*	**0.001**
Trastuzumab interruptions due to drop in LVEF	8*	1	1	**0.002**

* $P < 0.05$ compared to other groups, † $P < 0.05$ from baseline

CIHR IRSC

Alberta CANCER FOUNDATION

Conclusions

- Prophylactic intervention with ACE inhibitor or Beta blocker helped preserve LVEF on trastuzumab
- Fewer interruptions in trastuzumab
- Similar to findings from PRADA trial (N=120) which showed preservation of LVEF with angiotensin receptor blocker
- Small trial (N=94)

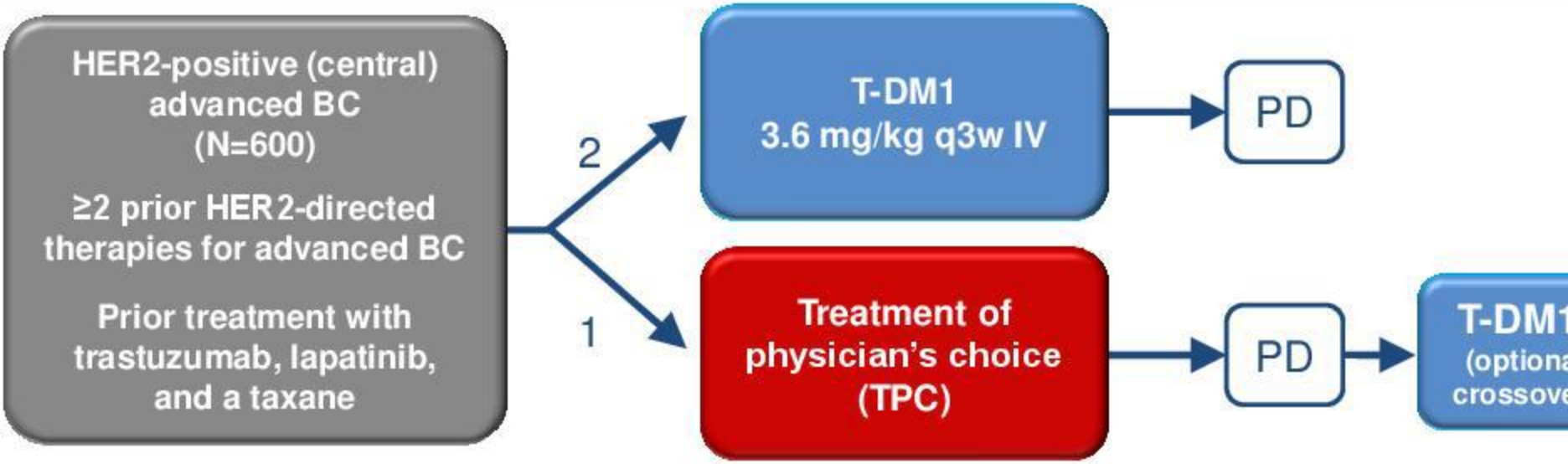
San Antonio Breast Cancer Symposium, December 8-1

Trastuzumab emtansine (T-DM1) improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: final overall survival results from the phase 3 TH3RESA study

Hans Wildiers,[1] Sung-Bae Kim,[2] Antonio Gonzalez Martin,[3] Patricia M. LoRusso,[4] Jean-Marc Ferrero,[5] Tanja Badovinac-Crnjevic,[6] Ron Yu,[7] Melanie Smitt,[7] Ian E. Krop[8]

[1]University Hospitals Leuven, Leuven, Belgium; [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [3]MD Anderson Cancer Center, Madrid, Spain; [4]Yale Cancer Center, Yale University Medical Center, New Haven, CT, USA; [5]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; [6]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [7]Genentech, Inc, South San Francisco, CA, USA; [8]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

TH3RESA Study Schema



Stratification factors: World region, number of prior regimens for advanced BC, presence of visceral dise

Co-primary endpoints: PFS by investigator and OS

Key secondary endpoints: ORR by investigator and safety

[a]First patient in: Sept, 2011. Study amended: Sept, 2012 following EMILIA 2nd interim OS results to allow patients in the TPC arm to receive T-DM1 after documented PD.

Baseline Characteristics

Characteristic	TPC (n=198)	T-DM1 (n=404)
Age, %		
<65 years	82.8	85.4
65–74 years	14.1	11.4
≥75 years	3.0	3.2
World region, %		
United States	24.2	24.5
Western Europe	42.9	42.3
Other	32.8	33.2
Race, %		
White	81.3	80.4
Asian	12.1	14.1
Other[a]	6.6	5.4
ECOG PS,[b] %		
0	41.4	44.8
1	51.0	49.8
2	7.6	5.5

[a]Multi-racial patients are included in the Other category.
[b]Two patients in the T-DM1 arm had missing ECOG PS scores.

Characteristic	TPC (n=198)	T-DM1 (n=404)
ER and/or PR-positive, %	52.0	51.5
Visceral involvement, %	75.8	74.8
Disease extent at study entry, %		
Metastatic	94.4	96.8
Unresectable locally advanced/recurrent BC	5.6	3.2
Number of prior regimens (excluding hormonal) for advanced BC,[a] median (range)	4 (1–19)	4 (1–14)
≤3, %	39.4	32.6
4–5, %	32.8	37.1
>5, %	27.8	30.3
Brain metastasis at baseline, %	13.6	9.9

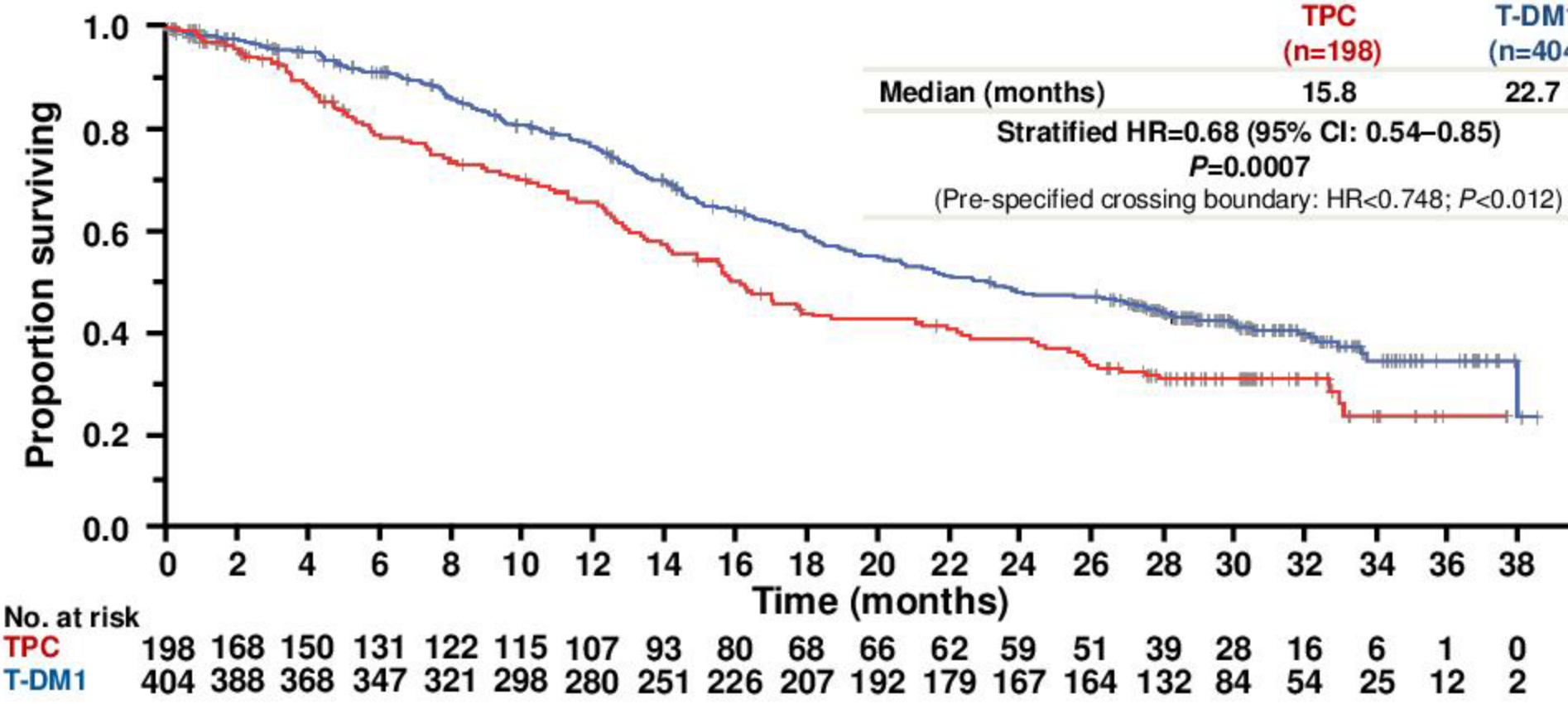
[a]Two patients in the T-DM1 arm had missing information for prior treatment in the advanced BC setting.

Treatment of Physician's Choice Regimen

TPC treatment regimen	TPC (n=184[a])	
Combination with HER2-directed agent, %	**83.2**	
Chemotherapy[b] + trastuzumab	68.5	**Trastuzumab-containing 80.4**
Lapatinib + trastuzumab	10.3	
Hormonal therapy + trastuzumab	1.6	
Chemotherapy[b] + lapatinib	2.7	
Single-agent chemotherapy,[b] %	**16.8**	

[a]Includes patients who received study treatment. Excludes one patient who was randomized to the TPC arm but received two cycles of T-DM1 by mistake.
[b]The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.

Final OS Analysis



Grade ≥3 AEs With Incidence ≥2% in Either Arm

	TPC (n=184)		T-DM1 (n=403)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nonhematologic AEs, %				
Diarrhea	22.3	**4.3**	12.7	0.7
Dyspnea	13.0	3.8	11.7	2.5
Asthenia	17.9	3.3	19.1	1.0
Abdominal pain	12.5	2.7	7.4	1.2
AST increased	7.1	2.7	12.4	2.5
Fatigue	26.1	2.7	30.8	2.2
ALT increased	5.4	2.2	9.2	1.5
Cellulitis	3.8	2.2	1.7	0.5
Pulmonary embolism	2.2	2.2	0.5	0.5
Hematologic AEs, %				
Neutropenia	21.7	**15.8**	7.7	2.5
Febrile neutropenia	3.8	**3.8**	0.2	0.2
Anemia	11.4	3.3	11.4	3.5
Leukopenia	6.0	2.7	2.2	0.5
Thrombocytopenia[a]	3.8	2.7	20.6	**6.0**

Shading indicates grade ≥3 AEs with >3% difference between the TPC and T-DM1 arms.
[a]The incidence of grade ≥3 hemorrhage of any type (basket term) was 4.2% (T-DM1) and 0.5% (TPC).

Conclusions

- T-DM1 improved OS compared to TPC among HER2-positive MBC pretreated with taxane, trastuzumab, lapatinib by 6.9 months
  - 15.8 to 22.7 months
  - OS benefit seen despite crossover by 50% of TPC
- Favorable safety profile despite longer treatment duration
- Solidifies role of T-DM1 in treatment of previously treated HER2-positive MBC