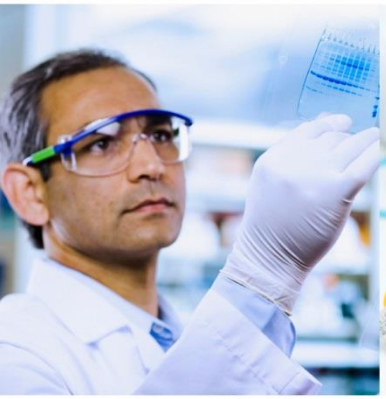
GASCO 2017 San Antonio Breast Cancer Symposium Review

HER2-Positive Breast Cancer and Survivorship

Amelia Zelnak, MD, MSc
Atlanta Cancer Care
Northside Hospital Cancer Institute




NORTHSIDE HOSPITAL
CANCER INSTITUTE

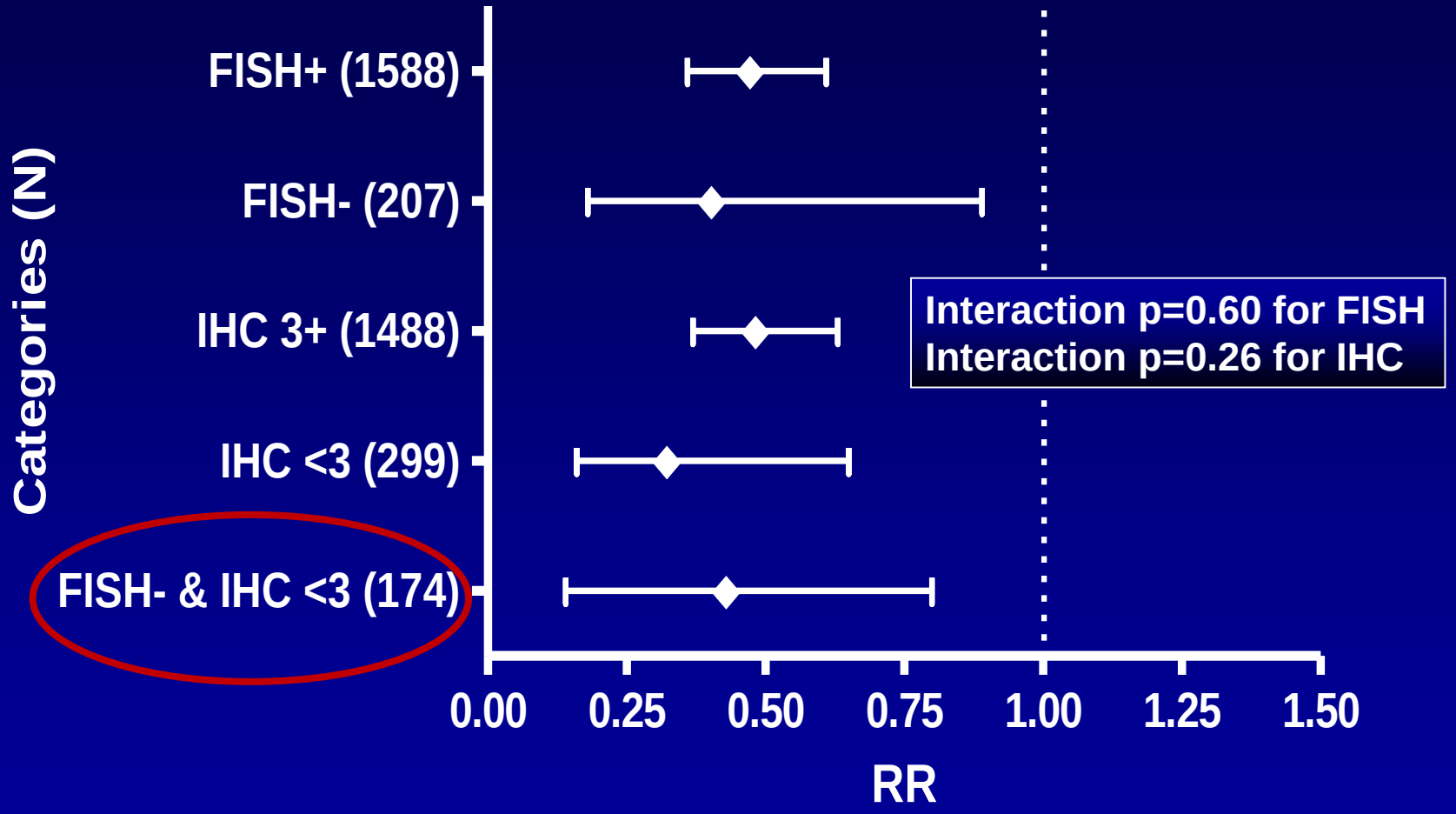
Disclosure

- **I, Amelia Zelnak, declare that neither I nor any member of my family has a financial arrangement or affiliation with any corporate organization offering financial support or grant monies for this continuing medical education activity or with any corporate organization that might have an interest in the subject being presented.**

NSABP B-47 (NRG Oncology) Phase III RCT Comparing Adjuvant Chemotherapy with AC→Weekly Paclitaxel or TC x 6 with or without Trastuzumab for 1 Year in High-risk, Invasive Breast Cancer Negative for HER2 by ISH and with IHC 1+ or 2+ (HER2-Low IBC)

Louis Fehrenbacher, Reena S. Cecchini, Charles E. Geyer, Jr., Priya Rastogi, Joseph P. Costantino, James N. Atkins, John Crown, Jonathan Polikoff, Jean-Francois Boileau, Louise Provencher, Christopher Stokoe, Timothy D. Moore, André Robidoux, Virginia Borges, Kathy S. Albain, Sandra M. Swain, Soonmyung Paik, Eleftherios P. Mamounas, Norman Wolmark

RR of ACTH/ACT for DFS (NSABP B-31)

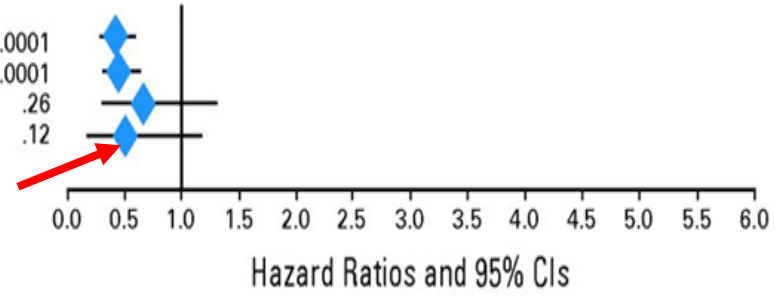


Note: RR adjusted for ER and nodal status

N9831 Outcomes by HER2 Status

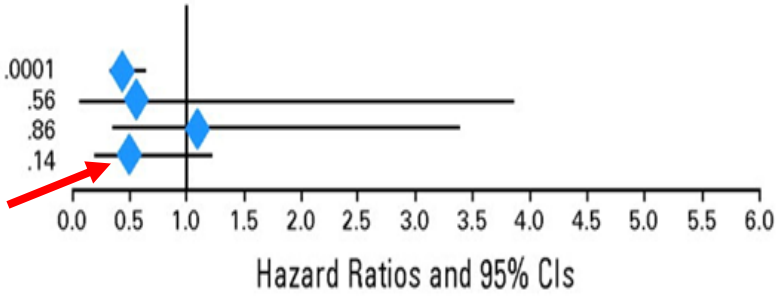
A

Subgroup	n	HR*	95% CI	P
IHC or FISH *HER2*/CEP17 RATIO				
IHC 3+	1,512	0.46	0.33 to 0.63	< .0001
FISH ≥ 2.0	1,639	0.49	0.36 to 0.68	< .0001
IHC 0, 1, 2+	333	0.69	0.36 to 1.32	.26
FISH < 2.0	156	0.54	0.25 to 1.17	.12



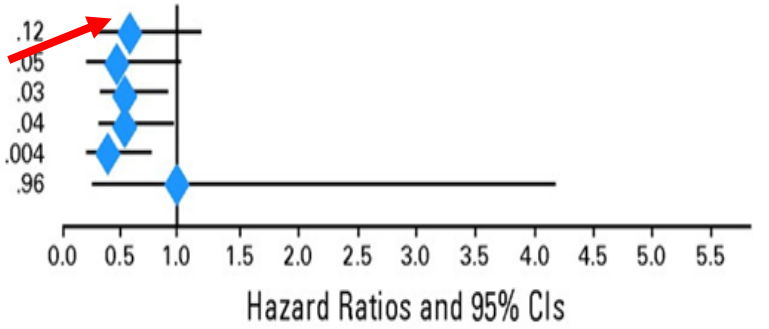
B

IHC/FISH *HER2*/CEP17 RATIO				
3+/ ≥ 2.0	1,408	0.45	0.32 to 0.63	< .0001
3+/ < 2.0	53	0.57	0.08 to 3.89	.56
0,1,2+/ ≥ 2.0	219	1.11	0.36 to 3.43	.86
0,1,2+/ < 2.0	103	0.51	0.21 to 1.23	.14



C

FISH *HER2*/CEP17 RATIO				
< 2.0	156	0.54	0.25 to 1.17	.12
2.0 - 5.0	253	0.42	0.18 to 1.01	.05
5.0 - 8.0	515	0.50	0.27 to 0.92	.03
8.0 - 11.0	473	0.51	0.27 to 0.95	.04
11.0 - 15.0	328	0.35	0.17 to 0.72	.004
≥ 15.0	70	0.96	0.21 to 4.35	.96

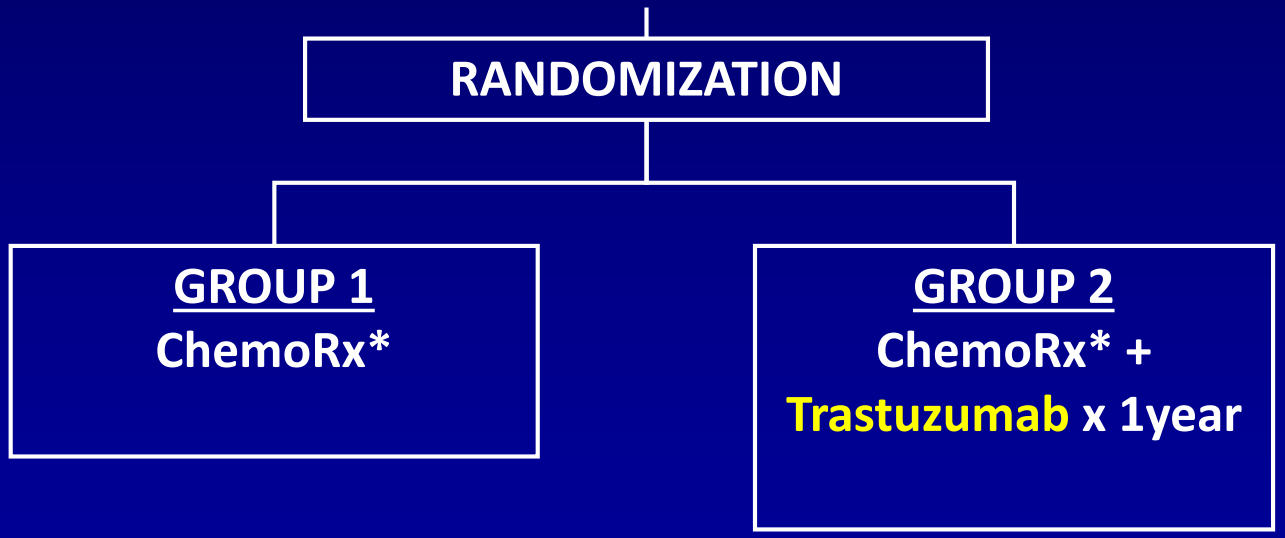


Perez EA, et al. J Clin Oncol. 2010;28:4307-15

B-47: Adjuvant Trastuzumab in HER2 Low Breast Cancer

STRATIFICATION

- HER2 IHC Score (1+, 2+)
- Number of Positive Nodes (0-3, 4-9, 10+)
- ER / PgR Status
- Intended ChemoRx regimen (AC→WP, TC)



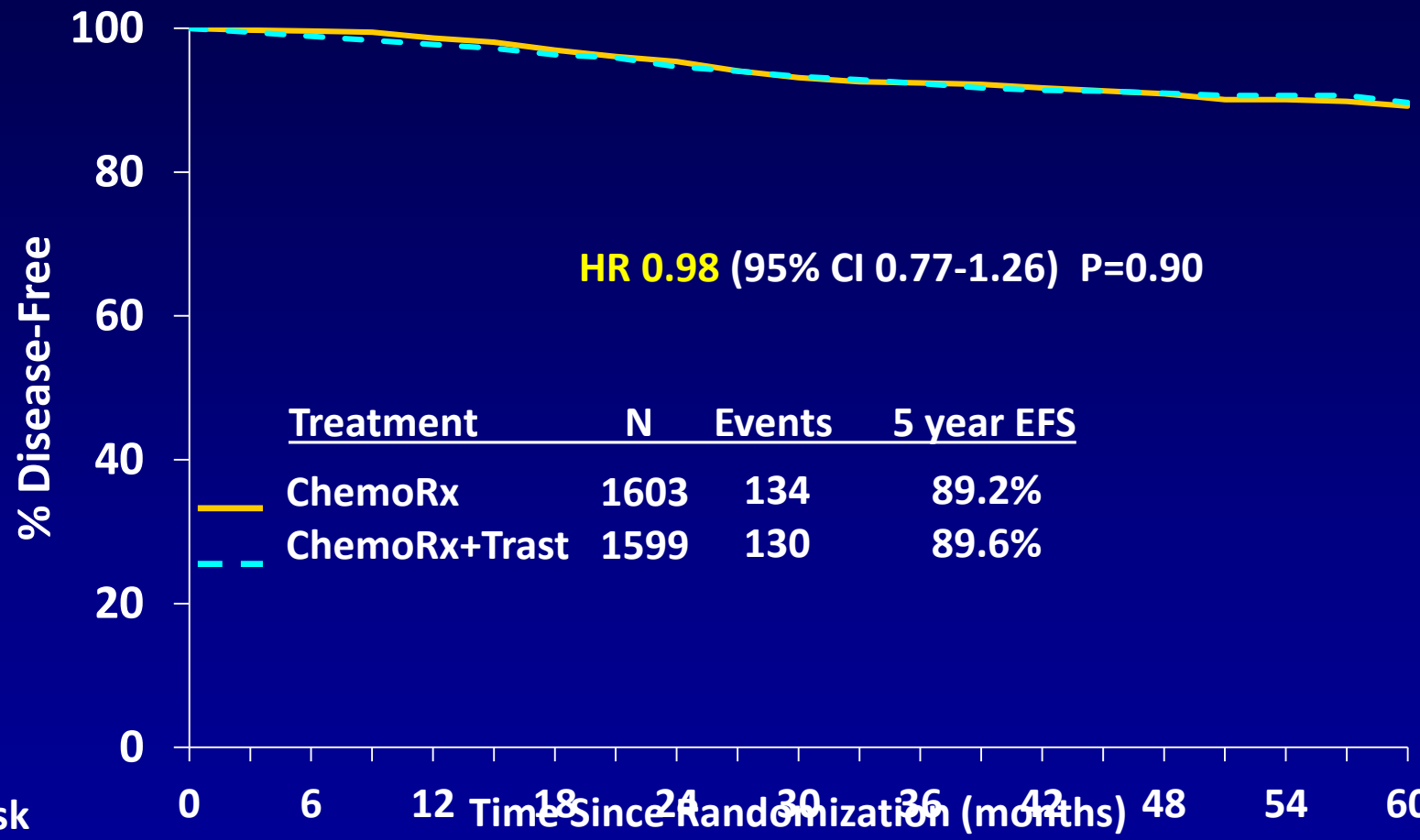
Hormonal therapy and radiation as indicated. Chemotherapy by MD Choice:

***AC→WP: Doxorubicin 60mg/m2 and Cyclophosphamide 600mg/m2 q2 or 3 wks x 4 followed by qwk paclitaxel x 12**
or TC: Docetaxel 75mg/m2 + Cyclophosphamide 600mg/m2 q3wk x 6

B-47: Patient Characteristics

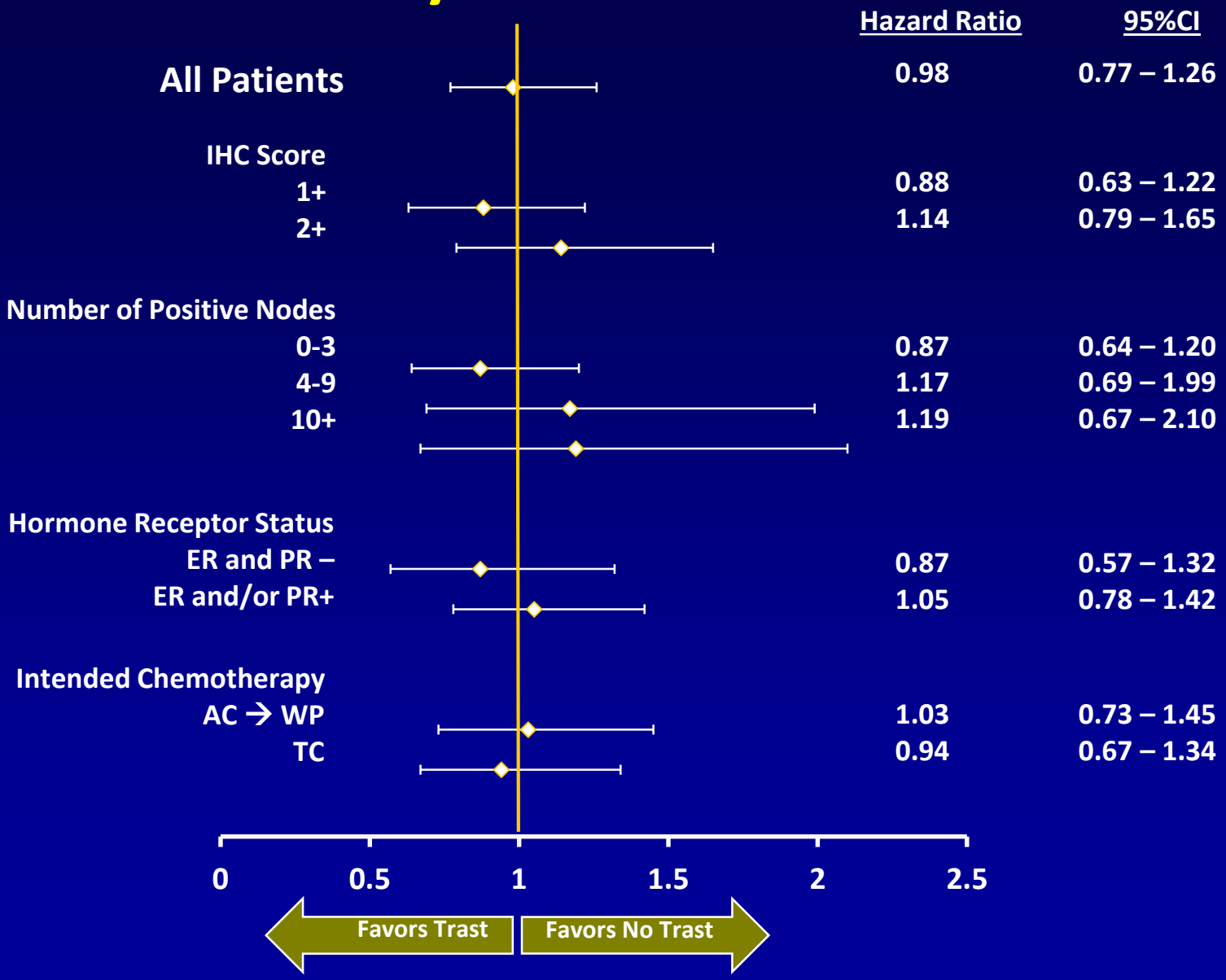
Characteristic	Cohorts	ChemoRx	ChemoRx + Trast
Age at entry (yrs)	≤49 ≥50	41.1% 58.9%	41.9% 58.1%
Race	White Black Other	84.0% 8.8% 7.2%	82.6% 10.7% 6.8%
Number of positive nodes	Negative 1 – 3 4 or more	21.5% 52.4% 26.1%	18.4% 53.0% 28.6%
ER/PgR status	Both Negative ER and/or PgR Positive	17.2% 82.8%	17.3% 82.7%
Intended chemotherapy	AC→WP TC	55.8% 44.2%	55.9% 44.1%
IHC Score	1+ 2+	56.2% 43.8%	57.7% 42.3%

B-47: Invasive Disease-Free Survival

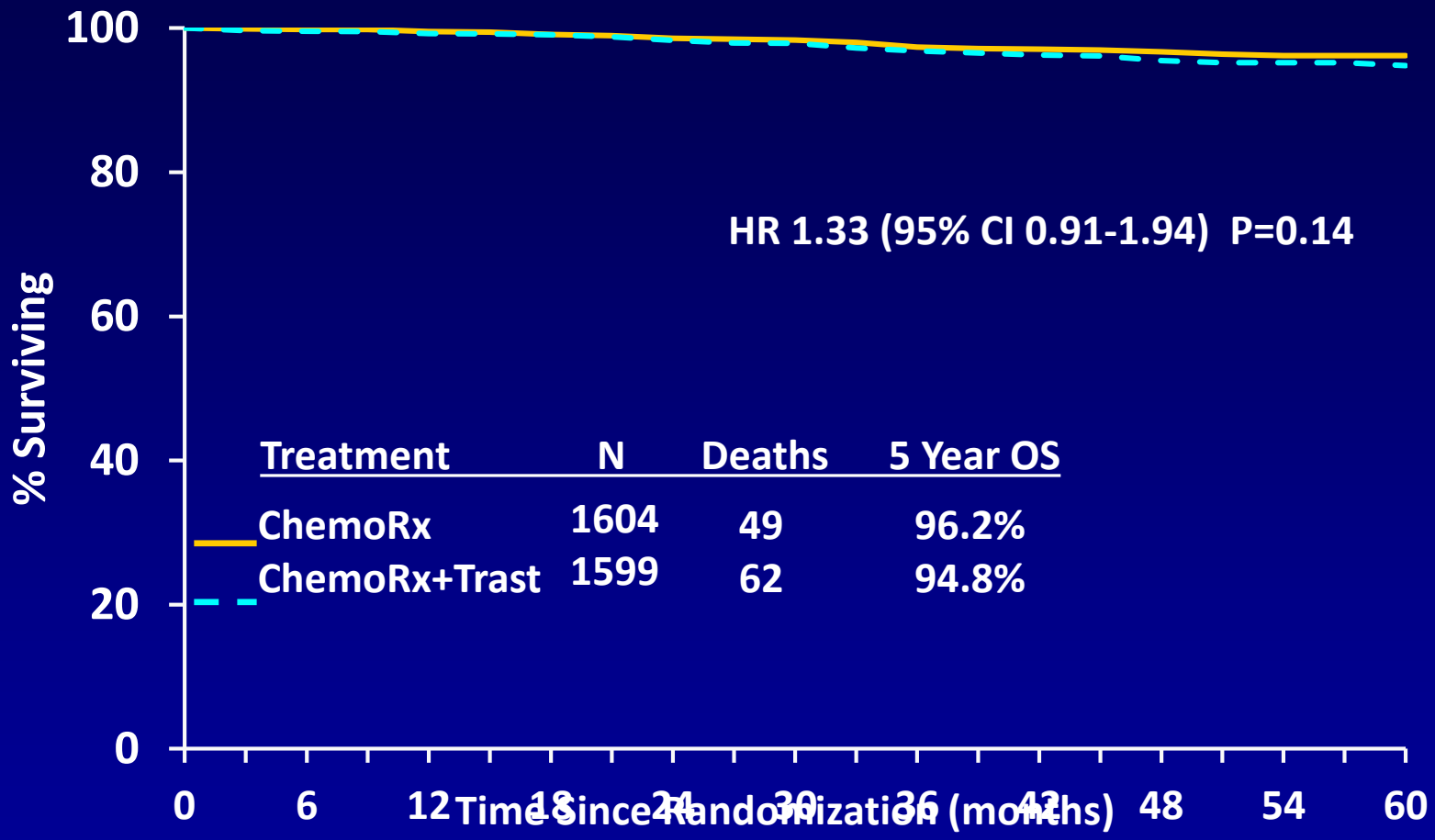


No. at Risk						
ChemoRx	1603	1558	1423	1003	595	140
ChemoRx+Trast	1599	1528	1403	1009	591	117

B-47: IDFS by Stratification Variables



B-47: Overall Survival



No. at Risk

ChemoRx	1604	1577	1507	1099	703	169
ChemoRx+Trast	1599	1563	1497	1113	683	149

Conclusions

- There is **NO** benefit of trastuzumab therapy in patients with FISH ratios <2.0 and IHC staining intensity of 1-2+

- The benefit of trastuzumab in central tested HER2-low patients identified retrospectively from 2 major adjuvant trials that used local testing for eligibility are not readily explained and not confirmed in this study

CTRC-AACR SAN ANTONIO BREAST CANCER SYMPOSIUM

Copy number aberration analysis to predict response to neoadjuvant anti-HER2 therapy: results from the NeoALTTO phase III trial

Sotiriou C, Brown D, Rothé F, Maetens M, Fumagalli D, Salgado R, Bradbury I, Pusztai L, Harbeck N, Gomez H, Chang TW, Coccia-Portugal MA, de Azambuja E, Nuciforo P, Baselga J, Piccart M, Loi S, Venet D.

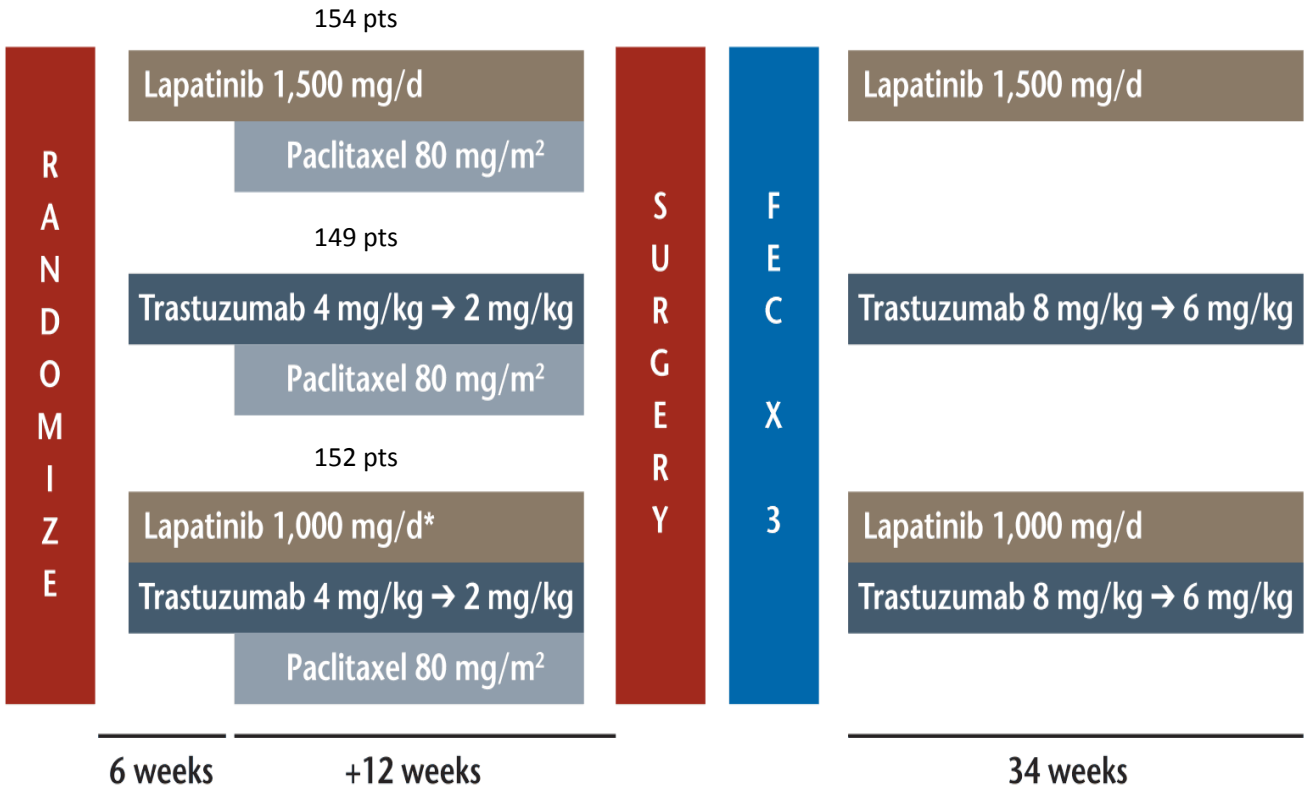
NEO-ALTTO

Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

NEO-ALTTO

Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

Study design

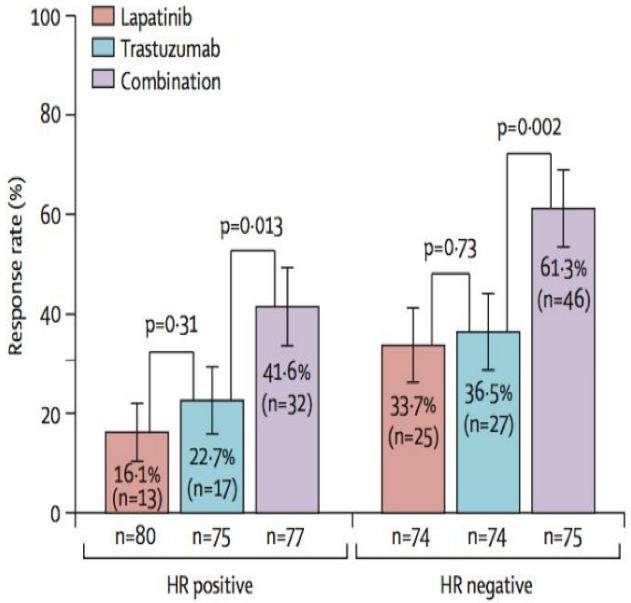


d = day; FEC = fluorouracil, epirubicin, cyclophosphamide

**Amendment: October 2, 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel; 54/152 had protocol-driven reduction.*

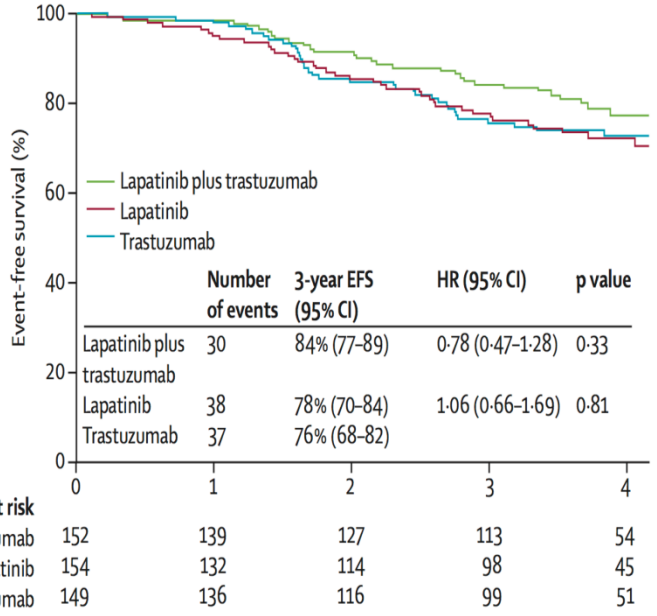
Trial results

Pathological complete response



Baselga *et al*. Lancet 2012

Event-free survival



	Number of events	3-year EFS (95% CI)	HR (95% CI)	p value
Lapatinib plus trastuzumab	30	84% (77–89)	0·78 (0·47–1·28)	0·33
Lapatinib	38	78% (70–84)	1·06 (0·66–1·69)	0·81
Trastuzumab	37	76% (68–82)		

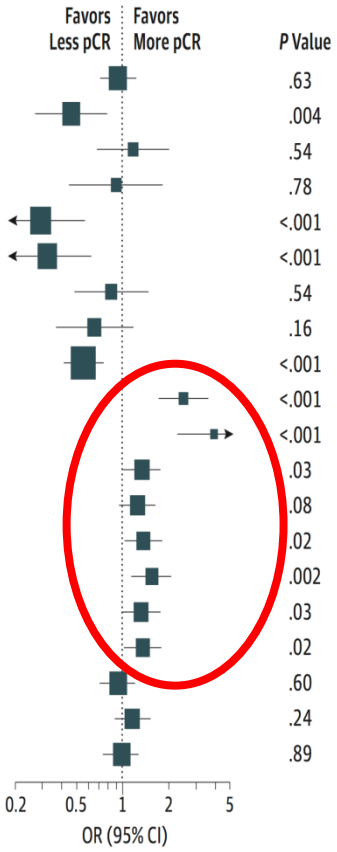
Number at risk					
Lapatinib plus trastuzumab	152	139	127	113	54
Lapatinib	154	132	114	98	45
Trastuzumab	149	136	116	99	51

de Azambuja *et al*. Lancet Oncology 2014

ESR1, ERBB2 and *immune signatures* were associated with pCR (N=254 pts, RNAseq)

A Univariate model

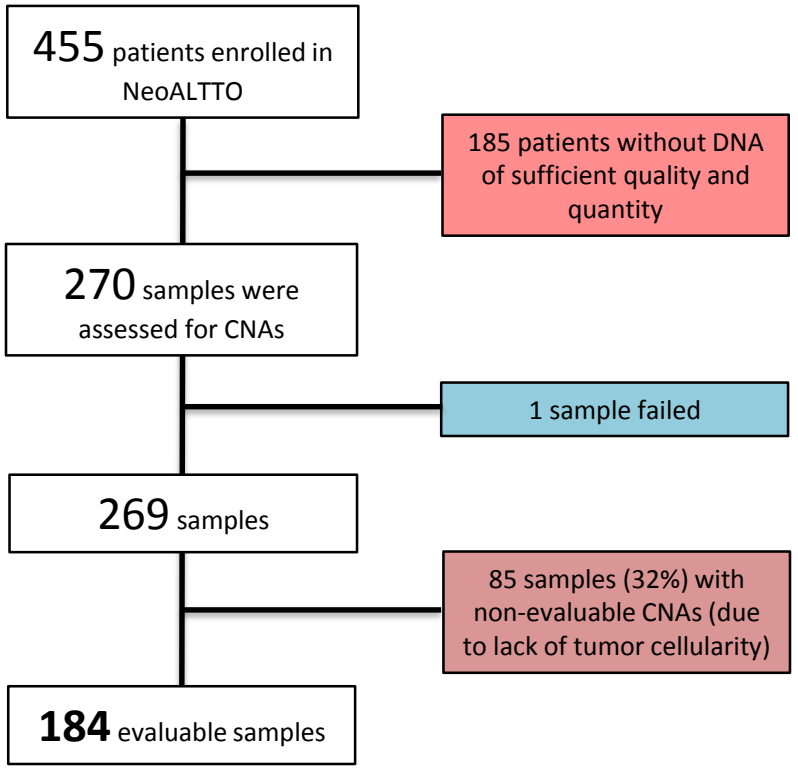
Parameter	OR (95% CI)	FDR
Age (continuous)	0.94 (0.72-1.2)	0.42
Estrogen receptor positive (yes vs no)	0.46 (0.27-0.78)	0.0065
Tumor size (≥T3 vs T2)	1.2 (0.70-2.0)	0.41
Lapatinib vs trastuzumab	0.91 (0.45-1.8)	0.49
Lapatinib vs combination	0.29 (0.15-0.55)	3.3×10^{-4}
Trastuzumab vs combination	0.32 (0.17-0.62)	0.0012
Grade (1-2 vs 3)	0.84 (0.49-1.5)	0.41
Nodal status (N0 vs N1-N3)	0.66 (0.37-1.2)	0.14
ESR1	0.56 (0.42-0.74)	1.2×10^{-4}
ERBB2/HER2	2.5 (1.7-3.6)	1.2×10^{-7}
HER2 enriched (PAM50)	4.0 (2.3-6.9)	1.8×10^{-6}
Immune1	1.3 (1.0-1.7)	0.034
Immune2	1.3 (0.97-1.6)	0.084
Immune3	1.4 (1.1-1.8)	0.024
Genomic Grade Index	1.6 (1.2-2.1)	0.0032
Aurka	1.3 (1.0-1.7)	0.036
AKT/mTOR	1.4 (1.0-1.8)	0.032
Stroma1	0.93 (0.72-1.2)	0.42
Stroma2	1.2 (0.90-1.5)	0.21
AR	0.98 (0.76-1.3)	0.53



Fumagalli *et al*. JAMA Oncol 2016

Study Design

- **Objective:** To investigate copy number aberrations (CNAs) and their association with: Pathological complete response and Event-free survival (EFS)
- **Methods:** Cytoscan HD, Affymetrix arrays, 2.75M probes, 750,000 SNPs
- **CNAs Evaluation**:
  - Integer level estimates of total copy number and major allele were obtained using Genome Alteration Print (GAP)
  - Recurrent CNAs were identified with GISTIC2
  - Genome instability index (GII) was defined as the median absolute deviation of the normalized copy number



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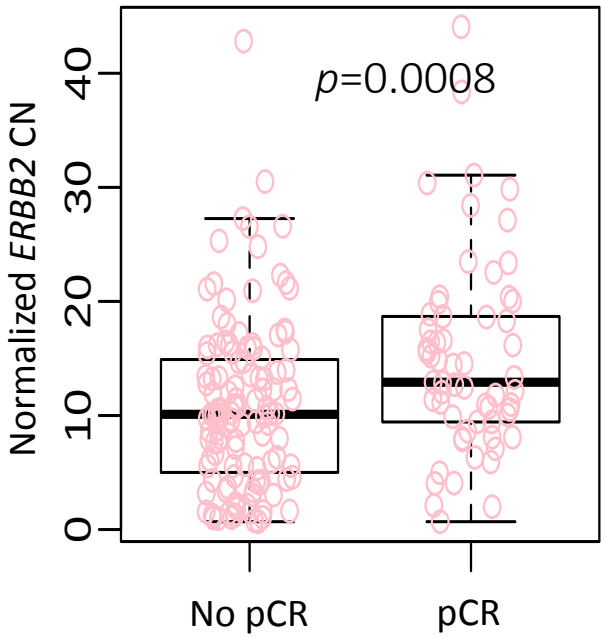
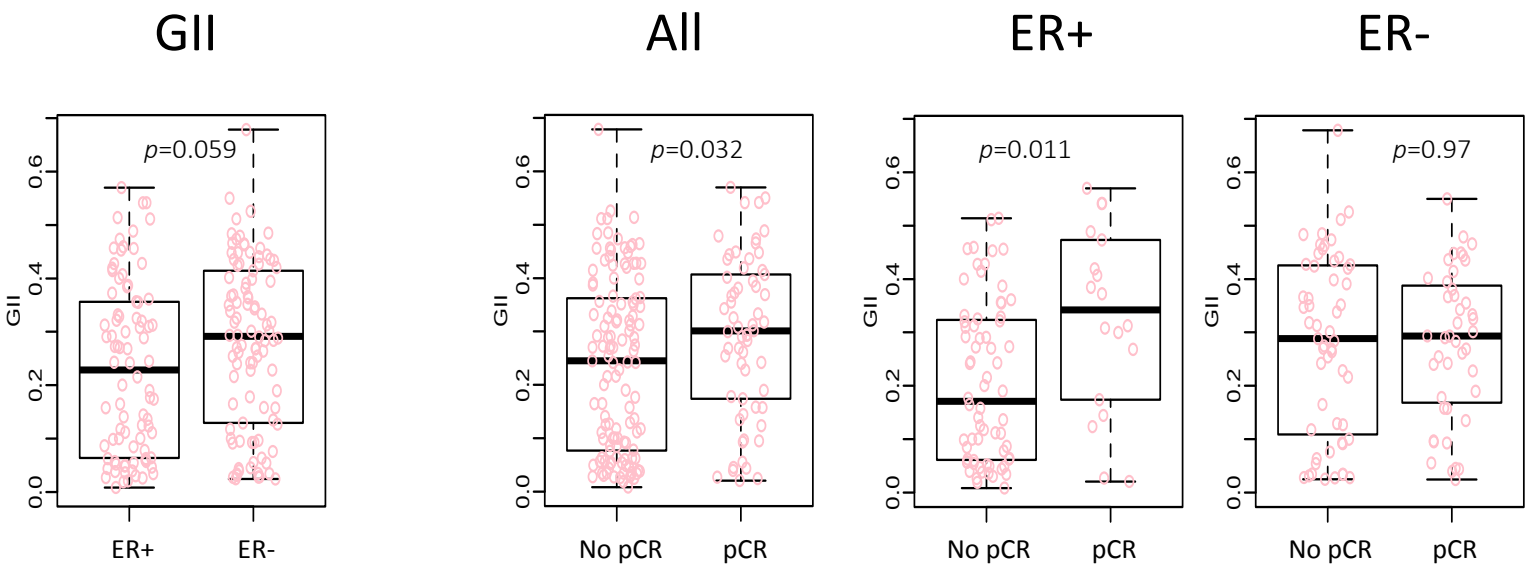
Copy number changes in cancer genes and pCR



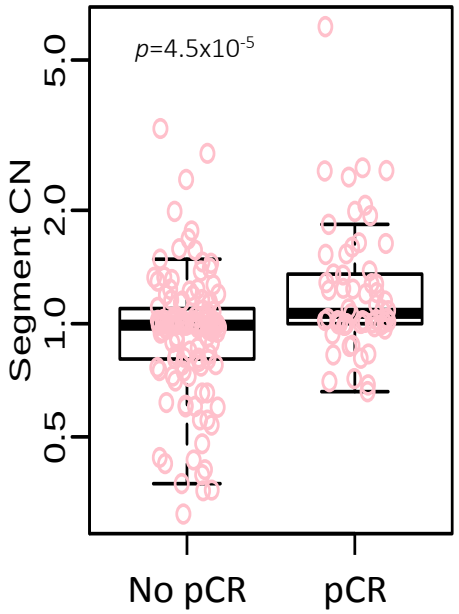
- Among cancer genes, only *ERBB2* was predictive of pCR
- *ERBB2* CN ***was not significant*** correcting for ERBB2 mRNA expression
- ERBB2 mRNA expression and HER2-enriched by PAM50 ***remained significant*** correcting for *ERBB2* CN

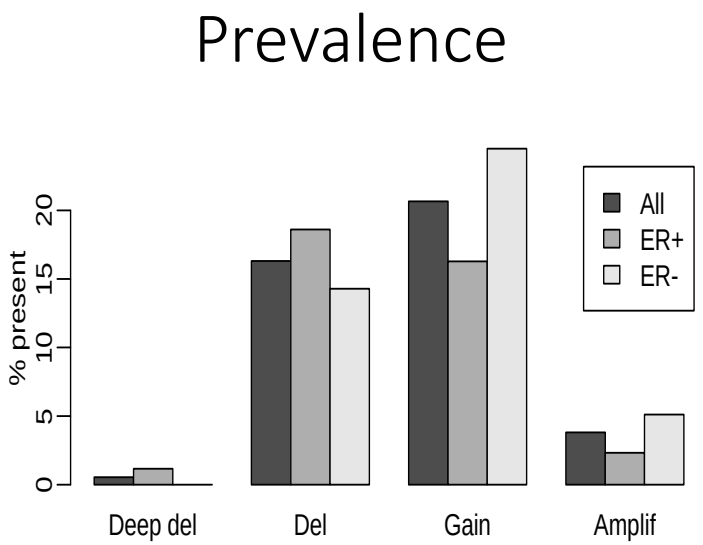
Genome instability index (GII) and pCR



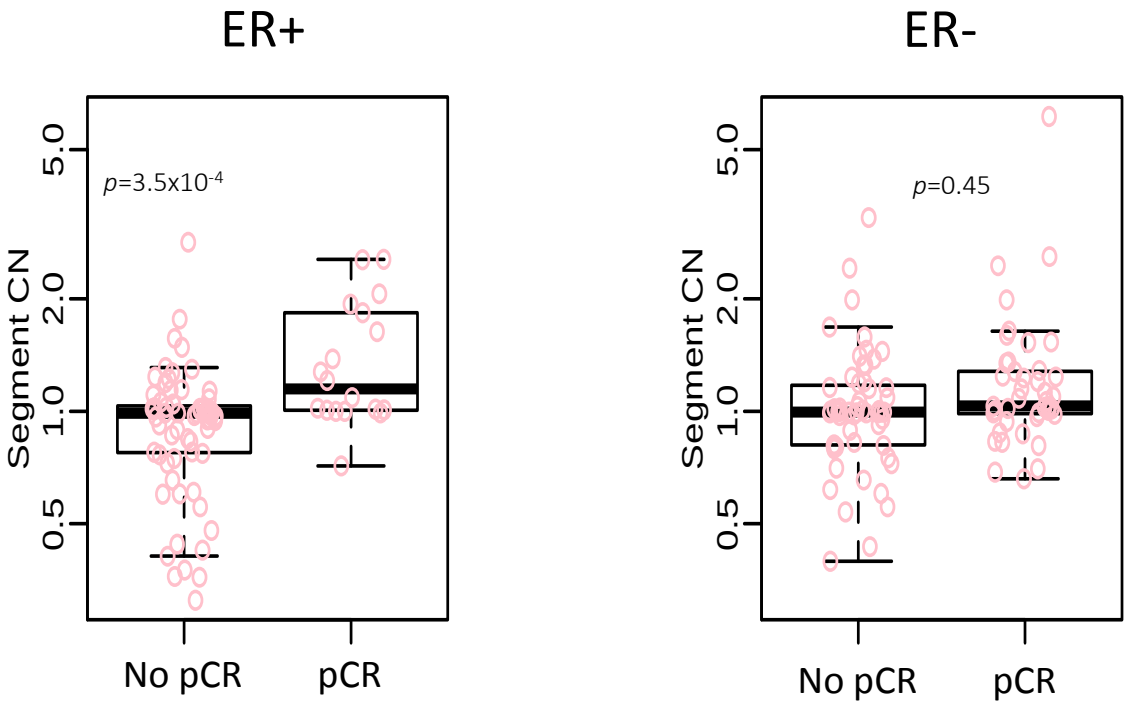
Interaction test: p=0.025

Identification of 6q23-24 segment associated with pCR (6.5 Mbases – harboring 39 genes)





6q23-24 segment is associated with pCR in ER+ tumors only



Interaction test: p=0.04

Conclusions

- High copy number level of ERBB2 was predictive of pCR, however ERBB2 mRNA and HER2-enriched by PAM50 were better predictors of pCR
- High genome instability index was associated with higher pCR rate in ER+ tumors
- A novel amplified region on 6q23-24 was shown to be predictive of pCR, in particular for ER+ tumors and warrants additional investigation
- Can we identify patients who are less likely to achieve a pCR with standard therapy? Can we develop more effective treatment options for these patients?

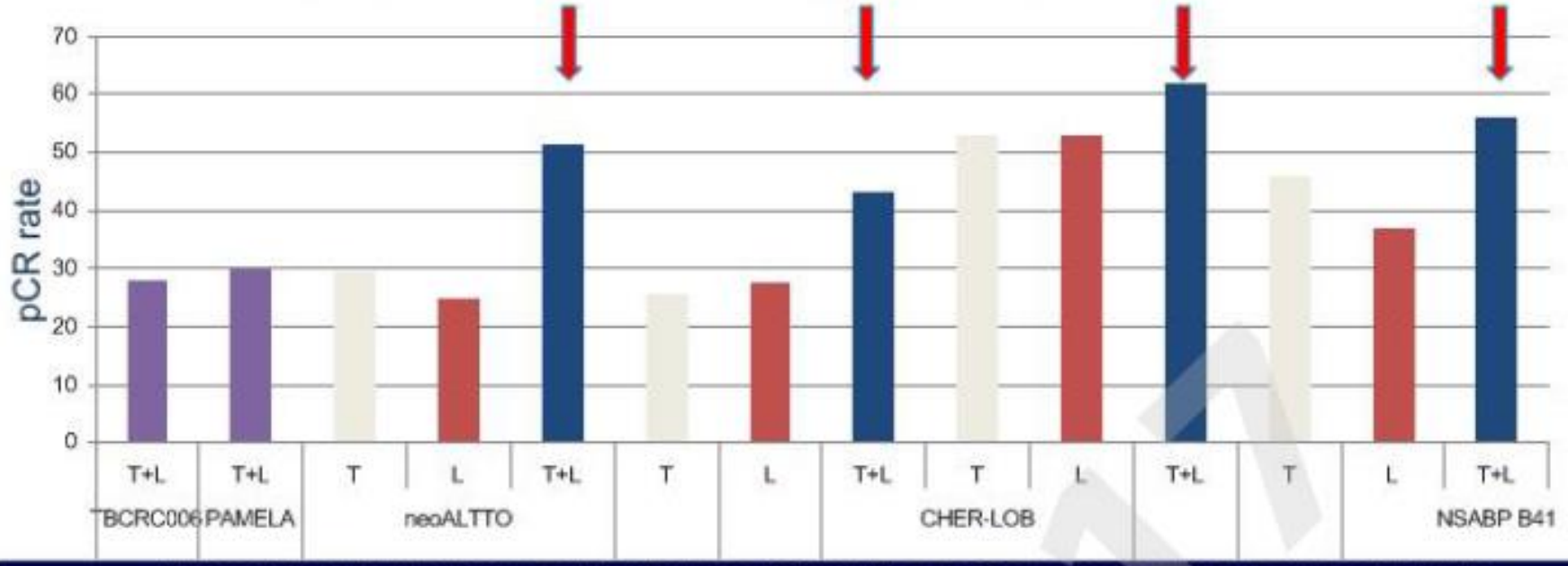
Event-free survival and gene expression signatures in CALGB (ALLIANCE) 40601

Ian E. Krop, David Hillman, Mei Polley, Maki Tanioka, Joel S. Parker, Lucas Huebner, N. Lynn Henry, Sara Tolaney, Chau Dang, Lyndsay Harris, Donald A. Berry, Charles M. Perou, Ann Partridge, Eric P. Winer, and Lisa A. Carey

on behalf of the Alliance for Clinical Trials in Oncology

Background

- Trastuzumab+lapatinib (HL) are synergistic
  - Neoadjuvant HL for 12-18 weeks is associated with pCR of 20-30%
  - Lapatinib increases pCR when combined with trastuzumab + chemotherapy



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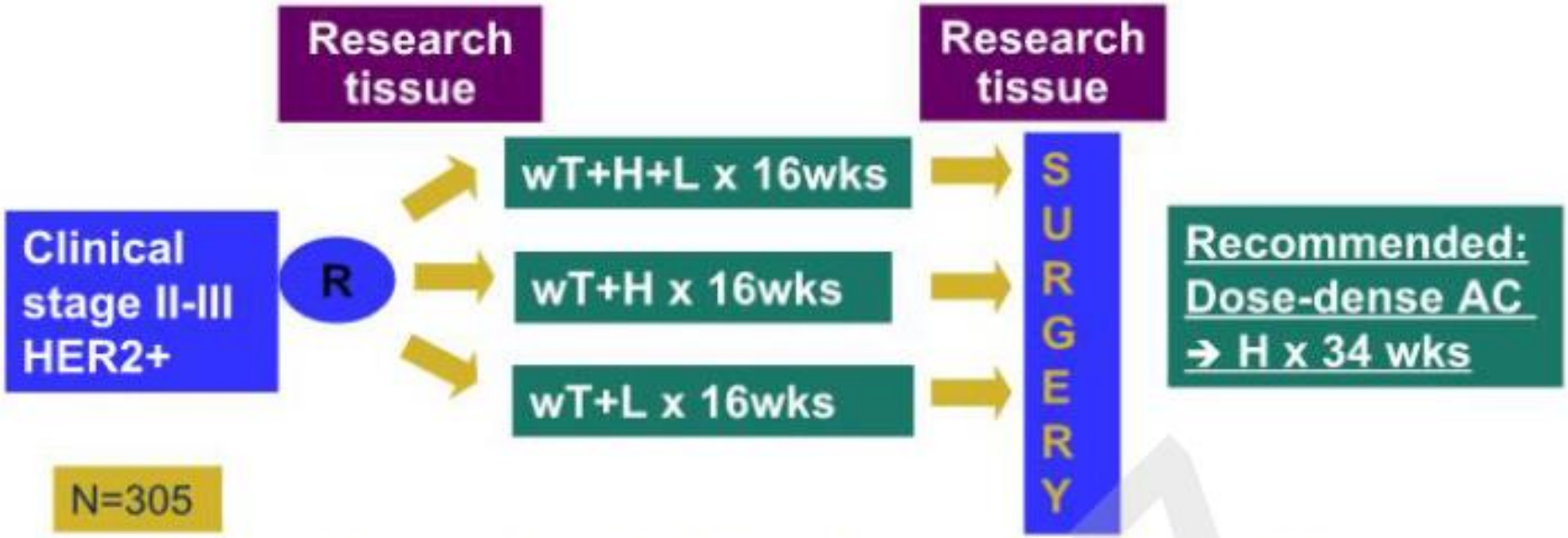
C40601: Phase 3 neoadjuvant study evaluating dual HER2 therapy in HER2+ BC

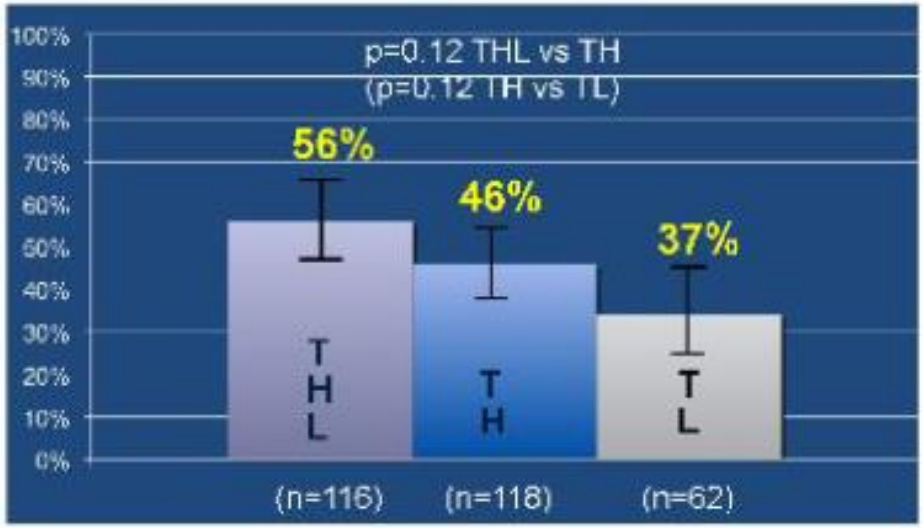


wT= weekly paclitaxel, H=trastuzumab, L=lapatinib

Carey et al, JCO 2015

Primary Endpoint

- In-breast pCR to dual therapy (THL) versus single (TH)
  - 56% versus 46% (p=0.12)



Carey et al, JCO 2015

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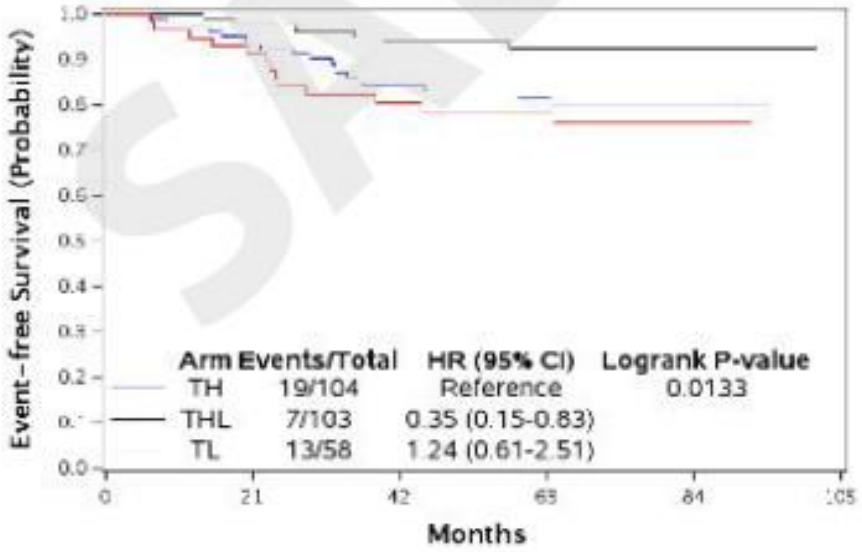
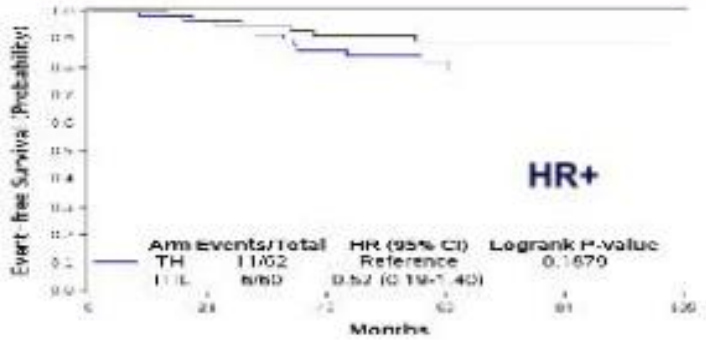
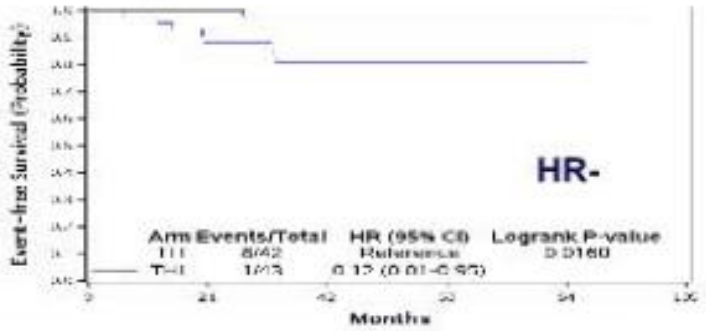
EFS by Treatment Arm







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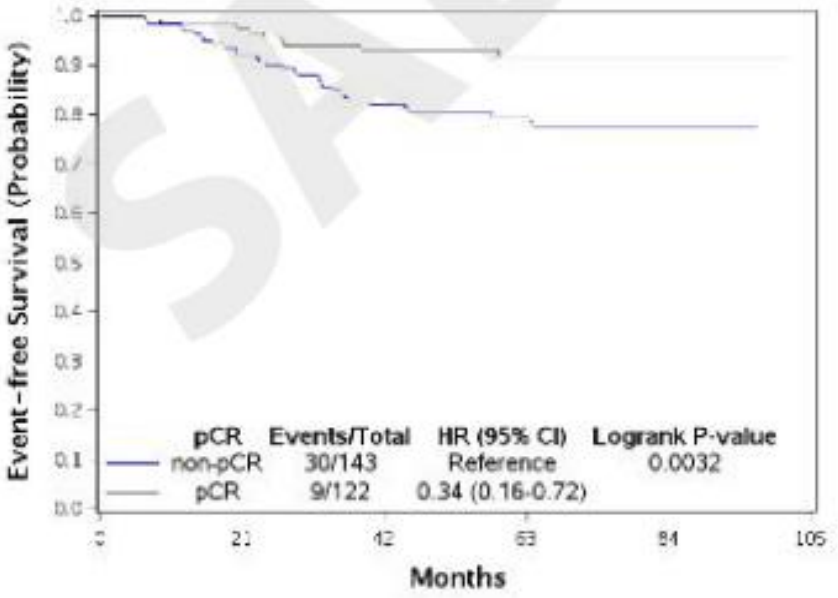
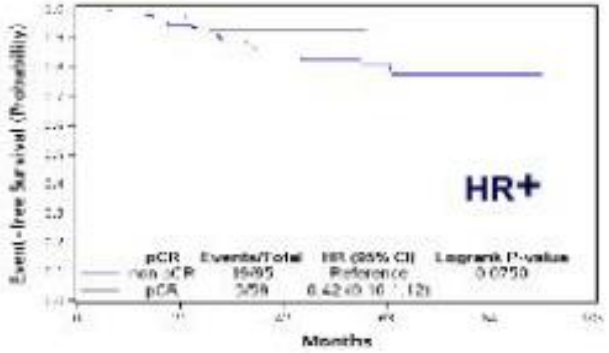
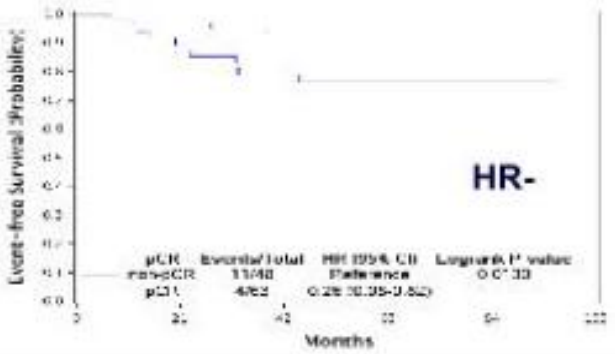
EFS by pCR Status







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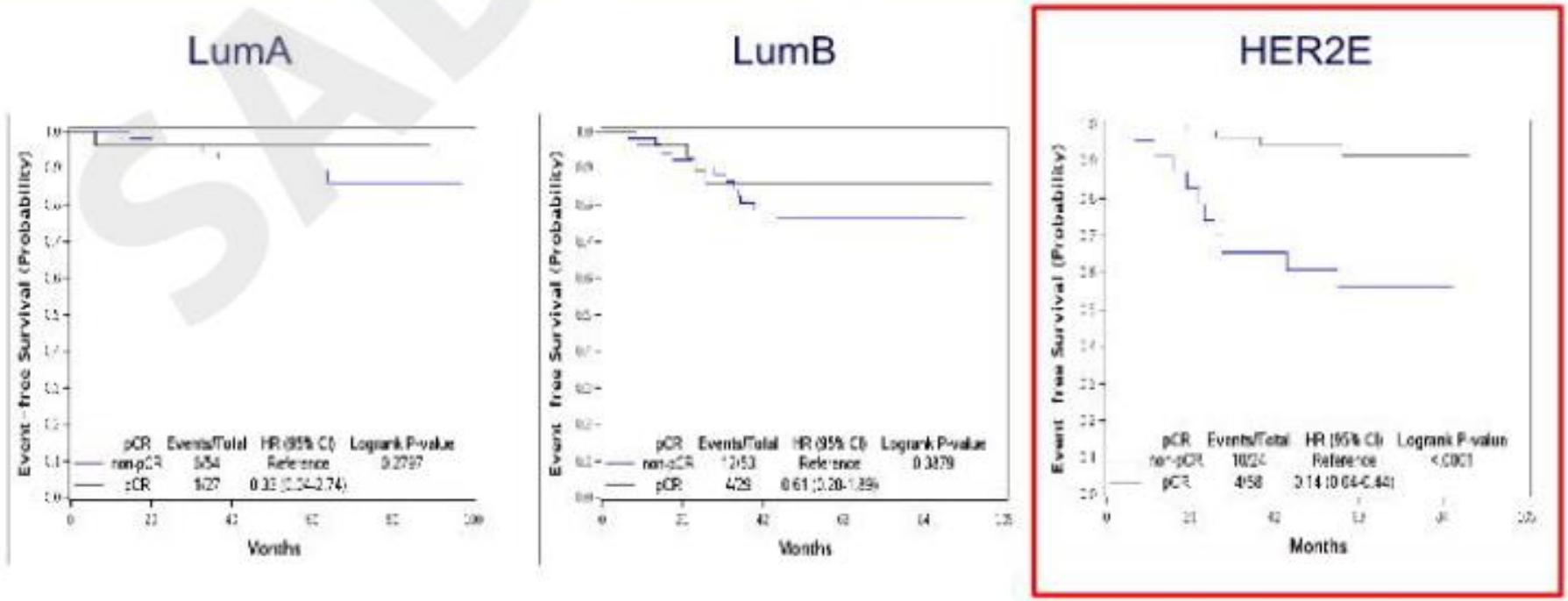
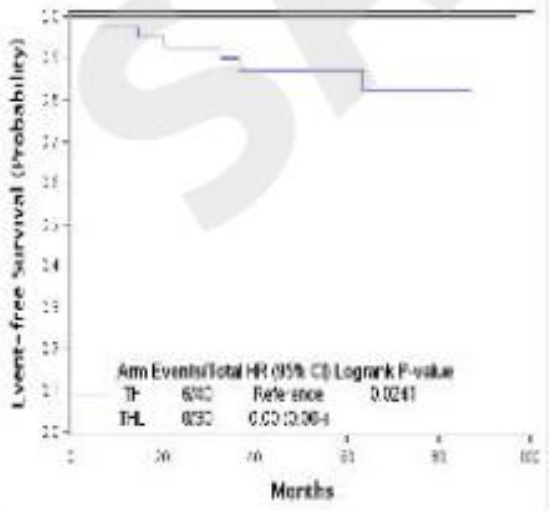
EFS: Impact of pCR by subtype

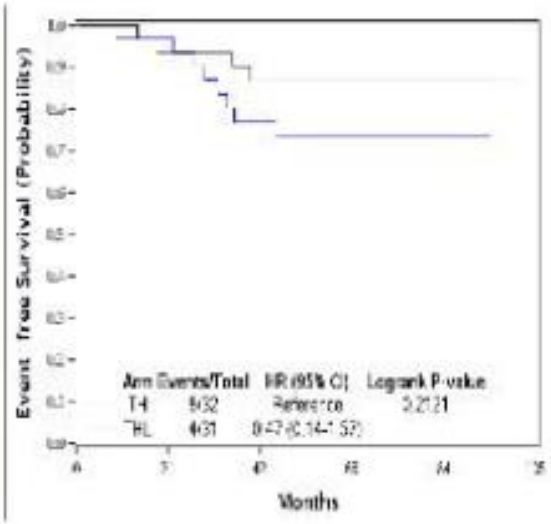


EFS: Rx Effect by Intrinsic Subtype

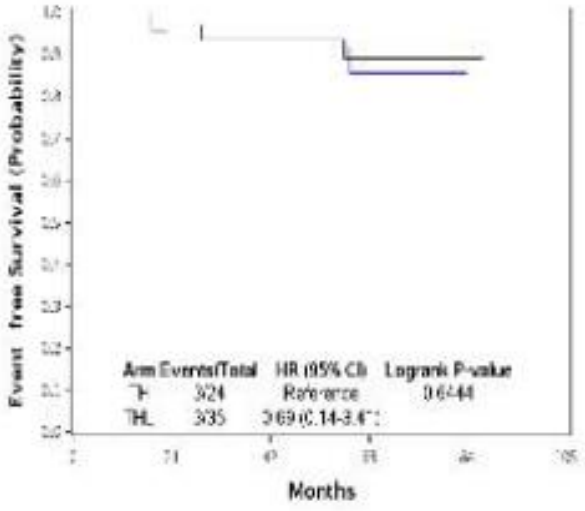
LUM A



LUM B



HER2 E



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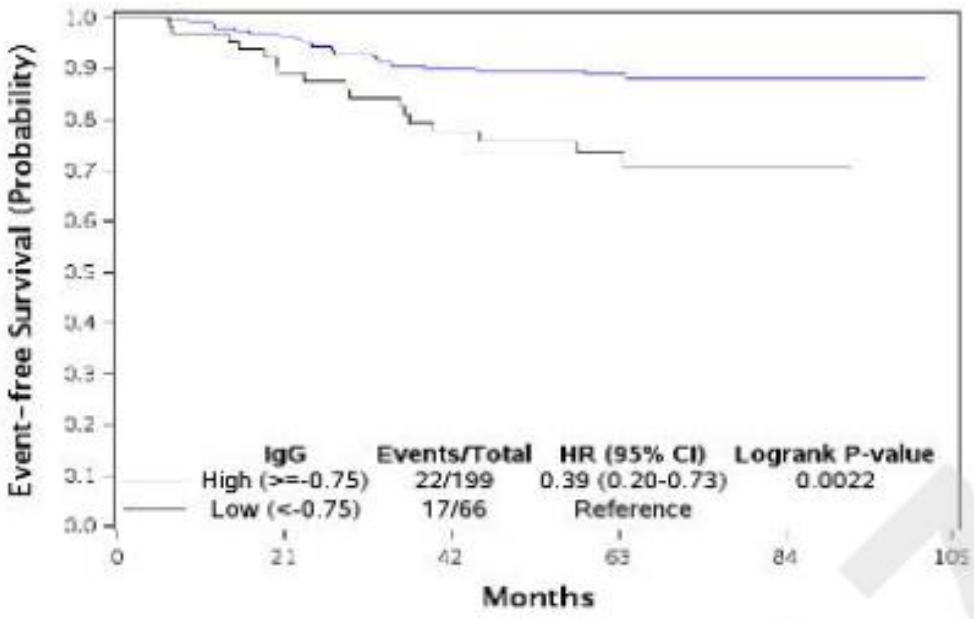
EFS by IgG Signature



*Lower quartile vs upper 3 quartiles

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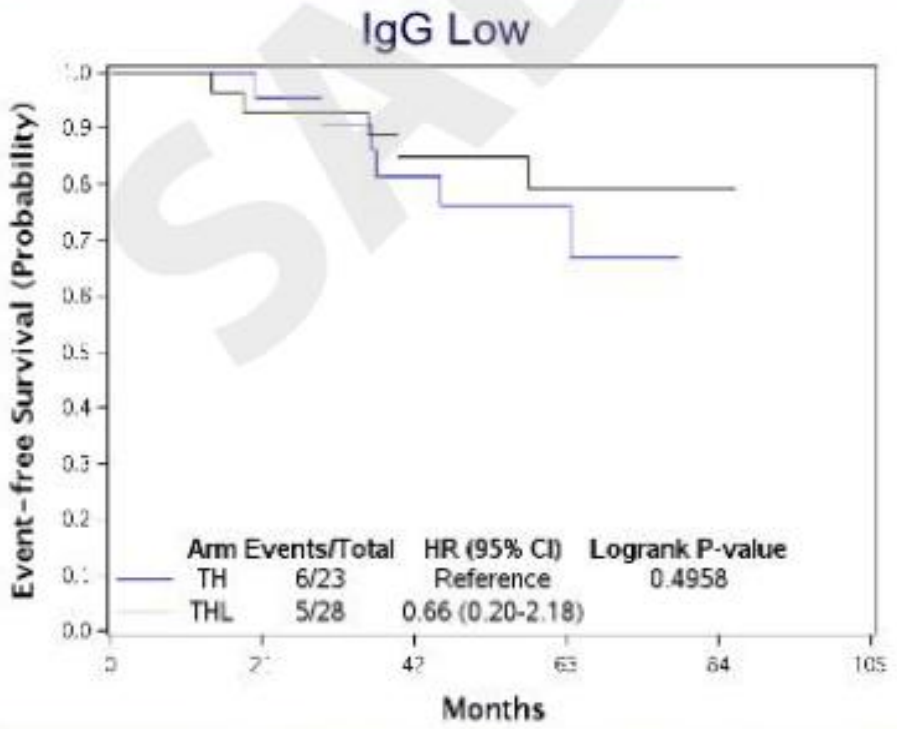
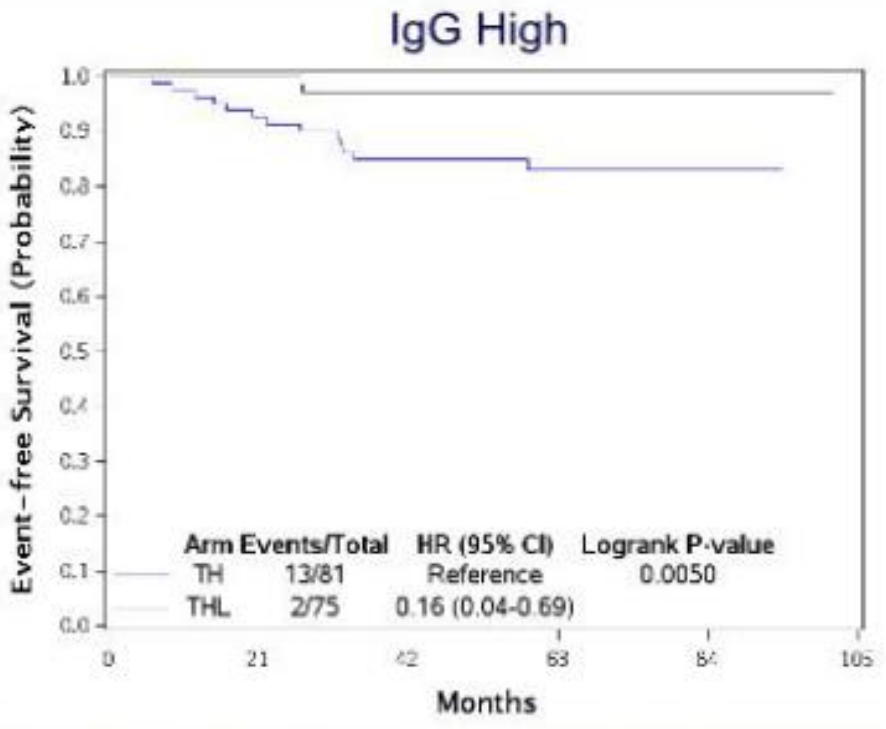
EFS: Rx Effect by IgG Signature





Conclusions

- Addition of neoadjuvant lapatinib to trastuzumab/taxane regimen was associated with improved EFS
- pCR was associated with a favorable outcome
  - Most evident in HR-negative and HER2-enriched subtype
- Immune activation by RNA was independent predictor of pCR and EFS
- EFS benefit of dual HER2-therapy primarily seen in Luminal A tumors (contrasting with effect of pCR)

FBCG

San Antonio Breast Cancer Symposium – December 5-9, 2017

BIG
Breast International Group

A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer

The Synergism Or Long Duration (SOLD) trial

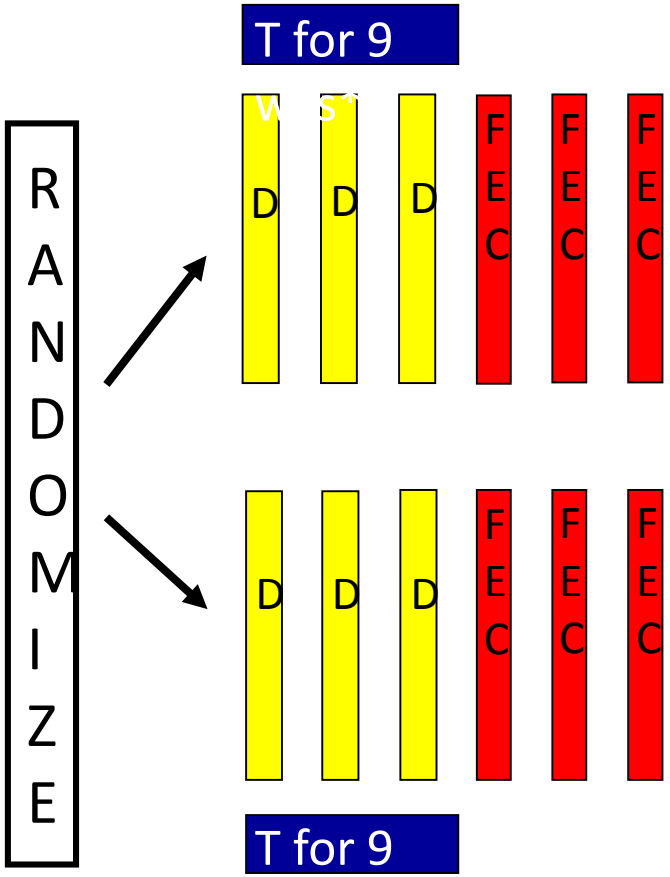
H Joensuu, J Fraser, H Wildiers, R Huovinen, P Auvinen, M Utriainen, P Nyandoto, KK Villman, P Halonen, H Granstam-Björneklett, L Lundgren, T Turpeenniemi-Hujanen, J Yachnin, D Ritchie, T Huttunen, R Paridaens, P Canney, VJ Harvey, PL Kellokumpu-Lehtinen, H Lindman

SOLD design

Docetaxel (D) 80/100 mg/m^2 iv 3-wkly

$F_{600}E_{75}C_{600}$ iv 3-wkly

Trastuzumab (T)



*Wkly iv, or 3-wkly either iv or sc

In both groups:

- Locoregional RT given according to the institutional practice
- Endocrine therapy for a minimum of 5 yrs when cancer ER/PR +ve

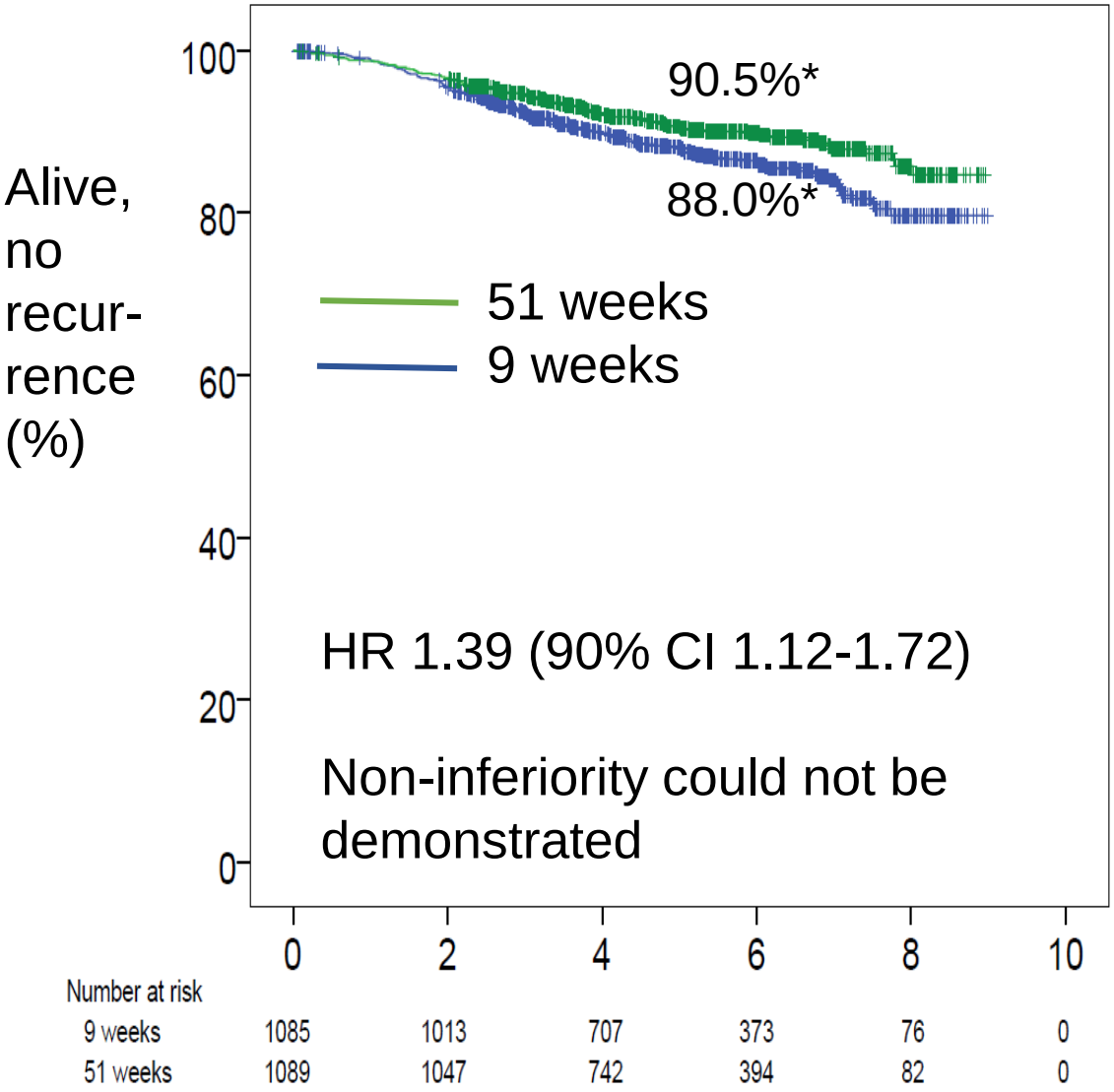
T to complete 1 year trastuzumab

**14 times 3-weekly, either iv or sc

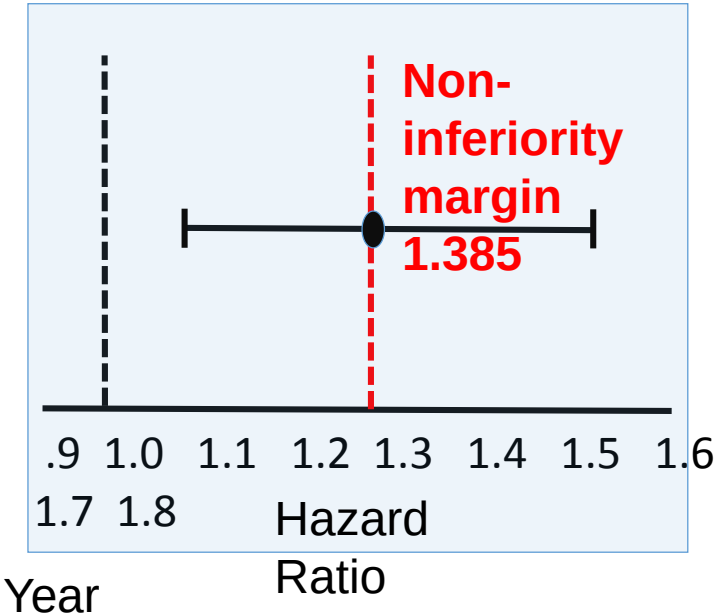
Key baseline characteristics

Characteristic	9-week group (n=1,085)	1-year group (n=1,089)
Median age (range) – years (range)	56 (23-82)	56 (27-79)
Premenopausal	33 %	33 %
Breast tumor diameter		
≤10 mm	12 %	14 %
11-21 mm	44 %	42 %
21-50 mm	41 %	42 %
>50 mm	3 %	3 %
Axillary lymph nodes with cancer		
0	60 %	60 %
1-3	30 %	29 %
>3	11 %	11 %
Ductal histological type	92 %	92 %
Estrogen receptor-positive	66 %	66 %
Progesterone receptor-positive	46 %	47 %

Disease-free survival



*5-year DFS estimate



Overall survival

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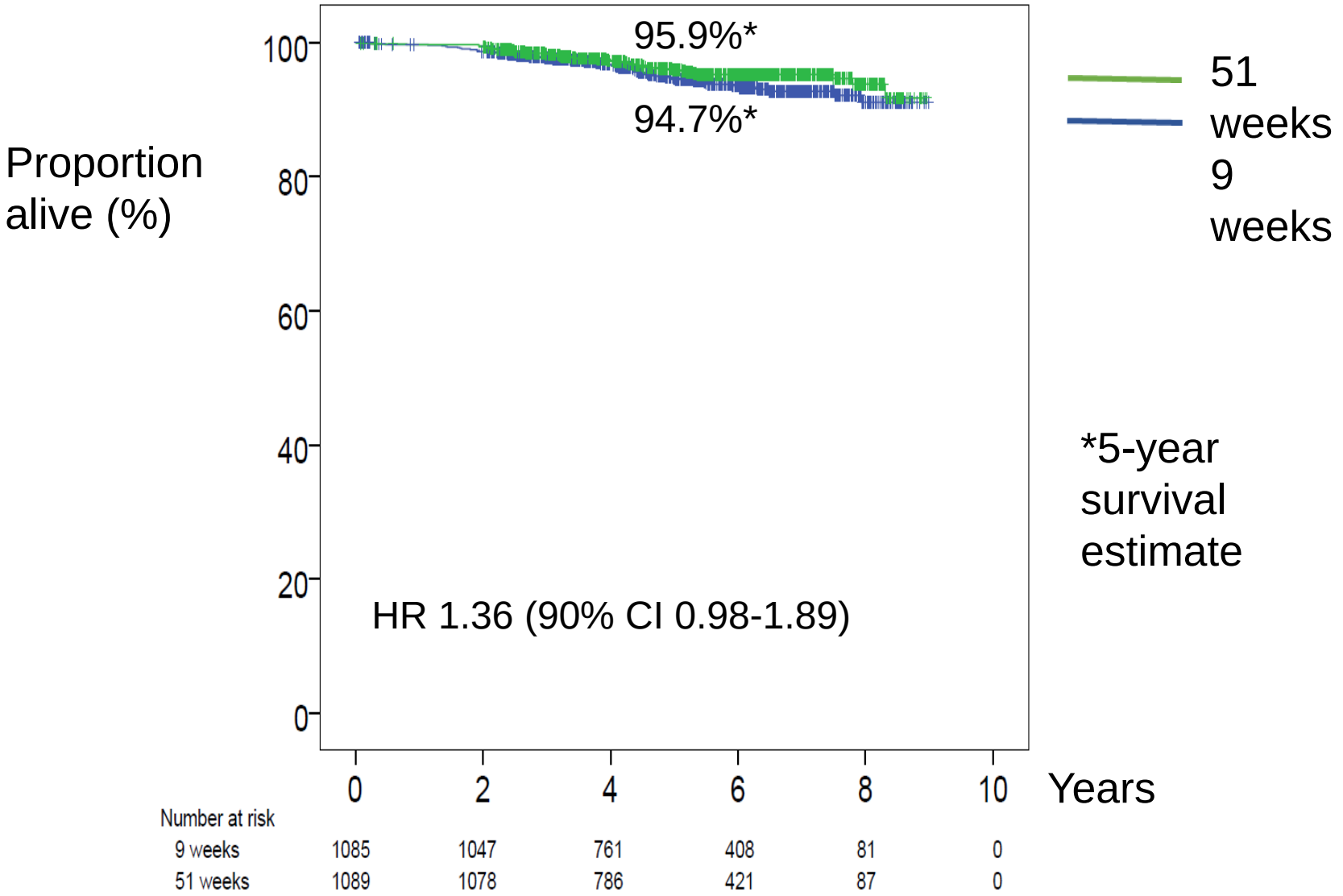


Conclusions

- I am **NOT SOLD** on 9 weeks of trastuzumab
- 12 months remains the standard of care

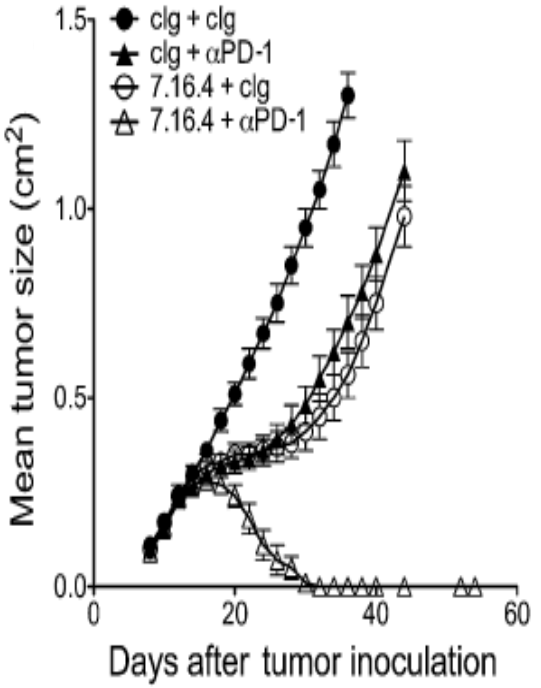
Phase Ib/II Study Evaluating Safety and Efficacy of Pembrolizumab and Trastuzumab in Patients with Trastuzumab-Resistant HER2-positive Advanced Breast Cancer: Results from the PANACEA Study (IBCSG 45-13/BIG 4-13/KEYNOTE-014)

Sherene Loi, Anita Giobbie-Hurder, Andrea Gombos, Thomas Bachelot, Rina Hui, Giuseppe Curigliano, Mario Campone, Laura Biganzoli, Herve Bonnefoi, Guy Jerusalem, Rupert Bartsch, Manuela Rabaglio-Poretti, Rosita Kammler, Rudolf Maibach, Mark J. Smyth, Angelo Di Leo, Marco Colleoni, Giuseppe Viale, Meredith M. Regan, Fabrice André

On behalf of the International Breast Cancer Study Group and Breast International Group

Background: Anti-tumor immunity & HER2-positive breast cancer

- HER2-positive breast cancer has high levels of T cell infiltration
- TILs are associated with improved prognosis and response to trastuzumab and chemotherapy[1,2]
- Trastuzumab has been shown to have immune mediated mechanisms of action[3,4]
- Preclinical studies suggest immune-mediated mechanisms of trastuzumab resistance that can be overcome with checkpoint inhibition combinations[5]



[1] Loi et al, J Clin Oncol 2013; [2] Loi et al, Ann Oncol 2014 [3] Clynnes et al Nat Med 2002
[4] Park et al, Cancer Cell 2011; [5] Stagg, Loi et al, PNAS 2011

Study Design: PANACEA IBCSG 45-13/BIG 4-13/KEYNOTE-014

Patients

- Centrally confirmed HER2+
- ECOG 0-1
- Tumor biopsy sample <1yr
- Measurable disease RECIST 1.1
- No limit of prior systemic treatment
- Documented PD on trastuzumab or TDM-1

PD-L1 + → Phase Ib Pembrolizumab 2mg/kg and 10mg/kg IV + trastuzumab Q3W

Phase II Pembrolizumab 200mg IV + trastuzumab Q3W

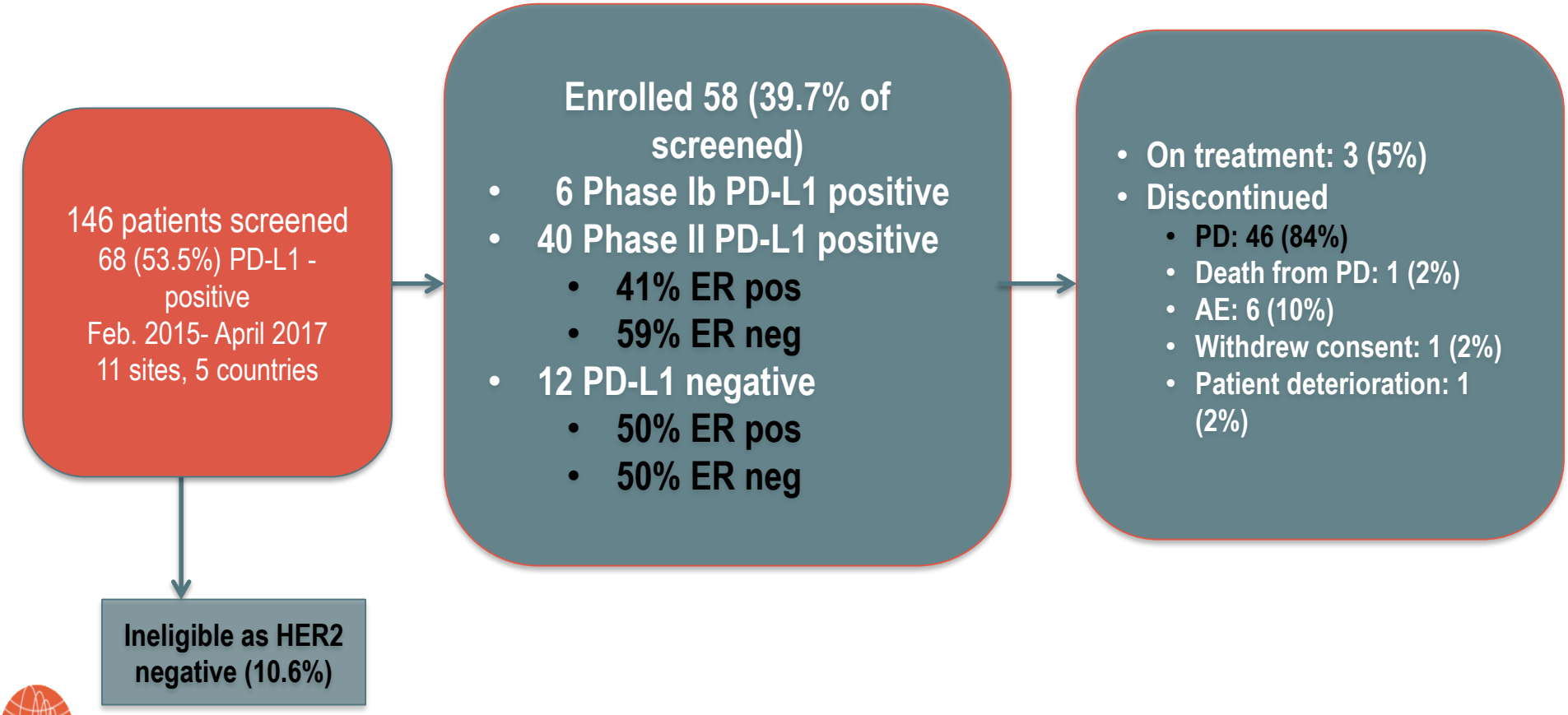
PD-L1 - → Phase II Pembrolizumab 200mg IV + trastuzumab Q3W

Protocol specified follow-up. Treatment until progression, toxicity, patient withdrawal, investigator decision, or maximum 2 years

PD-L1 Positive was QualTek ≥1% tumor or stroma; Q[2]: CPS ≥1%

Enrollment and Disposition

Median follow-up: 13.6 months



Baseline Characteristics

Characteristic N (%)	Phase Ib PD-L1 positive; n=6	Phase II PD-L1 positive; n=40	Phase II PD-L1 negative; n=12	Overall n=58
Age yrs. median (range)	49 (38-57)	49 (28-72)	56.5 (43-61)	**50.5 (28-72)**
ER negative	4 (66%)	23 (57.5%)	6 (50%)	**33 (56.9%)**
positive (≥ 1%)	2 (33%)	17 (42.5%)	6 (50%)	**25 (43.1%)**
Prior trastuzumab-containing therapy	6 (100%)	40 (100%)	12 (100%)	**58 (100%)**
Additional anti-HER2 therapy				
No	1 (16.7%)	6 (15%)	0 (0%)	**7 (12.1%)**
Yes	5 (83.3%)	34 (85%)	12 (100%)	**51 (87.9%)**
T-DM1	4	29	9	**42**
Pertuzumab	3	10	4	**17**
Other	1	17	8	**26**
Prior chemotherapy (Anth/Taxane)	6 (100%)	40 (100%)	12 (100%)	**58 (100%)**
Median time from Dx met disease to enrolment; months (range)	15.5 (6-83.6)	40.8 (1.1-111)	71.5 (9.9-179.1)	**40 (1.1-179.1)**

Most Common AEs[1] at Least Possibly Related; N=58

Adverse Event	Pts N (%)	G1	G2	G 3	G4
Fatigue	12 (21%)	7	5		
Diarrhea	8 (14%)	6	2		
Arthralgia	8 (14%)	6	2		
Headache	6 (10%)	4	2		
Nausea	6 (10%)	6			
Dyspnea	5 (9%)	2	1	1	1
Myalgia	5 (9%)	5			

No cardiac events reported
No DLTs in Phase Ib

Immune-related AEs

- Any grade, n=11 (19.0%)
- Grade ≥ 3, n=6 (10.3%)
- Led to discontinuation, n=4 (6.9%)

Most common Immune AEs

- Any grade thyroid, n=4 (6.9%)
- Pneumonitis
  - All grades, n=4 (6.9%)
  - Grade≥3, n=2 (3.4%)

[1] Grade is reported as worst grade for patient

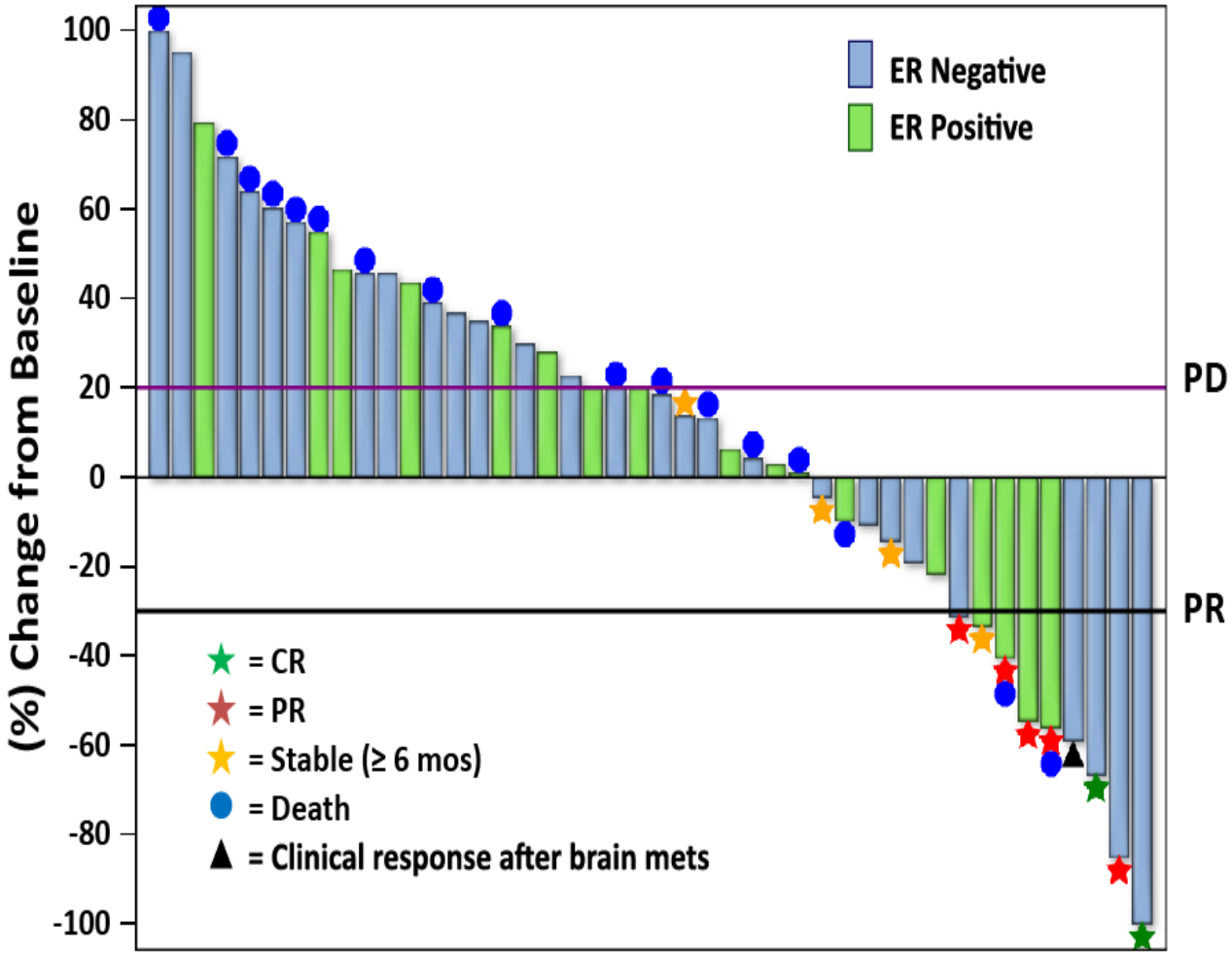
Best Overall Response (RECIST 1.1)

	PD-L1 Positive Phase Ib, n=6	PD-L1 Positive Phase II, n=40	PD-L1 Negative Phase II, n=12
ORR n (%) [90%CI]	**1 (17%) [1-58]**	**6 (15%) [7-29]**	**0 (0%) [0-18]**
DCR[1] n (%) [90%CI]	1 (17%) [1-58]	10 (25%) [14-49]	0 (0%) [0-18]
Best overall response, n (%)			
Complete Response	**1 (17%)**	**1 (2.5%)**	**-**
Partial Response	**-**	**5 (12.5%)**	**-**
Stable Disease	**-**	**7 (17.5%)**	**2 (16.7%)**
Progressive Disease	**5 (83%)**	**25 (62.5%)**	**9 (75.0%)**
Not Evaluable	**-**	**2 (5.0%)**	**1 (8.3%)**

Overall PD-L1 + cohort **ORR 15.2% [7-27]** **DCR 24% [14-36]**

[1]DCR: CR, PR, or SD ≥ 6 months

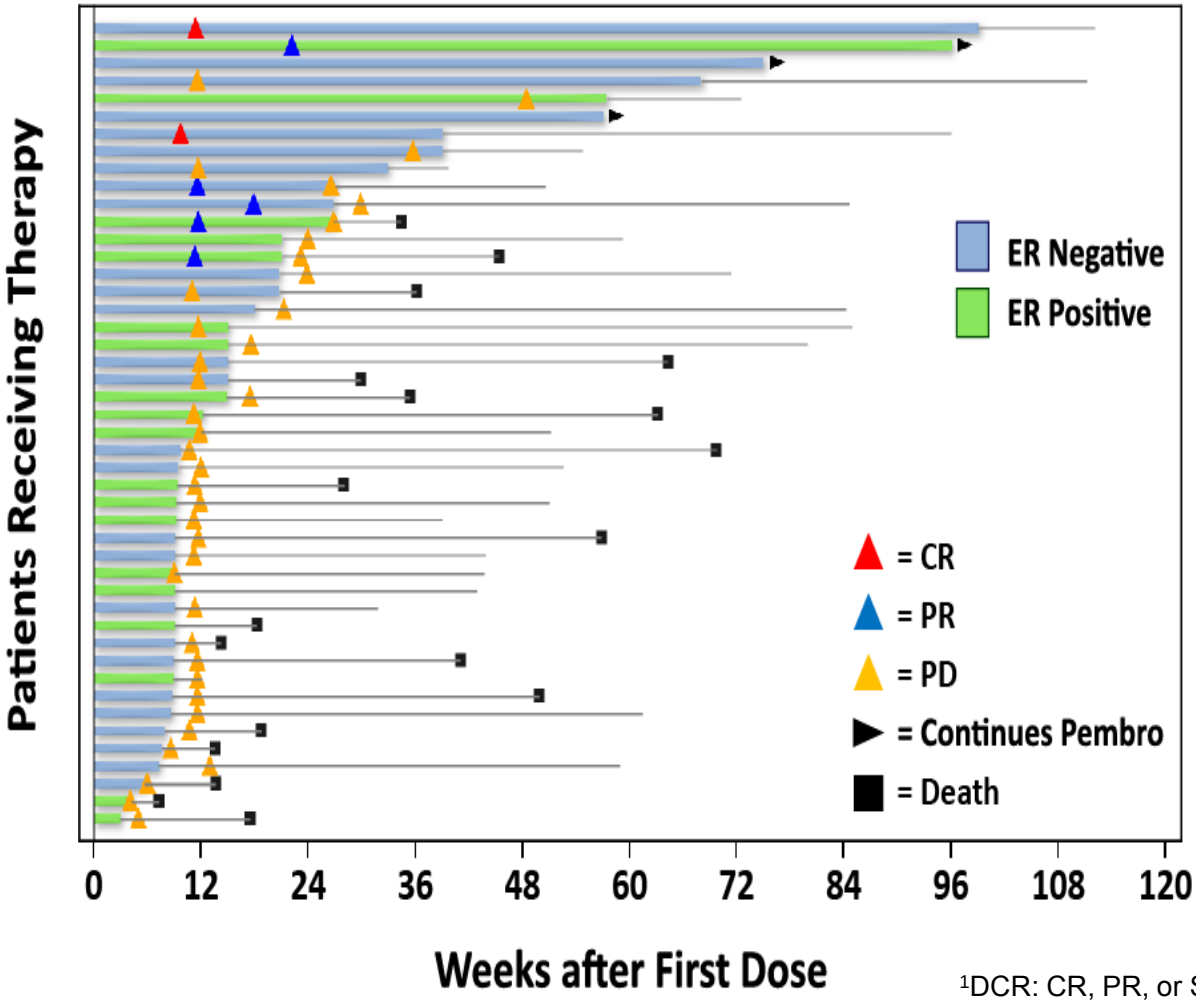
Maximum Change from Baseline in Target Lesions: PD-L1 Positive Cohort (N=44)



N=44 as excludes 2 patients without follow-up measurements of target lesions

▲ brain met not detected at screening in a patient with PR

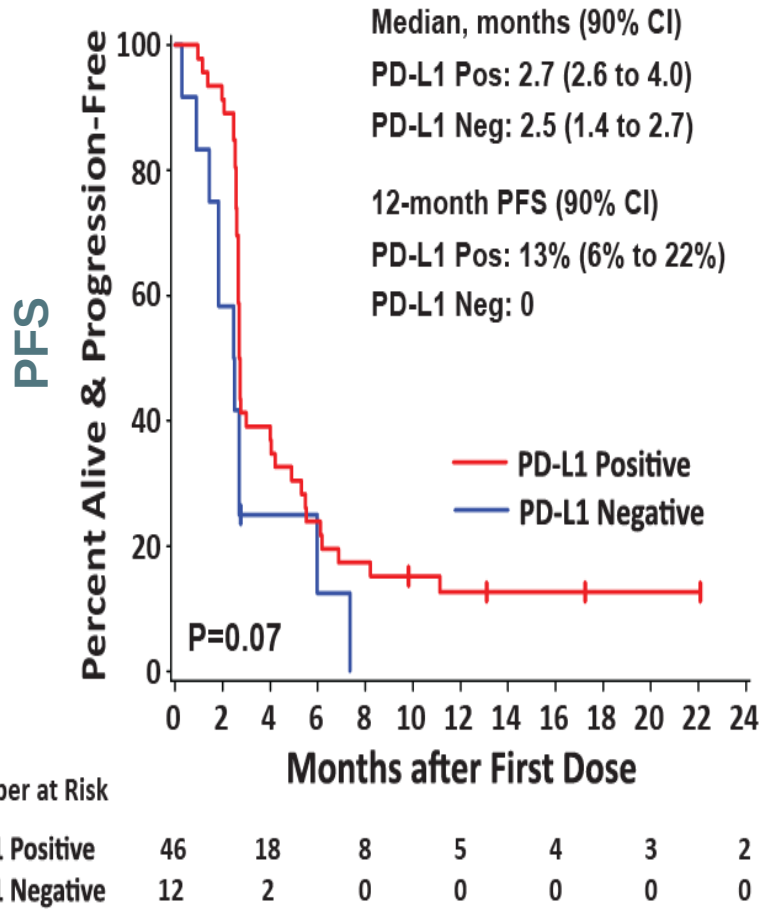
Disease Control: PD-L1 Positive Cohorts

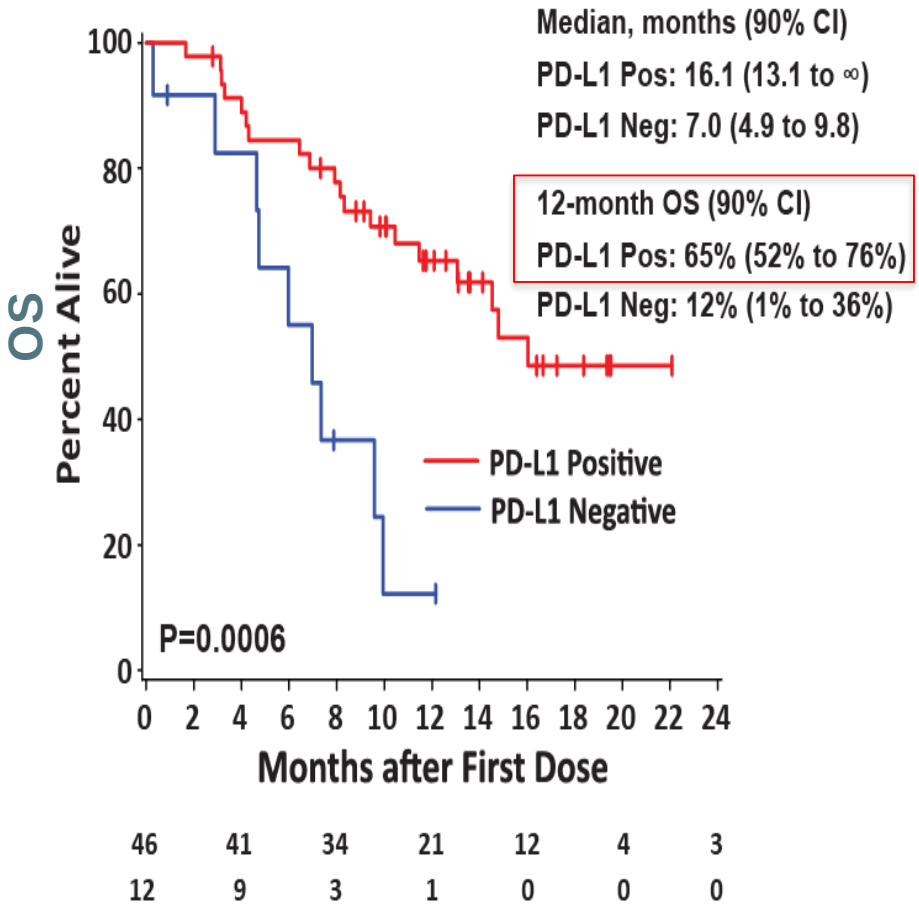


- **Median duration of disease control[1]: 11.1 months (90% CI: 6.2 -∞)**
- Median DoR[2]: 3.5 months (90% CI: 2.7 - ∞)
- Mean DoR[2]: 10 months (90% CI: 2.7-23.1)
- **Five patients (10.8%) continue with no progression at time of reporting**

[1]DCR: CR, PR, or SD ≥ 6 months, [2] timing from first restaging at 12 weeks

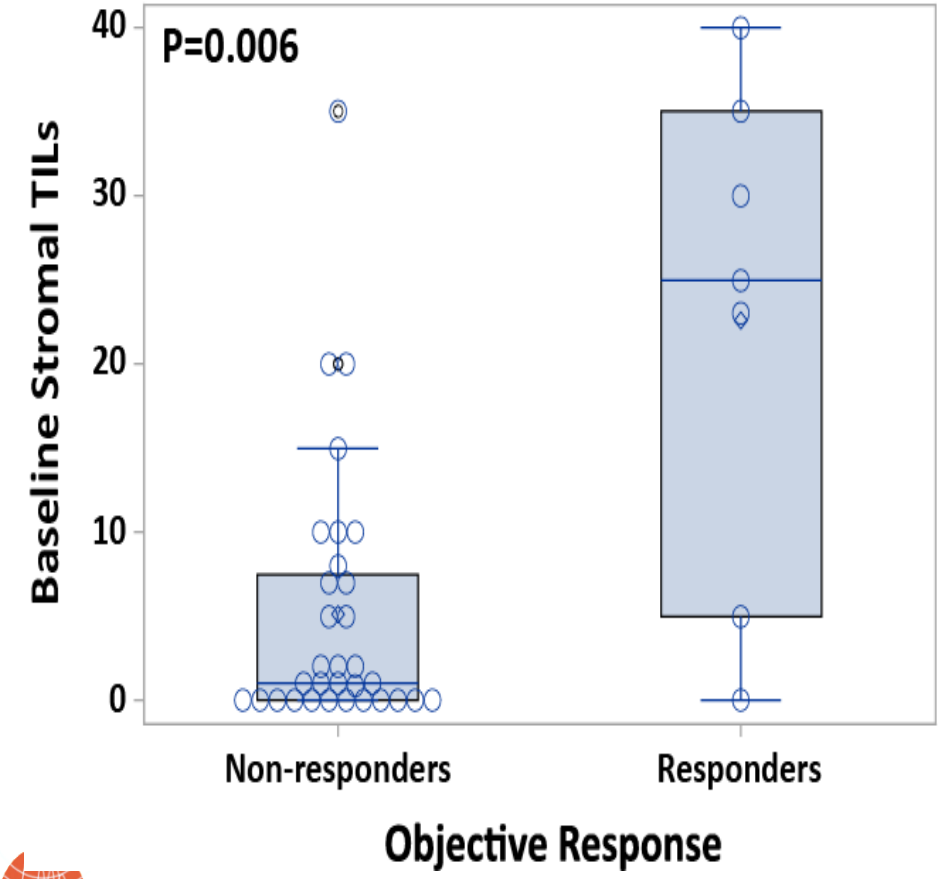
PFS and OS by PD-L1 Status



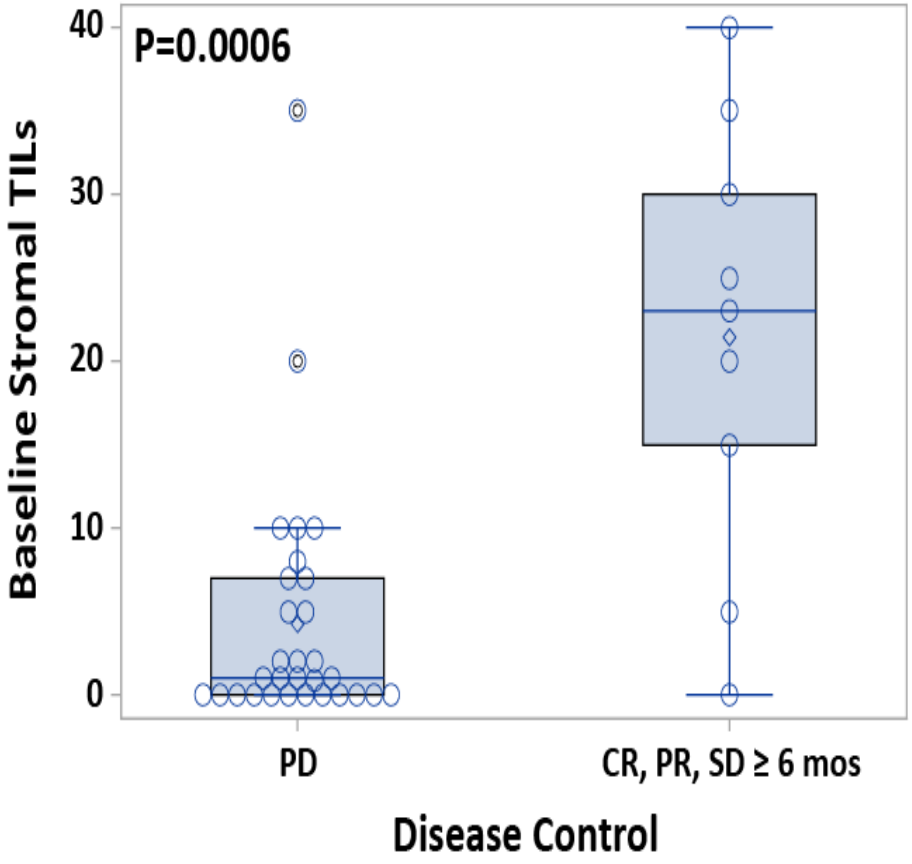


Higher sTILs Associated with Better Response and Disease Control: PD-L1 Positive Cohorts

Baseline sTILs and ORR



Baseline sTILs and DCR



Conclusions

- Combination of pembrolizumab with trastuzumab showed encouraging responses in PD-L1 positive, trastuzumab-resistant mHER2+ patients (ORR 15%, DCR 25%)
  - No responses observed in PD-L1 negative patients
  - Stromal TIL levels associated with responses

- Heavily pretreated HER2+ MBC is poorly immunogenic (most had low TILs)

- Future directions in IO in mHER2+ should focus on combinations with effective anti-HER2 therapy and investigate use earlier in disease course

San Antonio Breast Cancer Symposium, December 5-9, 2017

Imperial College London

A phase III multicentre double blind placebo controlled trial of celecoxib versus placebo in primary breast cancer patients

(REACT Randomised EuropeAn Celecoxib Trial)

EudraCT Number: 2004-000049-39

R. C. Coombes, Holly Tovey, Lucy Kilburn, Janine Mansi, Carlo Palmieri, John Bartlett, Jonathan Hicks, Andreas Makris, Abigail Evans, Sibylle Loibl, Carsten Denkert, Elisabeth Murray, Robert Grieve, Robert Coleman, Marcus Schmidt, Peter Klare, Mahdi Rezai, Beate Rautenberg, Nicole Klutinus, Uwe Rhein, Kelly Mousa, Tessa Dibble, Susana Ricardo-Vitorino, Gunter von Minckwitz, Judith Bliss ***on behalf of the REACT trial management group and investigators***

NORTHSIDE HOSPITAL CANCER INSTITUTE

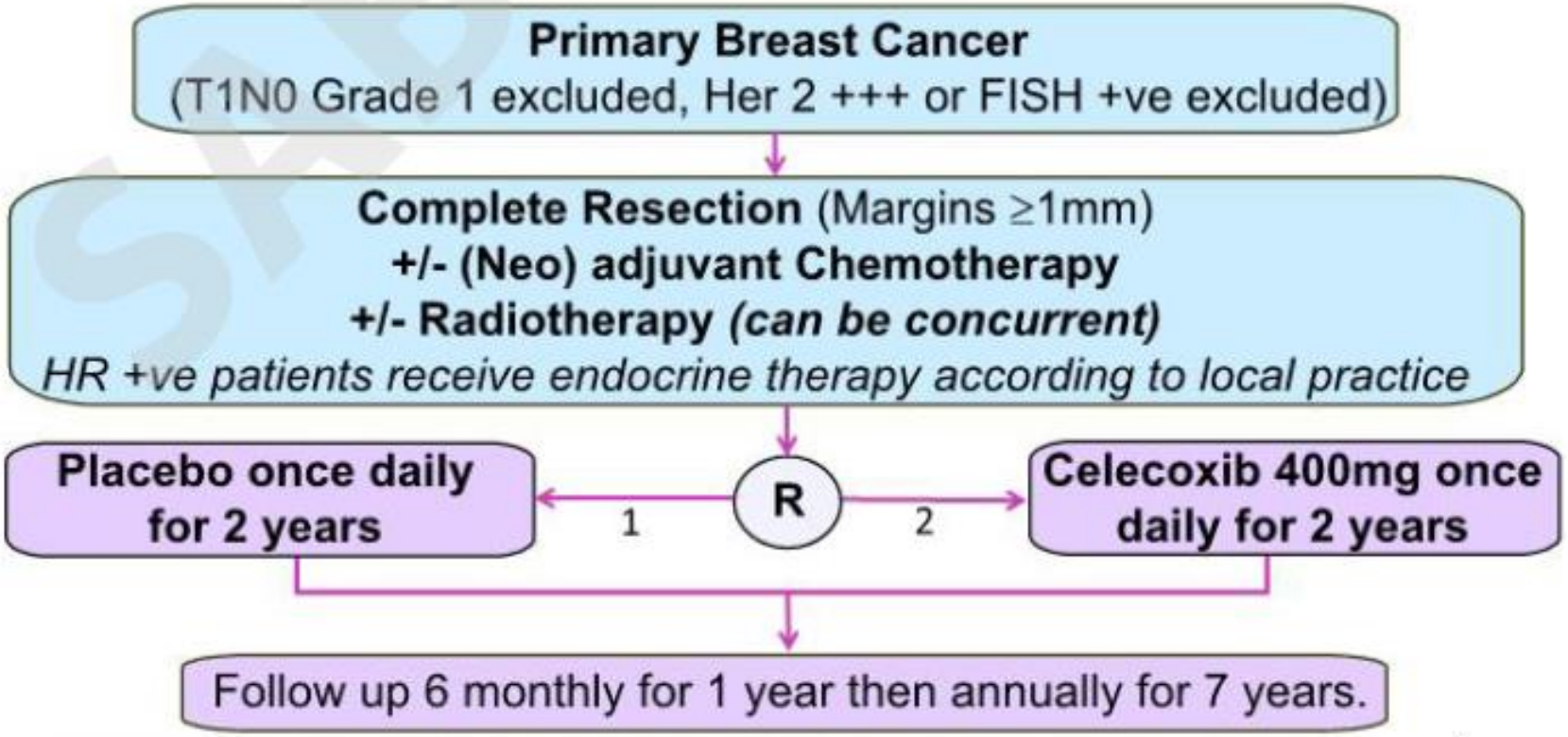
San Antonio Breast Cancer Symposium, December 5-9, 2017

Background and rationale

- Elevated levels of COX-2 have been associated with cancer progression
- COX-2 is transcriptionally regulated; its promoter is activated by multiple transcription factors, either alone or in combination. This leads to breast cancer (BC) progression.
- COX-2 enhances the aromatase pathway, particularly in estrogen receptor positive BCs.

San Antonio Breast Cancer Symposium, December 5-9, 2017

Trial Design



NORTHSIDE HOSPITAL
CANCER INSTITUTE

Baseline Characteristics

- 2639 patients: 1825 recruited in UK; 814 recruited in Germany

		Celecoxib	Placebo
Age	Median (IQR)	55.2 (48-63)	55.3 (48-63)
Menopausal status	Pre	554 (31%)	275 (31%)
	Post	1,209 (69%)	601 (69%)
Prior chemotherapy	Neoadjuvant	305 (17%)	153 (18%)
	Adjuvant	1,006 (57%)	506 (58%)
	Both	7 (<1%)	6 (1%)
	None	444 (25%)	211 (24%)

Baseline Characteristics

		Celecoxib	Placebo
Tumour size	≤2cm	852 (48%)	405 (46%)
	2-5cm	769 (44%)	381 (44%)
	>5cm	108 (6%)	64 (7%)
Grade	G1	93 (5%)	29 (3%)
	G2	917 (52%)	471 (54%)
	G3	741 (42%)	370 (42%)
Biological subgroup	Triple negative	480 (27%)	224 (26%)
	ER/PgR+ & HER2-	1,280 (73%)	651 (74%)
Nodes involved	0 nodes	911 (52%)	444 (51%)
	1-3 nodes	589 (33%)	285 (33%)
	4+ nodes	249 (14%)	142 (16%)

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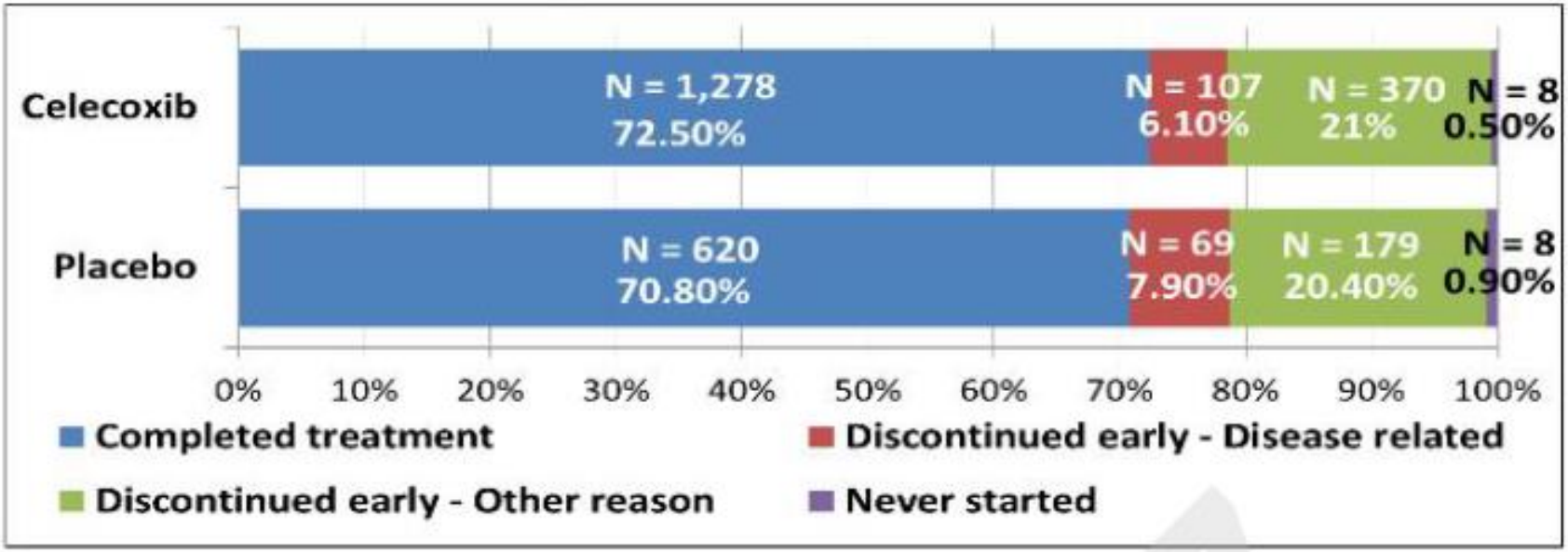
Treatment Compliance

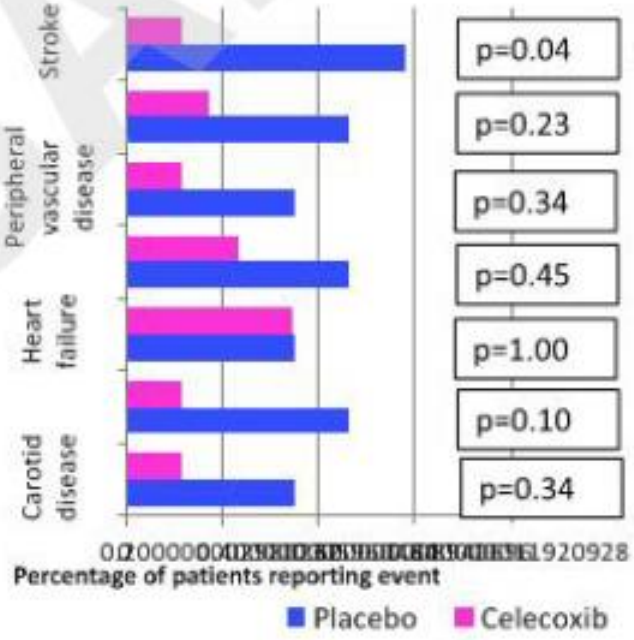


Median time on treatment: 24 months (IQR: 19.6 – 24.4)

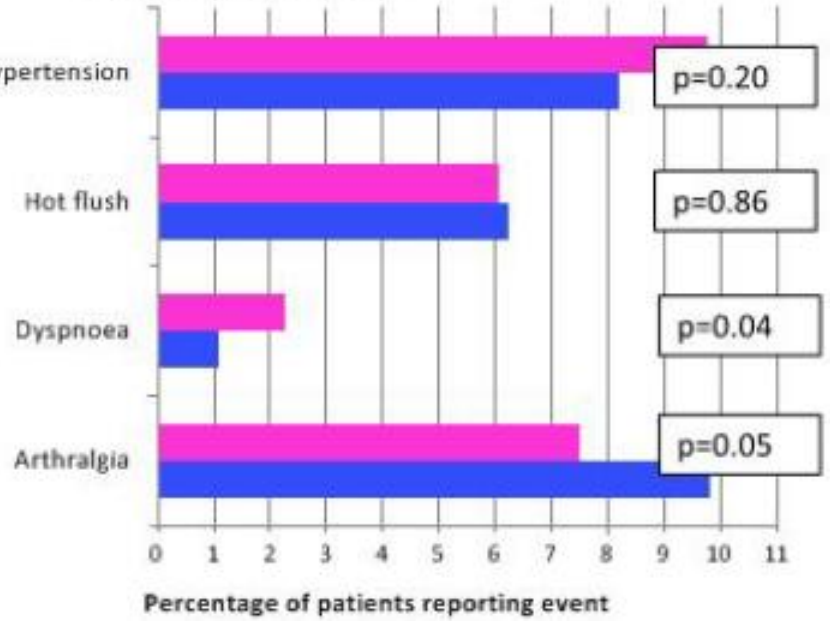
712 (81%) placebo, 1,418 (80%) celecoxib completed at ≥1 year

Safety

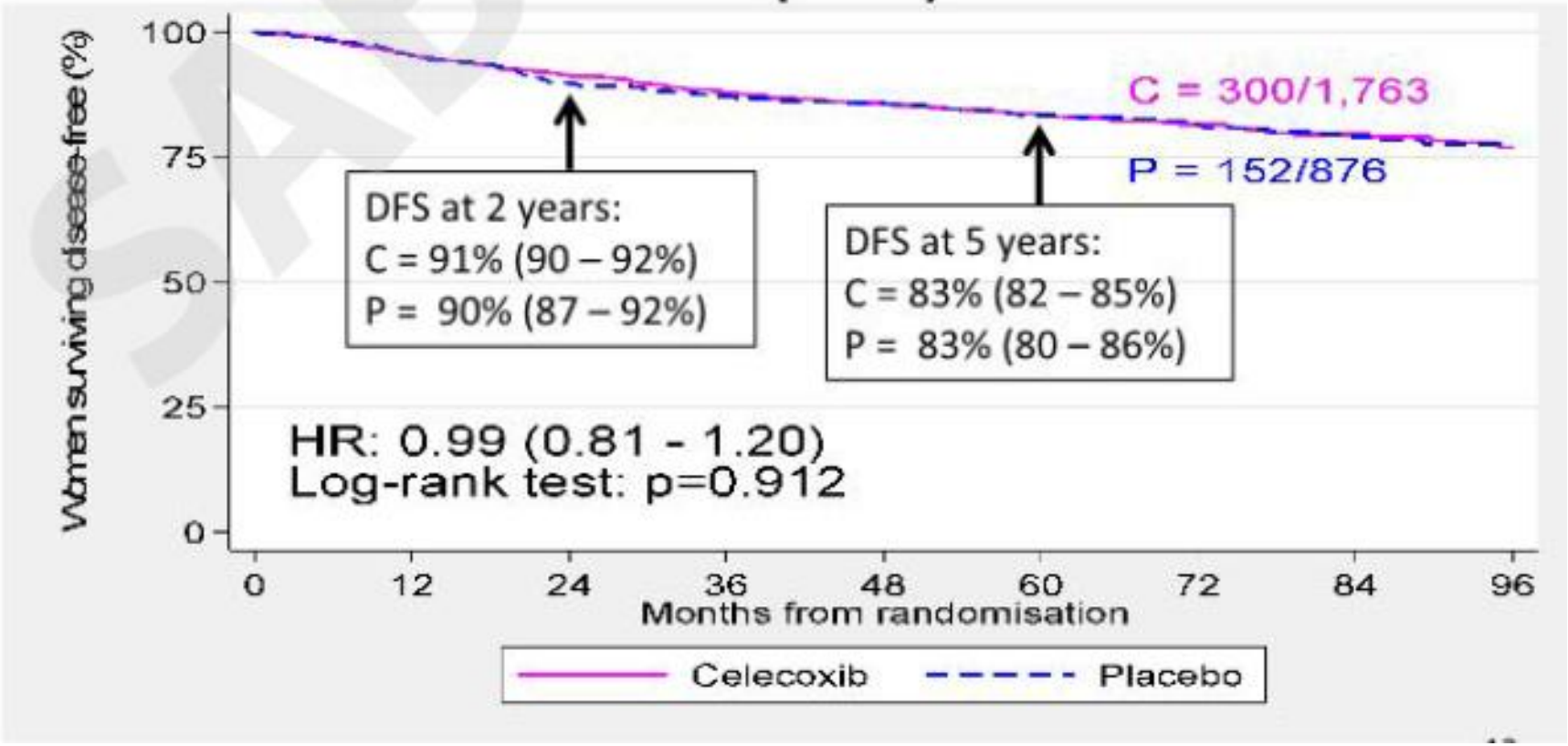
Pre-specified cardiovascular events



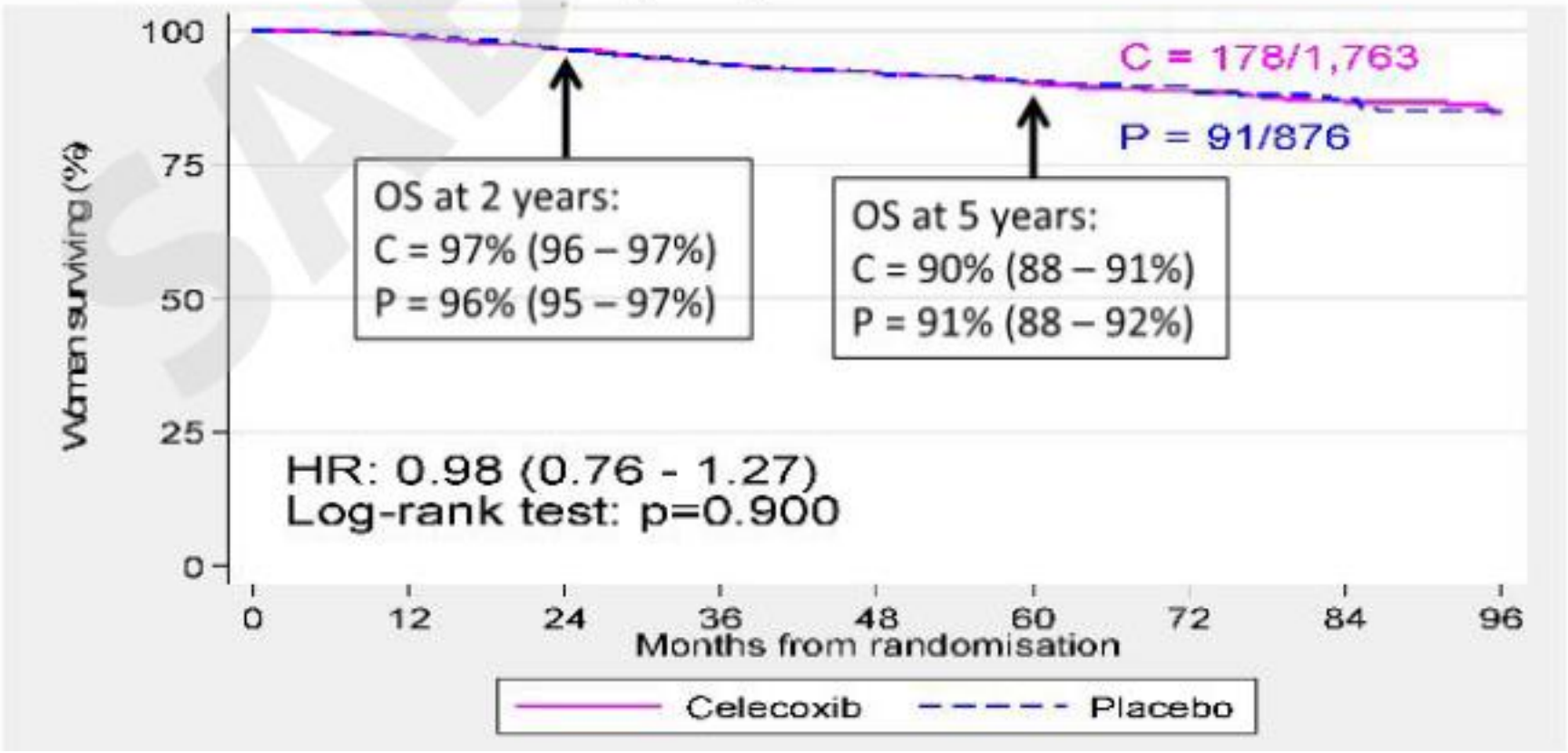
Other events with > 5% prevalence, >1% difference between treatments or statistically significant difference



Disease Free Survival (DFS)



Overall Survival (OS)



Conclusions

- No DFS or OS benefit with celecoxib
- No significant toxicity
- Subgroup analysis did not identify a predictor of benefit. Translational research is underway to look for a possible “celecoxib signature”
- Studies are ongoing evaluating NSAIDs (Alliance ABC Trial) in early-stage breast cancer

Randomized Blinded Sham- and Waitlist-Controlled Trial of Acupuncture for Joint Symptoms Related to Aromatase Inhibitors in Women with Early Stage Breast Cancer (SWOG 1200)

Dawn L. Hershman, Joseph M. Unger, Heather Greenlee, Jillian Capodice, Danika L. Lew, Amy Darke, Alice Kengla, Marianne K. Melnik, Carla W. Jorgensen, William H. Kreisle, Lori M. Minasian, Michael J. Fisch, N. Lynn Henry, Katherine D. Crew

STUDY DESIGN

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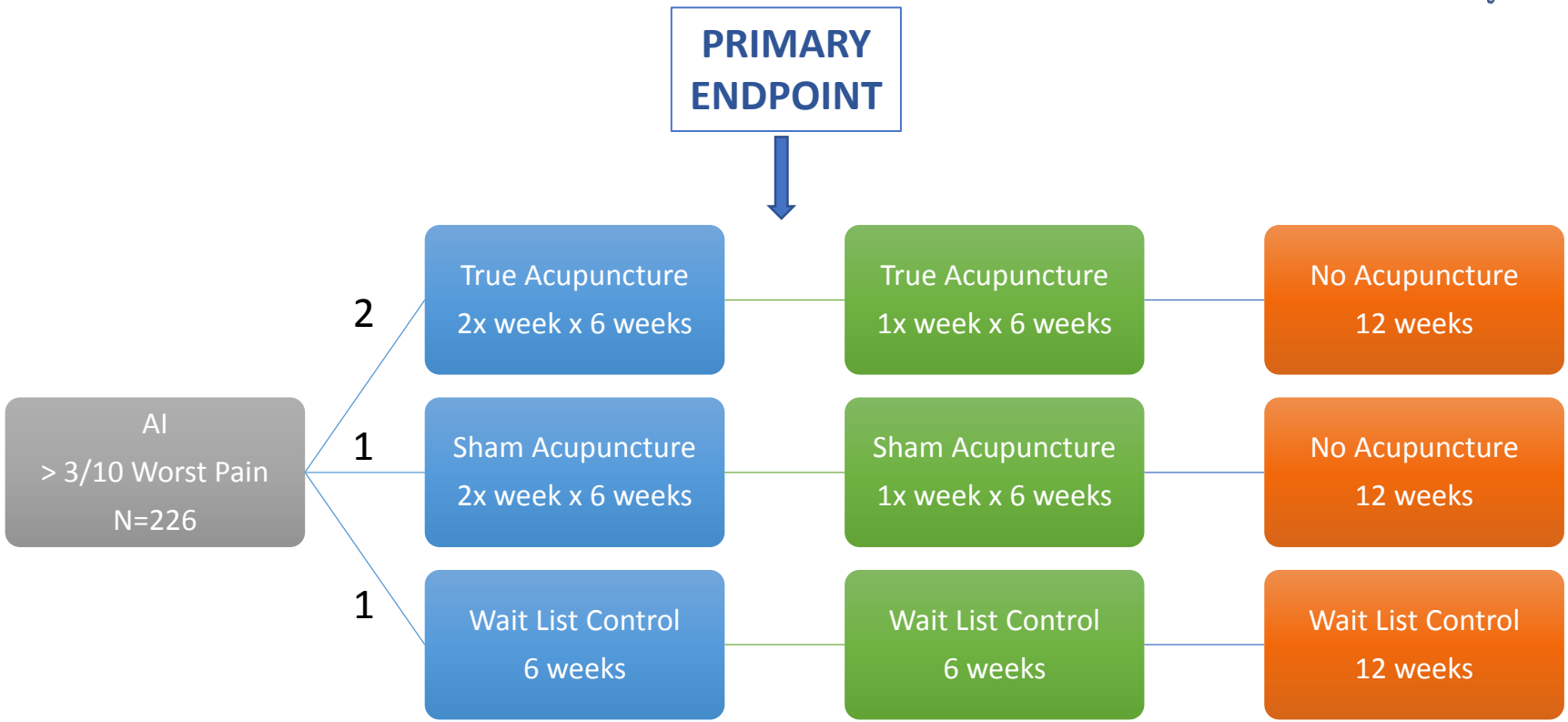

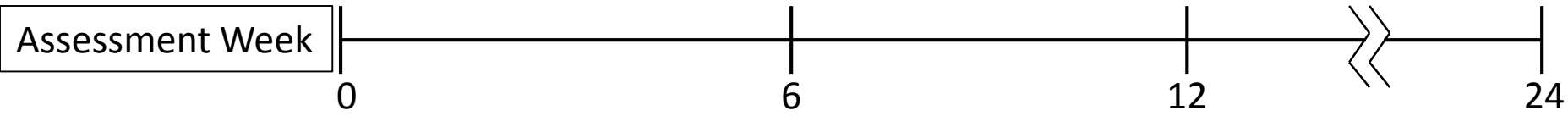

ELIGIBILITY

- Stage 1-3 hormone sensitive breast cancer
- Third-generation AI for at least 30 days prior to registration
- Score of ≥3 (range, 0-10) on the worst pain item of the BPI
- Symptoms started or increased since starting AI
- No opioids or corticosteroid and no alternative/physical therapy for the treatment of joint pain within 28 days prior to registration
- No prior acupuncture treatment for joint symptoms at any time, but allowed for other reasons >12 months prior

INTERVENTION

- **True Acupuncture**
  - Standard Traditional Chinese Medicine point prescription to reduce pain and decrease stress (30-45 min per session)
  - Full body, auricular and joint-specific acupuncture protocol tailored to the most painful joints
- **Sham Acupuncture**
  - Shallow needle insertion utilizing thin and short needles at non-acupuncture points
  - Four standardized points, auricular sham and joint-specific sham point protocols within the proximity of the specified anatomic area
- **Wait List Control**
  - True acupuncture offered after 24 weeks

Crew, KD. JCO,2010

PATIENT CHARACTERISTICS

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	Total (n=226)		True Acupuncture (n=110)		Sham Acupuncture (n=59)		Waitlist Control (n=57)	
Age, years								
Median	60.7		60.8		57.0		60.6	
Hispanic, N (%)	21	7%	11	10%	7	12%	3	5%
Race, N (%)								
White	193	88%	88	83%	54	93%	51	91%
Black	10	5%	6	6%	2	3%	2	4%
Asian	15	7%	11	10%	2	3%	2	4%
Prior Chemotherapy, N (%)	111	49%	56	51%	31	53%	24	42%
AI Therapy (median yrs)	1.1		1.0		1.1		1.1	
Prior Acupuncture, N (%)	44	19%	19	17%	13	22%	12	21%
Baseline Score – BPI WP			6.84		6.55		6.48	

6-WEEK RESULTS - WORST PAIN (BPI)

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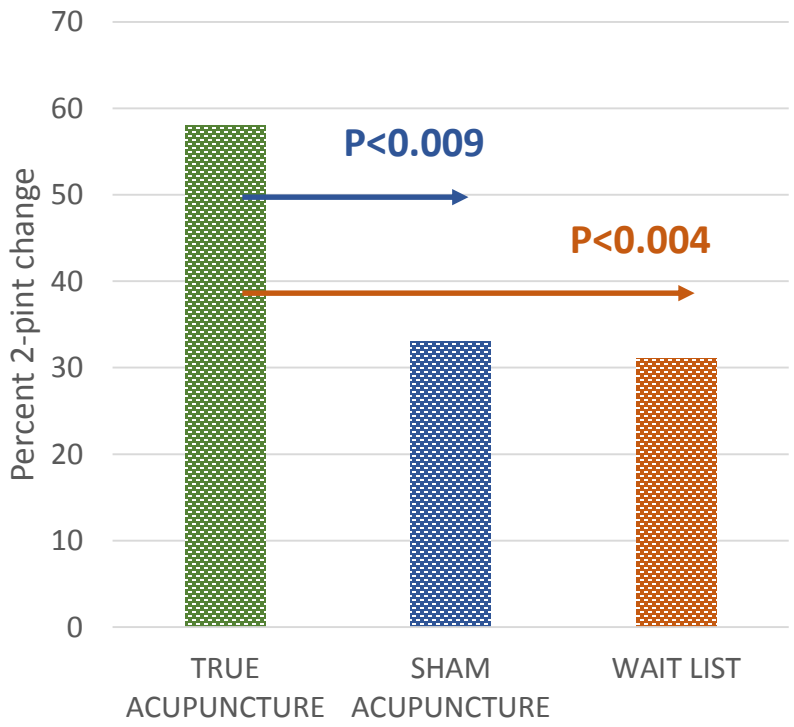
WORST PAIN	Fitted Difference*	P-value
True v. Sham	0.92 (0.20-1.65)	.01
True v. Waitlist	0.96 (0.24-1.67)	.01
Sham v. Waitlist	0.05 (-0.81-0.90)	.92

* Corrected for baseline score and study site

Percent with 2-point change



RESULTS - Other 6 Week Endpoints

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BPI AVERAGE PAIN	Fitted Difference	P-value
True v. Sham	0.60 (0.03, 1.17)	.04
True v. Waitlist	0.71 (0.15, 1.28)	.01
Sham v.	0.08 (-0.51,	79

BPI STIFFNESS	Fitted Difference	P-value
True v. Sham	1.00 (0.19, 1.81)	.02
True v. Waitlist	1.09 (0.26, 1.92)	.01
Sham v. Waitlist	0.17 (-0.62, 0.96)	.67

WOMAC	Fitted Difference	P-value
True v. Sham	9.27 (3.73, 14.82)	.001
True v. Waitlist	12.18 (6.76, 17.59)	<.0001
Sham v.	3.01 (-2.75,	0.31

M-SACRAH	Fitted Difference	P-value
True v. Sham	6.23 (0.92, 11.55)	.02
True v. Waitlist	9.40 (4.52, 14.28)	.0002
Sham v. Waitlist	4.26 (-1.32, 9.84)	.14

ADVERSE EVENTS

	True Acupuncture (n=106) Grade				Sham Acupuncture (n=55) Grade			
ADVERSE EVENTS	0	1	2	3	0	1	2	3
Bruising	**56**	**50**	0	0	**41**	**14**	0	0
Dizziness	101	5	0	0	55	0	0	0
Ear pain	105	1	0	0	54	1	0	0
Hematoma	105	1	0	0	55	0	0	0
Bleeding at injection site	103	3	0	0	53	2	0	0
Pain in extremity	105	1	0	0	55	0	0	0
Presyncope	105	0	1	0	54	0	1	0

Grade 1 bruising (47% vs. 25%) p=.01

- Patients on true acupuncture were more likely to believe they were receiving true acupuncture 6 weeks (68% vs. 36%, p<.0001).
- The intervention effect did not differ between those believing vs. not believing they were receiving true acupuncture at either 6 weeks (p=.16) using interaction tests.

Columbia University Medical Center
Herbert Irving Comprehensive Cancer Center

Weight Loss and Breast Cancer Incidence in Postmenopausal Women

Chlebowski RT, Luo J, Anderson GL, Barrington W, Redding K,

Simon MS, Manson JE, Rohan TE, Wactawski-Wende J, Lane D,

Strickler H, Mosaver-Rahmani Y, Freudenheim JL, Saquib N,

Stefanick ML

City of Hope National Medical Center

Women's Health Initiative Investigators

Participants and Methods

Participants in the Women's Health Initiative (WHI) Observational Study (n= 93,676)

- Postmenopausal, ages 50-79 years, with anticipated 3 year survival, recruited from 40 US Clinical Centers from 1993-1998
- 11.4 years mean follow-up through September 30, 2015

Measures

- Information on demographics, medical history and breast cancer risk factors collected at baseline by questionnaires
- Information on medication use collected at baseline during interviews including "in hand" medication container review.
- Mammograms were not protocol mandated but mammogram frequency wascllected annually

Baseline Characteristics by Weight Change Category

- Compared with the women with stable weight:
- Women who had ≥ 5% weight gain were more likely to be younger, Black and be heavier smokers (all P < .01)
- Women who had ≥ 5% weight loss were more likely to have higher BMI, but were less likely to be physically active or have used any menopausal hormone therapy (all P < .01)
- Other baseline characteristics including education, alcohol intake, history of estrogen alone or estrogen plus progestin, BCRAT risk score, bilateral oophorectomy, physical activity (MET-hrs/wk), BMI, and diabetes were similar among weight change category groups

Baseline Medication Use (%) by Weight loss Category

Weight change category	Metformin	NSAID
Stable Weight (within ± 5%) (n=41,139)	0.5%	8.7%
Weight gain (≥ 5%) (n=12,021)	0.7%	12.6%
Weight loss (≥ 5%) Intentional (n=4,829)	0.8%	10.3%
Weight loss (≥ 5%) Unintentional (n=3,346)	1.1%	12.2%

Metformin use rare

Measured Weight Change (pounds, mean, SD) by Weight loss Category Year 1- 3 (measured) and Year 3- 6 (self report)

Weight change category	Weight change Year 1-3	Weight change Year 3-6
Stable Weight (within ± 5%) (n=41,139)	+0.54 (4.07)	-2.80 (9.58)
Weight gain (≥ 5%) (n=12,021)	+18.51 (28.42)	-9.80 (31.33)
Weight loss (≥ 5%) Intentional (n=4,829)	-19.58 (27.12)	+2.55 (13.68)
Weight loss (≥ 5%) Unintentional (n=3,346)	-16.90 (18.69)	+1.82 (12.03)

Measured weight change from year 1-3 used in all analyses

Weight Change and Breast Cancer (n= 3,061) among 61,335 Postmenopausal Women after 11.4 Years (median) follow-up

- In multivariable–adjusted analyses, compared with the women with stable weight (n=41,139):
- Women who had ≥ 5% weight loss (n=8,175) had a significantly lower breast cancer incidence (HR 0.88 95% CI 0.78-0.98, P= 0.02)
- Adjustment for mammography frequency did not alter findings (HR 0.88 95% CI 0.78-0.99)
- Women who had ≥ 5% weight gain (n=12,021) did not have a higher overall breast cancer incidence (HR 1.02 95% CI 0.93-1.11). However, women with such weight gain had a significantly higher incidence of triple negative breast cancer (HR 1.54 95% CI 1.16-2.05)

Weight Change and Breast Cancer incidence including by Weight Loss Intentionality

% Weight change between baseline And Year 3	Breast cancer cases (N)	HR (95% CI) Multivariable-adjusted
Stable Weight (within ± 5%)	2,092	Reference
Weight gain (≥ 5%)	620	1.02 (0.93-1.11)
Weight loss (≥ 5%)	349	0.88 (0.78-0.98)
Intentional	229	0.91 (0.79-1.04)
Unintentional	120	0.82 (0.68-0.99)

Statistical test between intentional and unintentional weight loss groups found no significant difference (P=0.2)

Conclusions

- Accupuncture is an option for symptom management for patients with AI-induced arthralgias
  - The 12-week (18 session) intervention was ~ $1,250 ($65-$75/session)
  - Will insurance coverage change based on results?

- Findings from WHI suggest that interventions in postmenopausal women designed to generate weight loss may reduce breast cancer risk.