Best of ASCO
Breast Cancer Update

Georgia Society of Clinical Oncology
September 6, 2014

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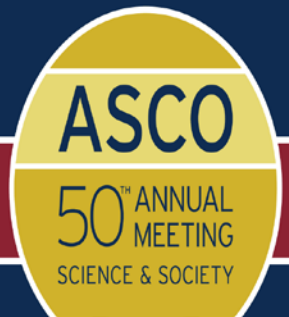
Randomized Comparison of Adjuvant Aromatase Inhibitor Exemestane plus Ovarian Function Suppression vs Tamoxifen plus Ovarian Function Suppression in Premenopausal Women with Hormone Receptor Positive Early Breast Cancer: Joint Analysis of IBCSG TEXT and SOFT

Olivia Pagani, MD
on behalf of the
TEXT and SOFT Investigators and
International Breast Cancer Study Group
(IBCSG)



TEXT and SOFT Designs

Enrolled: Nov03-Apr11

TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)

- Premenopausal
- ≤12 wks after surgery
- Planned OFS
- No planned chemo *OR* planned chemo

RANDOMIZE →

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

SUPPRESSION OF OVARIAN FUNCTION TRIAL (N=3066)

- Premenopausal
- ≤12 wks after surgery
- No chemo

OR

- Remain premenopausal ≤ 8 mos after chemo

RANDOMIZE →

- Tamoxifen x 5y
- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

Joint Analysis (N=4690)

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

Median follow-up 5.7 years

OFS=ovarian function suppression

Eligibility

- Premenopausal women with HR+ (ER and/or PgR≥10%) invasive breast cancer confined to breast +/- axillary nodes
- Proper local-regional treatment with no residual disease
- Randomized within 12 weeks of surgery for all women in **TEXT** and women in **SOFT** who did not receive chemotherapy
- Women in **SOFT** who received prior (neo)adjuvant chemotherapy randomized ≤8 months of chemotherapy completion when premenopausal status demonstrated
  - These patients were permitted to receive oral endocrine therapy prior to randomization

Treatments

Protocol treatment was for 5 years from randomization

- **Ovarian Function Suppression**

  TEXT

  - All women started with GnRH agonist triptorelin (IM q28d)
  - Triptorelin initiated concurrently with chemotherapy, if it was given
  - Bilateral oophorectomy or irradiation as alternatives to triptorelin after 6 months

  SOFT

  - Choice of OFS method

- **Oral endocrine therapy**
  - Exemestane 25 mg daily, or
  - Tamoxifen 20 mg daily
  - In TEXT started 6 to 8 weeks after initiation of OFS, or after chemotherapy if given

Endpoints

Primary

- Disease-free survival (DFS)
  - Invasive recurrence (local, regional, distant)
  - Invasive contralateral breast cancer
  - Second (non-breast) invasive malignancy
  - Death without prior cancer event

Secondary

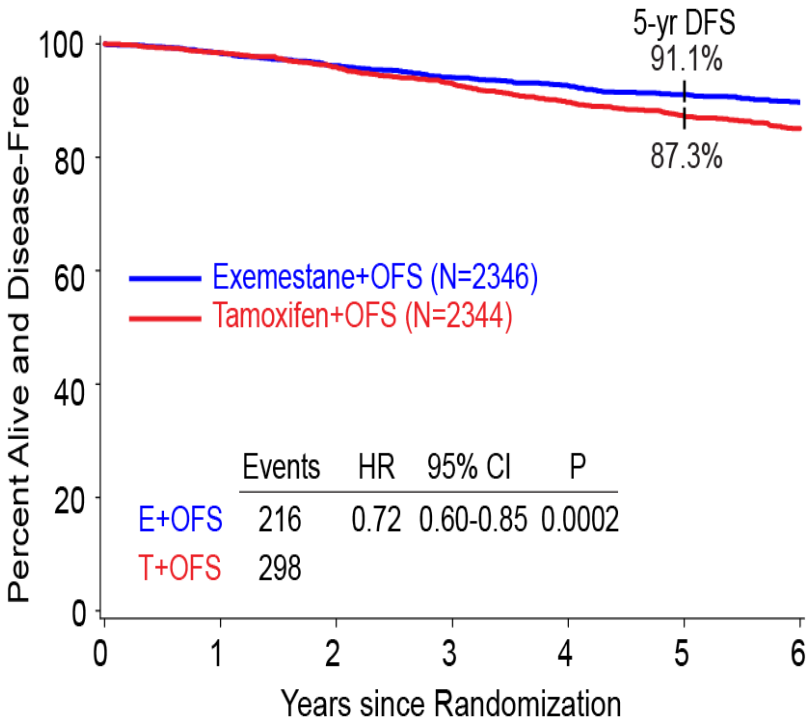
- Breast cancer-free interval (BCFI)
  - Invasive recurrence or contralateral breast cancer
- Distant recurrence-free interval (DRFI)
  - Distant recurrence
- Overall survival (OS)
  - Death from any cause

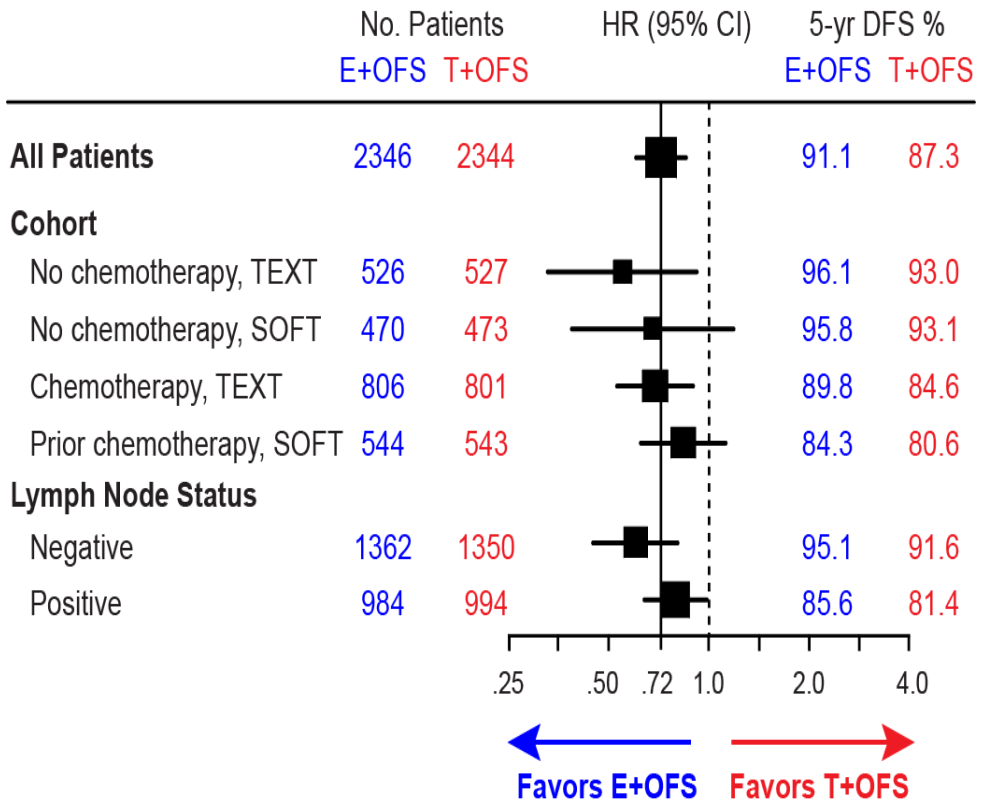
Characteristics

	No chemo TEXT (N=1053)	No chemo SOFT (N=943)	Chemo TEXT (N=1607)	Prior chemo SOFT (N=1087)	Overall (N=4690)
Age <40 yr	16%	9%	30%	49%	27%
LN +	21%	8%	66%	57%	42%
T-size >2cm	19%	15%	53%	47%	36%
HER2 +	5%	3%	17%	19%	12%
Surgery to random. (median)	1.5 mo	1.8 mo	1.2 mo	8.0 mo	1.6 mo

Exemestane+OFS Improved DFS

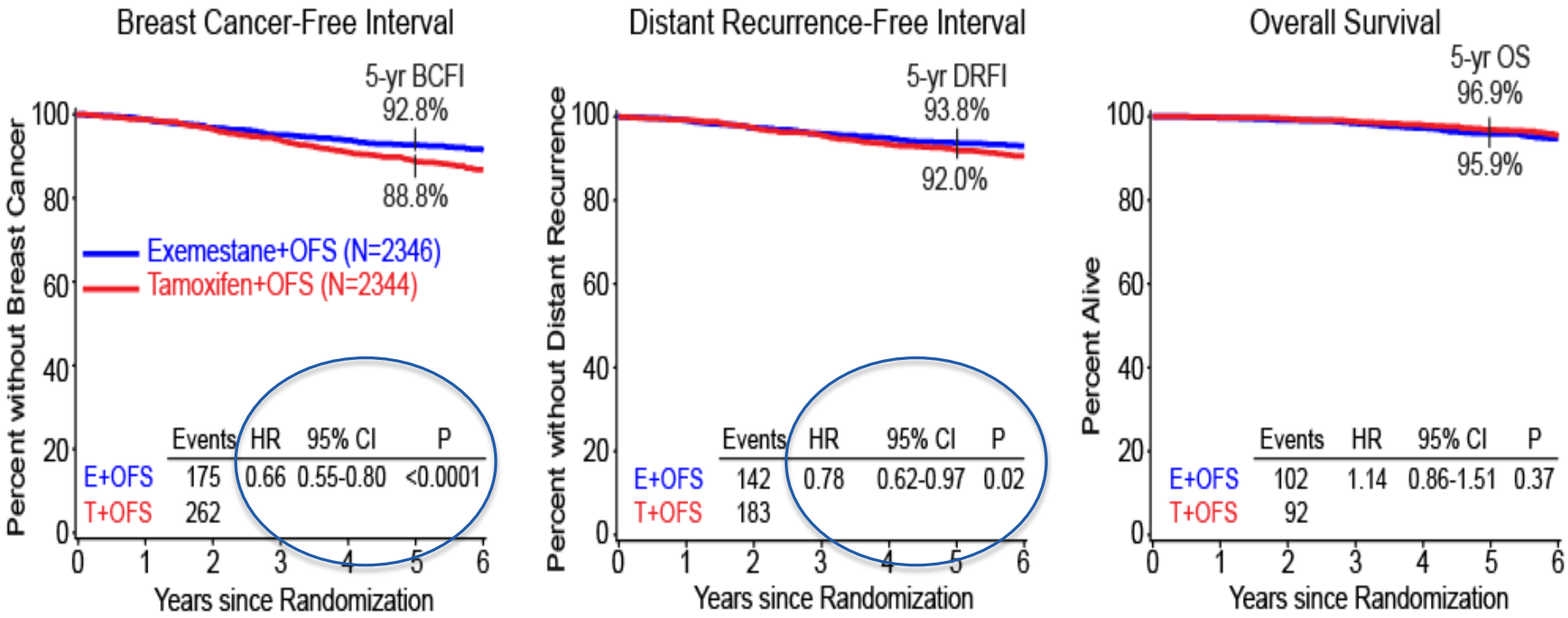
Difference 3.8% at 5 years





5.7 years median follow-up

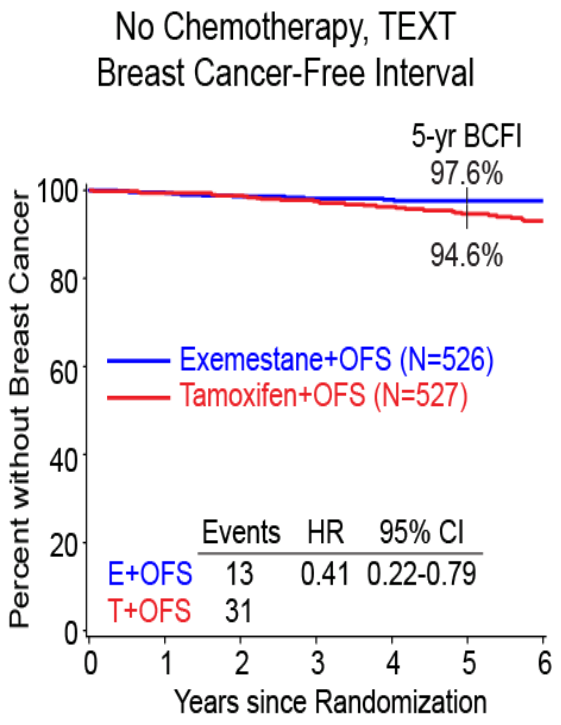
Exemestane+OFS Reduced Recurrence



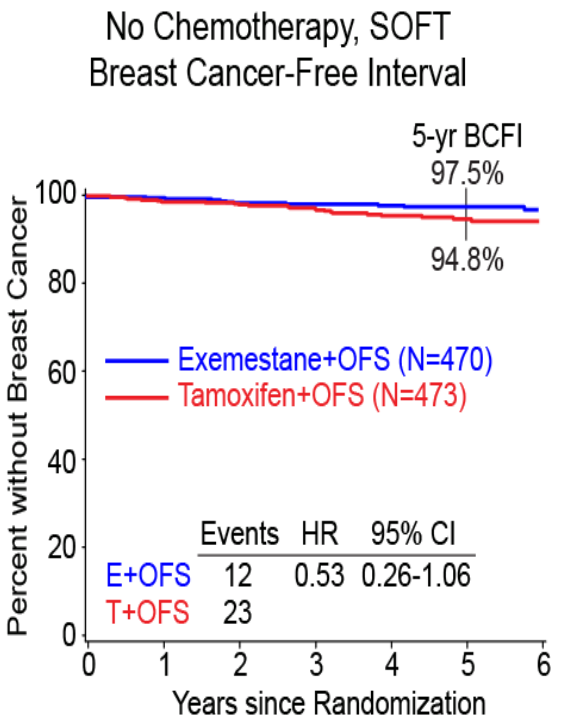
- 4% absolute improvement in 5-yr freedom from breast cancer for exemestane+OFS
- No significant difference in overall survival

Women Who Did Not Receive Chemotherapy

N=1996



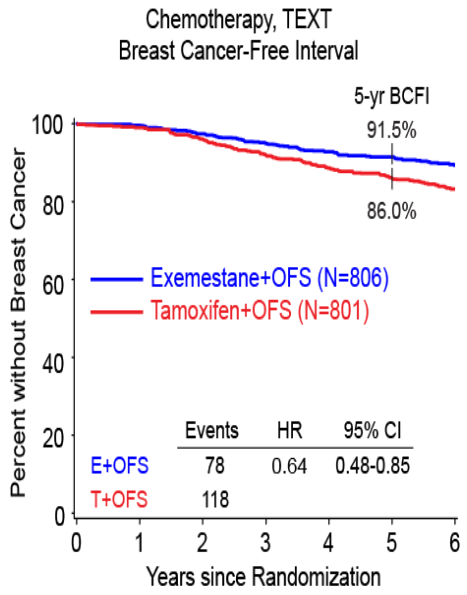
16% <40 years; 19% T-size >2cm; 21% N+

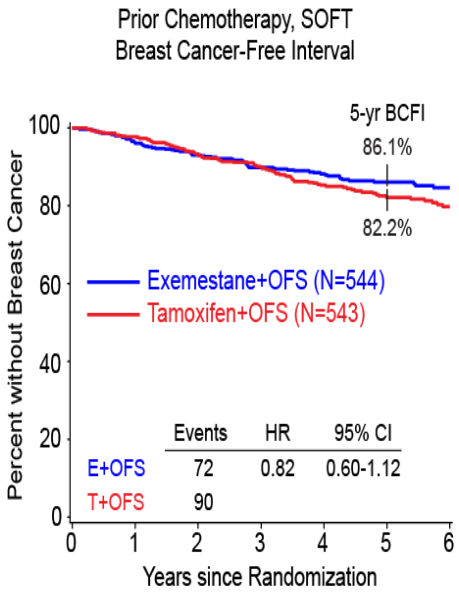


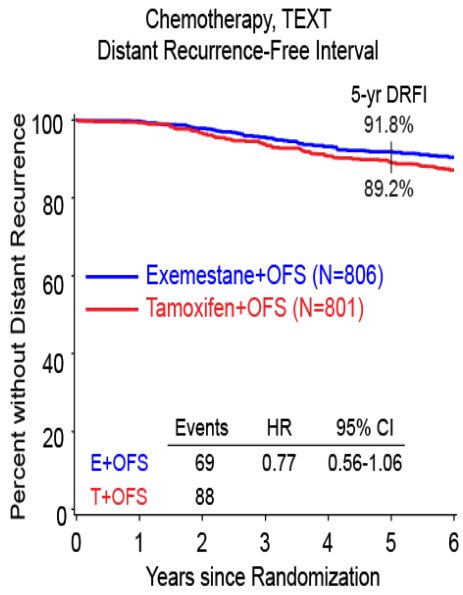
9% <40 years; 15% T-size >2cm; 8% N+

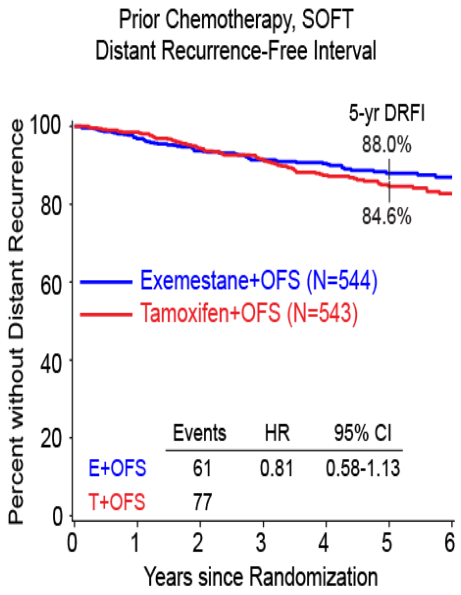
Some women have excellent prognosis with highly-effective endocrine therapy alone >97% breast cancer-free at 5 years when treated with exemestane+OFS

Women Who Received Chemotherapy









66% N+; 53% T-size >2cm; 30% <40 years

57% N+; 47% T-size >2cm; 49% <40 years

Absolute improvement with exemestane+OFS

- 5-yr freedom from breast cancer: 5.5% in TEXT and 3.9% in SOFT
- 5-yr freedom from distant recurrence: 2.6% in TEXT and 3.4% in SOFT

Selected Adverse Events

	Exemestane+OFS (N=2318)		Tamoxifen+OFS (N=2325)	
CTCAE v3.0	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Depression	50%	3.8%	50%	4.4%
Musculoskeletal	89%	11%	76%	5.2%
Osteoporosis (% T< -2.5)	39% (13%)	0.4%	25% (6%)	0.3%
Fracture	6.8%	1.3%	5.2%	0.8%
Hypertension	23%	6.5%	22%	7.3%
Cardiac ischemia/infarction	0.7%	0.3%	0.3%	0.1%
Thrombosis/embolism	1.0%	0.8%	2.2%	1.9%
CNS ischemia	0.7%	0.3%	0.3%	0.1%
CNS bleeding	0.6%	<0.1%	0.9%	0.1%
Hot flushes/flashes	92%	10%	93%	12%
Sweating	55%	--	59%	--
Vaginal dryness	52%	--	47%	--
Libido decrease	45%	--	41%	--
Dyspareunia	31%	2.3%	26%	1.4%

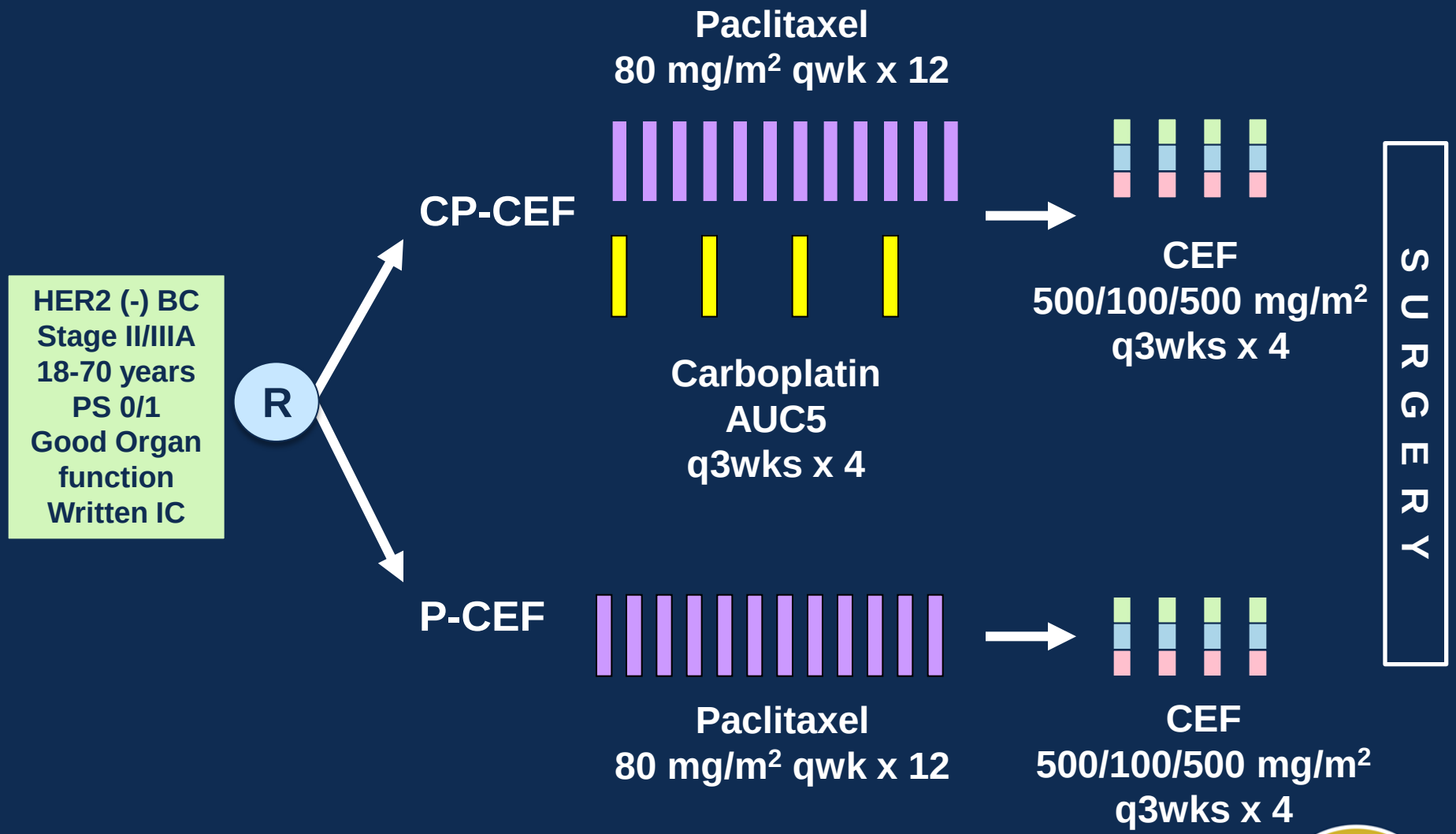
Conclusions: SOFT/TEXT

- Exemestane plus ovarian suppression had improved DFS compared to tamoxifen and is a reasonable option
- No difference in overall survival; longer follow-up is needed
- Results of tamoxifen alone arm not yet available
- Early cessation rate higher in exemestane arm
  - (16% vs 11%)
  - Side effect profile comparable to AIs in postmenopausal women
- Multiple unanswered questions:
  - Low risk patients: do short and long-term risks outweigh benefit?
  - Chemo-induced menopause: should we commit to 5 years of ovarian suppression or wait to switch to AI after confirming postmenopausal status
  - ABCSG12: similar trial (N=1803) of ovarian suppression with anastrozole versus tamoxifen did not show DFS advantage

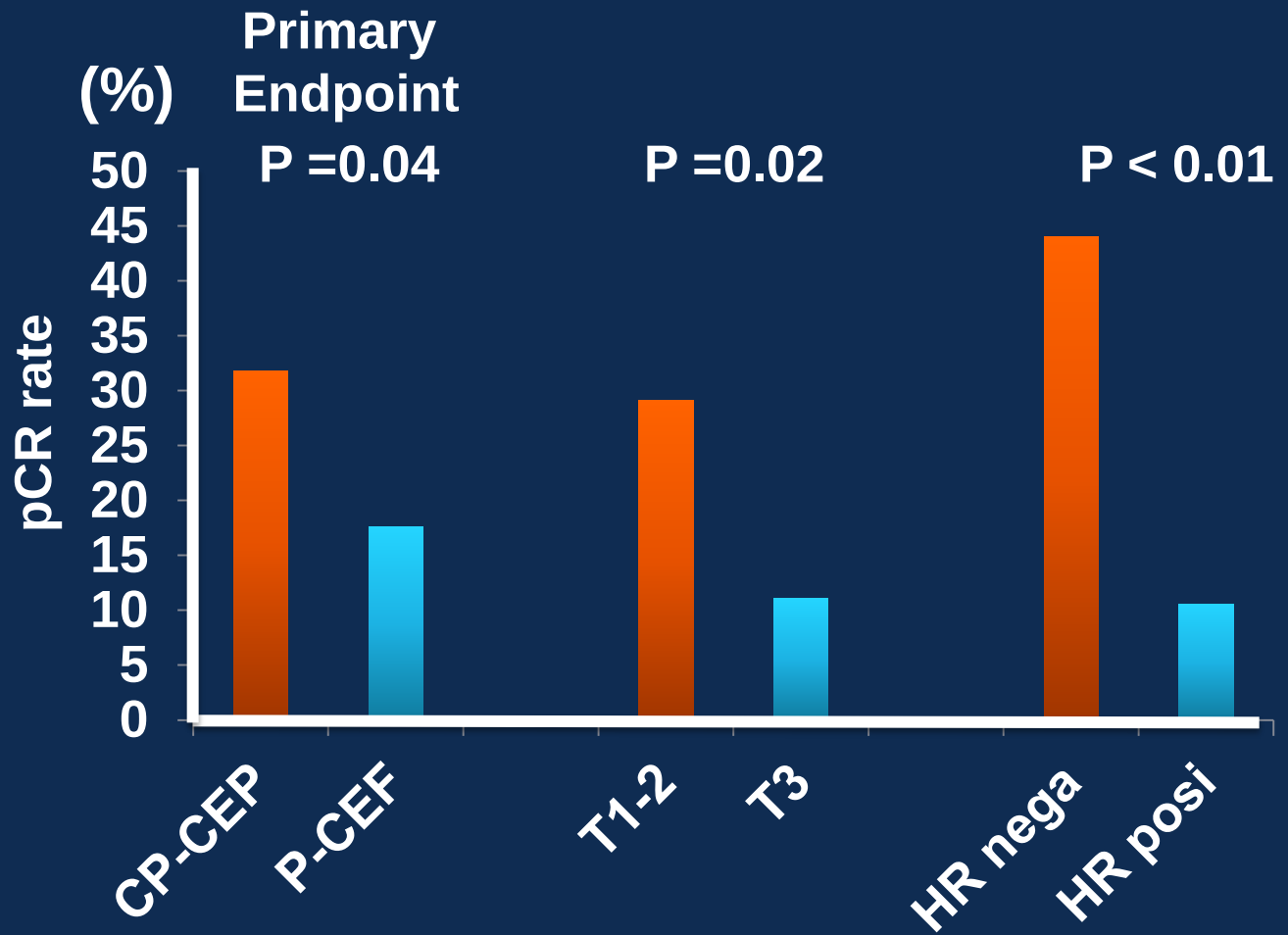
Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide / epirubicin / 5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer.

Kenji Tamura, Jun Hashimoto, Hitoshi Tsuda, Masayuki Yoshida, Hideko Yamauchi, Kenjiro Aogi, Satoru Shimizu, Hiroji Iwata, Norikazu Masuda, Naohito Yamamoto, Kenichi Inoue, Shinji Ohno, Katsumasa Kuroi, Tamie Sukigara, Yasuhiro Fujiwara, Masashi Andoh

Protocol Design

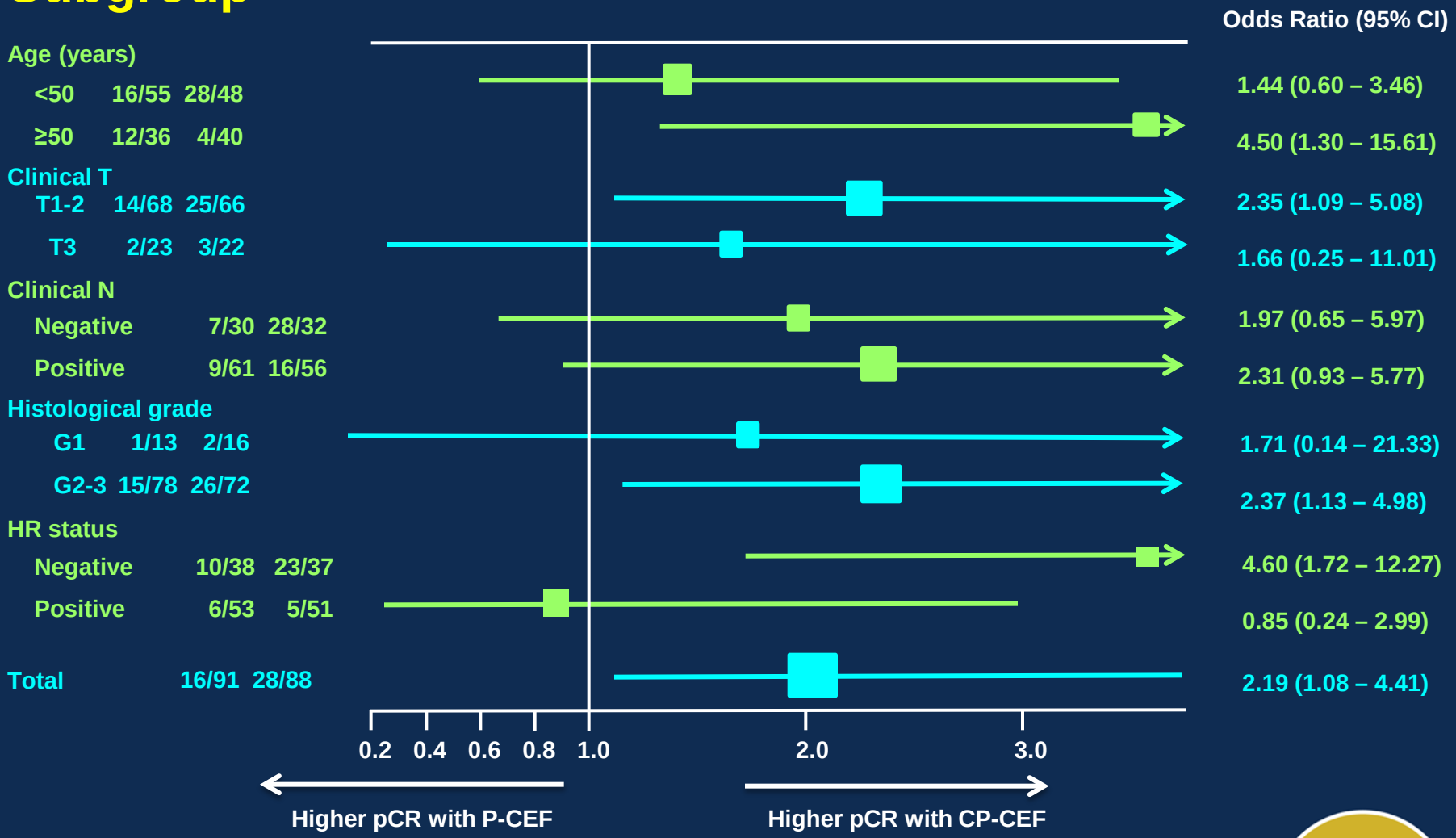


pCR rates by sub groups



Odds ratio	0.46	0.30	0.15

Odds rates / Subgroup Analysis



Adverse Events

Treatment arm	CP-CEF				P-CEF			
	All		CP phase		All		P phase	
Adverse events	G3%	G4%	G3%	G4%	G3%	G4%	G3%	G4%
Anemia	18.2	1.1	14.8	1.1	1.1	0	0	0
Neutropenia	46.6	19.3	52.3	5.7	17.6	20.9	8.8	1.1
Thrombocytopenia	1.1	0	1.1	0	0	0	0	0
Febrile neutropenia	20.5	0	2.3	0	15.4	0	0	0
Nausea	3.4	0	2.3	0	2.2	0	0	0
Vomiting	2.3	0	1.1	0	0	0	0	0
Fatigue	2.3	0	2.3	0	1.1	0	0	0
Infection	4.4	0	2.2	0	1.1	0	0	0
Sensory neuropathy	1.1	0	1.1	0	1.1	0	1.1	0

Pathological complete response (pCR) rates after carboplatin-containing neoadjuvant chemotherapy in patients with germline BRCA (gBRCA) mutation and triple negative breast cancer (TNBC) – Results from GeparSixto

Gunter von Minckwitz, Eric Hahnen, Peter A. Fasching, Jan Hauke, Andreas Schneeweiss, Christoph T. Salat, Mahdi Rezai, Jens U. Blohmer, Dirk M. Zahm, Christian Jackisch, Bernd Gerber, Peter Klare, Sherko Kümmel, Holger Eidtmann, Stephan Paepke, Valentina Nekljudova, Sibylle Loibl, Michael Untch, Rita Schmutzler

for the

GBG/AGO-B study groups

AGO-B
BREAST STUDY GROUP

GBG
GERMAN
BREAST
GROUP

Presented at the 2014 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.

Main Study Design

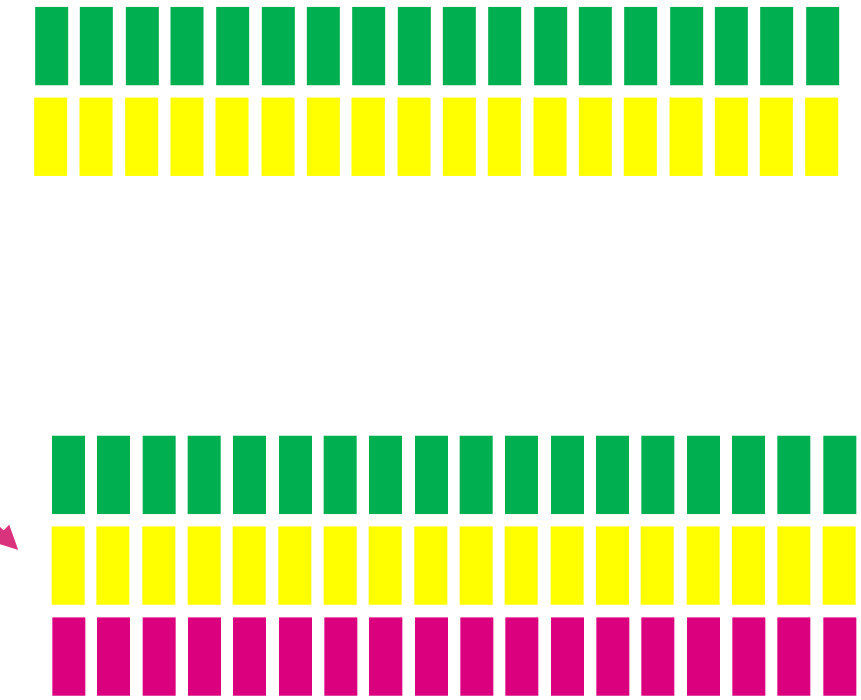
N=595

centrally confirmed TNBC or HER2-positive breast cancer

R

PM

PMCb



Surgery

Paclitaxel 80 mg/m² q1w

Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w

Carboplatin AUC 1.5-2* q1w

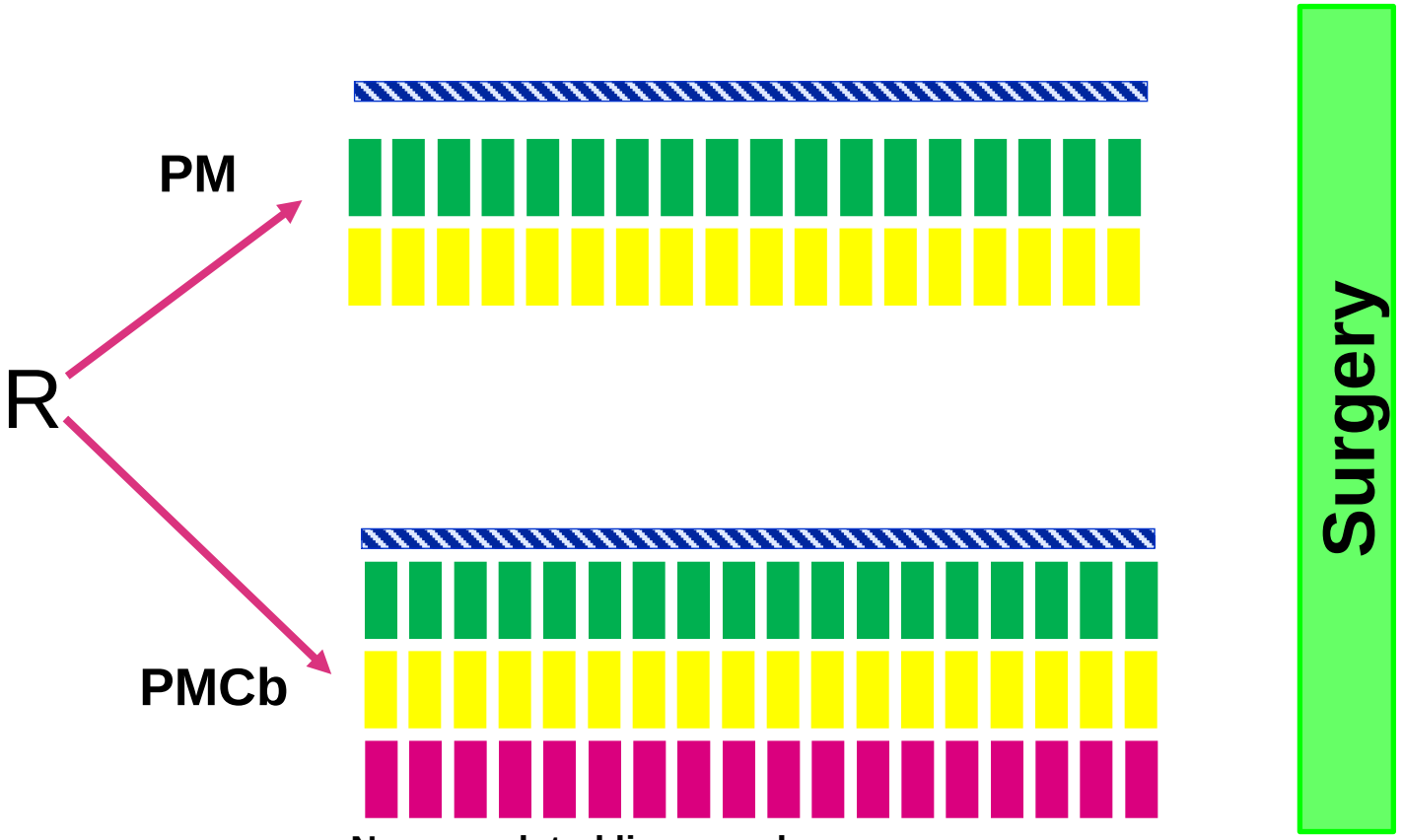
***reduced from AUC 2 to AUC 1.5 after enrolment of 330 patients**

von Minckwitz et al. Lancet Oncology, May 2014

Therapy in TNBC subgroup

N=315

centrally confirmed TNBC



Paclitaxel 80 mg/m² q1w

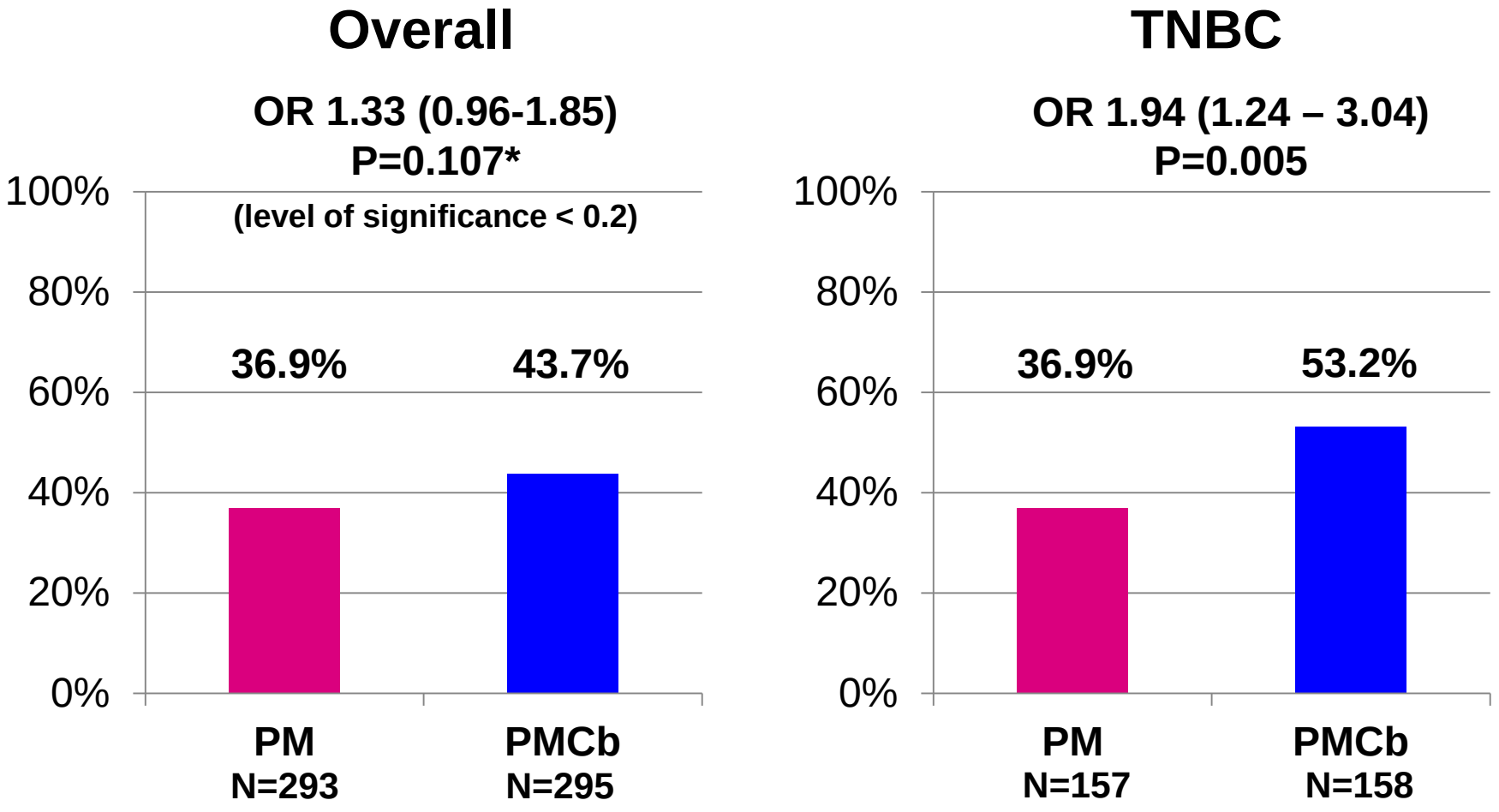
Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w

Carboplatin AUC 1.5-2 q1w

Bevacizumab 15 mg/kg q3w

von Minckwitz et al. Lancet Oncology, May 2014

pCR Rates (ypT0 ypN0)



von Minckwitz et al. Lancet Oncology, May 2014

Patients in GeparSixto (N=595)

- N=280 HER2-negative tumor
- N=21 no blood sample collected

Patients with TNBC included in analysis (N=294)

Multiplex Ligation Probe Amplification (MLPA) (N=294)
(to search for large deletions or dublications within BRCA 1/2)

- N= 6 alterations found

Fluidigm Genotyping (Sanger) (N=288)
(to search for most frequent (60%) recurrent pathogen mutations known for Germany)

- N=28 alterations found

Next generation sequencing (NGS) of a 26 HRD gene panel (N=260)

Completed (n=96)

- N= 8 alterations found

Still running (N=164)

Homopolymer Assay (Multiplicom) (N=164)

- N= 2 alterations found

further ≈ 8-10 alterations expected

AGO-B BREAST STUDY GROUP

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented at the 2014 ASCO Annual Meeting by Gunter von Minckwitz, M.D..
Presented data is the property of GBG and AGO-B.

GBG GERMAN BREAST GROUP

Characteristics of patients with TNBC

		PM (N=146)	PMCb (N=148)	
Age (median; yrs)		47.0	47.5	
Tumor size (median; cm)		3.0	3.0	
		%	%	
cT 3 / 4		13.7	8.1	
cN +		45.1	40.6	
Grade 3		77.4	72.3	
Family history for BC/OC*	(N=101)	34.9	33.8	
g*BRCA 1* alteration	(N= 35)	13.0	10.8	
g*BRCA 2* alteration	(N= 6)	1.4	2.7	
gRAD50/51C alteration	(N= 3)	1.4	0.7	
		15.8	14.2	

*assessed by a checklist of the German BRCA consortium to identify women at risk for germline alterations of >10%

pCR (ypT0/is ypN0) in all Patients with TNBC

Family history for BC/OC	*gBRCA/RAD* alteration: no (N=250)	*gBRCA/RAD* alteration: yes (N=44)
no (N=193)	43.9% (75/171)	45.5% (10/22)
yes (N=101)	49.4% (39/79)	81.8% (18/22)

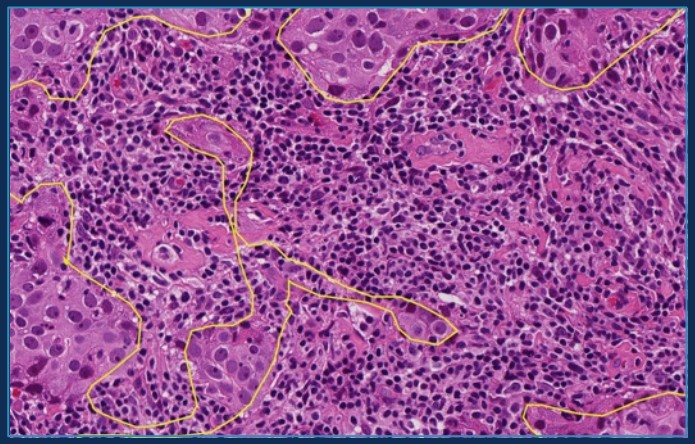
Expression of immune genes in triple-negative and HER2-positive breast cancer in the neoadjuvant GEPARSIXTO trial: Prediction of response to carboplatin-based chemotherapy

Carsten Denkert, Gunter von Minckwitz, Jan C. Brase, Silvia Darb-Esfahani, Stephan Gade, Ralf Kronenwett, Christoph Salat, Sherene Loi, Christian Schem, Christos Sotiriou, Keyur Mehta, Peter Klare, Karin Fisch, Jens-Uwe Blohmer, Hans Tesch, Sherko Kümmel, Kristin Krappmann, Manfred Dietel, Michael Untch, Sibylle Loibl

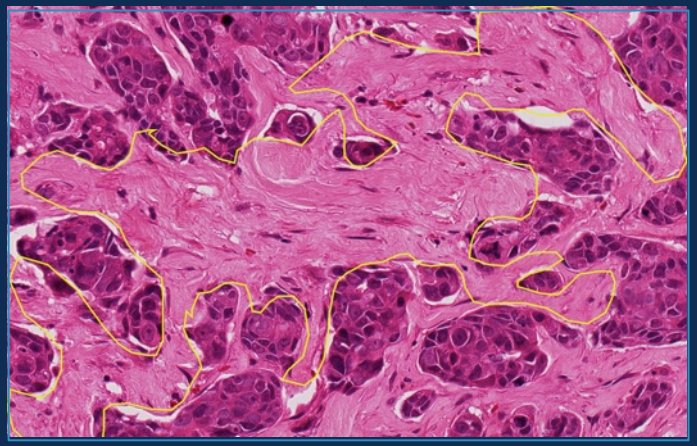
PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

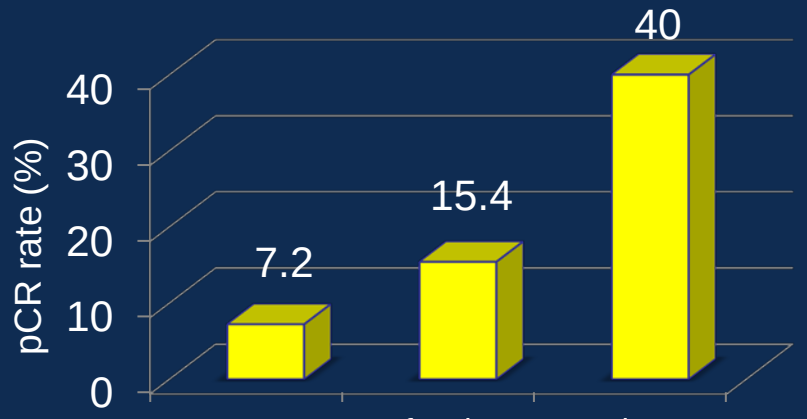
Background: Tumor-infiltrating lymphocytes are linked to chemotherapy response and prognosis in breast cancer

Lymphocyte-predominant breast cancer (LPBC)
= more that 60% TILs

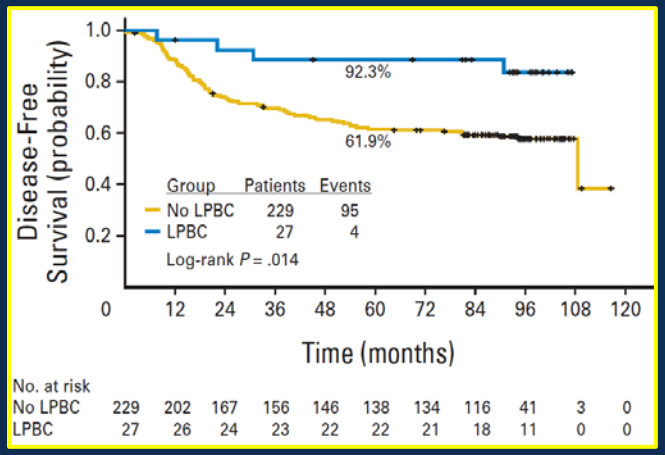


non-LPBC



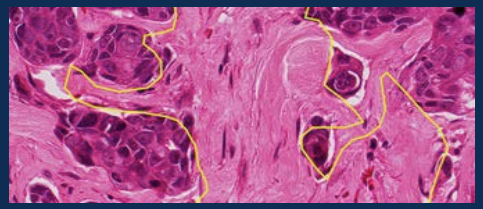


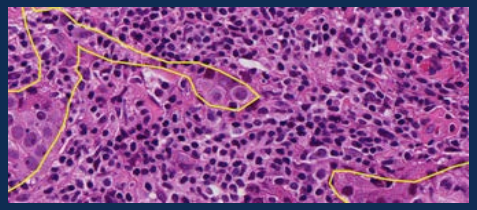
Denkert et al, JCO, 2010

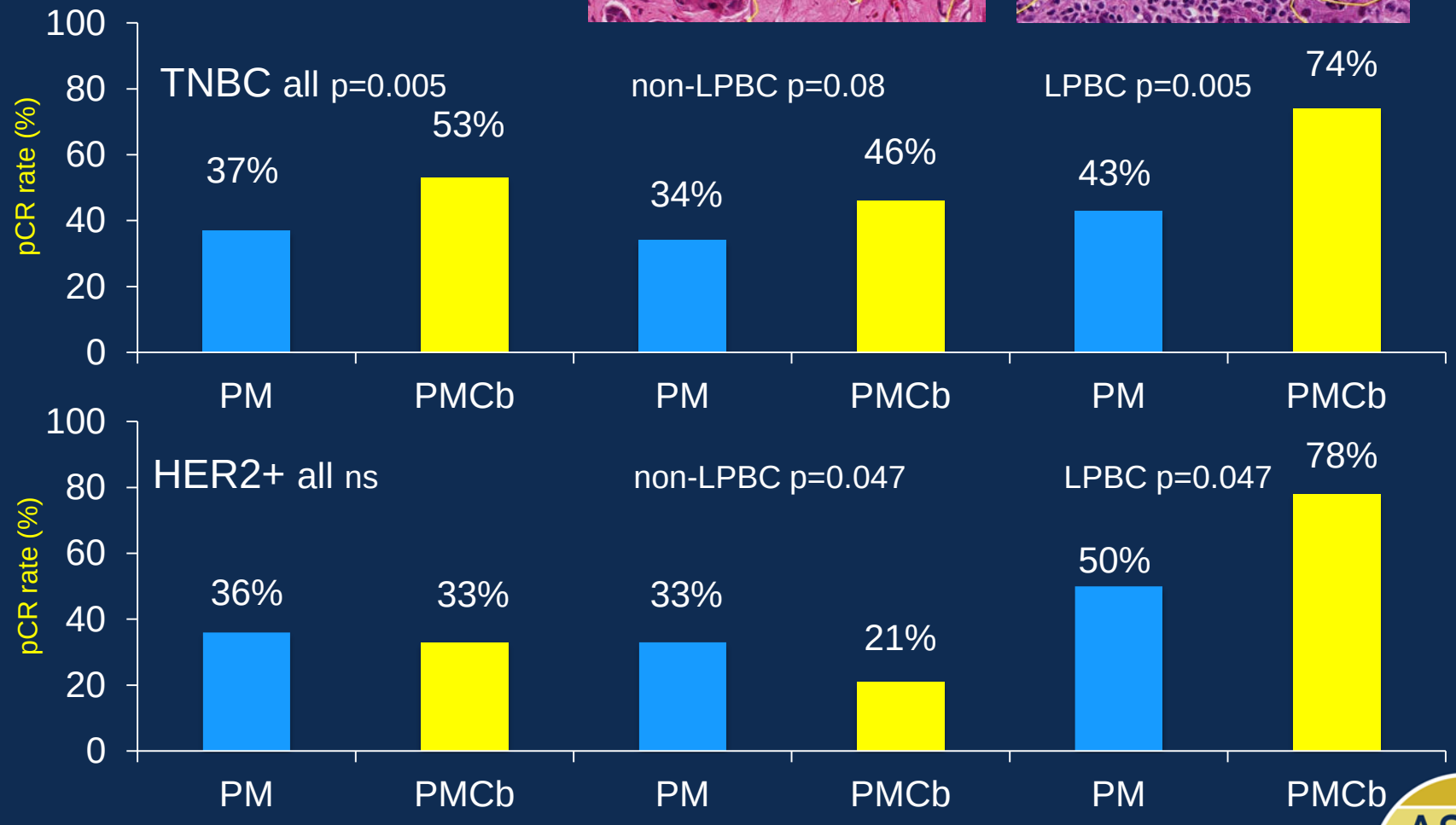


Loi et al, JCO, 2013 – BIG2-98

Background – Tumor-infiltrating lymphocytes (TILs)





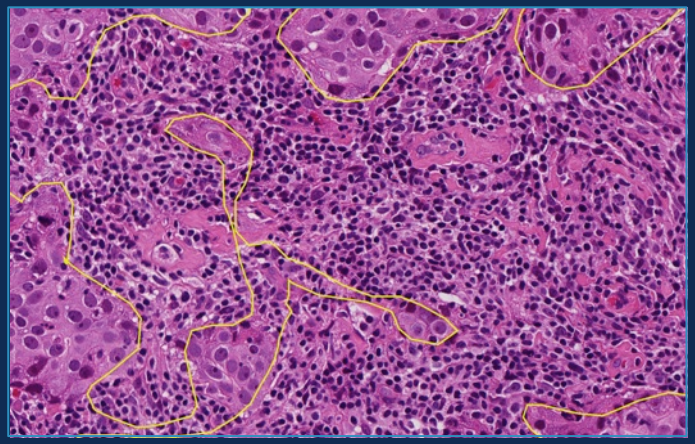


von Minckwitz et al. , ASCO 2013 & Lancet Oncology 2014
Denkert et al. SABCS 2013

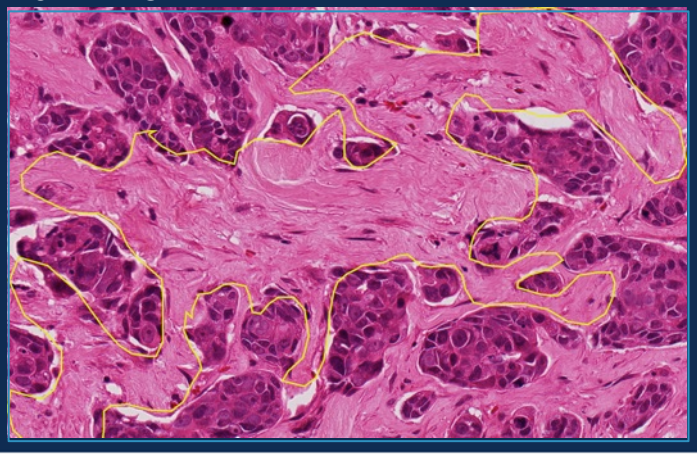
Further molecular characterization of immune infiltrate

morphological classification

Lymphocyte-predominant breast cancer (LPBC)
= more that 60% TILs



non-LPBC



molecular characterization

Hypothesis:

Immunosuppressive regulators:

PD1, PDL1,

CTLA4, IDO1, FOXP3

Immune activation:

T-Cells: CD8A, CCL5

B-Cells: IGKC, CD21, CD80

Chemoattractants:

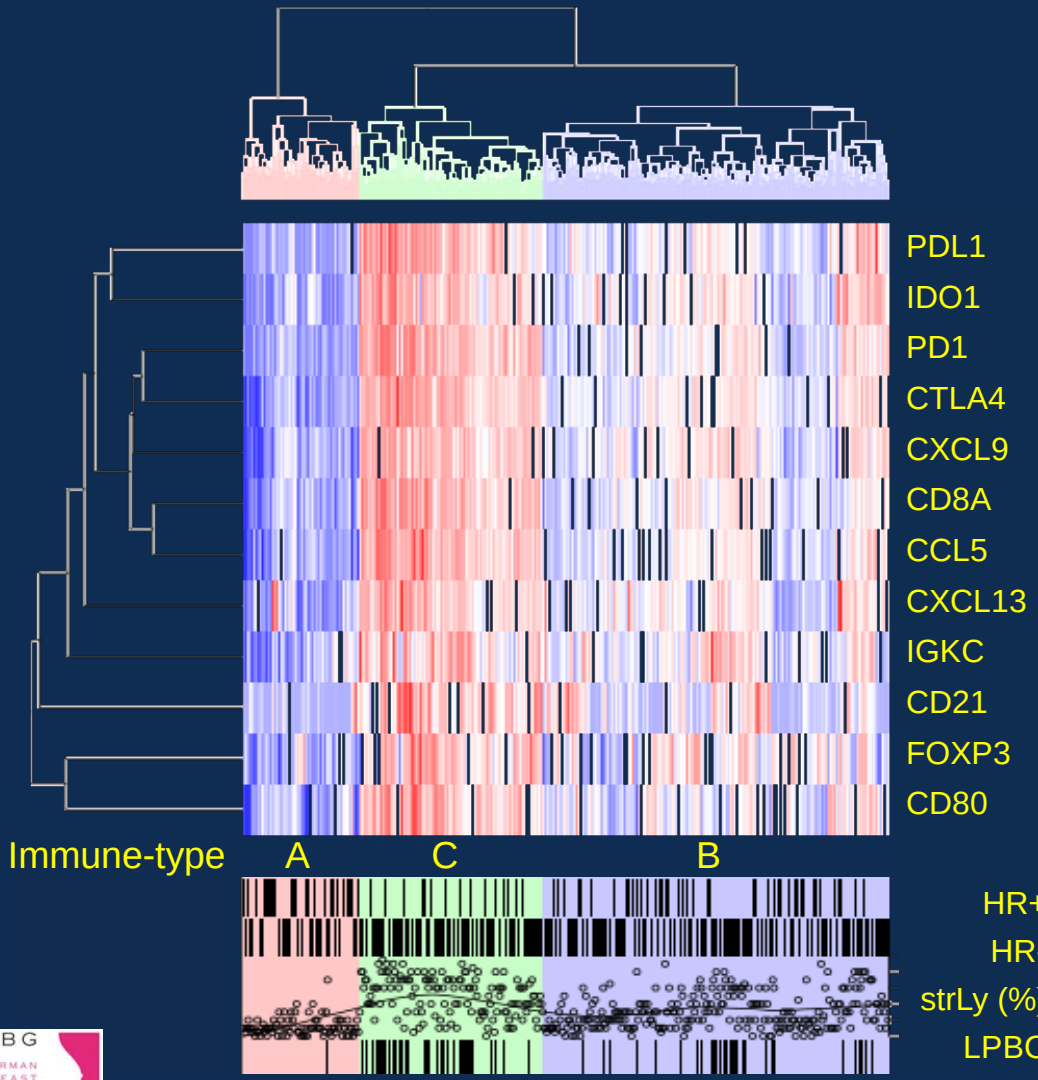
CXCL9, CXCL13

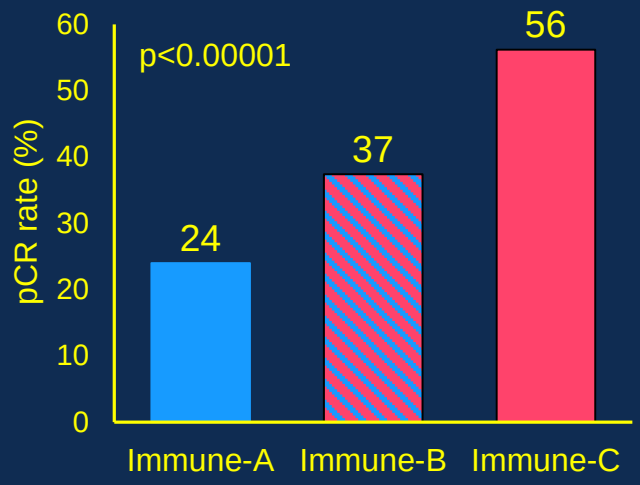
Methods

- Are mRNA markers better than TILs for diagnostic approaches?
- n=481 FFPE core biopsies from GeparSixto
- 12 immunologically relevant mRNAs
  - measured by quantitative RT-PCR
  - CXCL9, CCL5, CD8A, CD80, CXCL13, IGKC, CD21, IDO1, PD-1, PDL1, CTLA4, FOXP3
- evaluation of TILs based on H&E morphology

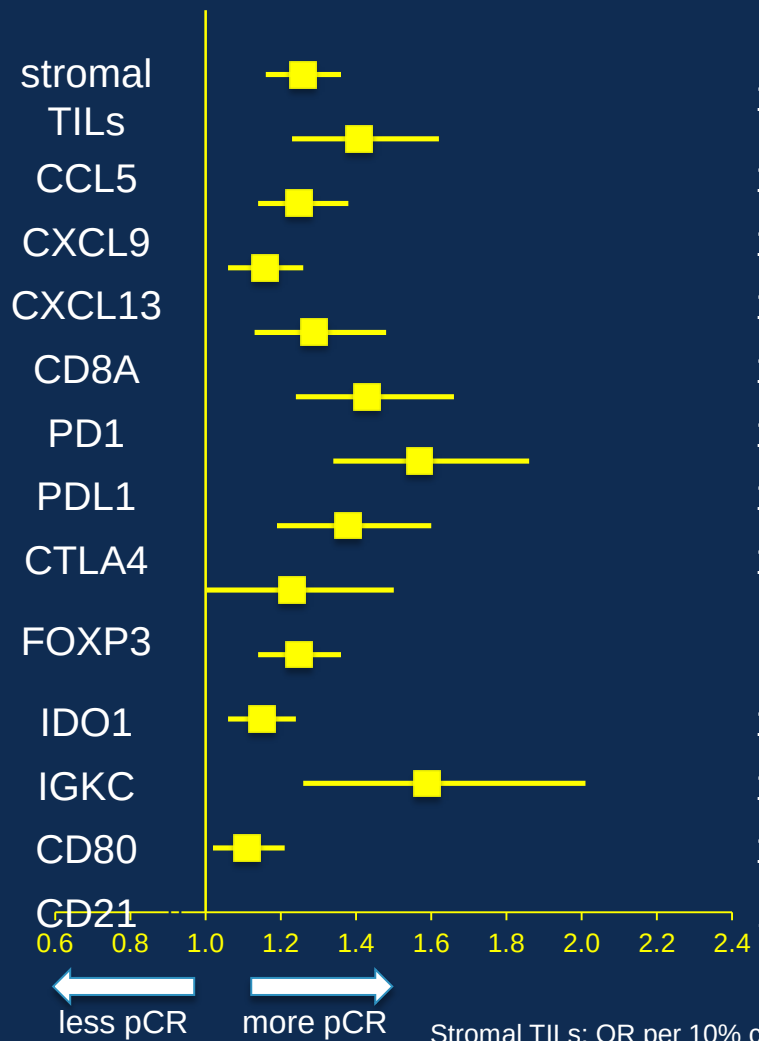
  (Denkert et al, SABCS 2013; Denkert et al, JCO, 2010)

Three different immune subtypes: correlation with response rate





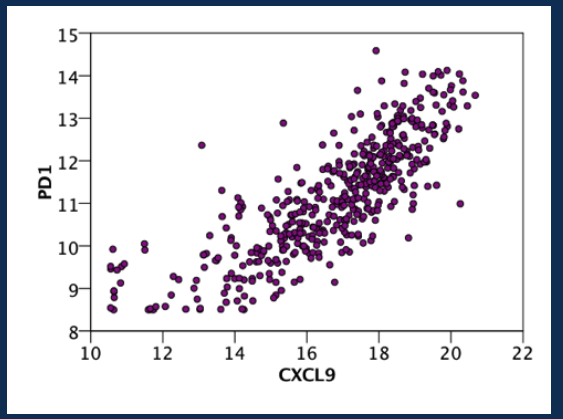
Immune markers were significantly linked to increased pCR rates – all cases (n=481)



	univariate OR (95% CI)	univariate p-value	multivariate p-value	interacti. w. CbTx p-value
stromal TILs	1.26 (1.16-1.36)	0.00000001	0.0000005	0.007
CCL5	1.41 (1.23-1.62)	0.000001	0.00001	0.002
CXCL9	1.25 (1.14-1.38)	0.000006	0.003	0.09
CXCL13	1.16 (1.06-1.26)	0.001	0.006	ns
CD8A	1.29 (1.13-1.48)	0.0002	0.001	0.01
PD1	1.43 (1.24-1.66)	0.000001	0.00002	0.02
PDL1	1.57 (1.34-1.86)	0.00000003	0.000001	0.09
CTLA4	1.38 (1.19-1.60)	0.00001	0.0001	0.06
FOXP3	1.23 (1.003-1.50)	0.05	0.02	ns
IDO1	1.25 (1.14-1.36)	0.0000005	0.00003	0.03
IGKC	1.15 (1.06-1.24)	0.0004	0.002	ns
CD80	1.59 (1.26-2.01)	0.0001	0.0002	ns
CD21	1.11 (1.02-1.21)	0.01	ns	ns

Stromal TILs: OR per 10% change, mRNA markers: OR per 1 dCt value (l≈ doubling of mRNA)

Immune markers were significantly linked to increased pCR rates – all cases (n=481)



CD8A	1.29 (1.13-1.48)	0.0002	0.001	0.01
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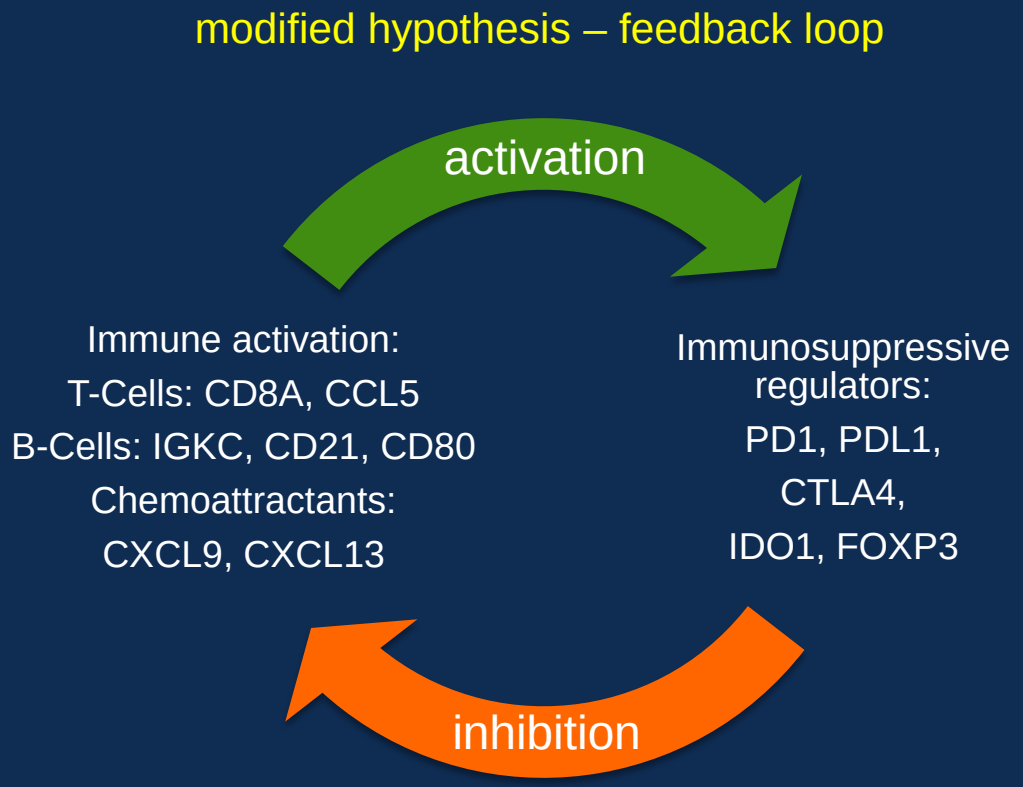
CTLA4	1.38 (1.19-1.60)	0.00001	0.0001	0.06
FOXP3	1.23 (1.003-1.50)	0.05	0.02	ns
CD21	1.11 (1.02-1.21)	0.01	ns	ns

Stromal TILs: OR per 10% change, mRNA markers: OR per 1 dCt value (l≈ doubling of mRNA)

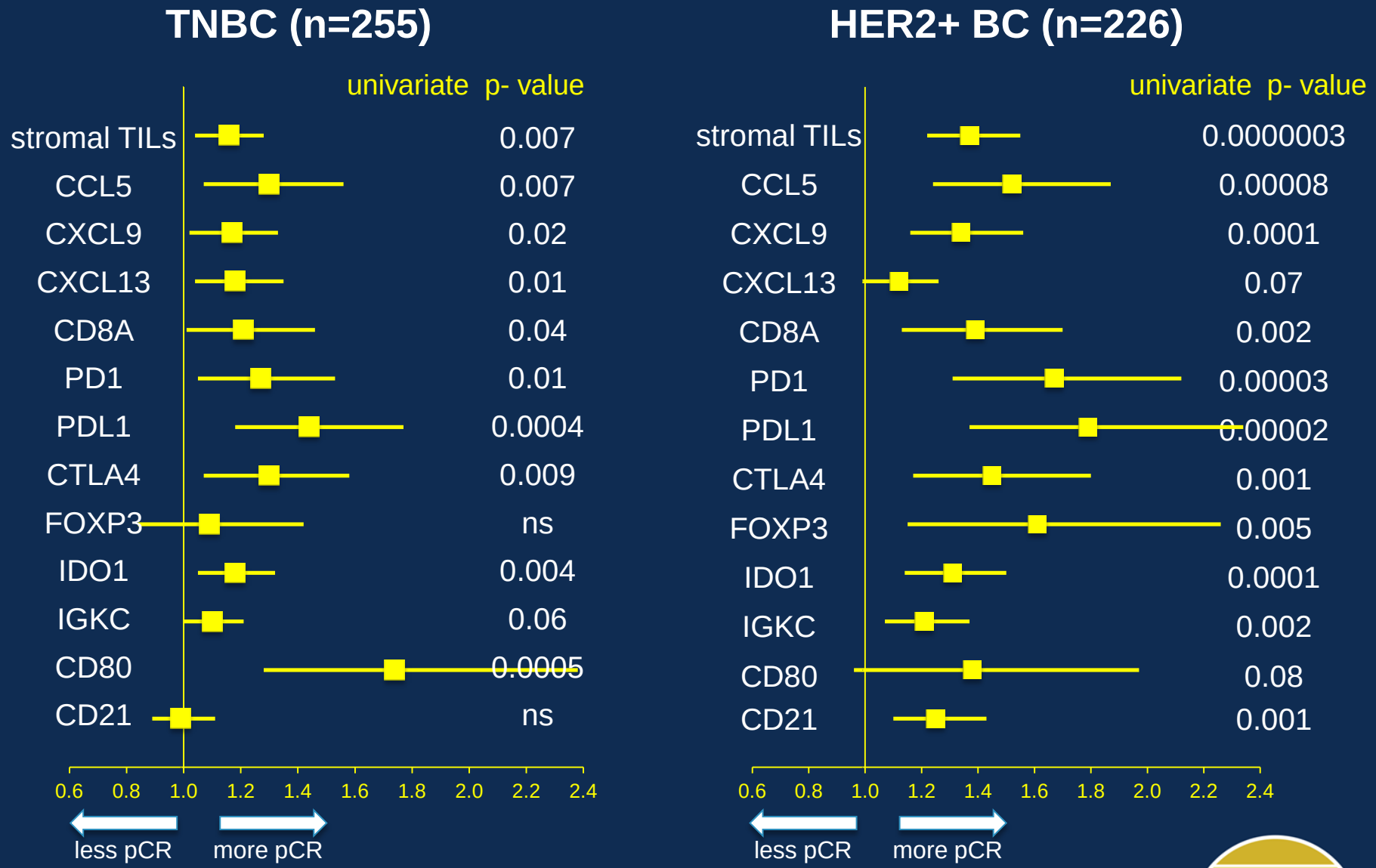
Conclusion - Immune-regulatory checkpoint markers

- Expression of PD1, PDL1, CTLA4, IDO1 and FOXP3 cannot be used to monitor anti-immune activity (because these markers are positively correlated with other immune mRNA markers and with therapy response).

- These markers are expressed in parallel to the pro-immune markers, suggesting a feedback activation of immuno-suppressive pathways in parallel to the immune reaction.



Immune markers in different subtypes



Comparison of immune mRNAs and TILs for response prediction

	all cases	TNBC	HER2+
	p-value for immune mRNA	p-value for immune mRNA	p-value for immune mRNA
CCL5	0.04		
CXCL9			
CXCL13			
CD8A			
PD1	0.09		
PDL1	0.005	0.04	0.06
CTLA4			
FOXP3			
IDO1	0.05	0.08	
IGKC			
CD80	0.07	0.005	
CD21			

- Exploratory multivariate analysis including TILs, mRNA markers and clinical markers:
- TILs are significant in all analyses
- immune mRNAs are only significant in selected analyses

- TILs contain similar information as immune mRNAs

Conclusions: Neoadjuvant Carboplatin

- Addition of carboplatin to weekly paclitaxel or to pegylated doxorubicin/paclitaxel improved pathologic complete response among triple negative breast cancer patients
- Similar to findings from CALGB 40603 in triple negative breast cancer
- Optimal dosing of carboplatin is unclear
- In GEPARSIXTO, increase of pCR rate with carboplatin was highest in patients with family history and alterations of *gBRCA/RAD*
- Assessment of tumor-infiltrating lymphocytes and other immune markers have been linked to improved response to neoadjuvant therapy

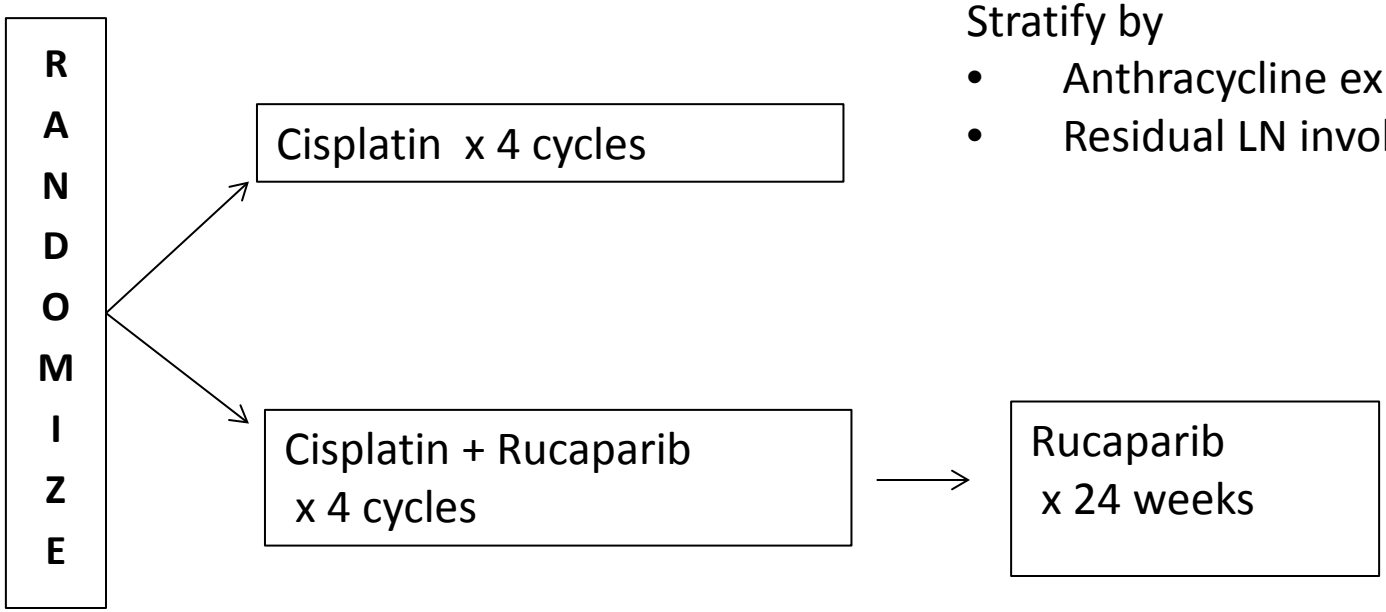
Abstract 1019: Cisplatin with or without PARP inhibitor, rucaparib, after preoperative chemotherapy in patients with triple-negative breast cancer (TNBC): Hoosier Cancer Research Network BRE09-146

Sujaata Dwadasi, Yan Tong, Tom Walsh, Michael A. Danso, Cynthia X. Ma, Paula Silverman, Mary-Claire King, Susan M. Perkins, Sunil S. Badve, Kathy Miller

Eligibility Criteria

- Histologically or cytologically confirmed triple negative invasive breast cancer, stage I-III at diagnosis
  - Patients with ER+ and/or PR+ allowed ONLY if they are known carriers of a deleterious mutation in BRCA1 or BRCA2.
- Completed neoadjuvant chemotherapy with an anthracycline and/or a taxane.
  - No prior cisplatin. Prior carboplatin allowed.
- Completed definitive resection of primary tumor with substantial residual disease based one of the following
  - Miller-Payne class 0-2[4]
  - Residual Disease Burden (RCB) classification II or III[5]
  - Residual lymph node (N1-N3) involvement
  - Residual 2 cm invasive disease in the breast
- Radiation therapy completed if indicated.

Study Schema



Stratify by

- Anthracycline exposure vs. not
- Residual LN involvement vs. not

Cisplatin 75 mg/m^2 D1
Rucaparib (combined therapy)
RP2 - 24 mg IV D1,2,3 cycle 1, escalate to 30 mg C2-4
Rucaparib monotherapy
30 mg IV or 100 mg po weekly x 24 weeks

Patient Characteristics	Cisplatin (n = 65)	Cisplatin + Rucaparib (n = 63)
Median age	48 (27-69)	47 (21-75)
African American	20%	17.5%
Known BRCA1 or 2 mutation at entry	BRCA 1 – 1 BRCA 2 - 2	BRCA 1 – 1 BRCA 2 - 2
Deleterious BRCA mutation by BROCA analysis*	21.5%	12.7%
Neoadjuvant Chemo Anthracycline Taxane Carboplatin	 66% 92% 0	 48% 89% 9.5%
Radiation Therapy	86%	86%
Median residual tumor	1.9 cm (0-9)	1.9 cm (0-11.5)
Median residual LN+	1 (0-15)	1 (0-38)
Median Residual Cancer Burden	2.6 (0-5.0) (n=53)	2.7 (0-5.3) (n=59)

*BROCA analysis available in 101 patients

1 YEAR DISEASE FREE SURVIVAL

	Cisplatin	Cisplatin + Rucaparib
All patients (ITT)	82.7%	82.5%
Deleterious BRCA mutation by BROCA analysis	84.6%	100%

BIG
Breast International Group

ALTTO
Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

Alliance for Clinical Trials in Oncology

First results from the phase III ALTTO trial (BIG 02-06; NCCTG 063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer (EBC)

Martine Piccart-Gebhart, Andrew P. Holmes, José Baselga, Evandro de Azambuja, Amylou Dueck, Giuseppe Viale, Jo Anne Zujewski, Aron Goldhirsch, Sergio Santillana, Kathleen Pritchard, Antonio C. Wolff, Christian Jackisch, Istvan Lang, Michael Untch, Ian Smith, Frances Boyle, Binghe Xu, Henry Gomez, Richard D. Gelber and Edith A. Perez

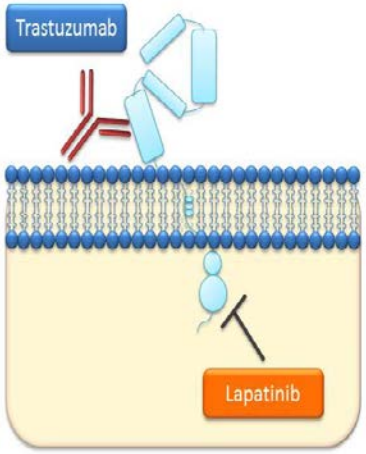
On behalf of the ALTTO Study Team

gsk

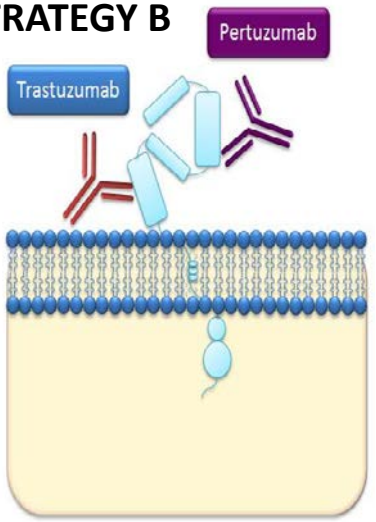
ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

AVAILABLE RESULTS OF DUAL HER2 BLOCKADE PRIOR TO ASCO 2014

STRATEGY A



STRATEGY B



Advanced Disease
↑ PFS and OS
(2 trials)

EGF104900 (N= 296)

Cleopatra (N= 808)

Neoadjuvant setting
Significant ↑ ↑ pCR
(4 trials)

NeoALTTO (N= 455)

Cherlob (N= 121)

LPT 109096 (N= 78)

NeoSPHERE (N= 417)

Non significant ↑ pCR
(2 trials)

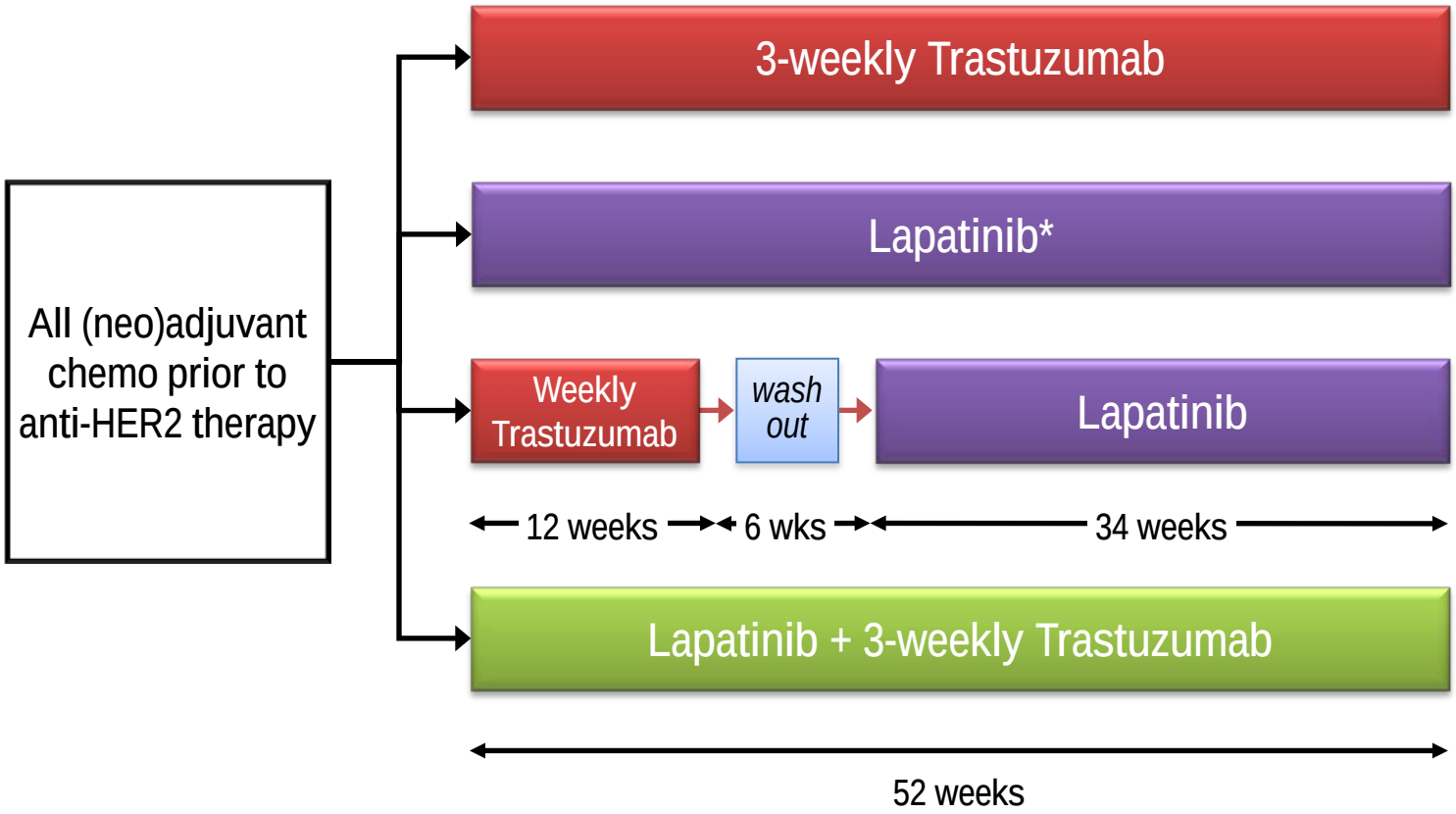
NSABP B-41 (N= 529)
CALGB 40601 (N= 305)

Adjuvant setting

ALTTO (N= 8,381)

APHINITY (N= 4,805)

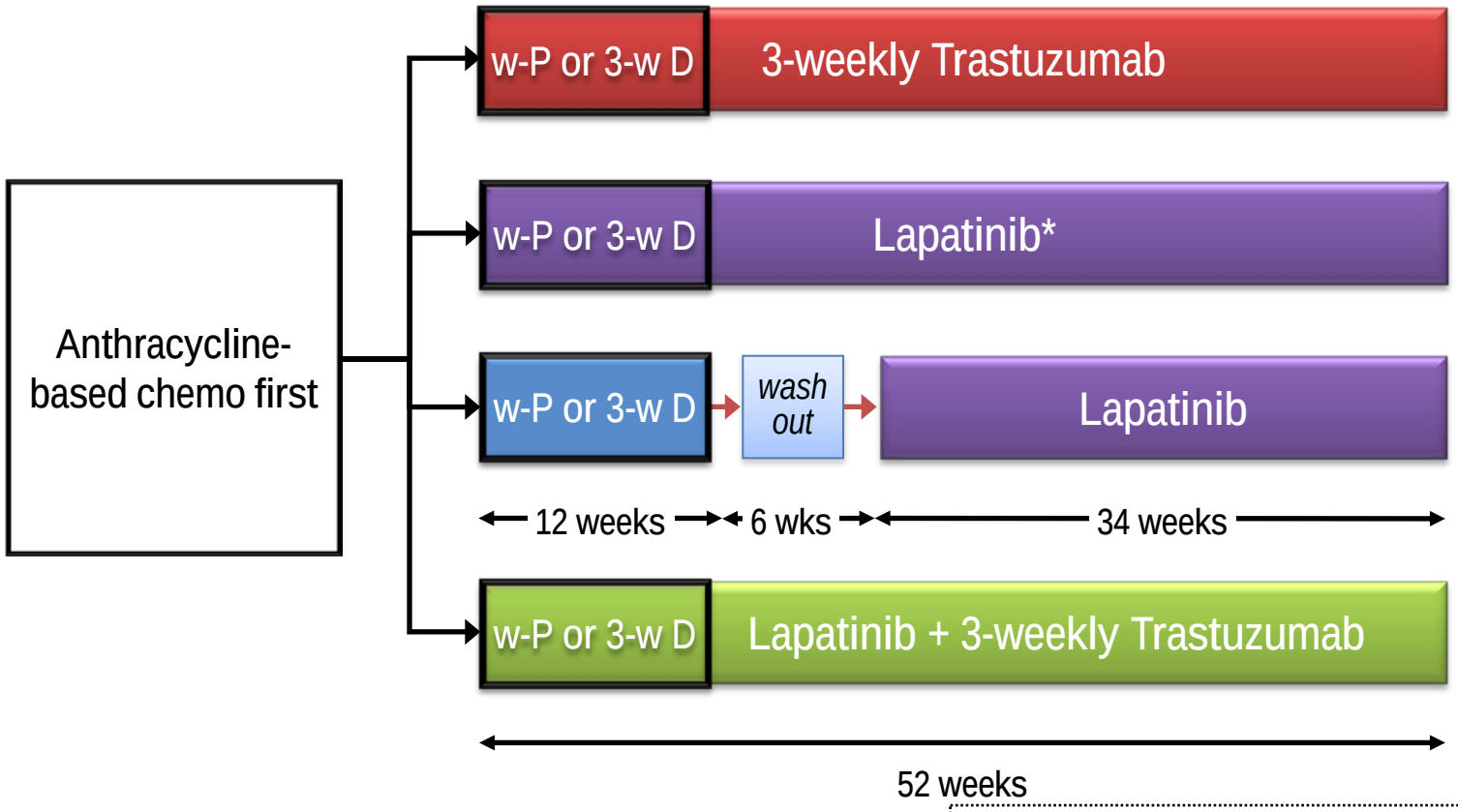
DESIGN 1: SEQUENTIAL ANTI-HER2 THERAPY AFTER ALL CHEMOTHERAPY (N= 4,613)



All patients: radiotherapy, if indicated (concomitant with targeted therapy).
Hormone receptor-positive patients: endocrine therapy for at least 5 years.
**The L alone arm was closed on 18 Aug 2011 following IDMC recommendation*

Tras alone: 8 mg/kg → 6 mg/Kg iv, q21 days
Lap alone: 1500 mg po qd
Tras → Lap: *T* 4 mg/kg → 2 mg/Kg iv q7 days; *L* 1500 mg po qd
Tras + Lap: *T* 8 mg/kg → 6 mg/Kg iv, q21 days; *L* 1000 mg po qd

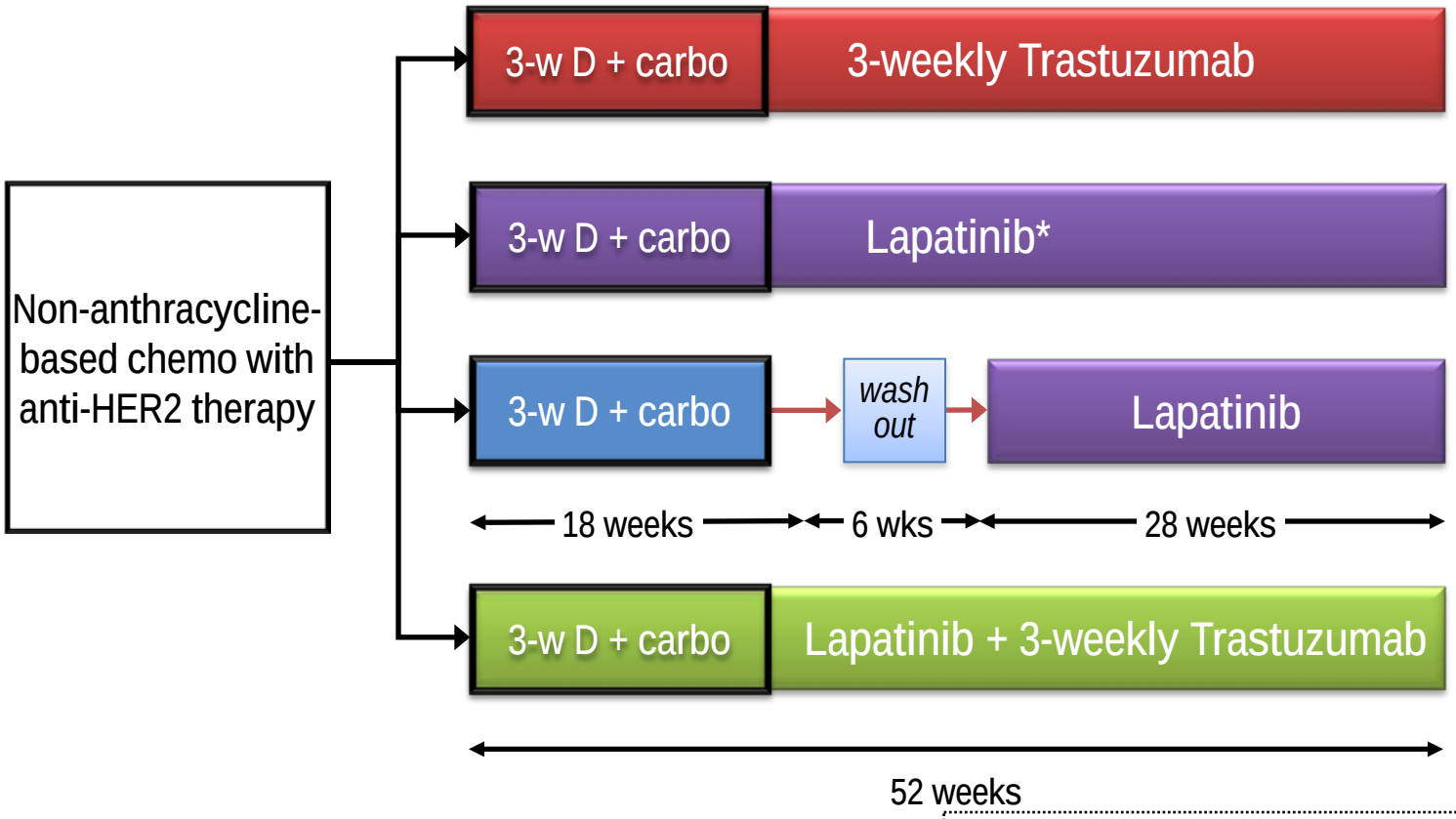
DESIGN 2: CONCURRENT ANTI-HER2 THERAPY AFTER ANTHRACYCLINE-BASED CHEMOTHERAPY (N= 3,337)



w-P: weekly paclitaxel (80 mg/m^2); 3-w D: q3 weeks docetaxel (75-100 mg/m^2)
All patients: radiotherapy, if indicated (concomitant with targeted therapy).
Hormone receptor-positive patients: endocrine therapy for at least 5 years.
**The L alone arm was closed on 18 Aug 2011 following IDMC recommendation*

Tras alone: 4 mg/kg → 2 mg/Kg iv, q7 days → 6 mg/Kg iv, q21 days
Lap alone: 750 mg po qd → 1500 mg qd
Tras → Lap: *T* 4 mg/kg → 2 mg/Kg iv q7 days; *L* 1500 mg po qd
Tras + Lap: *T* 4 mg/kg → 2 mg/Kg iv, q7 days → 6 mg/Kg iv, q21 days; *L* 750 mg po qd → 1000 mg qd

DESIGN 2B: CONCURRENT ANTI-HER2 THERAPY WITH A NON-ANTHRACYCLINE CHEMOTHERAPY (N= 431)



3-w D: q3 weeks docetaxel (75 mg/m^2); carbo: carboplatin (AUC 6)
All patients: radiotherapy, if indicated (concomitant with targeted therapy).
Hormone receptor-positive patients: endocrine therapy for at least 5 years.
**The L alone arm was closed on 18 Aug 2011 following IDMC recommendation*

Tras alone: 4 mg/kg → 2 mg/Kg iv, q7 days → 6 mg/Kg iv, q21 days
Lap alone: 750 mg po qd → 1500 mg qd
Tras → Lap: *T* 4 mg/kg → 2 mg/Kg iv q7 days; *L* 1500 mg po qd
Tras + Lap: *T* 4 mg/kg → 2 mg/Kg iv, q7 days → 6 mg/Kg iv, q21 days; *L* 750 mg po qd → 1000 mg qd

PRIMARY ENDPOINT

Disease-free survival (DFS) event: first occurrence of 1) **invasive breast cancer recurrence** at any site, 2) a **second primary cancer** (invasive contralateral breast cancer or non-breast malignancy, or 3) **death from any cause** as first event.

SECONDARY ENDPOINTS

- **Overall survival (OS)**
- Time to recurrence (TTR)
- Time to distant recurrence (TTDR)
- Cumulative incidence of brain metastases
- **Safety in general**
- **Cardiac safety**
- Presence or absence of cMYC gene amplification
- Expression levels of PTEN
- Presence or absence of p95 HER2 domain

CURRENT ANALYSIS PLAN

Statistical procedures for the two remaining pairwise comparisons are:

Comparison	Assumptions
L + T vs. T	Test superiority in ITT population at alpha = **0.025**
T→ L vs. T	Test non-inferiority in per protocol population (PPP) at alpha = **0.025**

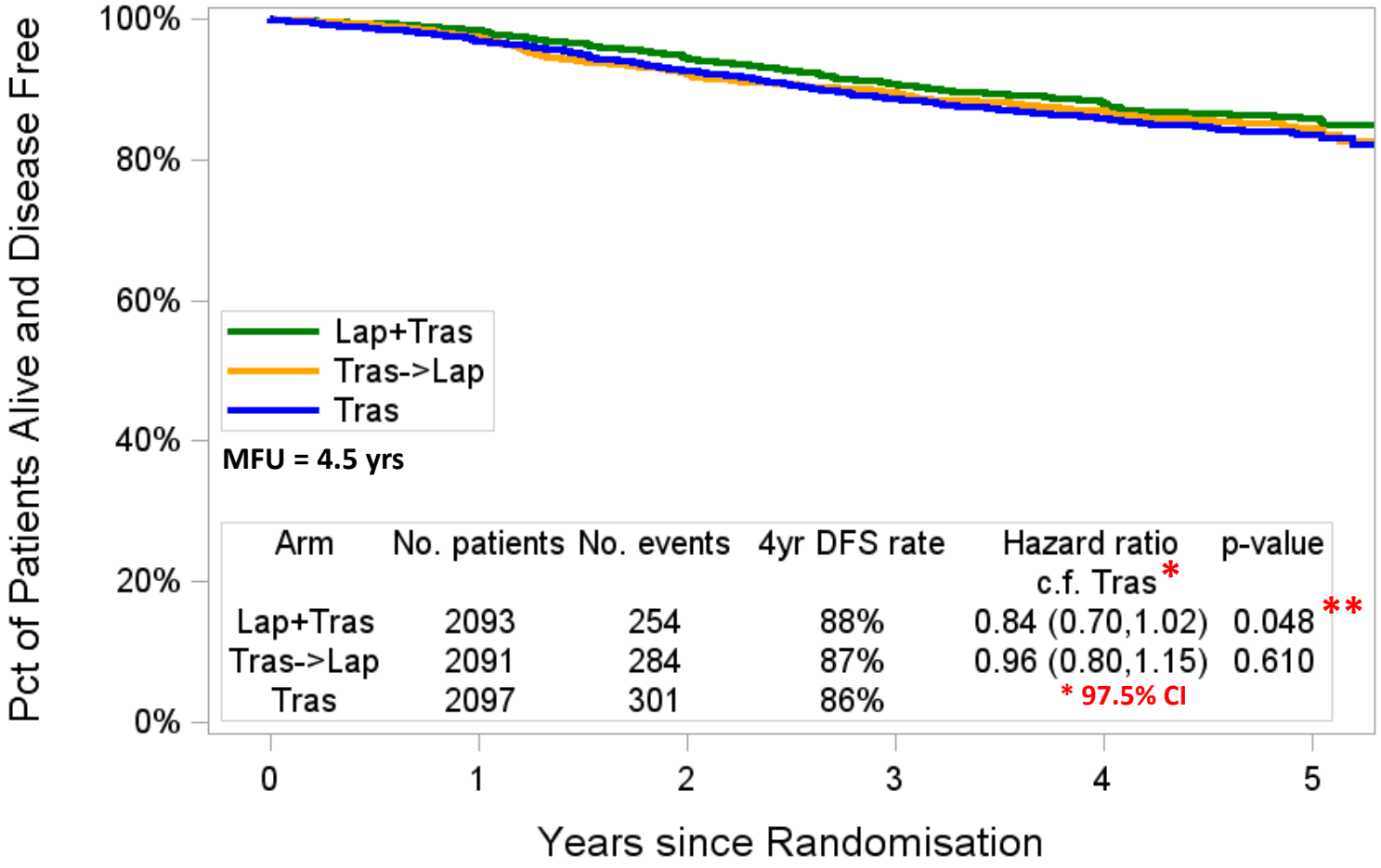
DISTRIBUTION OF THE STRATIFICATION FACTORS BY TREATMENT ARM

	L + T (N = 2,093)	T → L (N = 2,091)	T (N = 2,097)
Hormone Receptor Status			
Positive	1,203 (57%)	1,205 (58%)	1,200 (57%)
Negative	890 (43%)	886 (42%)	897 (43%)
Timing of chemotherapy			
Sequential (Design 1)	1,155 (55%)	1,143 (55%)	1,147 (55%)
Concurrent (Design 2 and 2B)	938 (45%)	948 (45%)	950 (45%)
Lymph Node Status			
Not applicable (neoadjuvant chemotherapy)	168 (8%)	170 (8%)	181 (9%)
Node negative	845 (40%)	842 (40%)	844 (40%)
1-3 positive nodes	617 (29%)	617 (30%)	603 (29%)
>=4 positive nodes	463 (22%)	462 (22%)	469 (22%)

DISTRIBUTION OF PATIENT CHARACTERISTICS BY TREATMENT ARM

	L + T (N = 2,093)	T → L (N = 2,091)	T (N = 2,097)
Menopausal Status			
Premenopausal	908 (43%)	929 (44%)	908 (43%)
Postmenopausal or male	1,185 (57%)	1,162 (56%)	1,189 (57%)
Pathological primary tumor size - largest diameter of invasive component			
Missing	27	41	38
≤ 2cm	937 (45%)	938 (46%)	942 (46%)
> 2cm to ≤ 5cm	1,002 (49%)	980 (48%)	990 (48%)
> 5cm	127 (6%)	132 (6%)	127 (6%)
Histologic grade			
Missing	10	7	9
Gx: Differentiation cannot be assessed	79 (4%)	61 (3%)	59 (3%)
G1: Well differentiated	51 (2%)	59 (3%)	48 (2%)
G2: Moderately differentiated	774 (37%)	793 (38%)	744 (36%)
G3: Poorly differentiated/undifferentiated	1,179 (57%)	1,171 (56%)	1,237 (59%)

DISEASE-FREE SURVIVAL (DFS) ANALYSIS



Arm	No. patients	No. events	4yr DFS rate	Hazard ratio c.f. Tras*	p-value
Lap+Tras	2093	254	88%	0.84 (0.70,1.02)	0.048**
Tras->Lap	2091	284	87%	0.96 (0.80,1.15)	0.610
Tras	2097	301	86%		

* 97.5% CI

Lap+Tras	2093	1938	1832	1672	1256	474
Tras->Lap	2091	1957	1822	1684	1261	476
Tras	2097	1959	1838	1658	1246	448

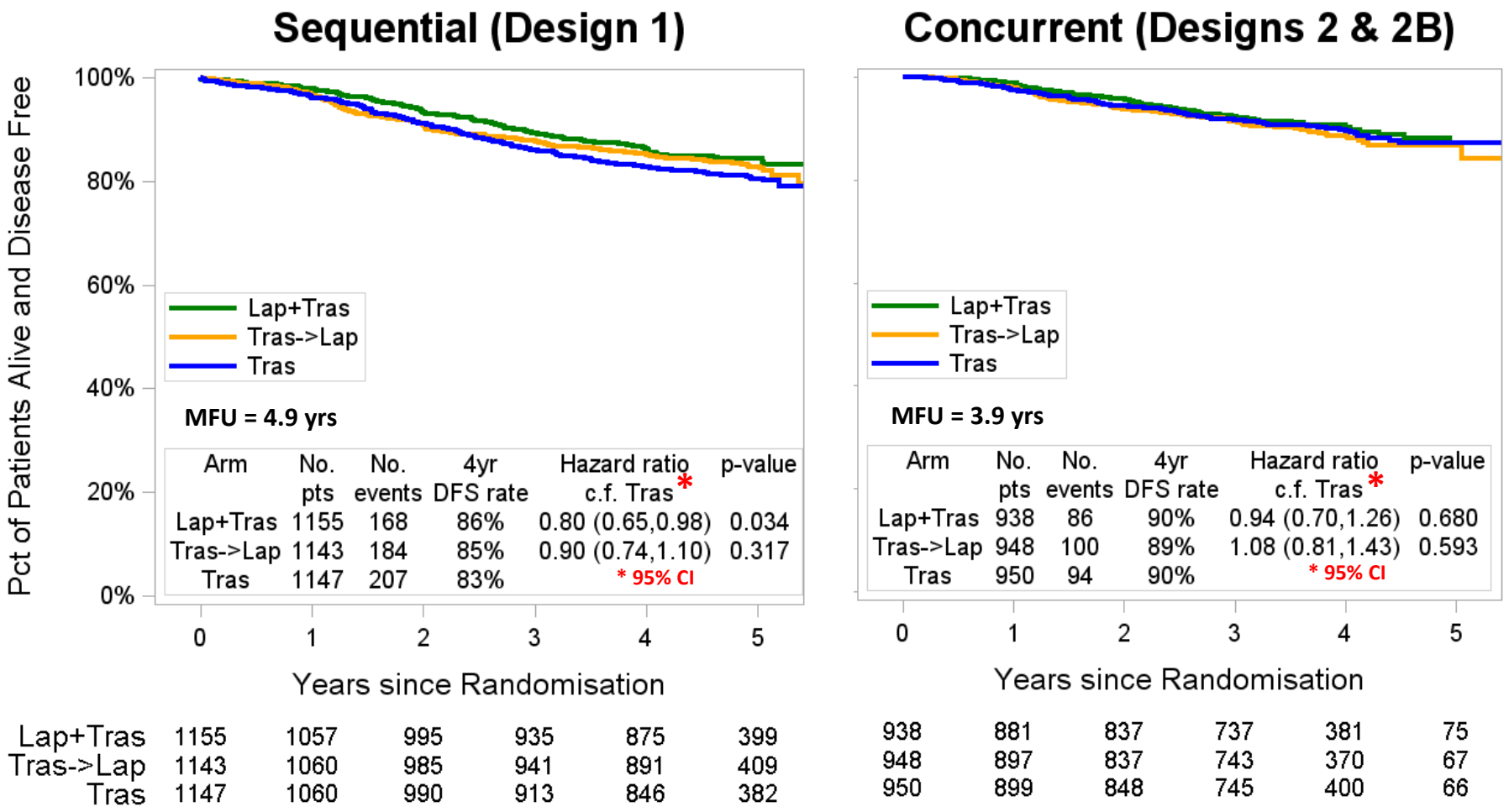
**p-value ≤ 0.025 required for statistical significance

DFS BY HORMONE RECEPTOR STATUS

Interaction tests p = 0.70 L + T

p = 0.60 T → L

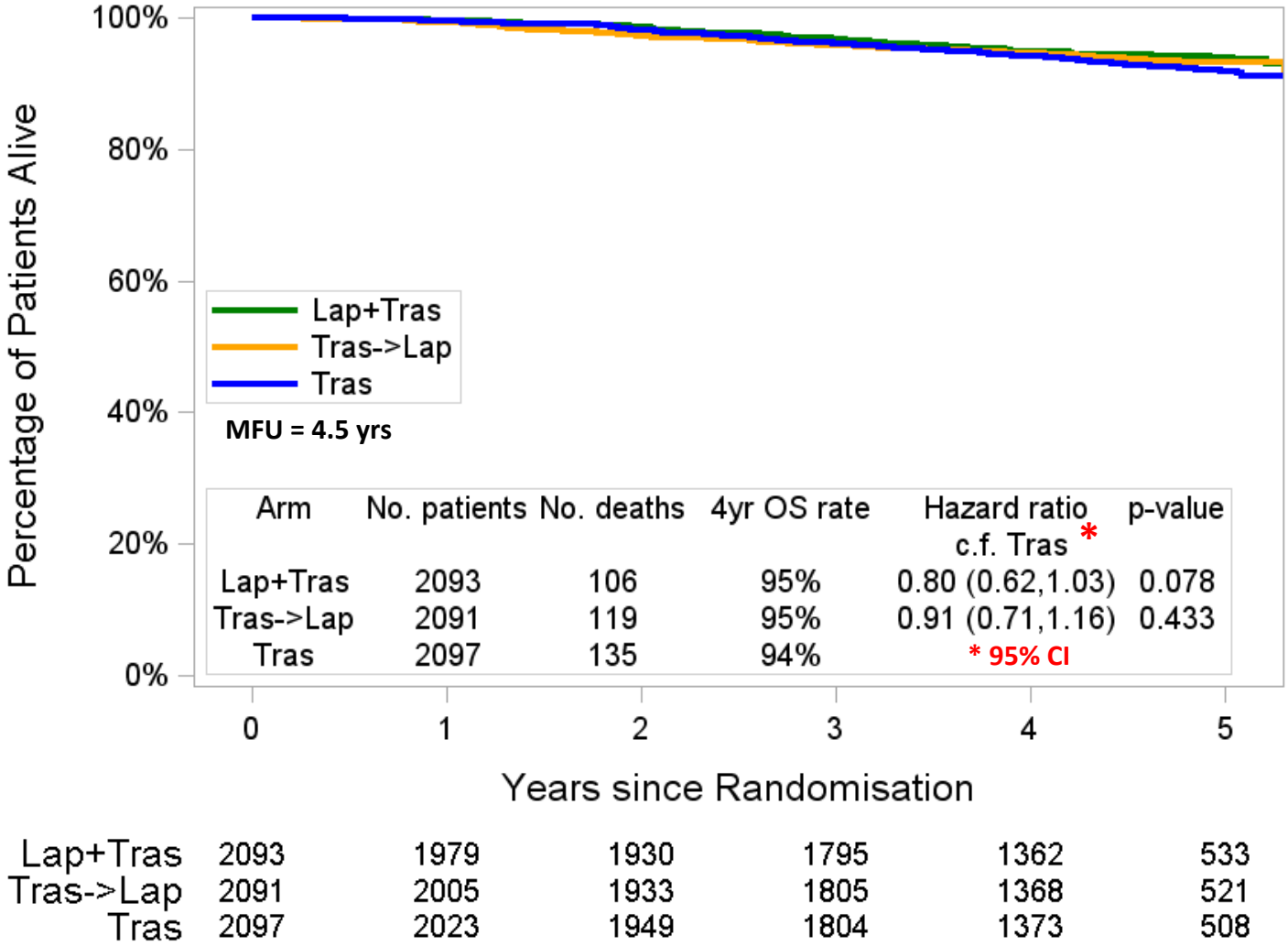
DFS BY CHEMOTHERAPY TIMING



Interaction tests p = 0.41 L + T

p = 0.31 T →L

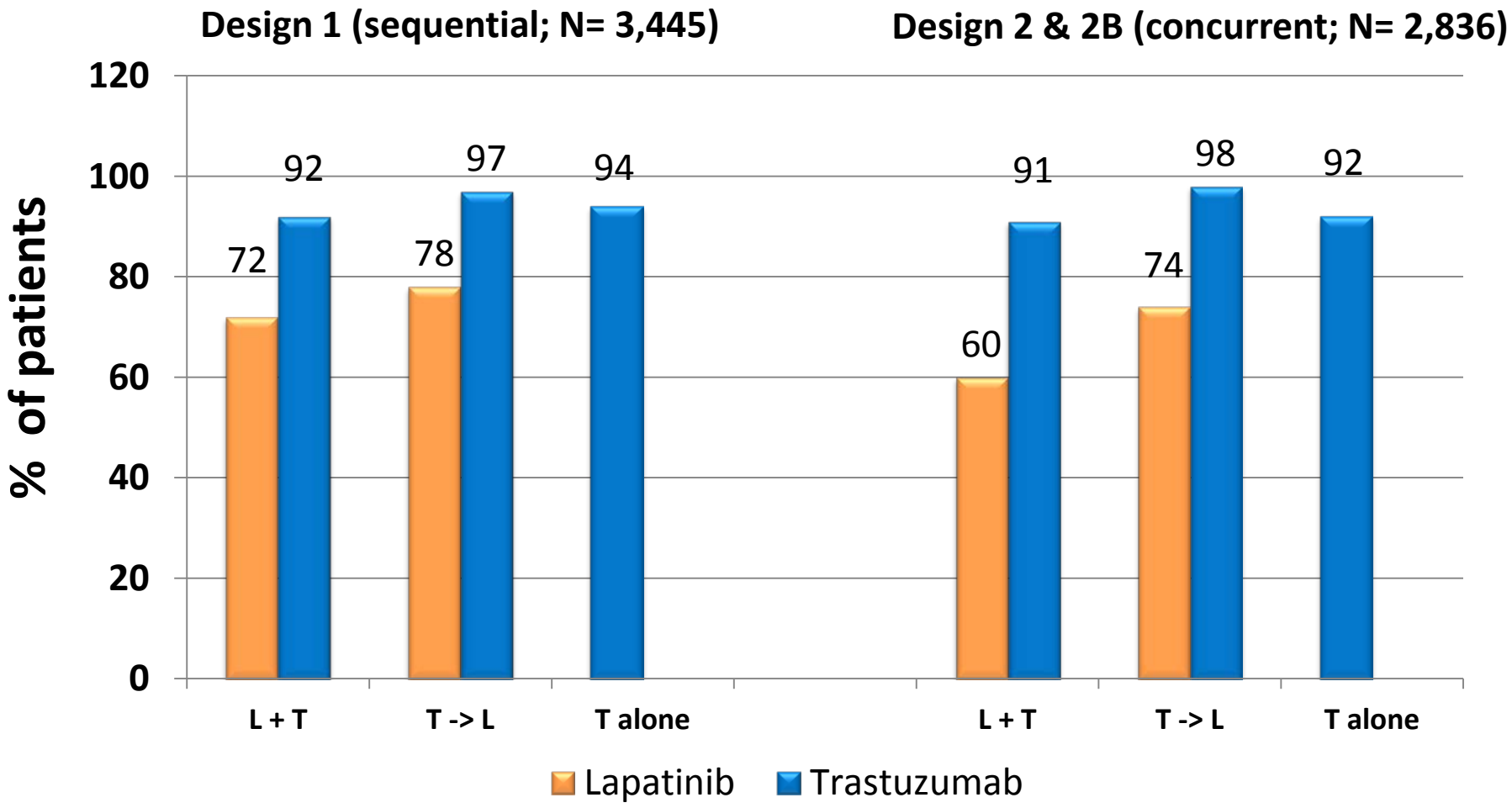
OVERALL SURVIVAL (OS) ANALYSIS



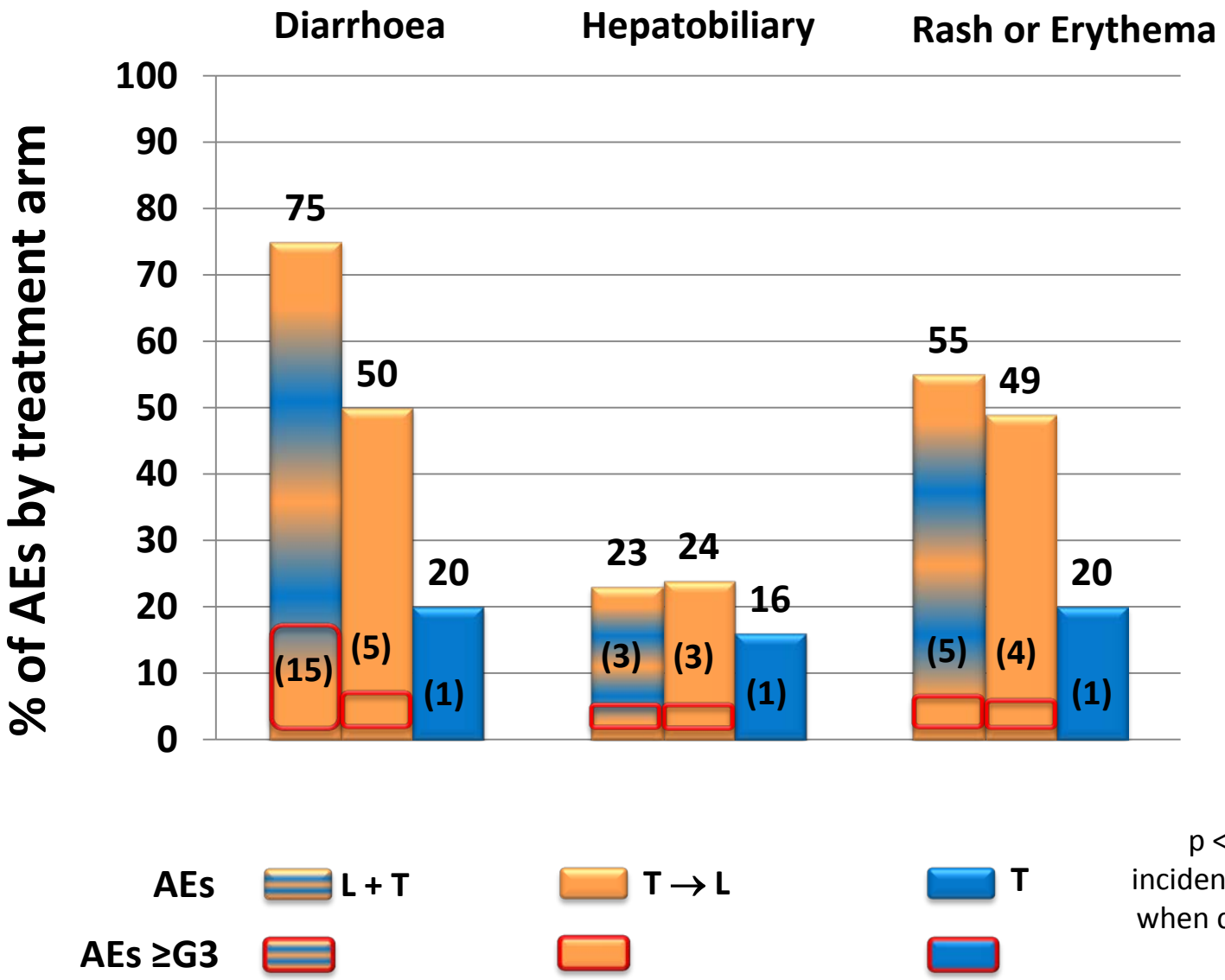
Arm	No. patients	No. deaths	4yr OS rate	Hazard ratio c.f. Tras *	p-value
Lap+Tras	2093	106	95%	0.80 (0.62,1.03)	0.078
Tras->Lap	2091	119	95%	0.91 (0.71,1.16)	0.433
Tras	2097	135	94%		

* 95% CI

PROPORTION OF PATIENTS RECEIVING ≥ 85% OF THE PLANNED DOSE OF ANTI-HER2 DRUGS



MAIN DIFFERENCES IN AEs BY TREATMENT ARM



$p < 0.001$ for incidence for all arms when compared to T

Conclusions

- The event rate was lower than anticipated: 555 DFS events for the L + T vs. T comparison at 4.5 years median follow-up instead of target of 850.
- The higher pCR observed with L + T vs. T in NeoALTTO (51.3% vs. 29.5%) did not translate into improved survival outcomes in ALTTO at 4.5 years median follow-up.
- Results of adjuvant pertuzumab trial (APHINITY) are anticipated to determine if higher pCR observed with trastuzumab plus pertuzumab (45.8% vs. 29%) in NeoSphere translates to improved long-term outcomes.

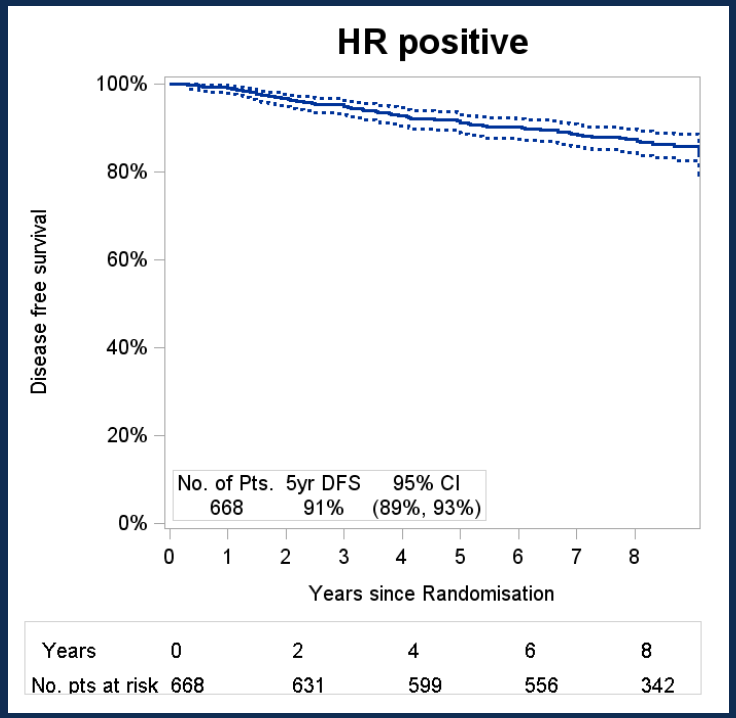
Efficacy Of Adjuvant Trastuzumab Compared With No Trastuzumab for Patients With HER2-Positive Breast Cancer And Tumors ≤ 2cm: A Meta-analysis Of The Randomized Trastuzumab Trials

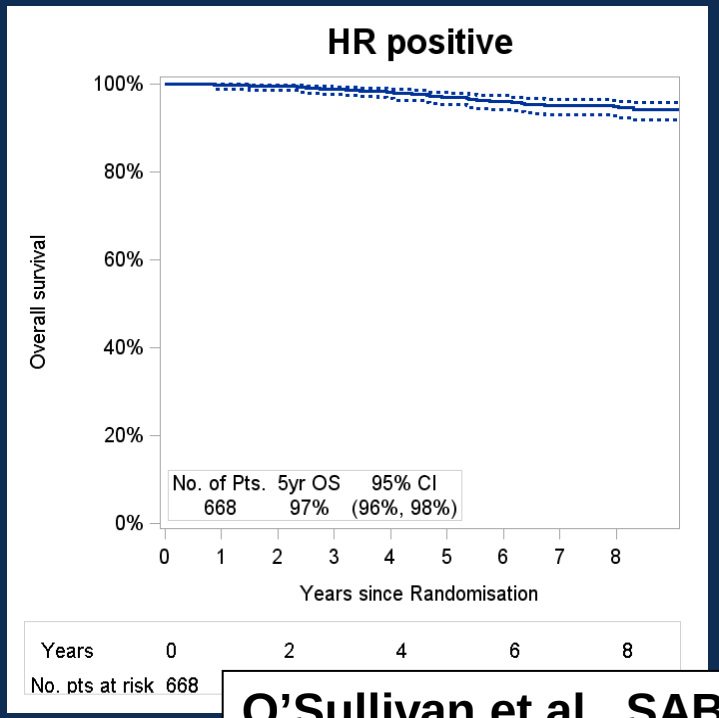
O'Sullivan CC, Bradbury I, de Azambuja E, Perez EA, Rastogi P, Spielmann M, Joensuu H, Ballman KV, Costantino JP, Delaloge S, Zardavas D, Piccart-Gebhart M, Zujewski JA, Holmes E, Gelber RD.

Long term follow up on behalf of the Trastuzumab Overview Group

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

Favorable Prognosis Seen for Patients with HER2-Positive BC and Hormone Receptor (HR)-Positive Tumors ≤ 2cm & 0/1 N+ Treated with Chemotherapy/ Hormones/ Trastuzumab





O'Sullivan et al., SABCS 2013

5 year DFS 91%

5 year OS 97%

"Is there an advantage of trastuzumab compared with no trastuzumab for patients with small tumors?"

Presented by: Ciara C. O'Sullivan email: ciara.o'sullivan@nih.gov

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Efficacy Analysis

- **Aim:**
  - Compare efficacy of trastuzumab vs. no trastuzumab in pts with small HER2-positive breast cancer (BC) in the adjuvant randomized trastuzumab trials

- **Methods:**
  - Analysis performed separately for hormone receptor (HR)-positive and HR-negative cohorts
  - Individual patient meta-analysis: tumors ≤ 2 cm (T1a, T1b and T1c) & 0-1, 2-3 and ≥ 4 positive nodes.

Trials Included in This Analysis

Trial	HER2+ Tumors	Timing of Trastuzumab	Duration of Trastuzumab	Chemotherapy regimen	Median follow up (years)
HERA	5,102	Sequential	1 or 2 years	Any – 94% A; 26% A and T	8.0
NCCTG N9831	3,505	Concurrent or sequential	1 year	AC→T AC→ w TH AC→ w T→H	8.7
NSABP B-31	3,222	Concurrent	1 year	AC→T AC→TH	9.4
PACS 04	528	Sequential	1 year	FEC→H DE→ H	5.0
FinHER	232	Concurrent	9 weeks	D+/-H→FEC V+/-H→FEC	5.6

A-doxorubicin; T-paclitaxel; w-weekly ; H-trastuzumab; F-5-fluorouracil; E-epirubicin; C-cyclophosphamide; D-docetaxel; V-vinorelbine

Presented by: Ciara C. O'Sullivan email:ciara.o'sullivan@nih.gov

HER2-Positive Tumors ≤ 2cm

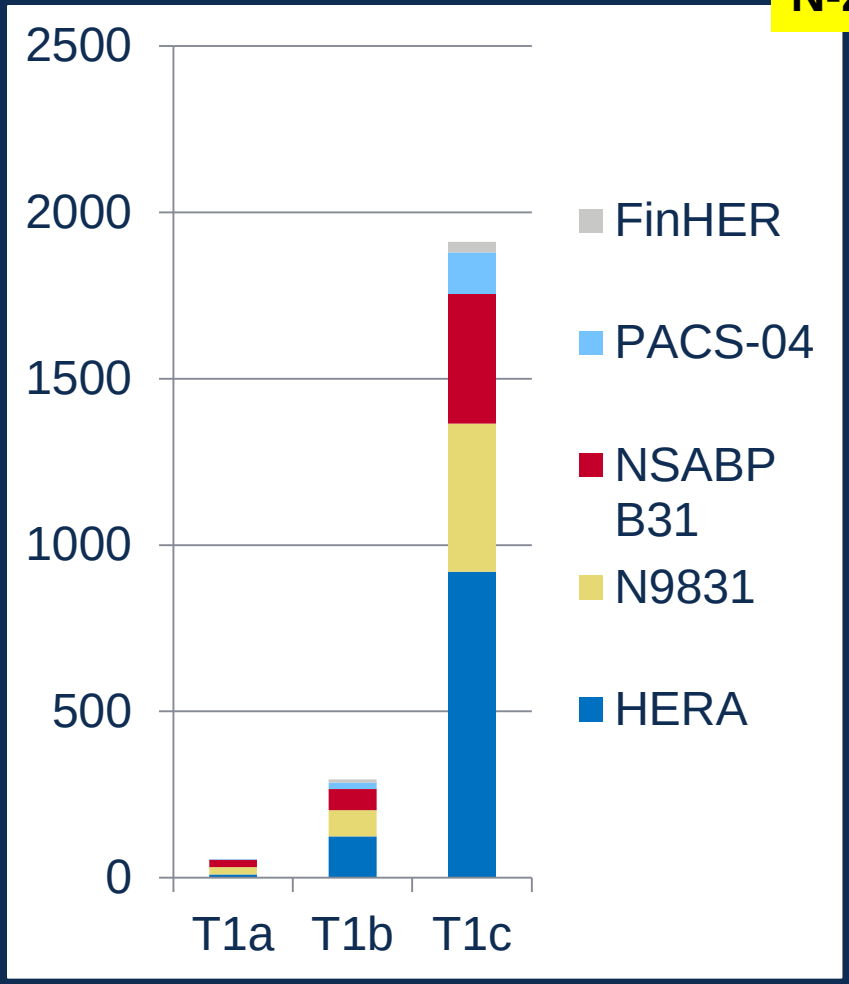
Trial	HER2+ Tumors	HER2+ Tumors ≤2cm	Received Trastuzumab	DID NOT receive Trastuzumab
HERA	5,102	2,002	1,320	682
NCCTG N9831	3,505	756	405	351
NSABP B-31	3,222	1,146	711	435
PACS 04	528	235	106	129
FinHER	232	81	46	35
TOTAL PTS	12,589	4,220	2,588	1,632

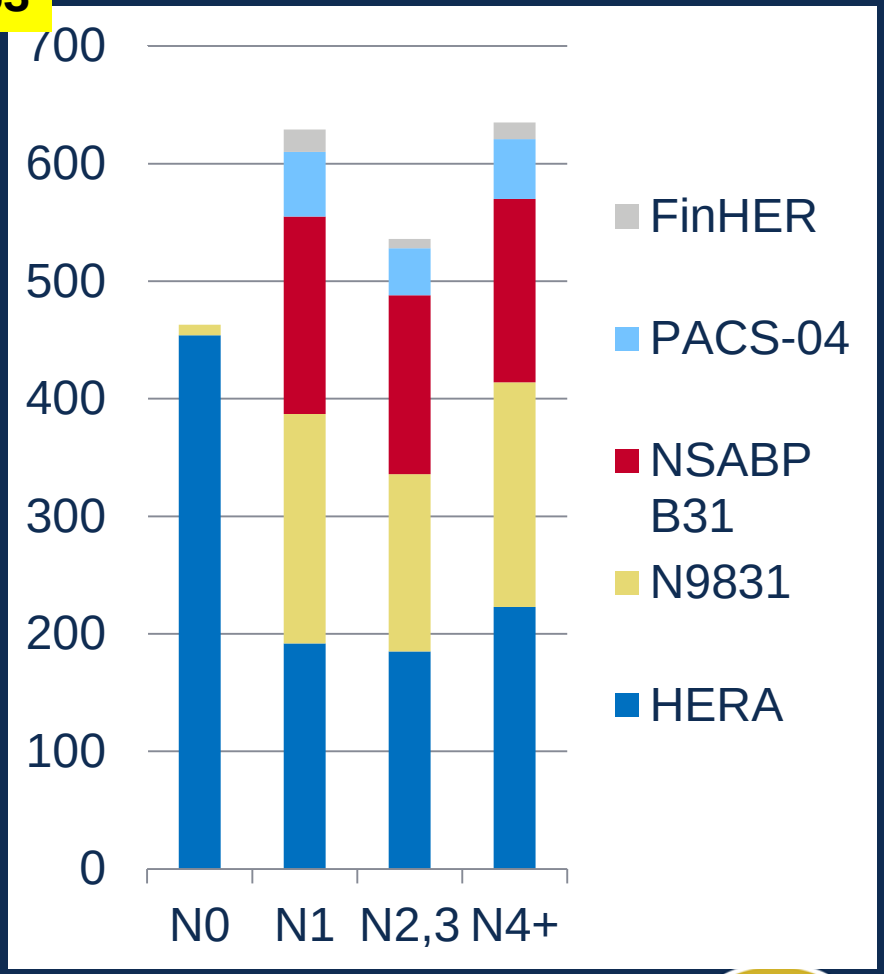
Presented by: Ciara C. O'Sullivan email: ciara.o'sullivan@nih.gov

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

RESULTS: HR-Positive Disease: Tumor Size (≤ 2cm) & Nodal Status

N-2,263

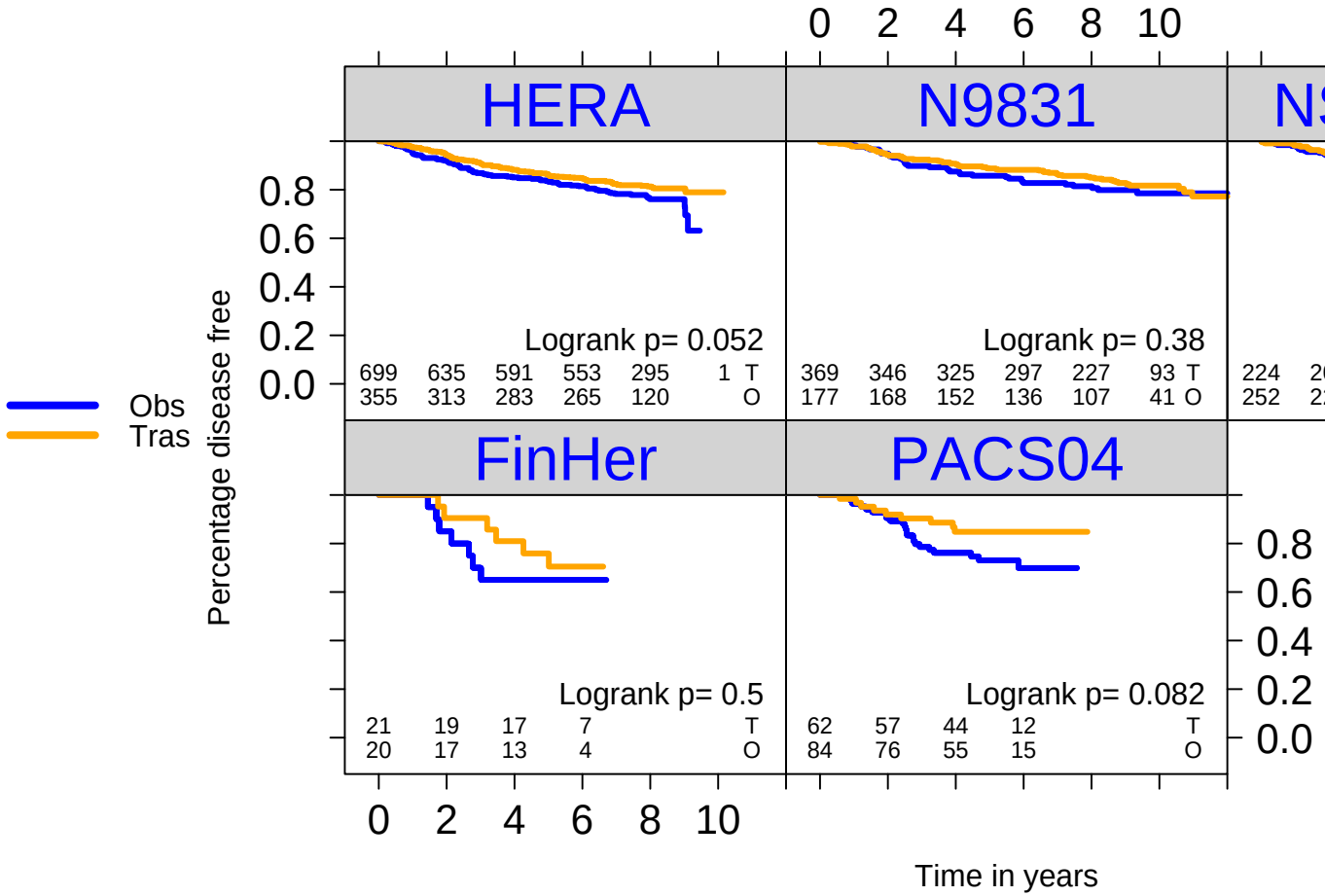




Presented by: Ciara C. O'Sullivan email: ciara.o'sullivan@nih.gov

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

DFS for HR-Positive Disease Treated With or Without Trastuzumab: Tumors ≤ 2cm



Study-to-study heterogeneity is not statistically significant

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Study Specific Hazard Ratios For Model Stratifying on Study, Including Overall Study and Nodal Status Effects in HR-Positive Cohort: Tumors ≤ 2cm

	Hazard Ratio	95% CI
Trastuzumab	0.7	0.58-0.85

Nodes	Hazard Ratio	95% CI
0	1.00	REF
1	1.38	0.99 - 1.94
2-3	1.55	1.11 - 2.18
≥4	2.73	2.00 - 3.73

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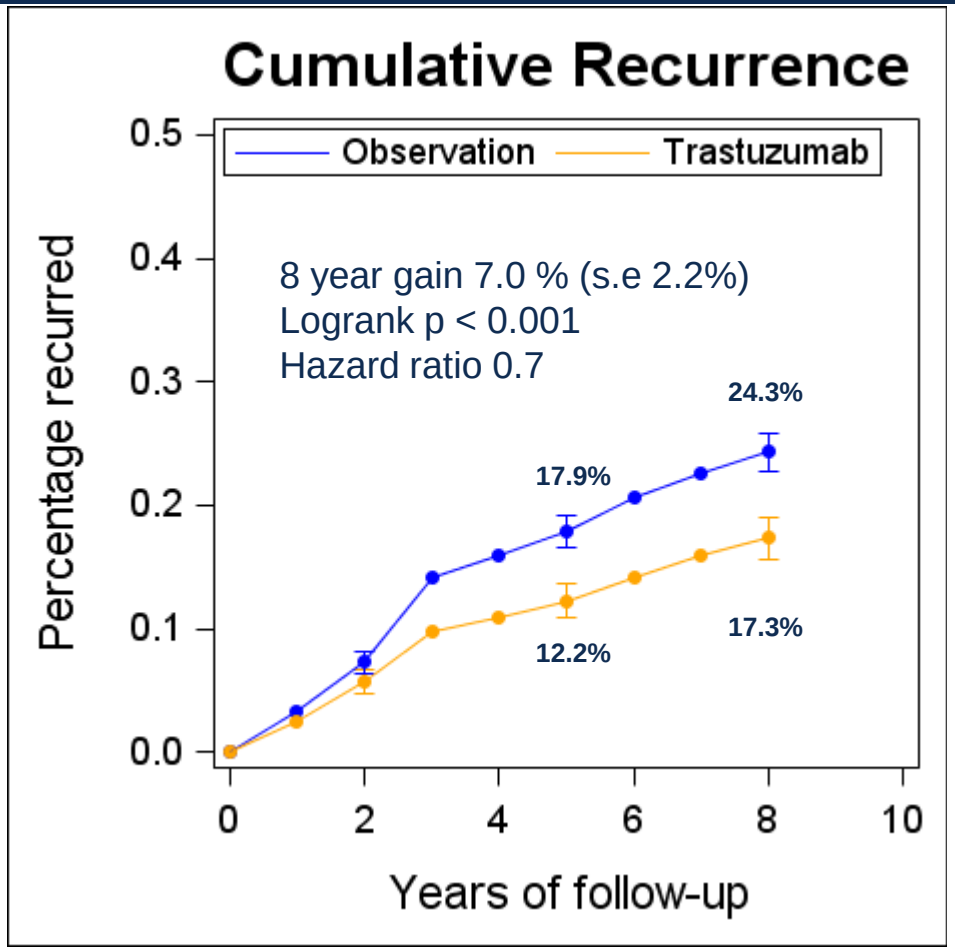
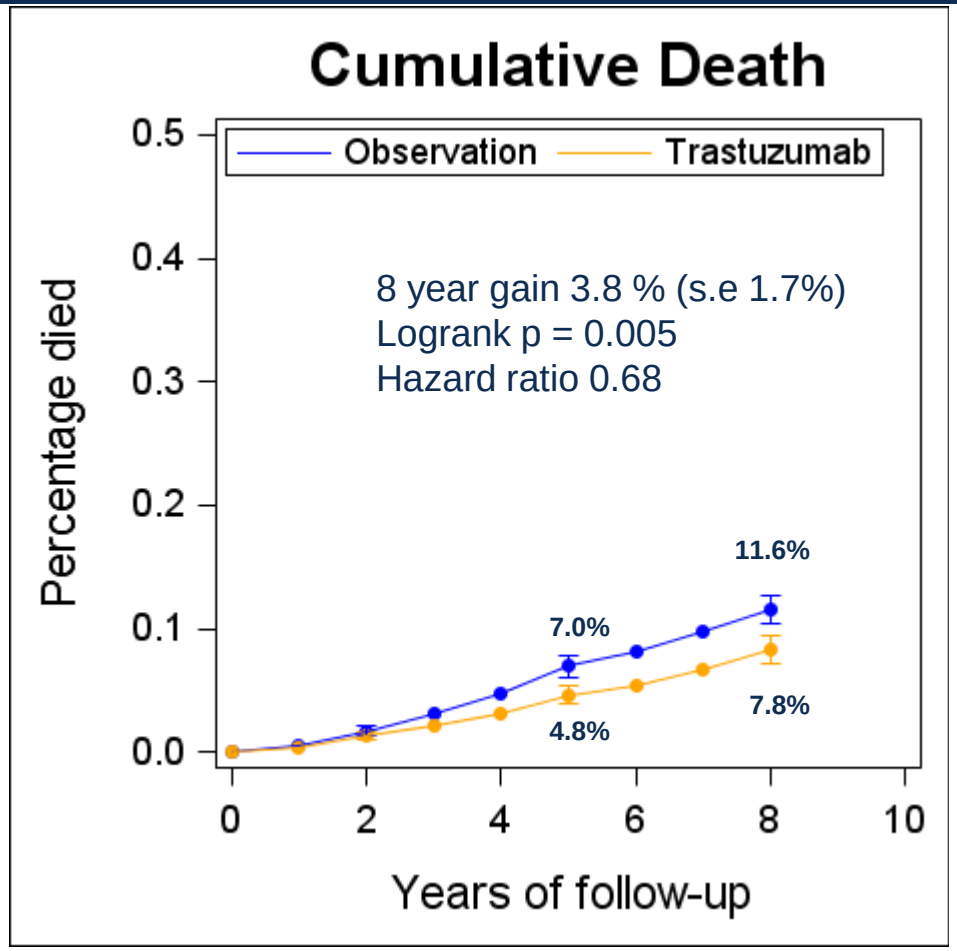
Cumulative Incidence of Recurrence or Death: HR-Positive Disease with Tumors ≤ 2cm





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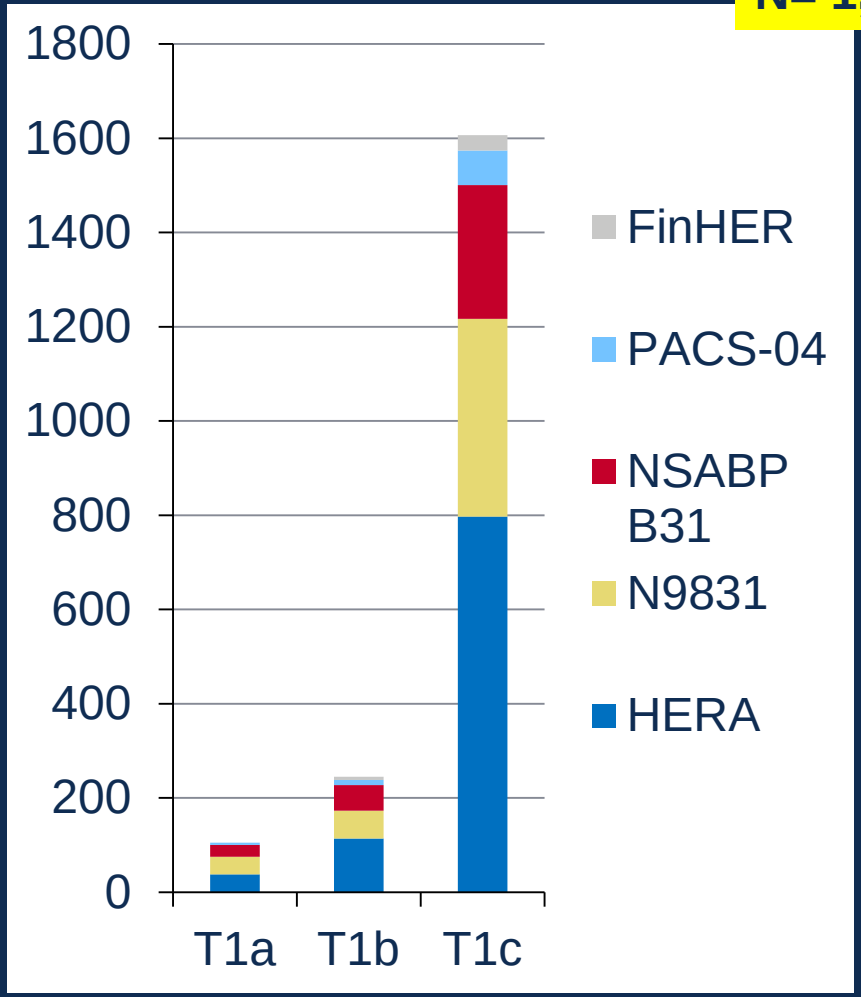
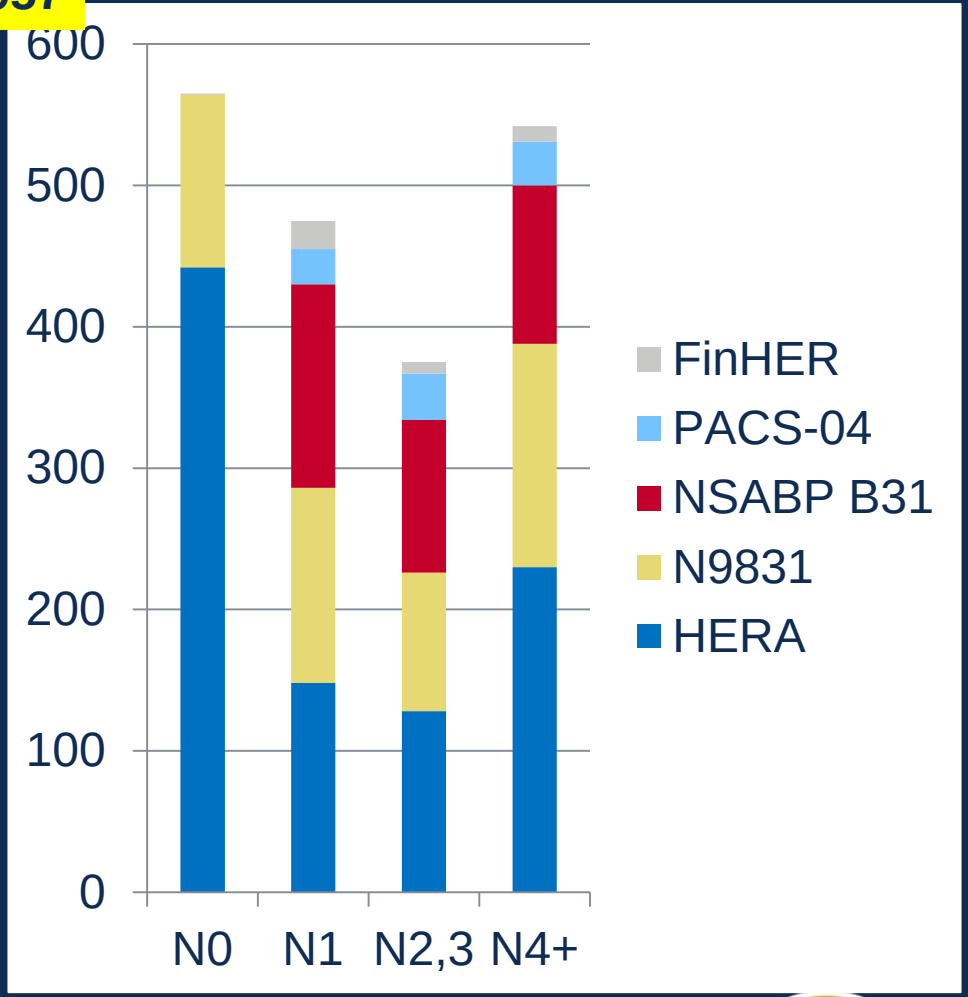
HR-negative disease : Tumor Size ≤ 2cm & Nodal Status

N= 1,957





Presented by: Ciara C.O'Sullivan **email: ciara.o'sullivan@nih.gov**

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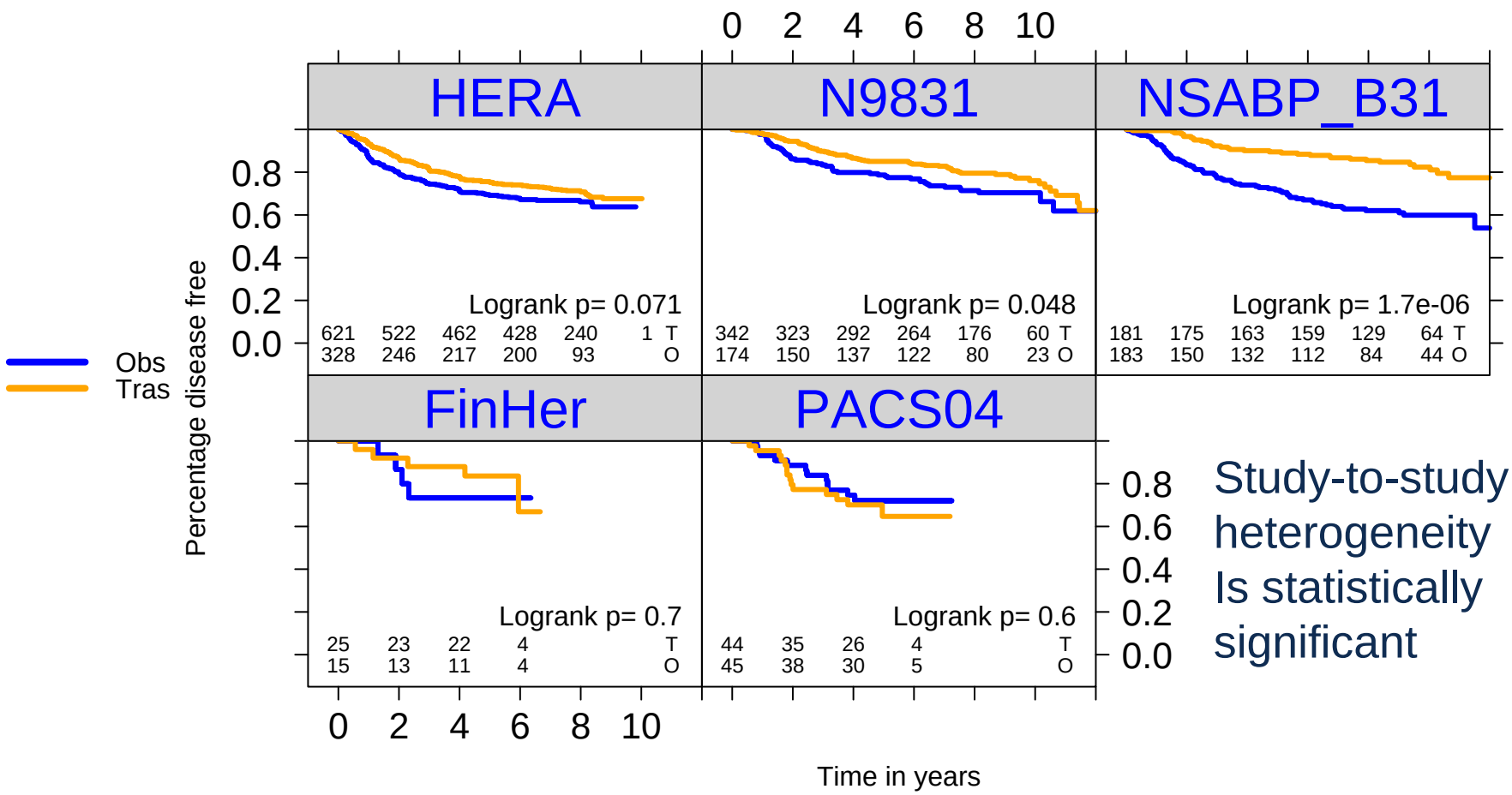
DFS for HR-Negative Disease Treated With or Without Trastuzumab: Tumors ≤ 2cm



Study-to-study heterogeneity Is statistically significant

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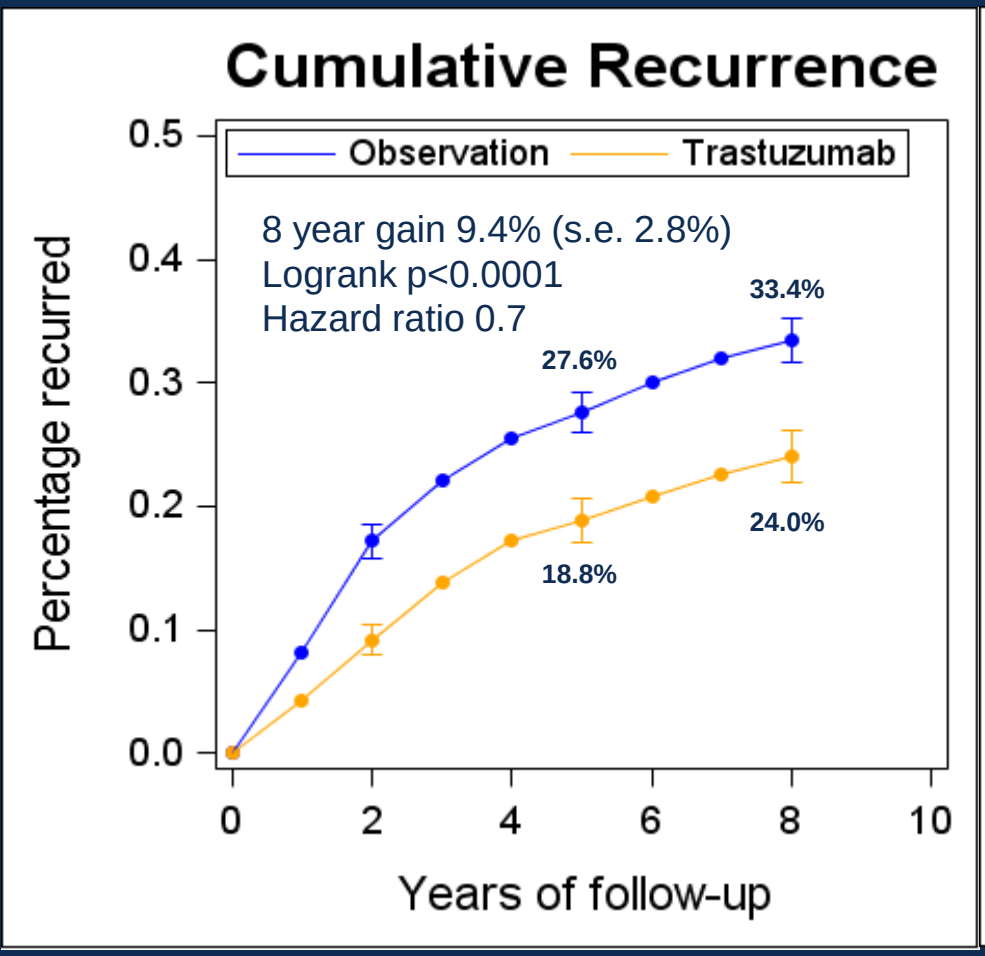
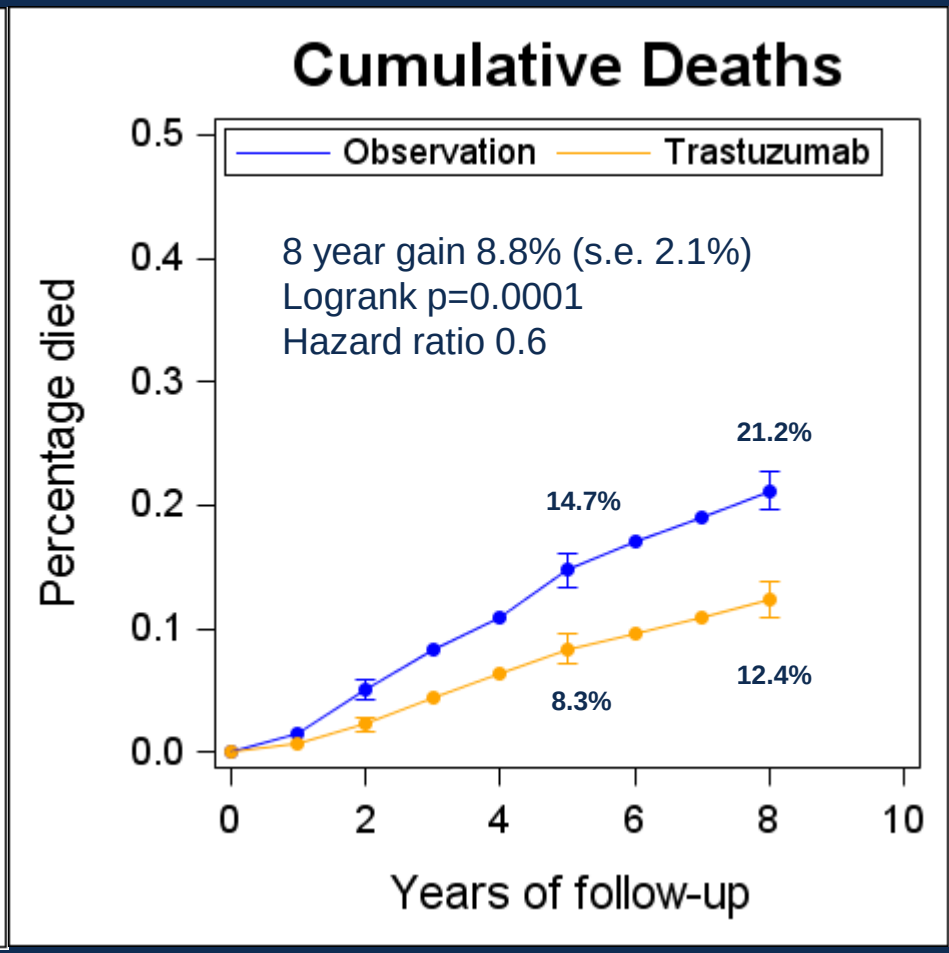
Cumulative Incidence of Recurrence or Death: HR-Negative Disease with Tumors ≤ 2cm





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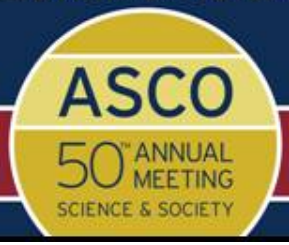
Conclusions

- Patients with tumors ≤ 2 cm benefitted substantially in terms of both DFS and OS from trastuzumab therapy
- Most patients included in analysis had T1c and positive axillary lymph nodes
- Benefit of trastuzumab-based chemotherapy among T1a-b, N0 tumors remains undefined.
- Benefit was similar in HR-negative and HR-positive patients

Prevention of Early Menopause Study (POEMS)-S0230

Phase III trial of LHRH analog during chemotherapy to reduce ovarian failure in early stage, hormone receptor-negative breast cancer: an international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance)

Halle C.F. Moore, Joseph M. Unger, Kelly-Anne Phillips, Frances Boyle, Erika Hitre, David Porter, Prudence A. Francis, Lori Minasian, Richard D. Gelber, Lori J. Goldstein, Henry L. Gomez, Carlos S. Vallejos, Ann H. Partridge, Shaker R. Dakhil, Silvana Martino, William E. Barlow, Carol J. Fabian, Frank L. Meyskens, Gabriel N. Hortobagyi, Kathy S. Albain

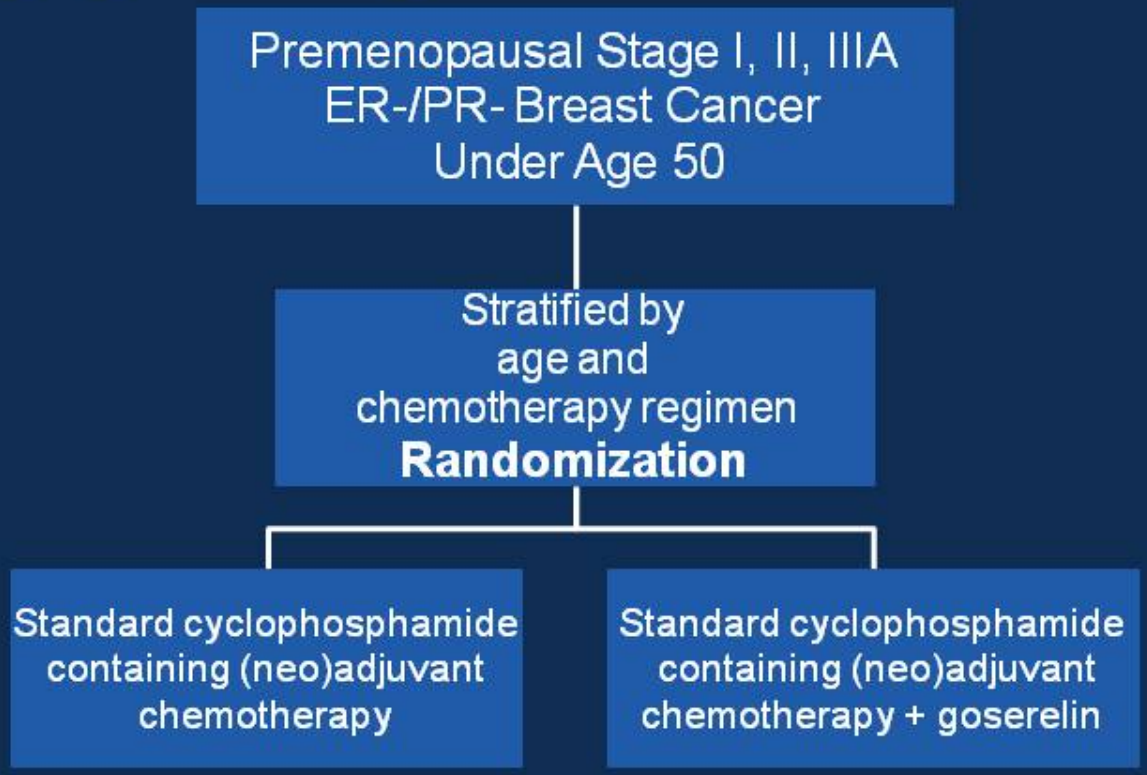


Presented By Halle Moore at 2014 ASCO Annual Meeting

Background

- Approximately 25% of breast cancers occur in women under age 50
- Ovarian failure is a common consequence of chemotherapy treatment
- Ovarian failure rates depend on chemotherapy regimen/duration, patient age and perhaps gonadal activity at time of chemotherapy administration

POEMS/S0230 Schema

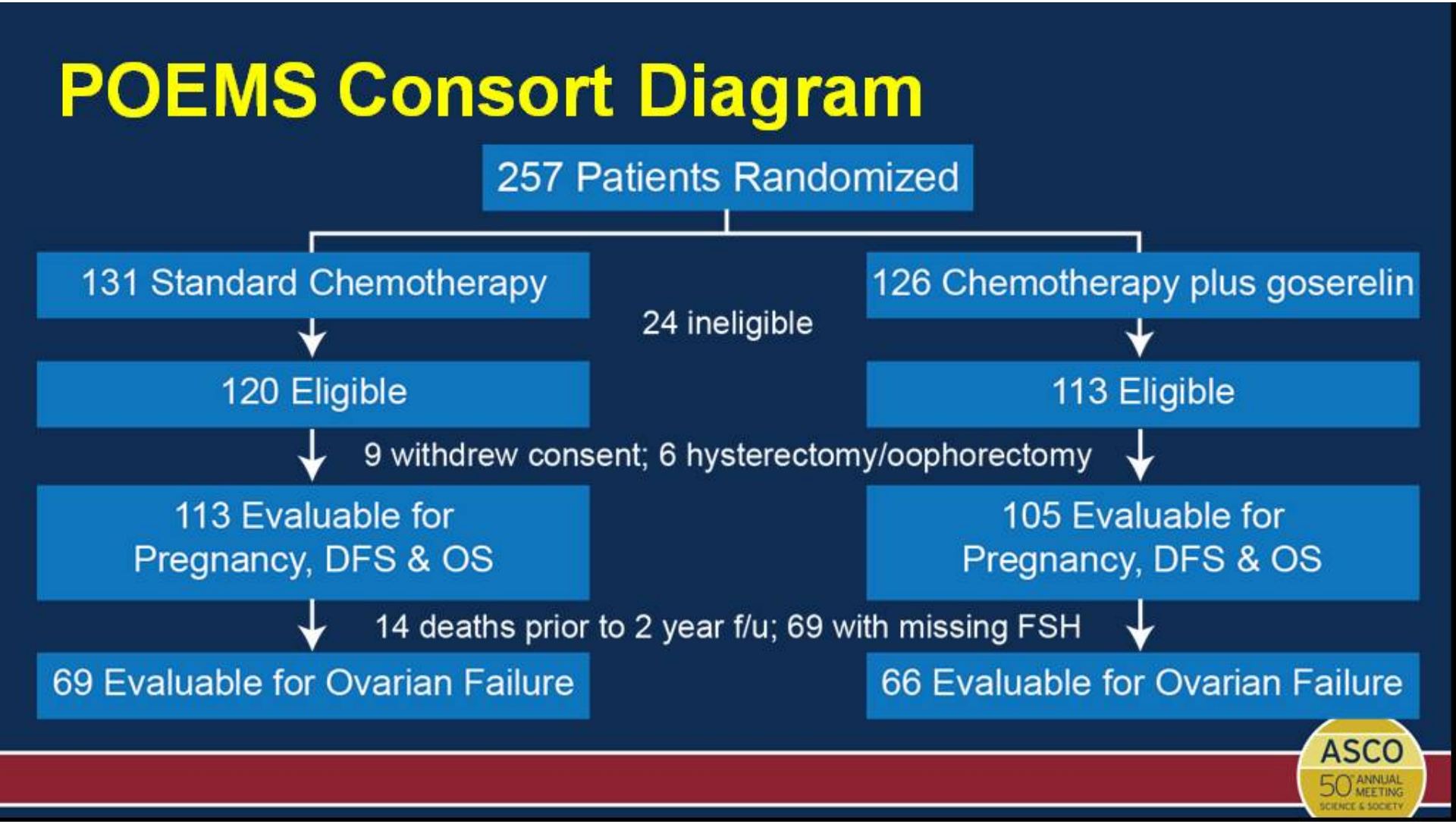


POEMS Objectives and Endpoints

- Primary
  - Ovarian Failure at 2 years
    - Defined as amenorrhea for the prior 6 months and FSH in the postmenopausal range
- Secondary
  - Ovarian dysfunction at 1 and 2 years
    - Defined as amenorrhea for preceding three months and FSH, estradiol and/or inhibin B levels in the postmenopausal range
  - Pregnancy Outcomes
- Exploratory
  - DFS and OS

Goserelin Administration

- Goserelin 3.6 mg SubQ every 4 weeks
- Started at least 1 week prior to first chemotherapy dose
- Continued for duration of chemotherapy
  - Last goserelin administered within 2 weeks of (before or after) the final chemotherapy dose


POEMS Consort Diagram
257 Patients Randomized
131 Standard Chemotherapy
126 Chemotherapy plus goserelin
24 ineligible
120 Eligible
113 Eligible
9 withdrew consent; 6 hysterectomy/oophorectomy
113 Evaluable for Pregnancy, DFS & OS
105 Evaluable for Pregnancy, DFS & OS
14 deaths prior to 2 year f/u; 69 with missing FSH
69 Evaluable for Ovarian Failure
66 Evaluable for Ovarian Failure
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Patients

	Standard Chemotherapy n=113	Chemotherapy + Goserelin n=105
Age in years: median (range)	38.7 (25-49)	37.6 (26-49)
Age <40 years	62%	65%
Age ≥40 years	38%	35%
Planned chemotherapy:		
3-4 month/cycle anthracycline	19%	23%
6-8 month/cycle anthracycline	71%	69%
3-4 month/cycle non-anthra.	4%	4%
6-8 month/cycle non-anthra.	6%	5%
Stage		
I	28%	22%
II	46%	53%
III	26%	24%

POEMS Ovarian Failure

	Standard Chemotherapy	Chemotherapy + Goserelin
Ovarian failure at 2 years	15/69 = 22%	5/66 = 8%

Logistic Regression Results:

Analysis	Odds Ratio	95% CI	p-value	
			One-sided	Two-sided
Univariate	0.30	0.10 – 0.87	p=.01	p=.03
Stratified*	**0.30**	**0.09 – 0.97**	**p=.02**	**p=.04**
Multivariate*	0.36	0.11 – 1.14	p=.04	p=.08

*Accounting for age and regimen through stratification ("Stratified") or covariate ("Multivariate") adjustment, respectively

POEMS Pregnancy

	Standard Chemotherapy n=113	Chemotherapy + Goserelin n=105	Adjusted OR	Adjusted P-value
Attempted pregnancy	18 (16%)	25 (24%)		p=.12
Achieved pregnancy	12 (11%)	22 (21%)	2.45	p=.03
Patients with ≥ 1 delivery	8 (7%)	16 (15%)	2.51	p=.05
Delivery or ongoing pregnancy	10 (9%)	19 (18%)	2.45	p=.04
Total number of babies	12	18		
Ongoing pregnancies	3	5		
Total adverse events				
Miscarriages	5	4		
Elective termination	3	2		
Delivery complication	2	2		

POEMS Disease Free Survival

Regression Covariates	HR (95% CI) p-value
Adjusted for age and regimen	0.47 (0.24-0.95) p=.04
Adjusted for age, regimen, & stage	0.49 (0.24-0.97) p=.04

POEMS Overall Survival

Regression Covariates	HR (95% CI) p-value
Adjusted for age and regimen	0.45 (0.19-1.04) p=.06
Adjusted for age, regimen, & stage	0.43 (0.18-1.00) p=.05

Conclusions

- Despite lower than planned accrual and incomplete follow-up data on 38% of patients, goserelin was associated with decreased rates of ovarian failure after chemotherapy and more successful pregnancies.
- Findings of improved DFS and OS are reassuring
- Study did not include hormone-receptor positive patients, so benefit and safety of goserelin in this setting is unclear
- For ER/PR-negative patients who are beginning chemotherapy should consider this option for the prevention of premature ovarian failure.