Review of adjuvant and neo-adjuvant abstracts from SABCS 2011 January 7th 2012

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Abstracts

- Delayed inhibition of HER2 in early stage breast cancer (Abstract S4-7)
- HER2-directed agents in the neo-adjuvant setting (S5-6, S5-4, S5-1)
- Management of patients non-responsive to pre-operative therapy (Abstracts S3-2, S3-6)

Results of a randomized, double-blind, multicenter, placebo-controlled (TEACH) study of adjuvant lapatinib in women with early stage ErbB2-overexpressing breast cancer

Goss et al

Abstract S4-7

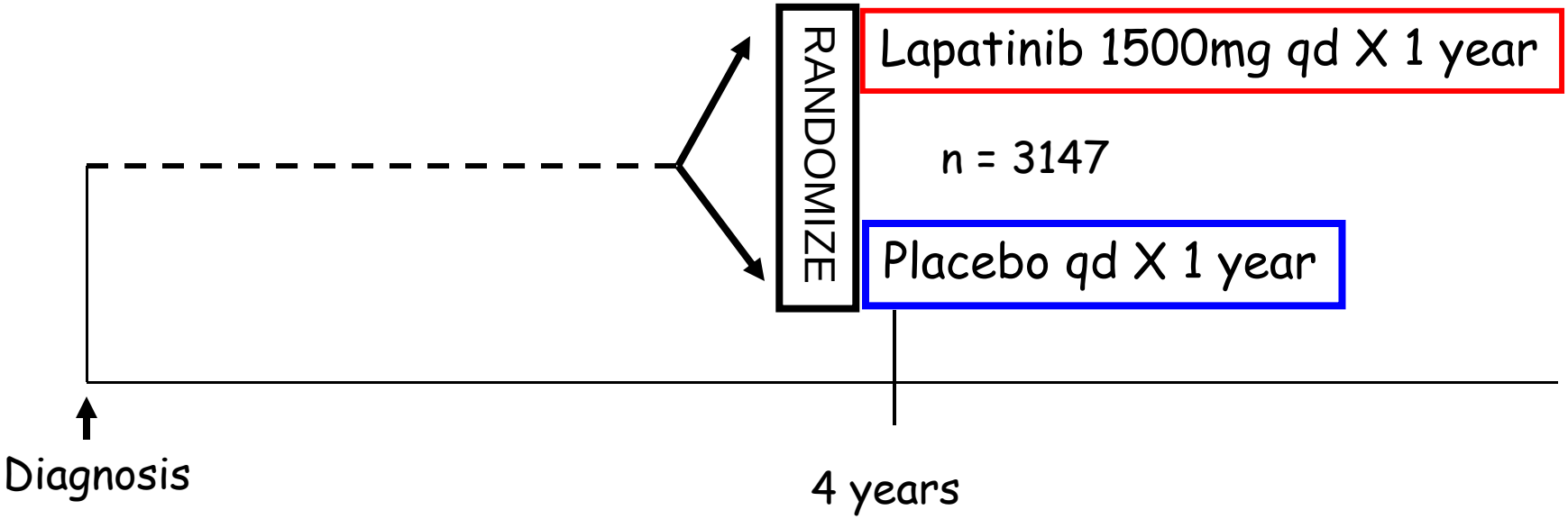
Study rationale

- At the time that results of the adjuvant trastuzumab trials were made available, many countries worldwide did not have access to trastuzumab
- TEACH trial designed to determine
  - The natural history of HER2-positive breast cancers and whether there was continued recurrences overtime
  - Whether delayed anti-HER2 therapy with lapatinib would decrease these delayed recurrences if they occurred

TEACH trial design

- Stage 1 -3c primary breast cancer
- HER2+ (3+ or FISH+)
- No prior trastuzumab
- (Neo) adjuvant chemotherapy
- Appropriate endocrine therapy

Stratification:
- Time from diagnosis ≤4 vs >4 years
- Lymph node + vs –
- ER+ and/or PR+ vs ER-, PR-



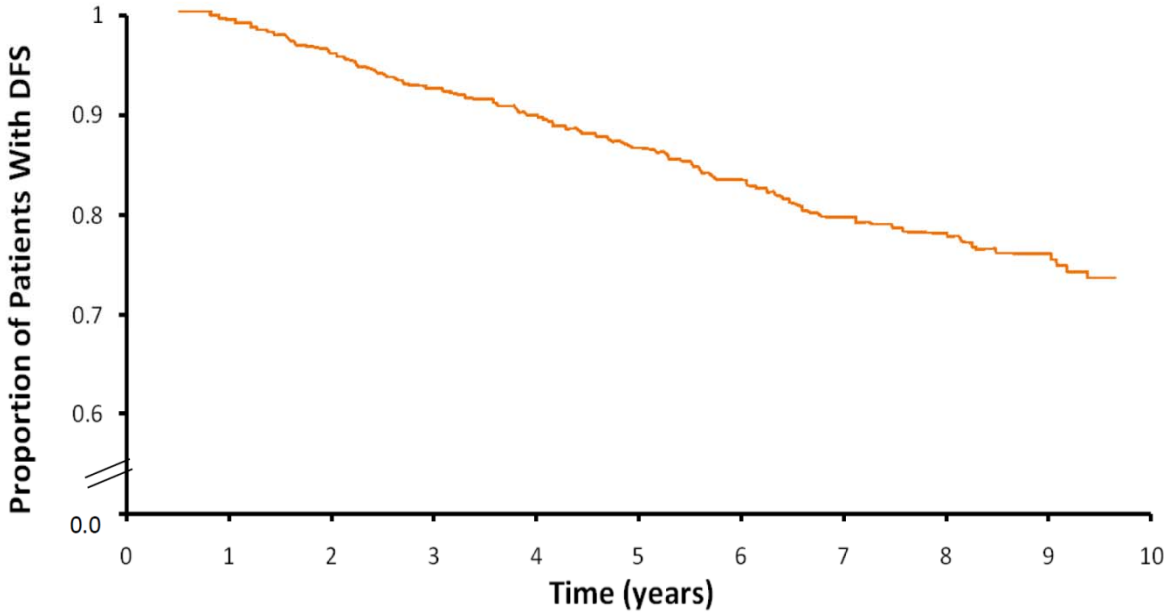
TEACH: Endpoints and statistics

- Primary endpoint: DFS
- Hypothesis: Lapatinib will decreases recurrence by 23% (requires HR of 0.769), assuming an annual recurrence rate of 7% in the lapatinib arm and 10% in the placebo arm

TEACH: Baseline characteristics

	Lapatinib N = 1571	Placebo N = 1576
Median age	51	52
Median time from initial diagnosis	2.7 years	2.75 years
Years since initial diagnosis:		
≤ 4 years	71%	72%
> 4 years	29%	28%
0 – 1 year	20%	21%
Hormone receptor status:		
ER and/or PR +	59%	59%
ER, PR-negative	41%	41%
Lymph node status:		
Positive	56%	56%

TEACH RESULTS: Ongoing Risk of Recurrence from Diagnosis in Placebo Arm

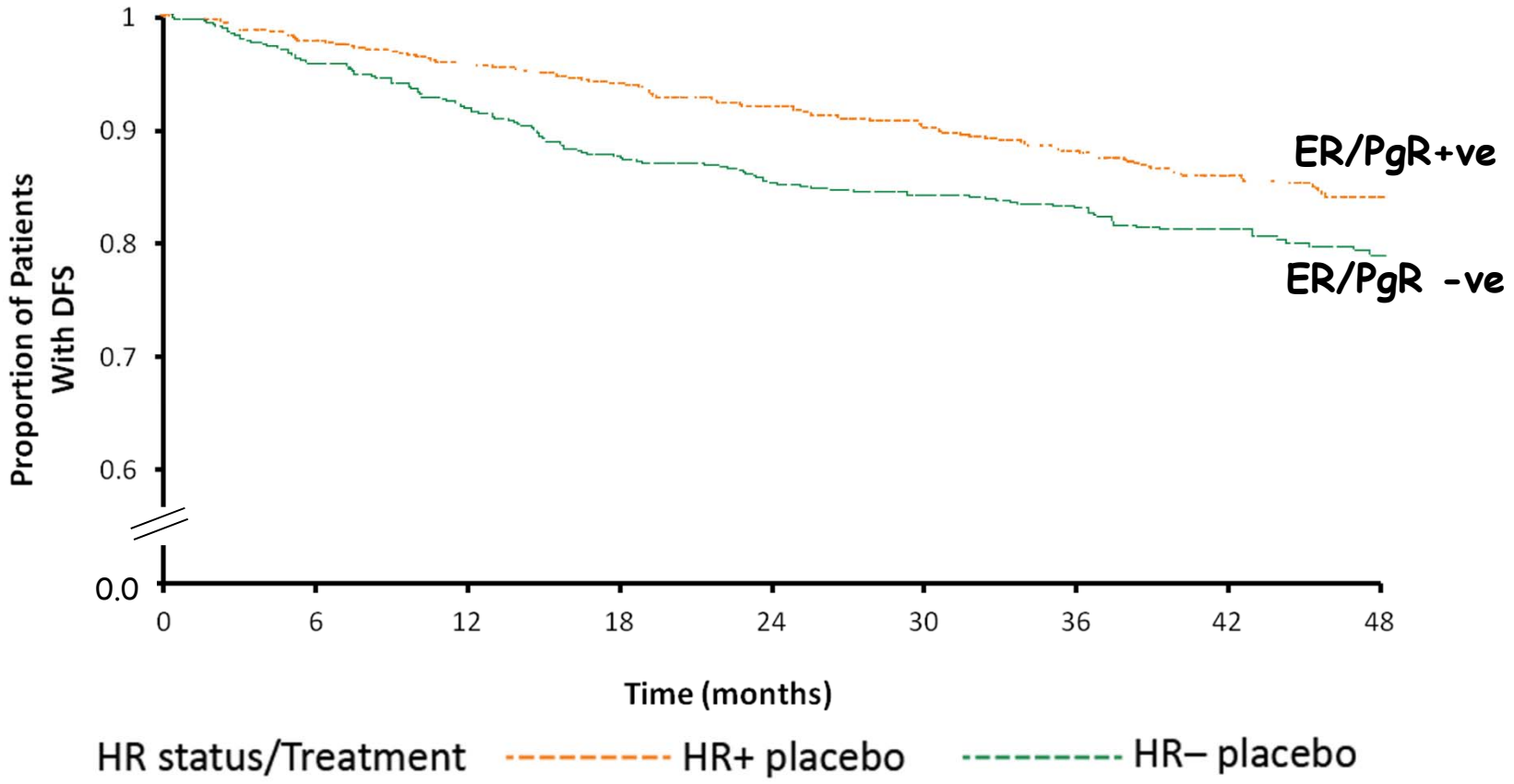


Year(s)	Disease-free Patients (%)
1	99.9%
2	96.7%
3	93.1%
4	91.0%
5	87.8%
6	84.4%
7	81.1%
8	79.2%
9	77.2%
10	74.9%

Number of patients at risk

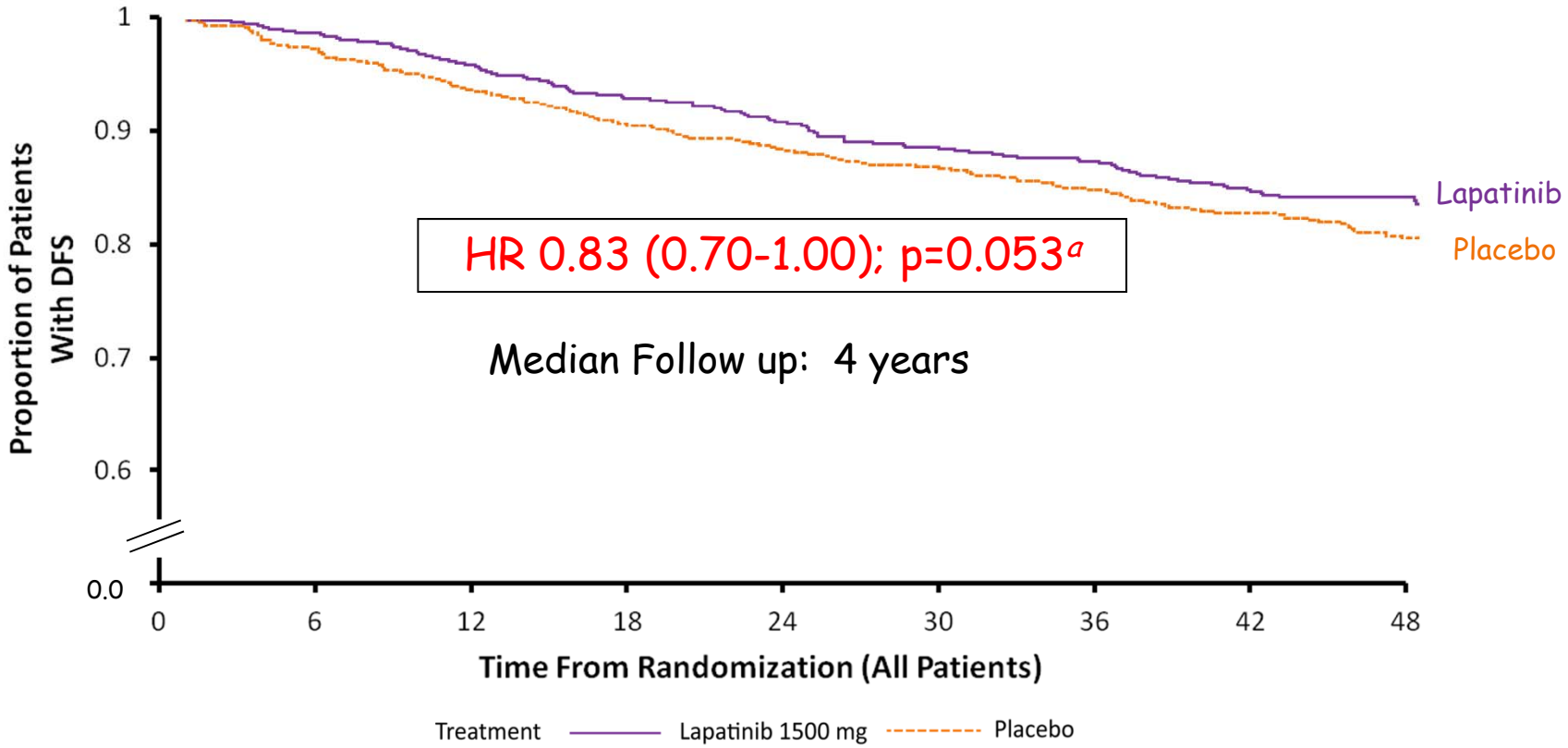
Placebo	1576	1569	1504	1430	1323	1043	781	539	310	181	96

TEACH: K-M Plot of DFS According to Hormone Receptor (HR) Status in untreated (placebo) ITT Population



Number of patients at risk									
HR+ placebo	927	880	845	814	789	757	626	420	193
HR– placebo	649	607	567	529	506	490	422	286	134

TEACH Primary Endpoint: K-M Plot of DFS in ITT Population—Time From Randomization

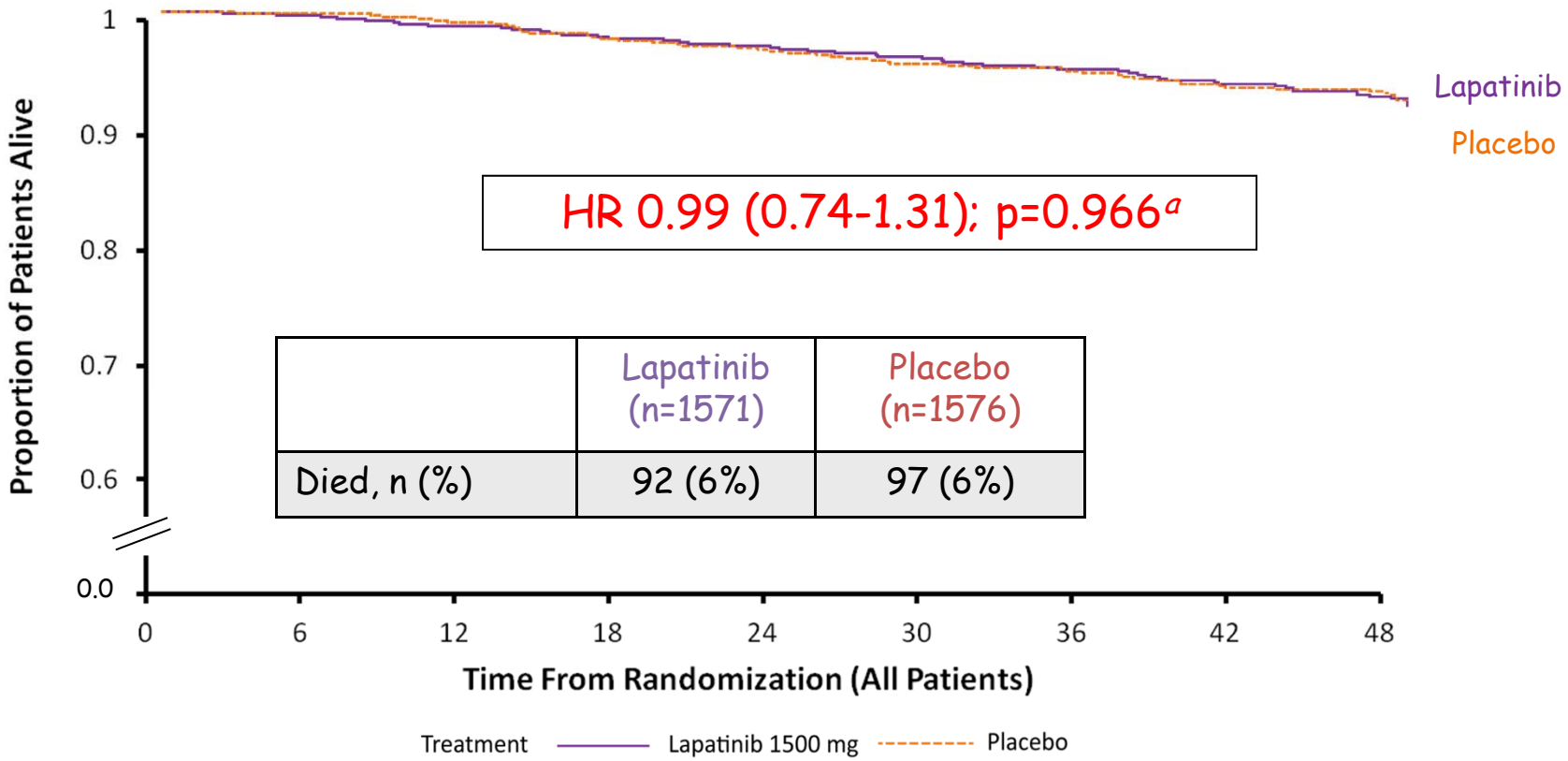


Number of patients at risk

Lapatinib 1500 mg	1571	1431	1349	1293	1233	1168	1001	661	299
Placebo	1576	1487	1412	1343	1295	1247	1048	706	327

[a]p value based on 2-sided stratified log-rank test

TEACH: K-M Plot of OS in ITT Population—Time From Randomization



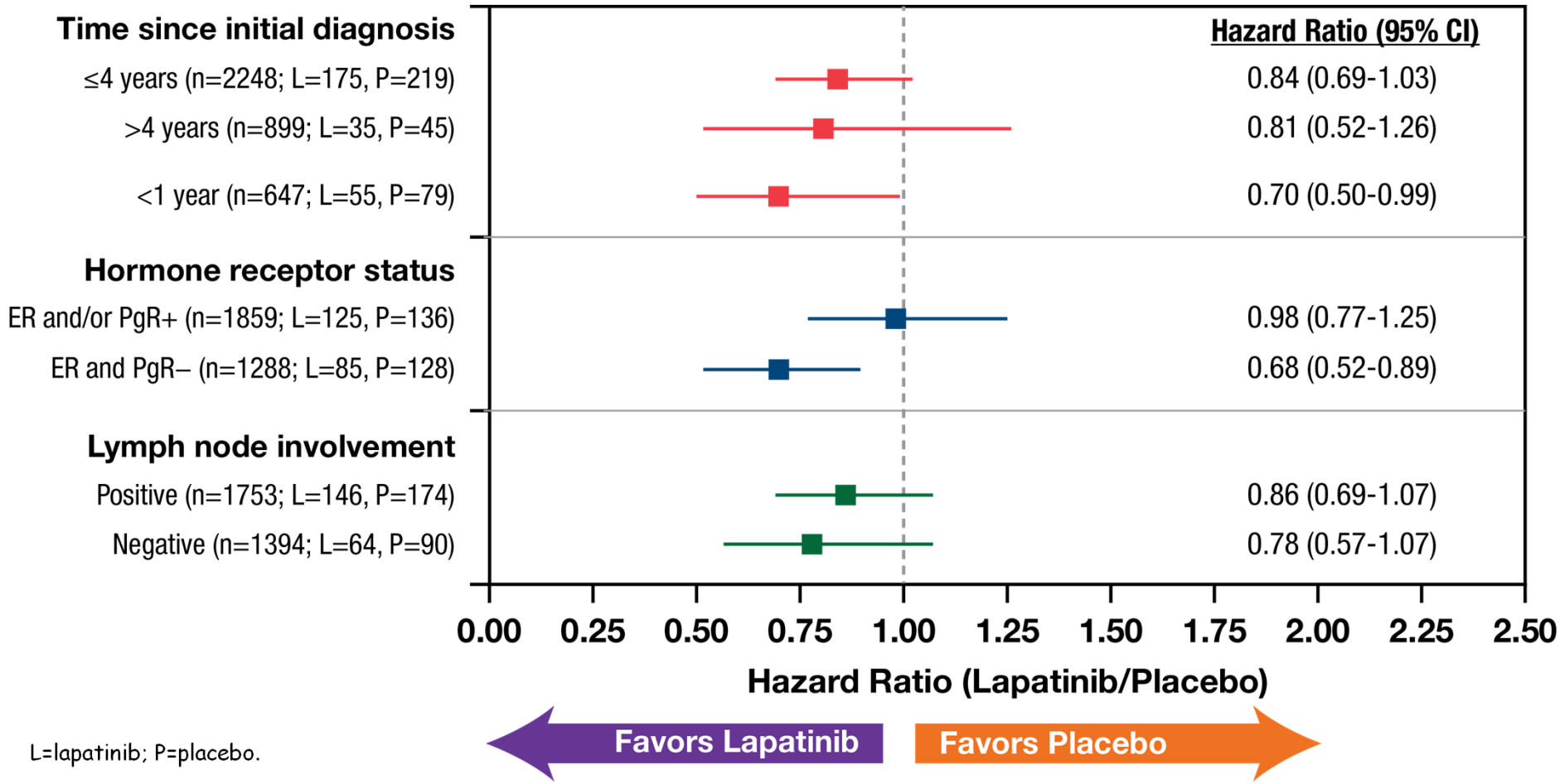
	Lapatinib (n=1571)	Placebo (n=1576)
Died, n (%)	92 (6%)	97 (6%)

Number of patients at risk

Lapatinib 1500 mg	1571	1518	1477	1444	1402	1340	1153	777	351
Placebo	1576	1555	1528	1487	1448	1389	1188	805	374

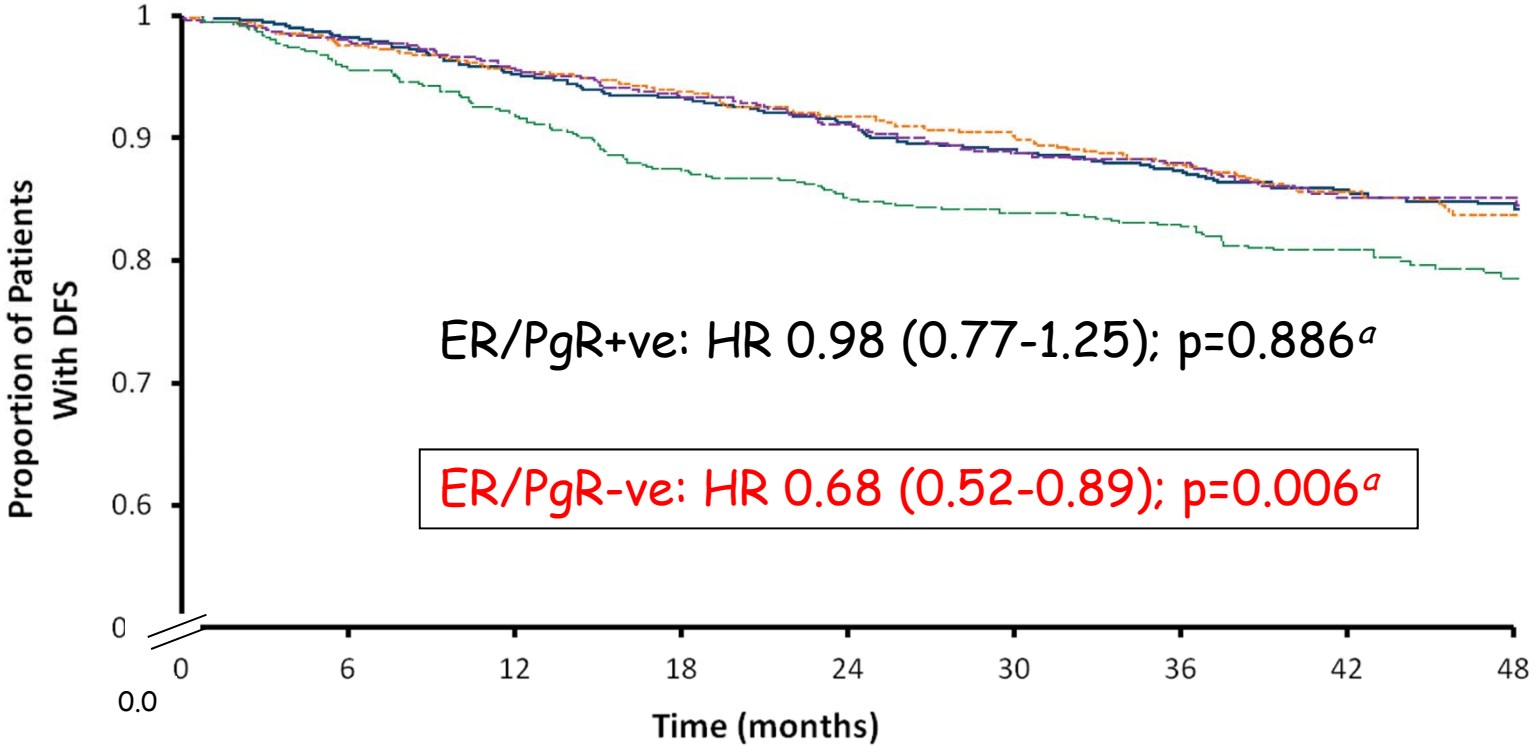
[a]p value based on 2-sided stratified log-rank test.

TEACH: Forest Plot of DFS for Subgroups in ITT Population



L=lapatinib; P=placebo.

TEACH: K-M Plot of DFS According to Hormone Receptor (HR) Status in <u>treated</u> ITT Population



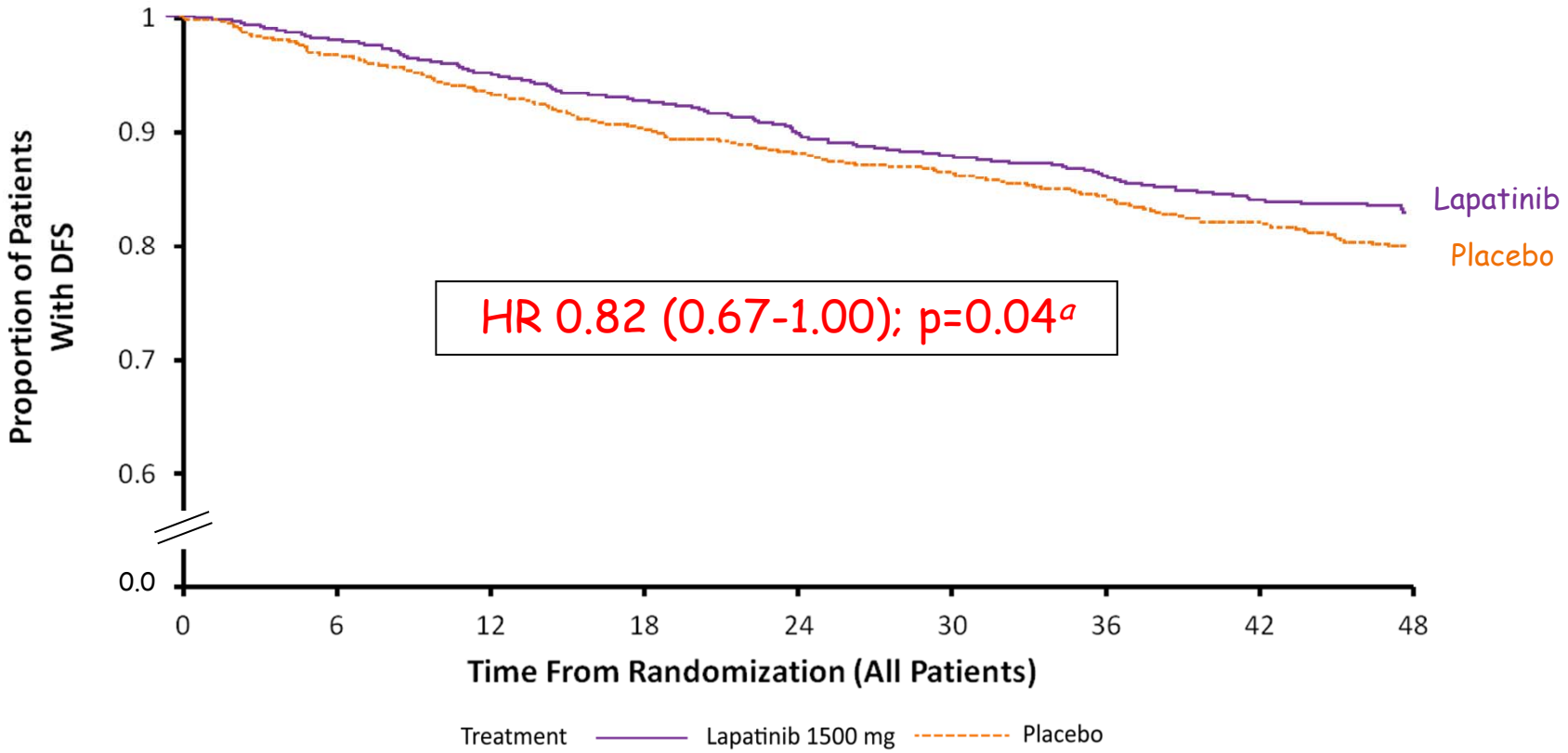
HR status/Treatment — HR+ lapatinib 1500 mg; HR+ placebo; HR– lapatinib 1500 mg; HR– placebo

Number of patients at risk

HR+ lapatinib 1500 mg	932	847	794	761	731	693	593	384	169
HR+ placebo	927	880	845	814	789	757	626	420	193
HR- lapatinib 1500 mg	639	584	555	532	502	475	408	277	130
HR- placebo	649	607	567	529	506	490	422	286	134

[a]p value based on 2-sided stratified log-rank test.

TEACH: K-M Plot of DFS in Confirmed FISH+ Population—Time From Randomization



Number of patients at risk

Lapatinib 1500 mg	1230	1137	1069	1026	980	934	810	533	245
Placebo	1260	1186	1125	1075	1035	993	840	578	275

[a]p value based on 2-sided stratified log-rank test.

TEACH: Sites of BRCA Recurrences and Second Primaries in Confirmed FISH+ Population

	Lapatinib 1500 mg (n=1230)	Placebo (n=1260)
Any recurrence of disease, second primary or contralateral BRCA, n (%)	157 (13%)	208 (17%)
Local recurrence	24 (2%)	37 (3%)
Regional recurrence	19 (2%)	25 (2%)
Distant recurrence	102 (8%)	133 (11%)
CNS	12 (<1%)	20 (2%)
Contralateral BRCA	10 (<1%)	13 (1%)
Second primary malignancy	22 (2%)	24 (2%)

TEACH: Time-to-First BRCA Recurrences in Confirmed FISH+ Population

	Lapatinib 1500 mg (n=1230)	Placebo (n=1260)
Any recurrence or contralateral BRCA, n (%)[a]	137 (11%)	183 (15%)
Patients with recurrence at yearly time points, %		
1 yr	3.7%	6%
2 yr	7.9%	10.5%
3 yr	10.6%	13.2%
Any recurrence HR (95% CI) 2-sided stratified log-rank p value[b]	0.79 (0.63-0.98) 0.033	
Patients with CNS recurrence at yearly time points, %		
1 yr	0.5%	0.7%
3 yr	1.1%	1.3%
CNS recurrence HR (95% CI) 2-sided stratified log-rank p value[b]	0.66 (0.33, 1.34) 0.286	

[a]Events not included were death and second primary cancer (competing risk).
[b]p value stratified by time from initial diagnosis, HR status, and lymph node involvement.

TEACH: Adverse events

- Lapatinib associated with more AEs, especially diarrhea and rash
- 20% drug discontinuation on lapatinib arm
- No significant difference in cardiac events between the two arms
- Lapatinib associated with elevated LFTs in 8% of patients

TEACH: conclusions

- Patients with HER2+ cancers who do not receive trastuzumab remain at an ongoing risk of recurrence up to 10 years (regardless of HR status)
- DFS was not significantly improved with delayed lapatinib in the ITT population but did benefit patients:
  - With ER/PR-negative cancers
  - Within one year of diagnosis

Neoadjuvant Pertuzumab and Trastuzumab Concurrent or Sequential with an Anthracycline-Containing or Concurrent with an Anthracycline-Free Standard Regimen: A Randomized Phase II Study (TRYPHAENA)

Schneeweiss et al

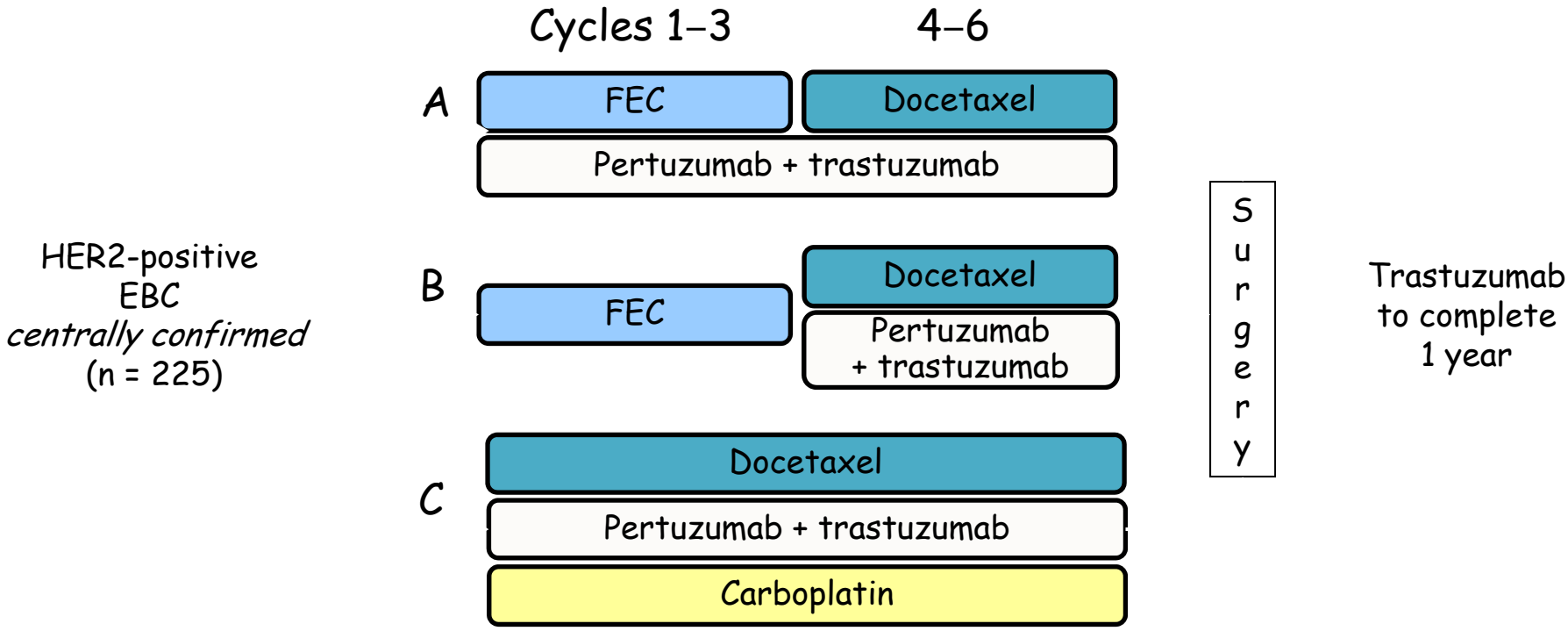
Abstract S5-6

Primary study objective

- To make a preliminary assessment of the tolerability of neoadjuvant treatment with pertuzumab and trastuzumab plus anthracycline-taxane-based or carboplatin-taxane-based standard chemotherapy regimens in HER2-positive EBC

EBC, early breast cancer; HER2, human epidermal growth factor receptor

Study design



- All 3 arms were experimental
- Study dosing q3w:
  - FEC: 500 mg/m^2, 100 mg/m^2, 600 mg/m^2
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m^2 (escalating to 100 mg/m^2 if tolerated, in Arms A and B only)

AUC, area under the plasma concentration-time curve; EBC, early breast cancer; FEC, 5-fluorouracil, epirubicin, cyclophosphamide

Study endpoints

- Primary endpoint:
  - Cardiac safety
    - Symptomatic LVSD (grade ≥3)
    - LVEF declines (≥10 percentage points and below 50%)
- Secondary endpoints:
  - Toxicity
  - pCR (defined as the absence of invasive tumor residues in the breast at surgery; remaining *in situ* lesions allowed; ypT0/is)
    - Study was not powered for formal comparison between arms
  - Clinical response rate
  - Rate of breast-conserving surgery
  - Disease-free survival and overall survival
  - Biomarker evaluation

LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; pCR, pathologic complete response

Baseline characteristics in the safety population

	FEC+H+P x3 → T+H+P x3 n = 72	FEC x3 → T+H+P x3 n = 75	TCH+P x6 n = 76
Median age, years (range)	49.0 (27–77)	49.0 (24–75)	50.0 (30–81)
ECOG PS 0, n (%)	65 (91.5)	66 (88.0)	67 (88.2)
1, n (%)	6 (8.5)	9 (12.0)	9 (11.8)
ER- and/or PR-positive, n (%)	39 (53.4)	35 (46.7)	40 (51.9)
ER- and PR-negative, n (%)	34 (46.6)	40 (53.3)	37 (48.1)
Disease type, n (%)			
Operable	53 (72.6)	54 (72.0)	49 (63.6)
Locally advanced	15 (20.5)	17 (22.7)	24 (31.2)
Inflammatory	5 (6.8)	4 (5.3)	4 (5.2)
HER2 IHC 0 and 1+, n (%)	1 (1.4)	0 (0.0)	0 (0.0)
2+, n (%)	5 (6.8)	1 (1.3)	2 (2.6)
3+, n (%)	67 (91.8)	74 (98.7)	75 (97.4)
HER2 FISH-positive, n (%)	69 (94.5)	69 (92.0)	73 (94.8)
FISH-negative, n (%)	0 (0.0)	1 (1.3)	2 (2.6)
Unknown, n (%)	4 (5.5)	5 (6.7)	2 (2.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; FISH, fluorescence *in situ* hybridization; H, trastuzumab; IHC, immunohistochemistry; P, pertuzumab; PR, progesterone receptor; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

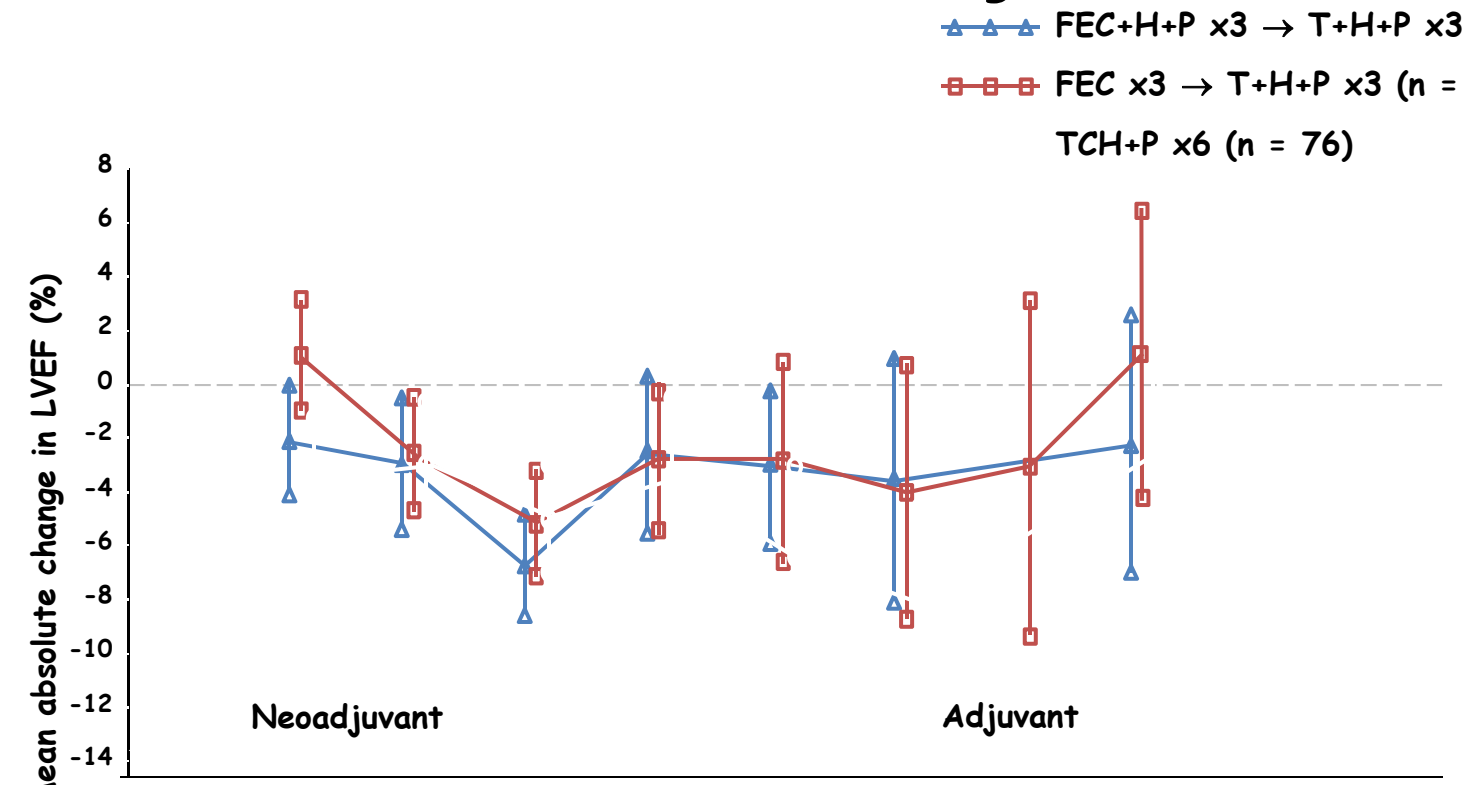
Cardiac events during neoadjuvant treatment

	FEC+H+P x3 → T+H+P x3 n = 72	FEC x3 → T+H+P x3 n = 75	TCH+P x6 n = 76
Symptomatic LVSD (grade ≥3), n (%)	0 (0.0)	2 (2.7)	0 (0.0)
LVSD (all grades), n (%)	4 (5.6)	3 (4.0)	2 (2.6)
LVEF decline ≥10% points and below 50%, n (%)	3 (4.2)	4 (5.3)	3 (3.9)

FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Mean change in LVEF

Central readings



Cycle	2	4	6	10	12	15	18	End of treatment	
Patients with assessment, n	66	64	69	36	34	19		15	FEC+H+P x3 → T+H+P x3
	65	58	65	33	27	18	13	10	FEC x3 → T+H+P x3
	62	62	68	35	28	17		16	TCH+P x6

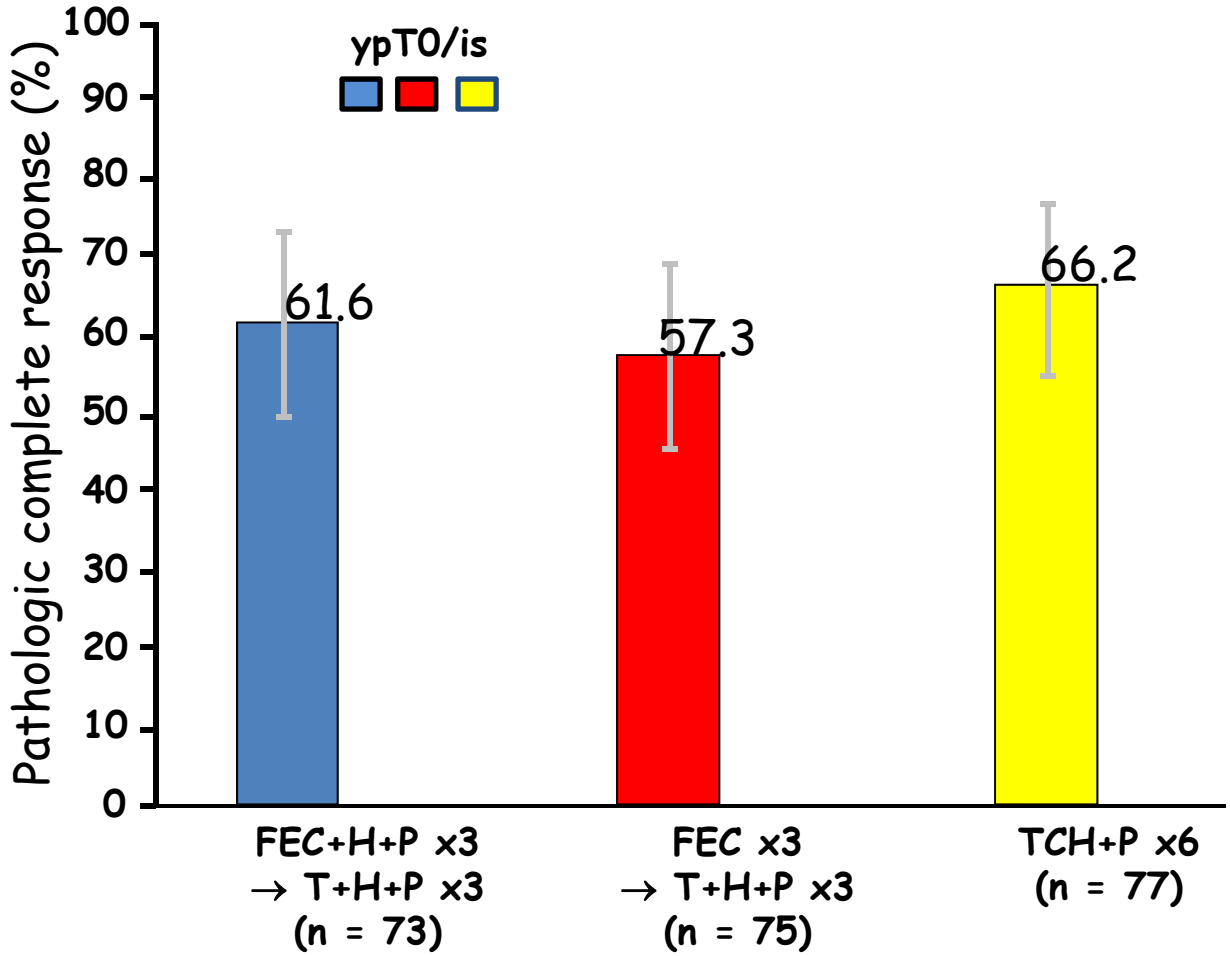
FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; LVEF, left ventricular ejection fraction; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

10 most common grade ≥3 adverse events excluding cardiac events during neoadjuvant treatment

Adverse event, n (%)	FEC+H+P x3 → T+H+P x3 n = 72	FEC x3 → T+H+P x3 n = 75	TCH+P x6 n = 76
Neutropenia	34 (47.2)	32 (42.7)	35 (46.1)
Febrile neutropenia	13 (18.1)	7 (9.3)	13 (17.1)
Leukopenia	14 (19.4)	9 (12.0)	9 (11.8)
Diarrhea	3 (4.2)	4 (5.3)	9 (11.8)
Anemia	1 (1.4)	2 (2.7)	13 (17.1)
Thrombocytopenia	0 (0.0)	0 (0.0)	9 (11.8)
Vomiting	0 (0.0)	2 (2.7)	4 (5.3)
Fatigue	0 (0.0)	0 (0.0)	3 (3.9)
Alanine aminotransferase inc.	0 (0.0)	0 (0.0)	3 (3.9)
Drug hypersensitivity	2 (2.8)	0 (0.0)	2 (2.6)

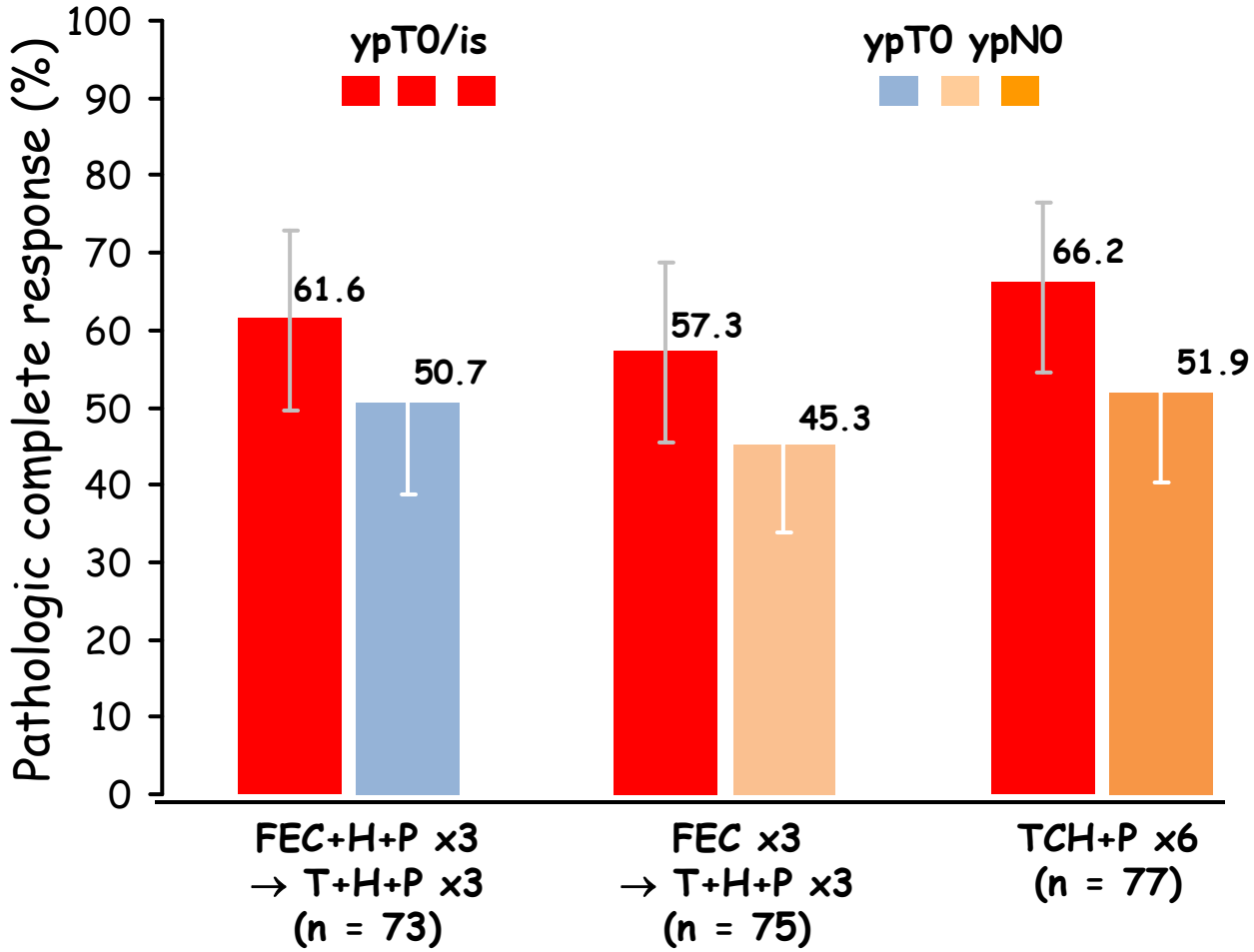
FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; inc., increased; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Pathologic complete response



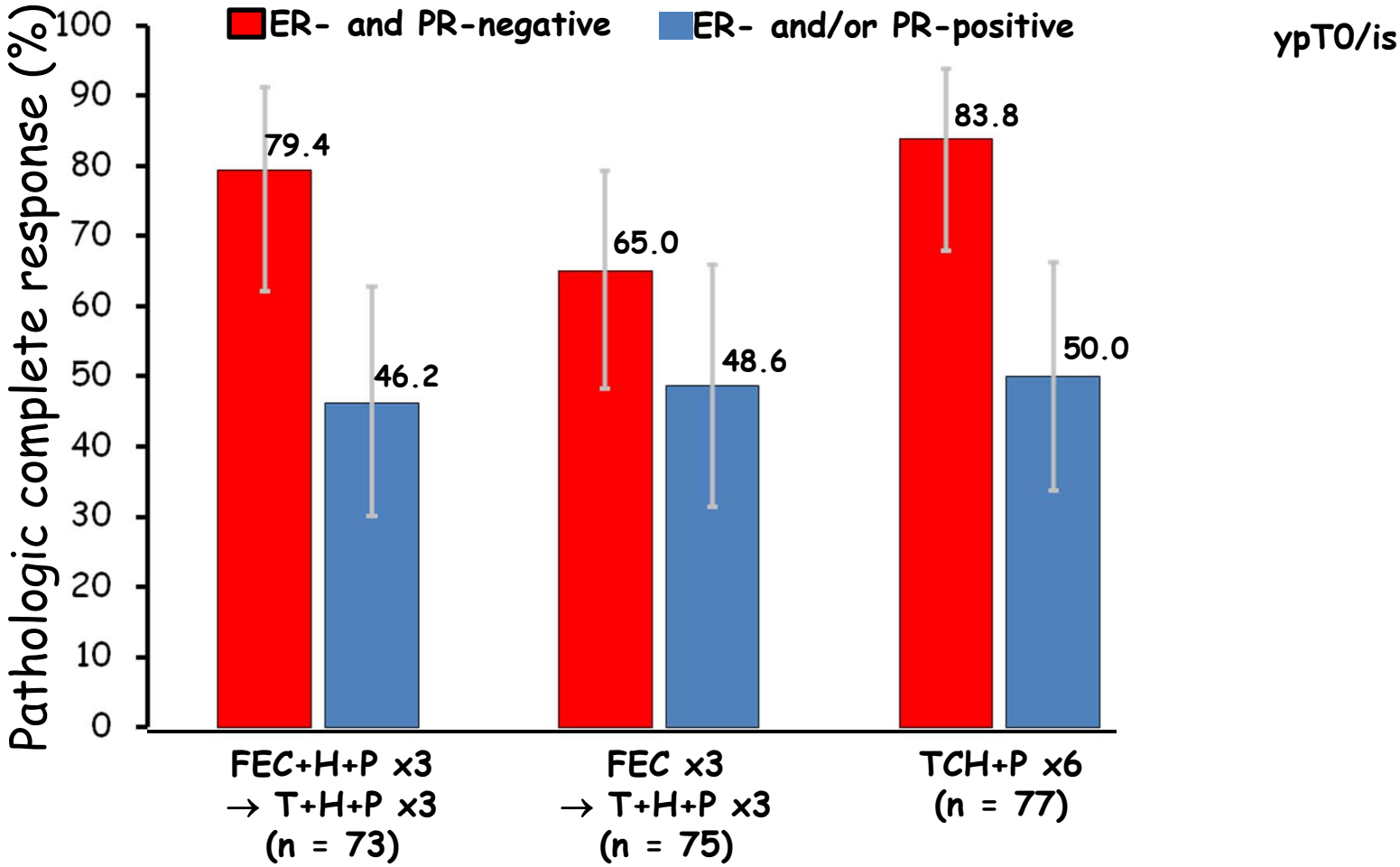
FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Pathologic complete response



FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Pathologic complete response by hormone receptor status



ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; PR, progesterone receptor; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

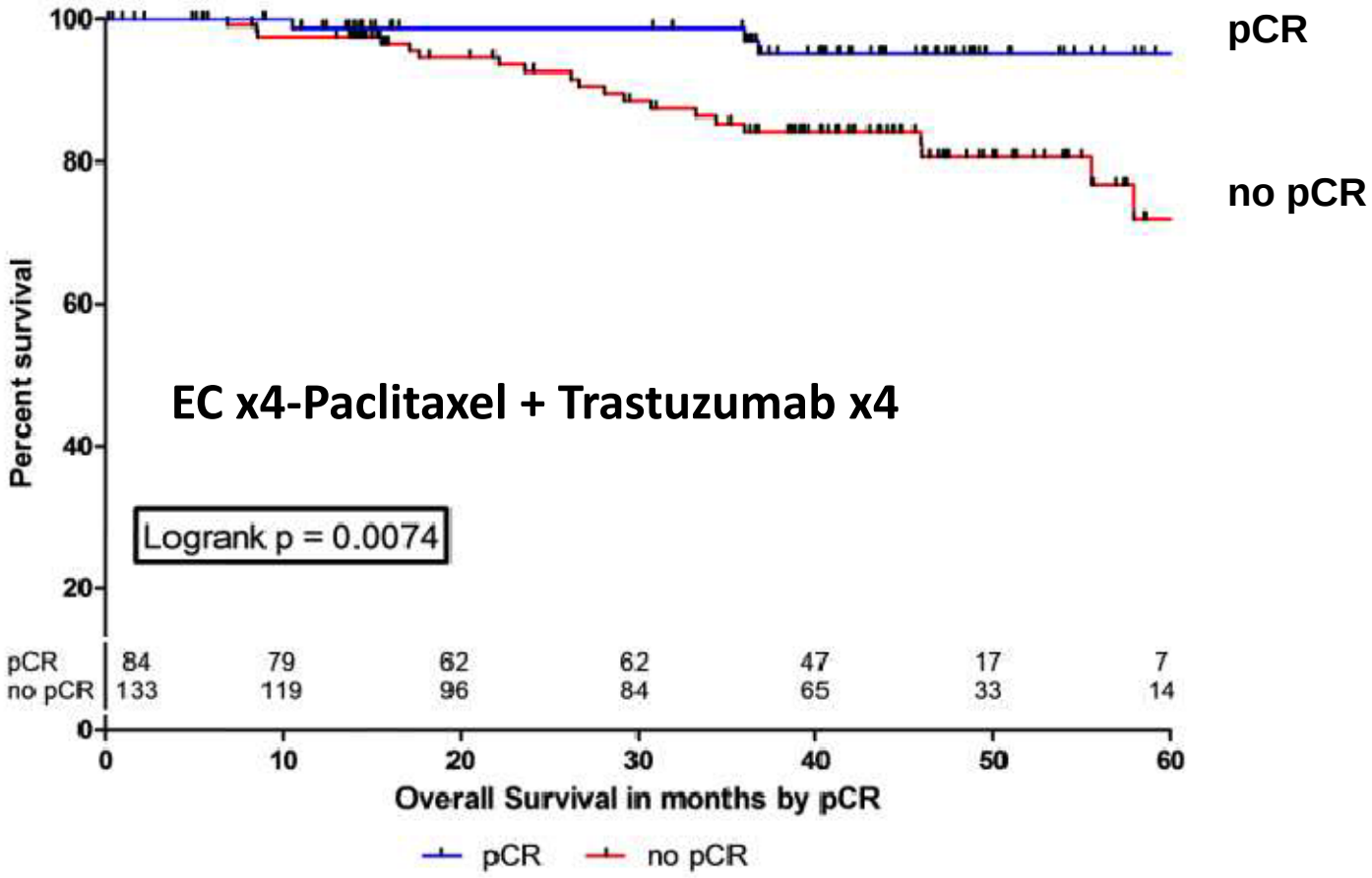
Summary and conclusions

- Results from TRYPHAENA indicate a low incidence of symptomatic and asymptomatic LVSD across all arms
  - Concurrent administration of pertuzumab plus trastuzumab with epirubicin resulted in similar cardiac tolerability compared with sequential administration or the anthracycline-free regimen
- Neutropenia, febrile neutropenia, leukopenia, and diarrhea were most frequently reported adverse events (grade ≥3) across all arms
- Regardless of chemotherapy chosen, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates (57–66%)
- Lower PCR in HR-positive versus HR-negative
- TRYPHAENA supports the ongoing APHINITY study, a Phase III trial to evaluate pertuzumab and trastuzumab plus standard chemotherapy in the adjuvant setting (NCT01358877)

Comparison of survival according to pathological complete response (pCR) in patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy with and w/o trastuzumab compared to patients with HER2-negative tumors

Loibl et al
Abstract S5-4

TECHNO Study - Overall Survival



Untch et al. J Clin Oncol 2011; 29:3351

Objectives

Definition of three subgroups:

- HER2-positive with trastuzumab
- HER2-positive without trastuzumab
- HER2-negative

Compare DDFS and OS in these subgroups:

- pCR vs. no pCR
- hormone receptor positive and -negative tumors

Methods

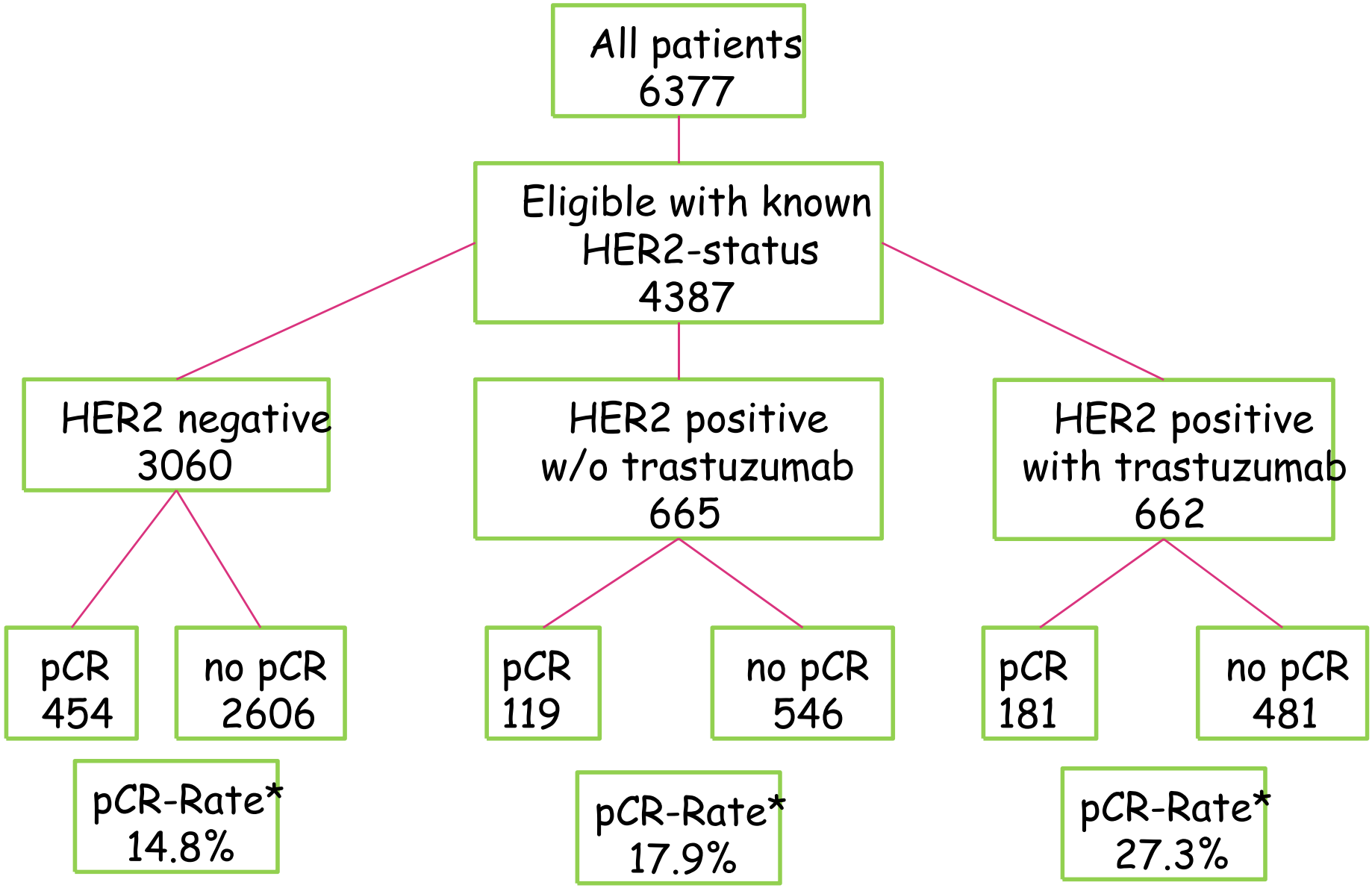
All neoadjuvant trials with follow-up were included

Known HER2 status (locally or centrally assessed)

Hormone receptor positivity was defined as ≥ 10% cells positive for estrogen and/or progesterone receptor (locally or centrally assessed)

pCR defined as no invasive and no non-invasive residuals in breast and lymph nodes (ypT0 ypN0)

Adjustment for trial

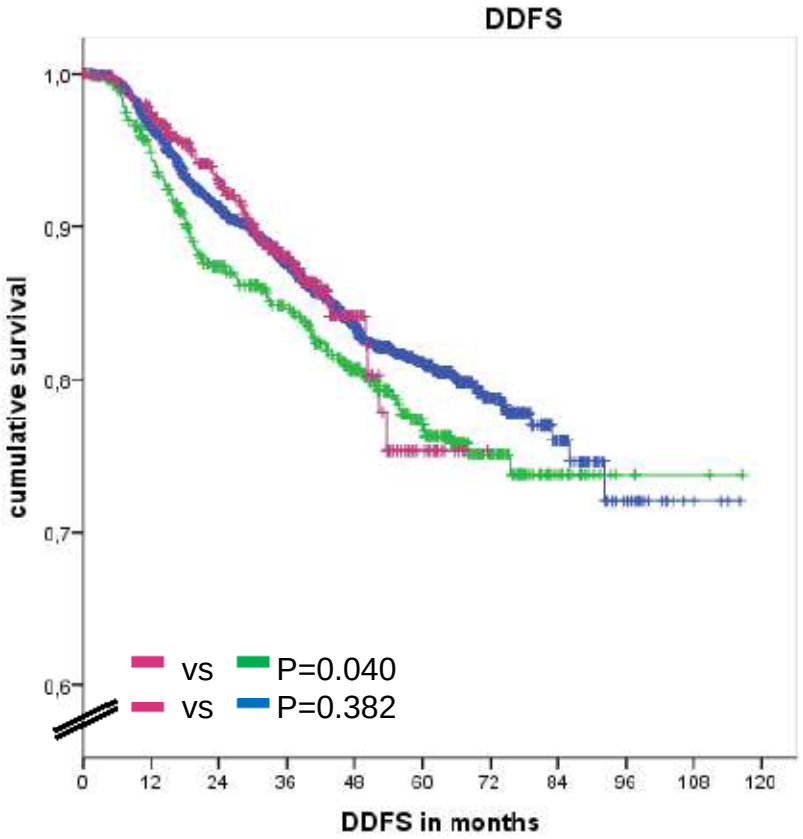


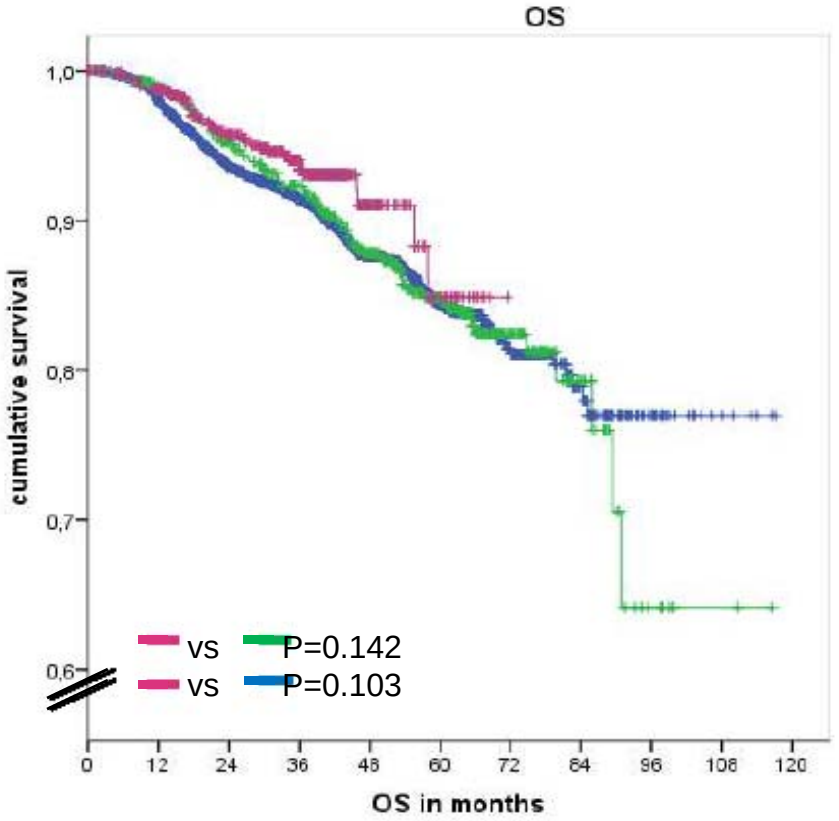
*ypT0 ypN0

Patients´ Characteristics

Age median	49 (22-81) years
	%
cT1-3	87
cN+	53
Ductal invasive	82
Grading 3	40
Hormone receptor positive	66
HER2-negative	70

DDFS and OS in the three subgroups



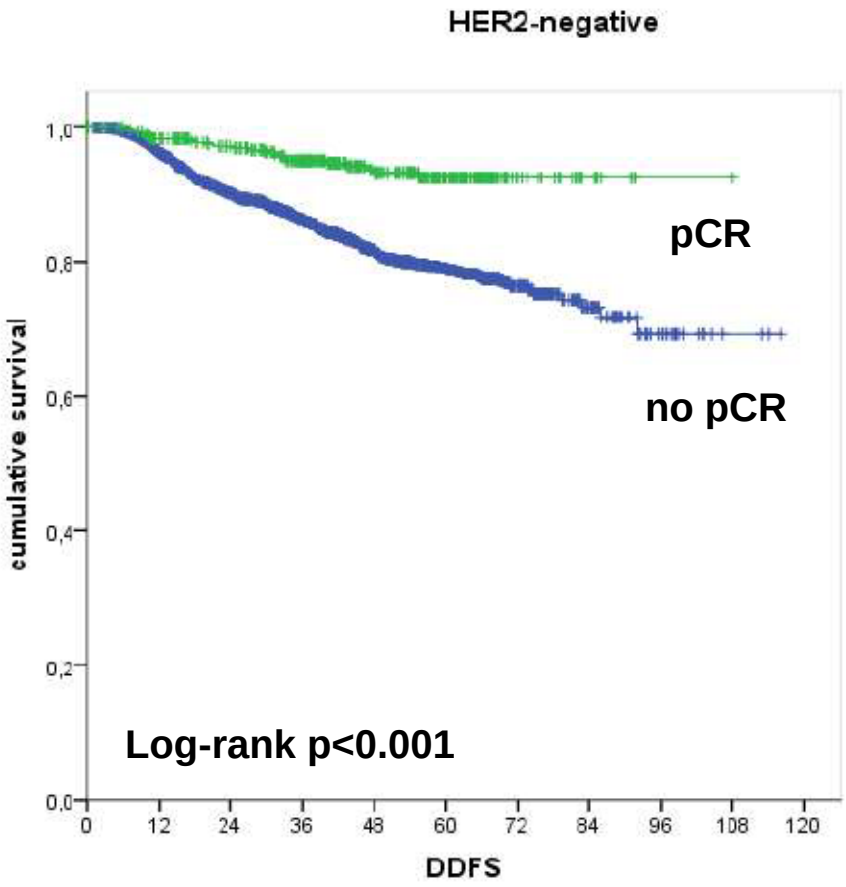


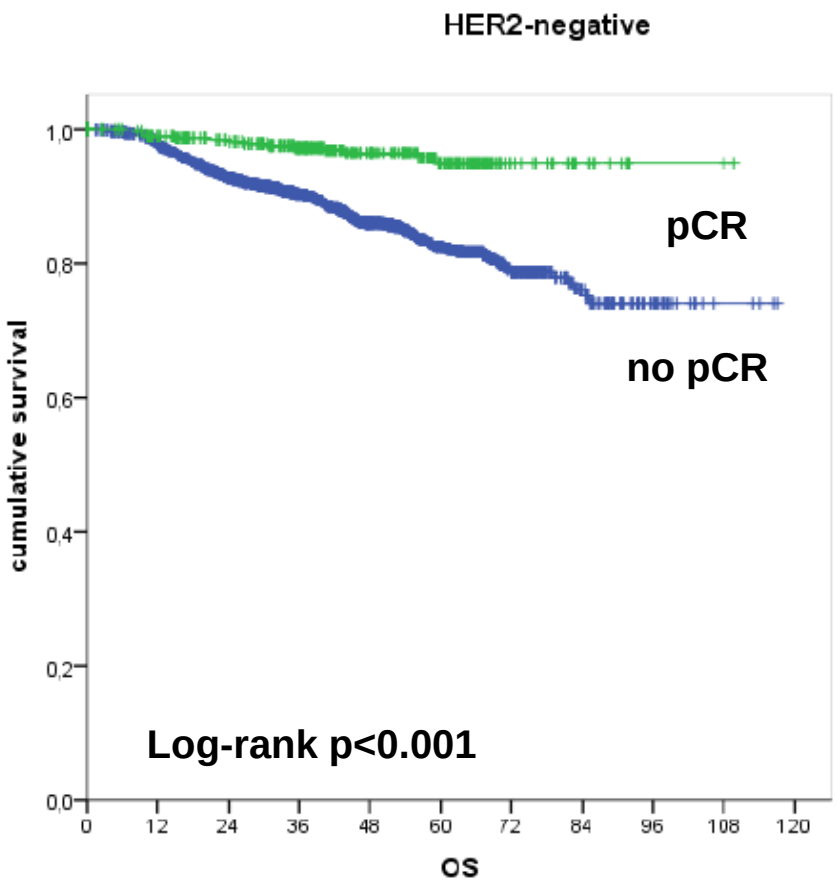
- n= 662 HER2+ with trastuzumab
- n= 3060 HER2 negative
- n= 665 HER2+; no trastuzumab

AGO-B BREAST STUDY GROUP

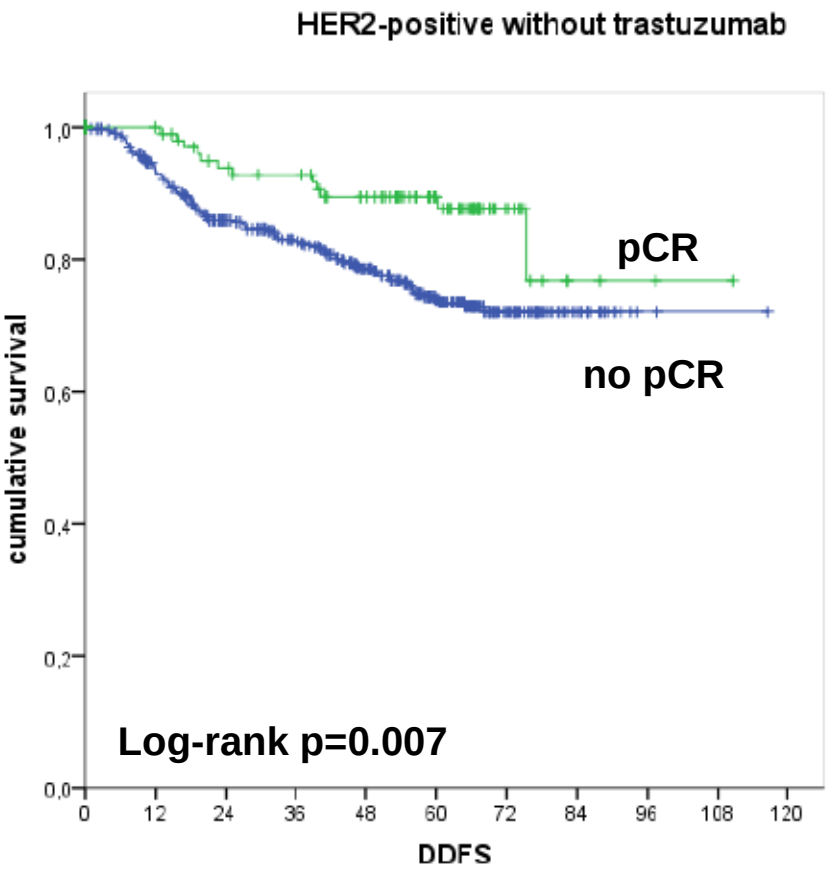
GBG GERMAN BREAST GROUP

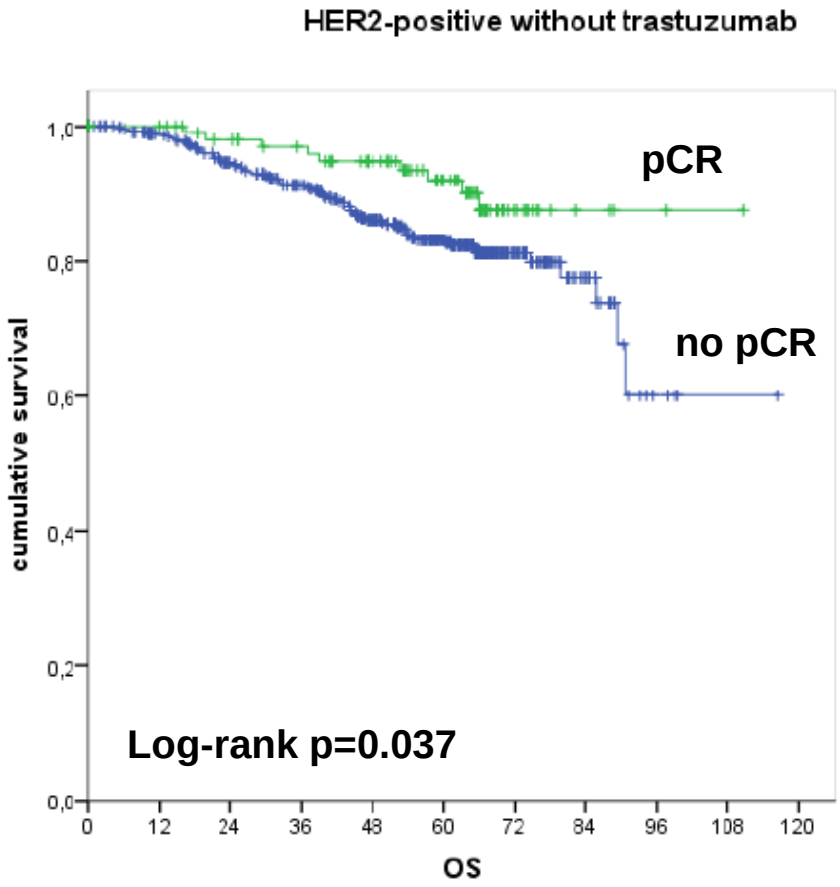
DDFS and OS by pCR – HER2-negative



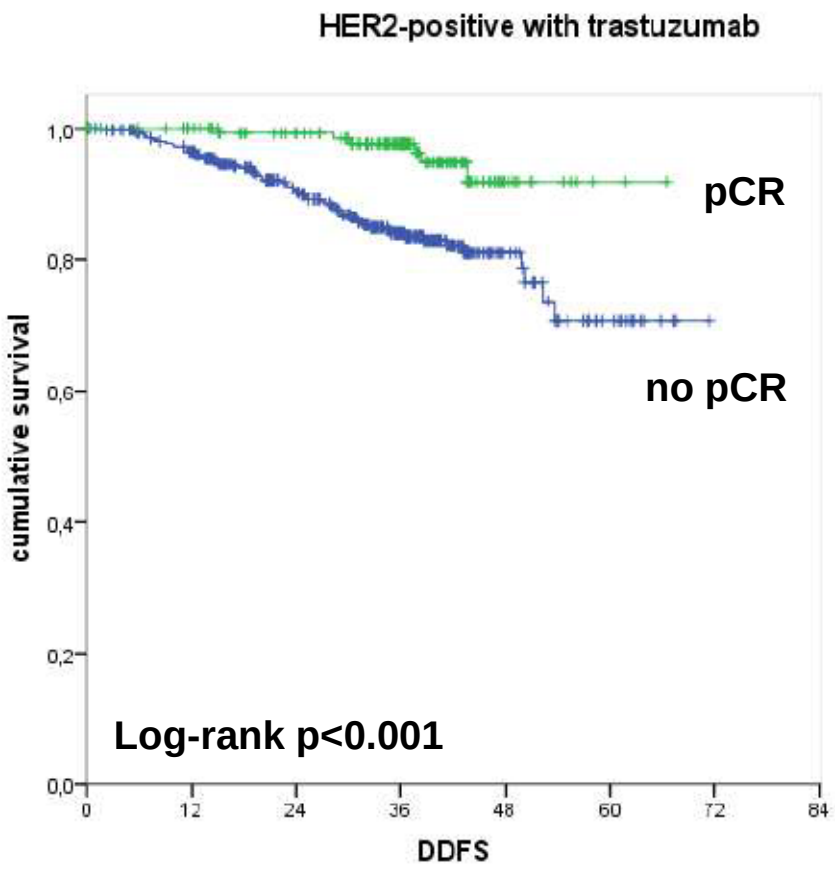


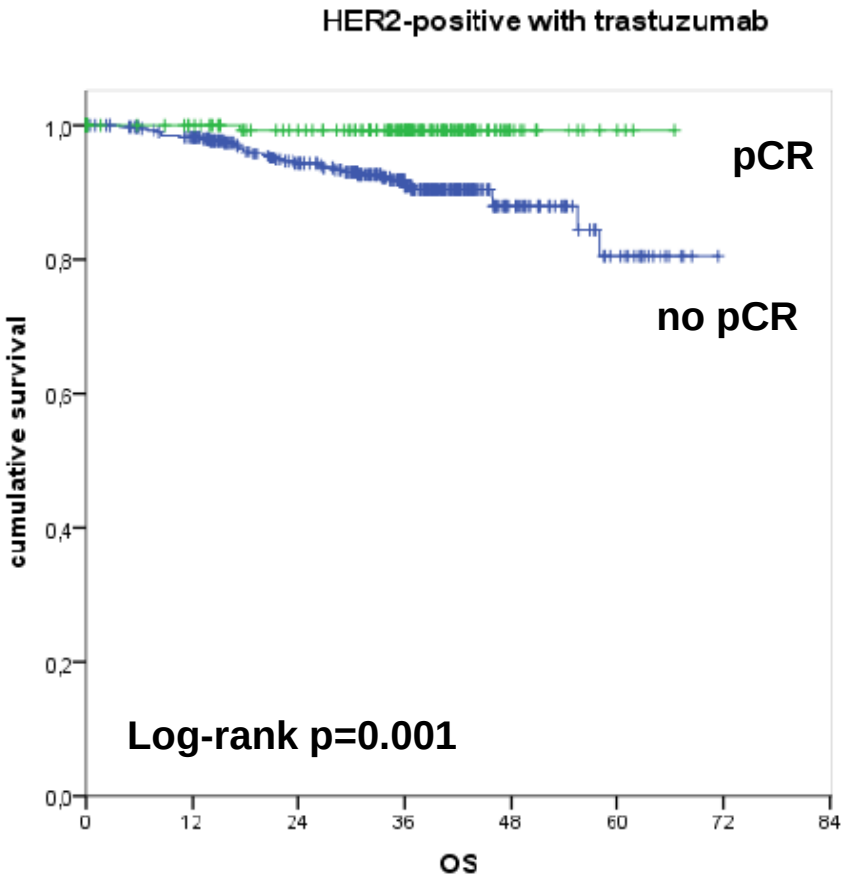
DDFS and OS by pCR – HER2-positive Without Trastuzumab





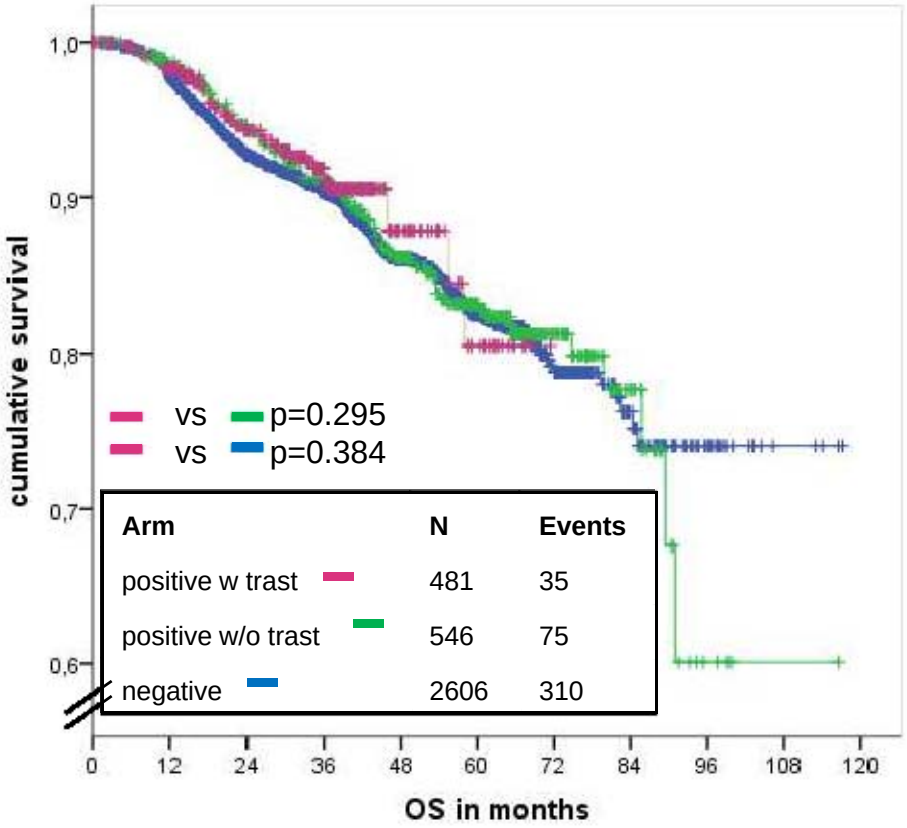
DDFS and OS by pCR – HER2-positive with Trastuzumab



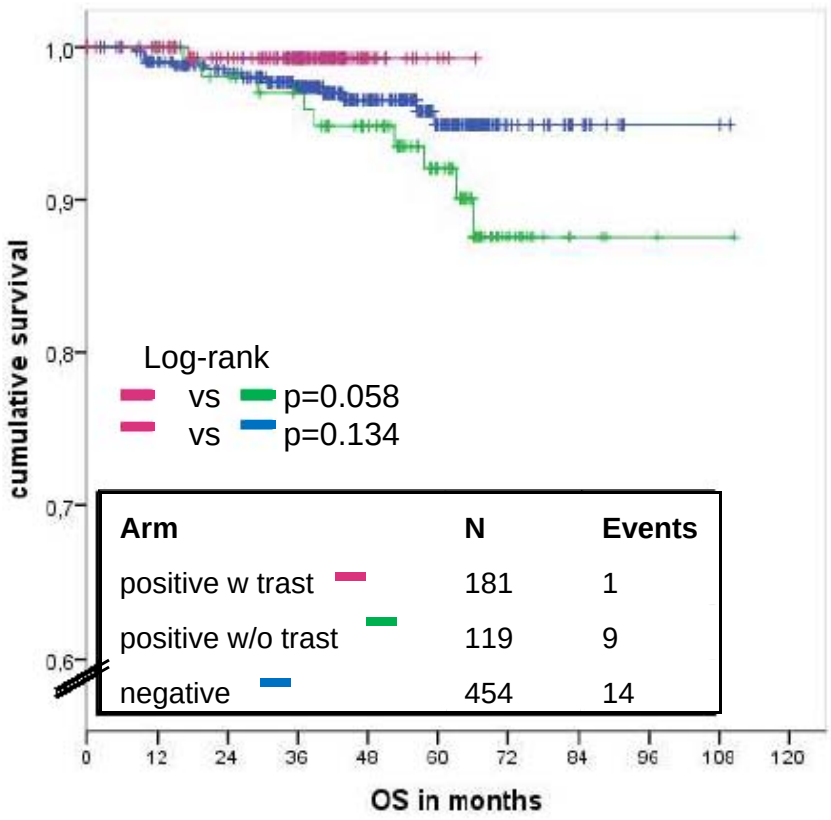


OS analysis by pCR

No pCR



pCR



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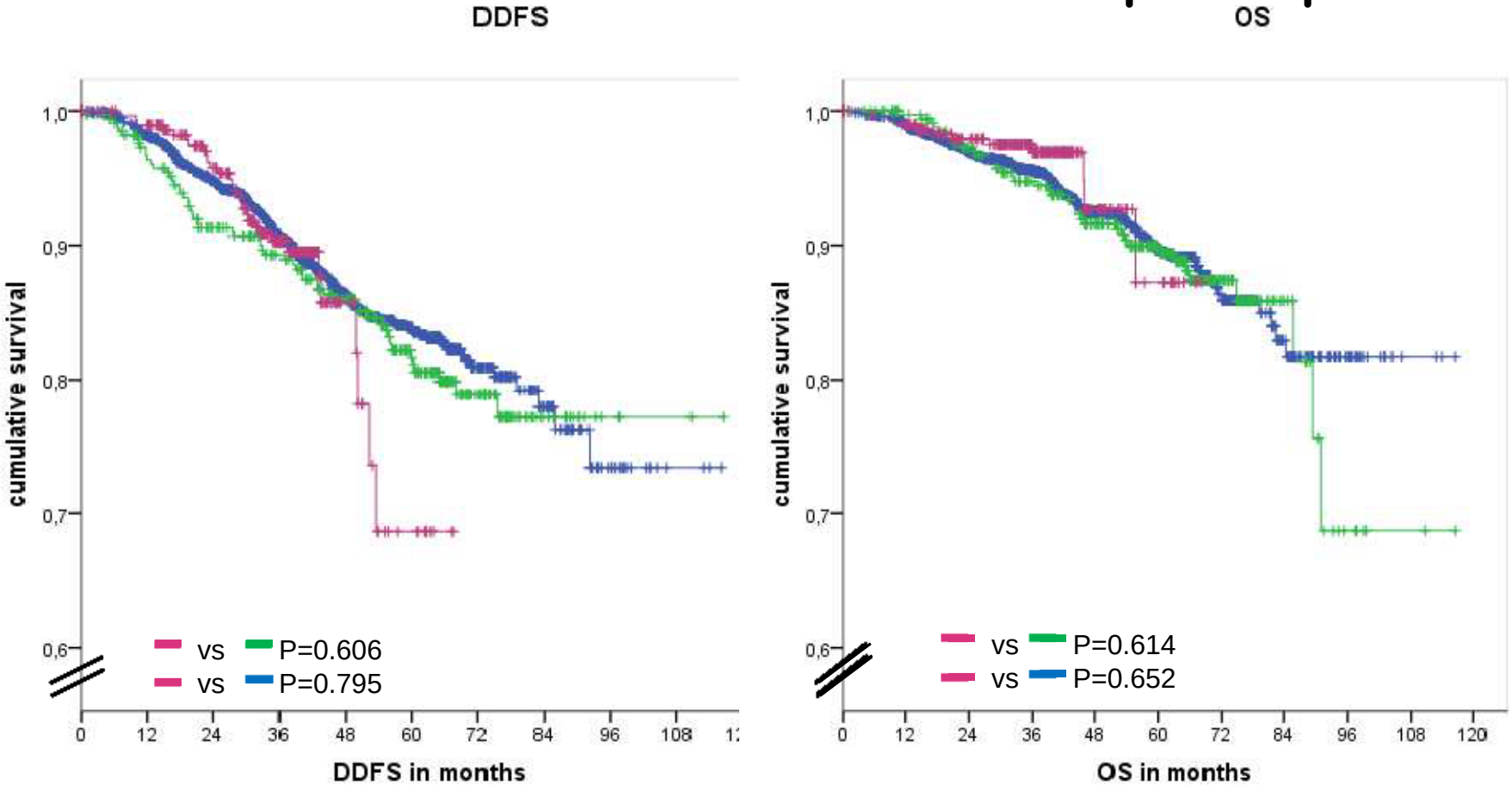
GBG GERMAN BREAST GROUP

DDFS and OS in Hormone Receptor-positive



n= 662 HER2+ with trastuzumab
n= 3060 HER2 negative
n= 665 HER2+; no trastuzumab

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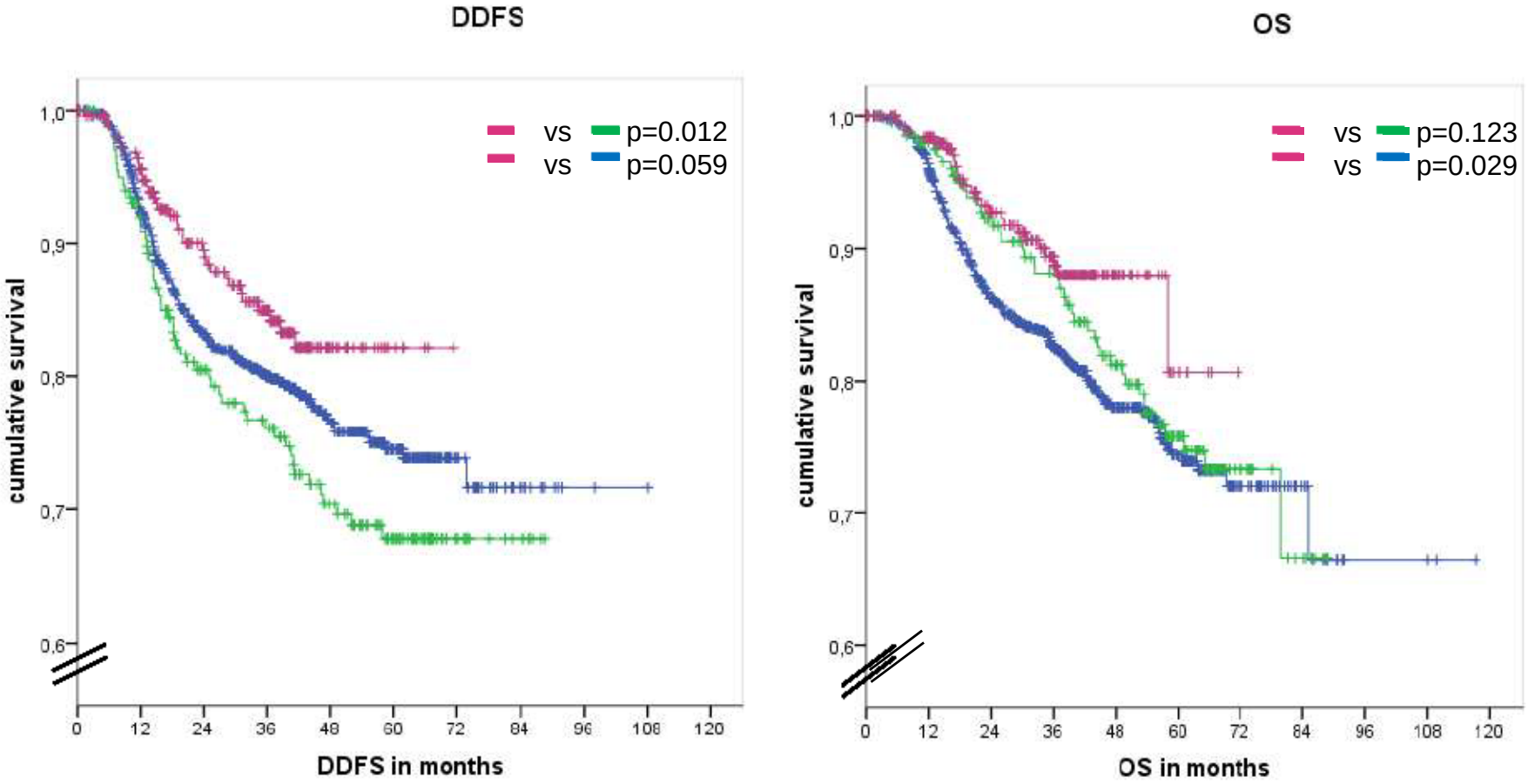
DDFS and OS in Hormone Receptor Negative



n= 662 HER2+ with trastuzumab
n= 3060 HER2 negative
n= 665 HER2+; no trastuzumab

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Summary

Patients with HER2-positive primary breast cancer treated with trastuzumab and chemotherapy achieve a higher pCR rat

DDFS and OS was significantly better with pCR in HER2-negative, HER2-positive non- trastuzumab and HER2-positive trastuzumab patients

In pCR patients OS tended to be superior with trastuzumab compared to HER2-positive, non-trastuzumab and HER2-negative patients

In particular HER2-positive, hormone receptor negative patients have a better DDFS and OS compared to HER2-positive, non-trastuzumab and HER2-negative patients

Neoadjuvant chemotherapy adapted by interim response improves overall survival of primary breast cancer patients – Results of the GeparTrio trial.

von Minckwitz et al

Abstract 3-2

Aims

To take advantage from the in vivo chemo-sensitivity test situation of neoadjuvant treatment

To develop specific treatment strategies for patients with or without response to 2 cycles TAC:

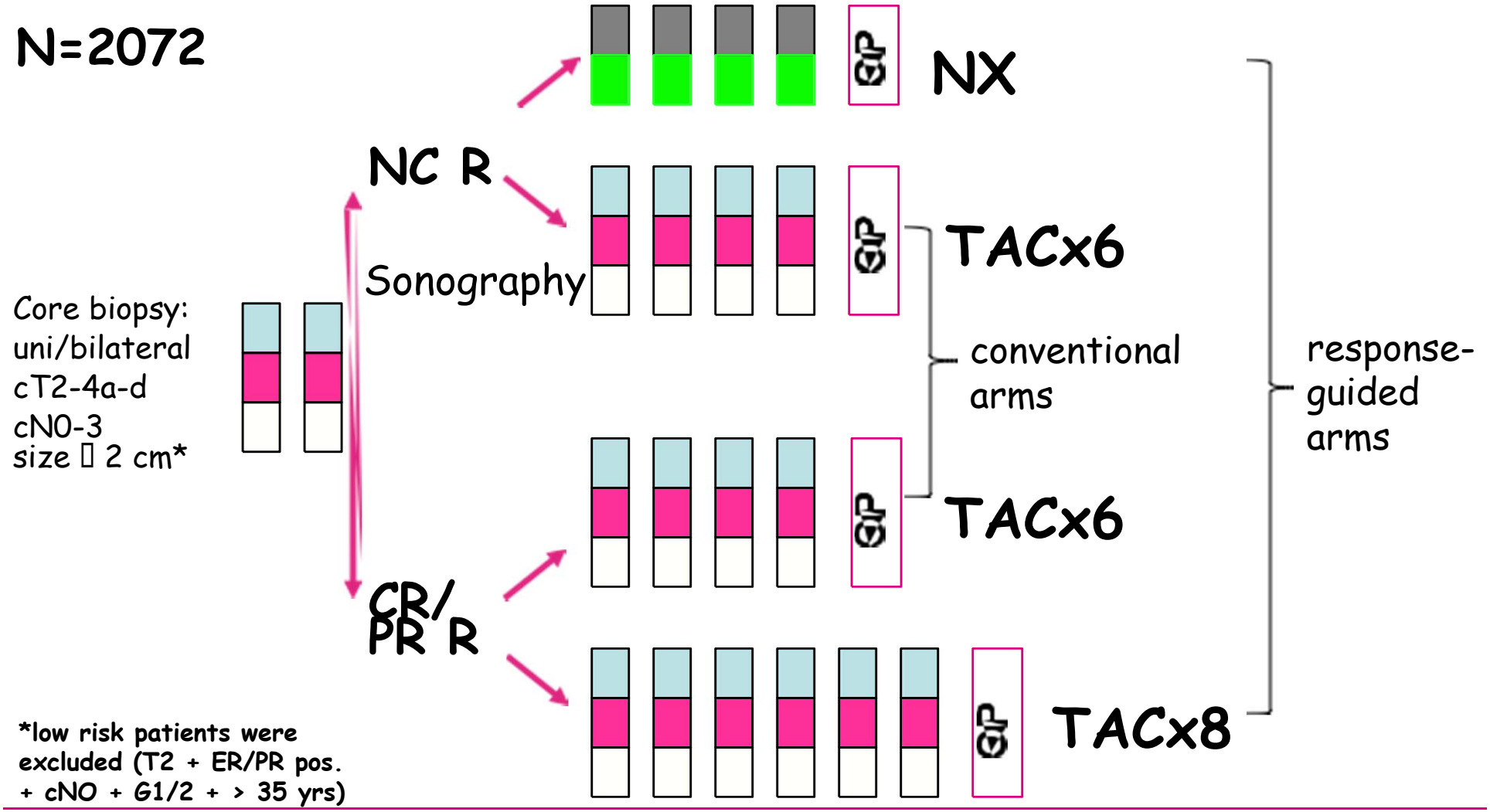
Responding patients:

→ treatment intensification by increased cycle number

Non-responding patients:

→ switch to non-cross resistant treatment

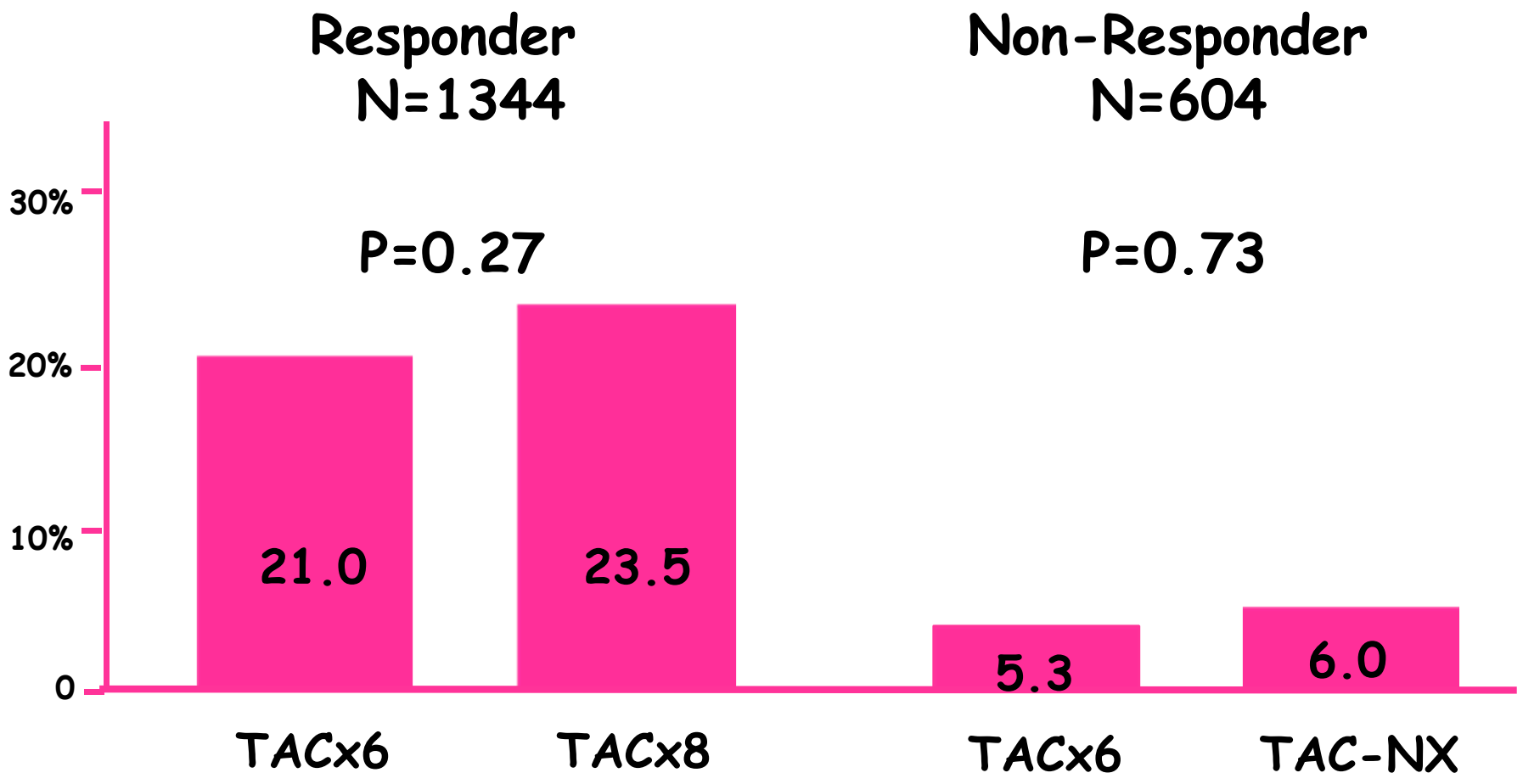
GeparTrio Trial Design



*low risk patients were excluded (T2 + ER/PR pos. + cNO + G1/2 + > 35 yrs)

von Minckwitz et al, JNCI 100: 542, 2008
von Minckwitz et al. JNCI 100; 552, 2008

Short Term Efficacy (pCR = ypT0 ypN0)



von Minckwitz et al, JNCI 100: 542, 2008
von Minckwitz et al. JNCI 100; 552, 2008

Objectives

Primary:

- Pathologic response (responder)
- Sonographic response (non-responder)

Secondary (actual with median follow up of 62 months):

- **To determine 5-year DFS and OS**
- **To examine treatment effects by breast cancer phenotype (post-hoc analysis)**

Study Population

Characteristic	Conventional TACx6 N=1025 %	Response-guided TACx8 or TAC-NX N=987 %
Age < 40 years	16.9	18.2
cT> 40 mm	60.5	61.5
cT4a-c	9.0	8.7
cT4d	4.6	4.3
cN +	55.3	54.7
Lobular type	13.8	13.1
Grade 3	41.0	35.1
HR-negative	36.8	34.4
HER2-positive	30.5	29.1

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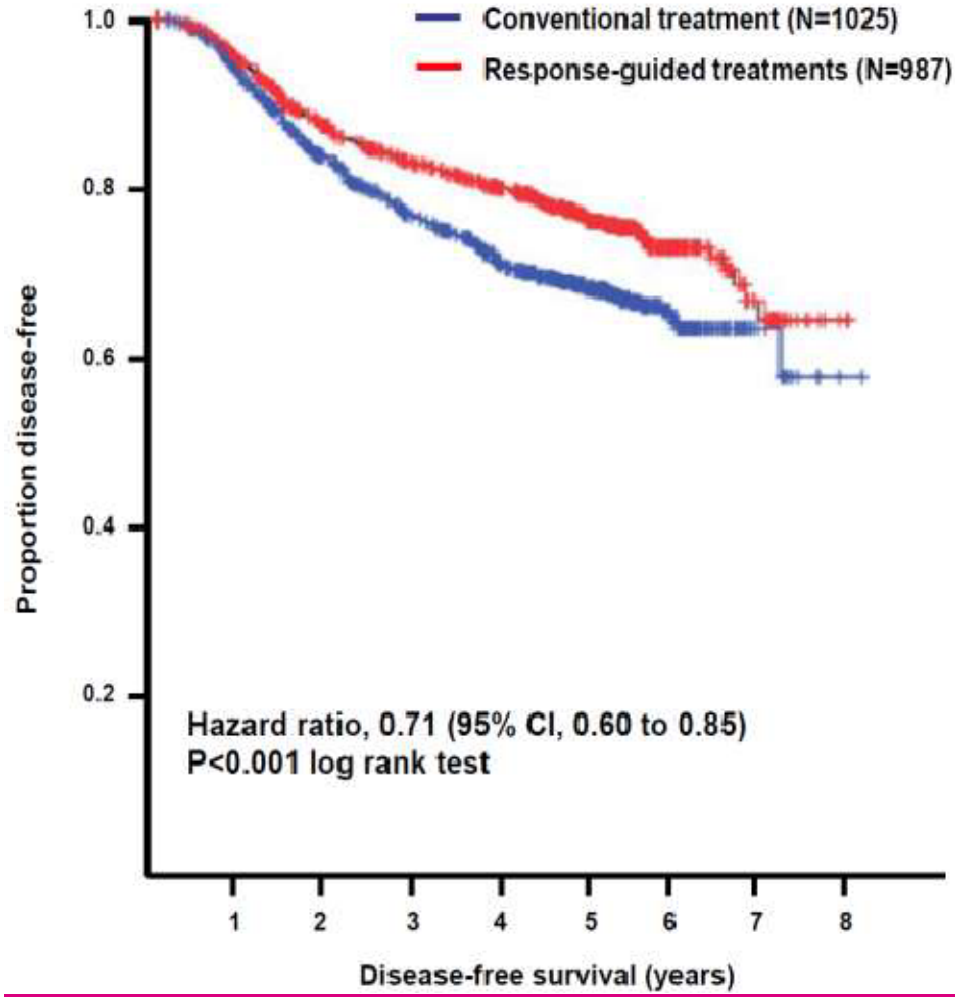
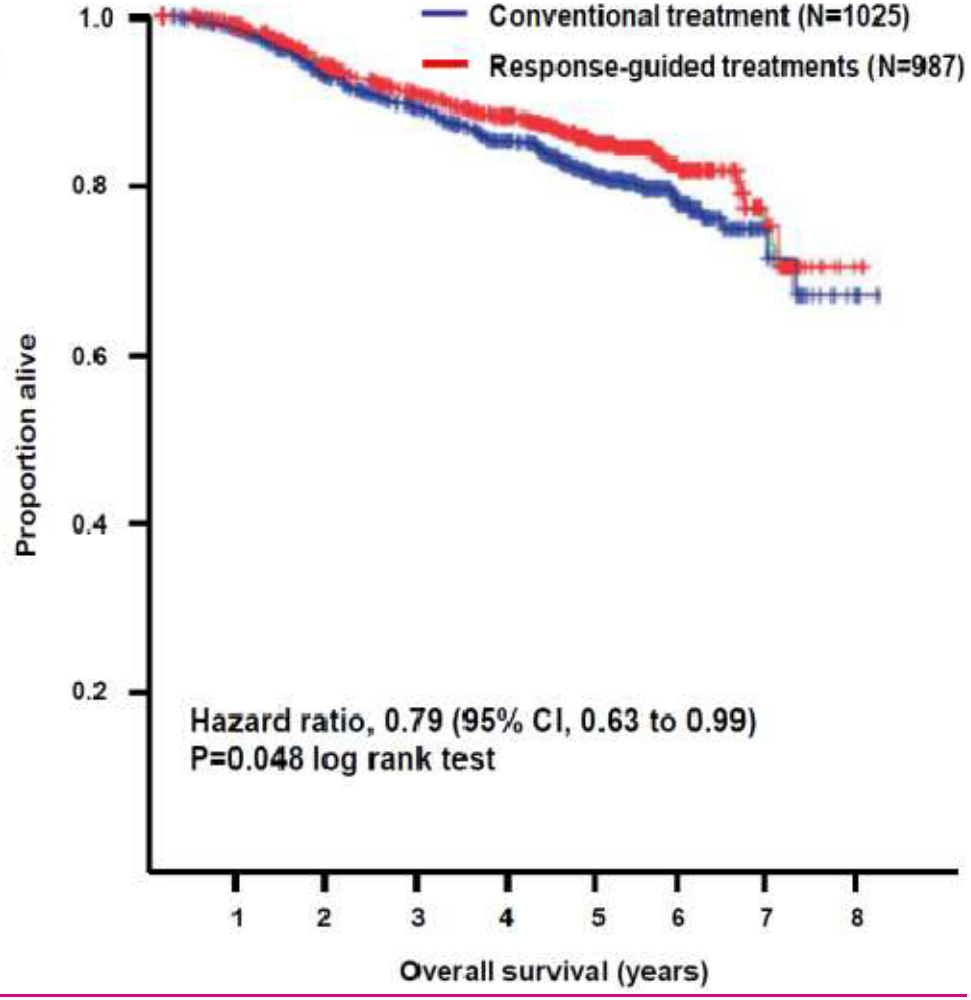
DFS and OS after conventional (TACx6) vs. response-guided (TACx8/TAC-NX) treatment



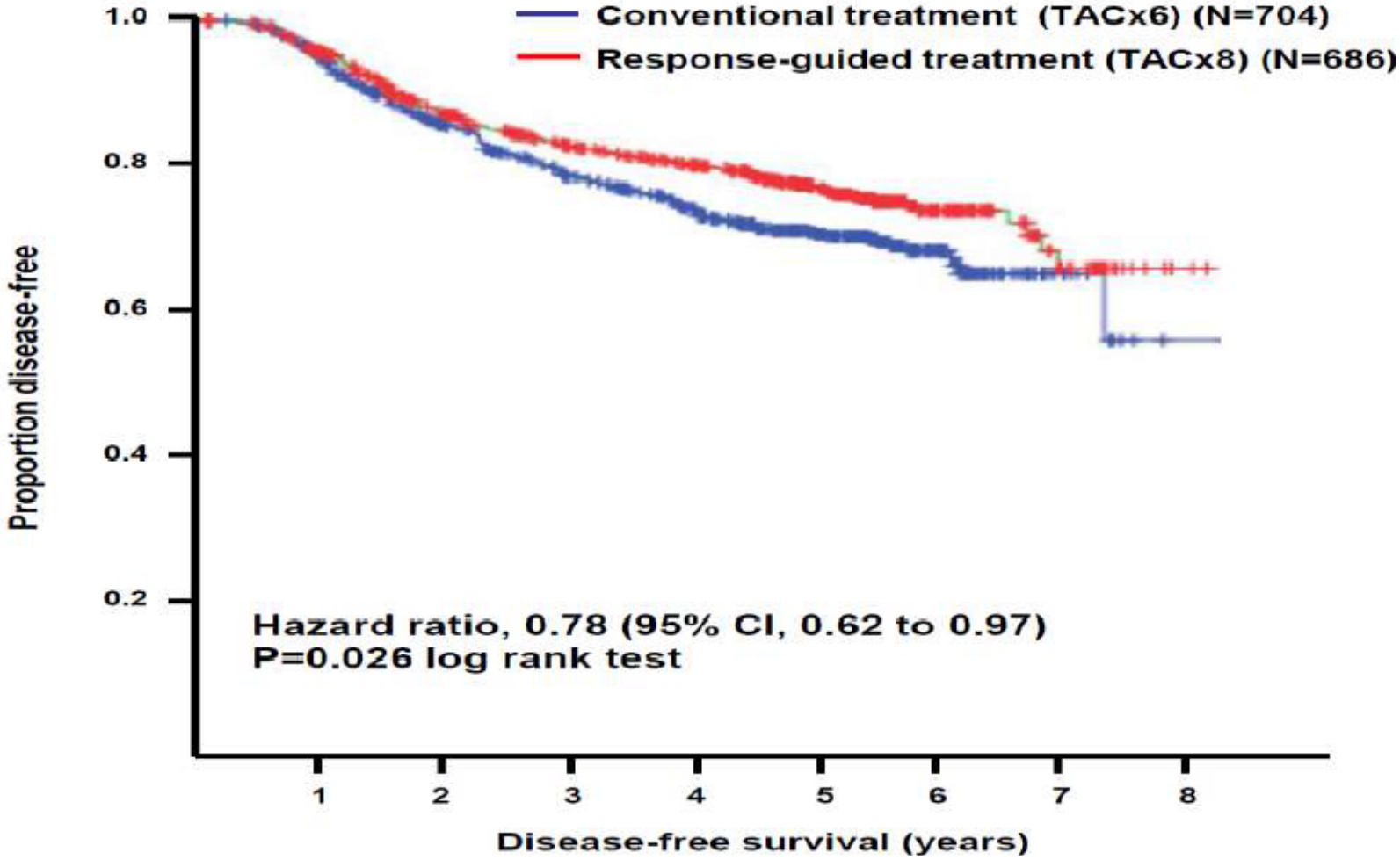


Median follow up 62 months

Adjusted Analysis for DFS

Variable	Group	HR	p-value
Treatment	Response-guided	0.71	0.001
Age	≥40 years	0.92	0.6
T-stage	cT1-3	0.60	<0.001
T-size	<40 mm	0.81	0.08
cN	negative	0.56	<0.001
Histological type	lobular	0.99	0.9
Grade	1-2	0.84	0.12
HR	positive	0.49	<0.001
HER2	negative	0.88	0.3

DFS after TACx6 vs TACx8 in responding patients



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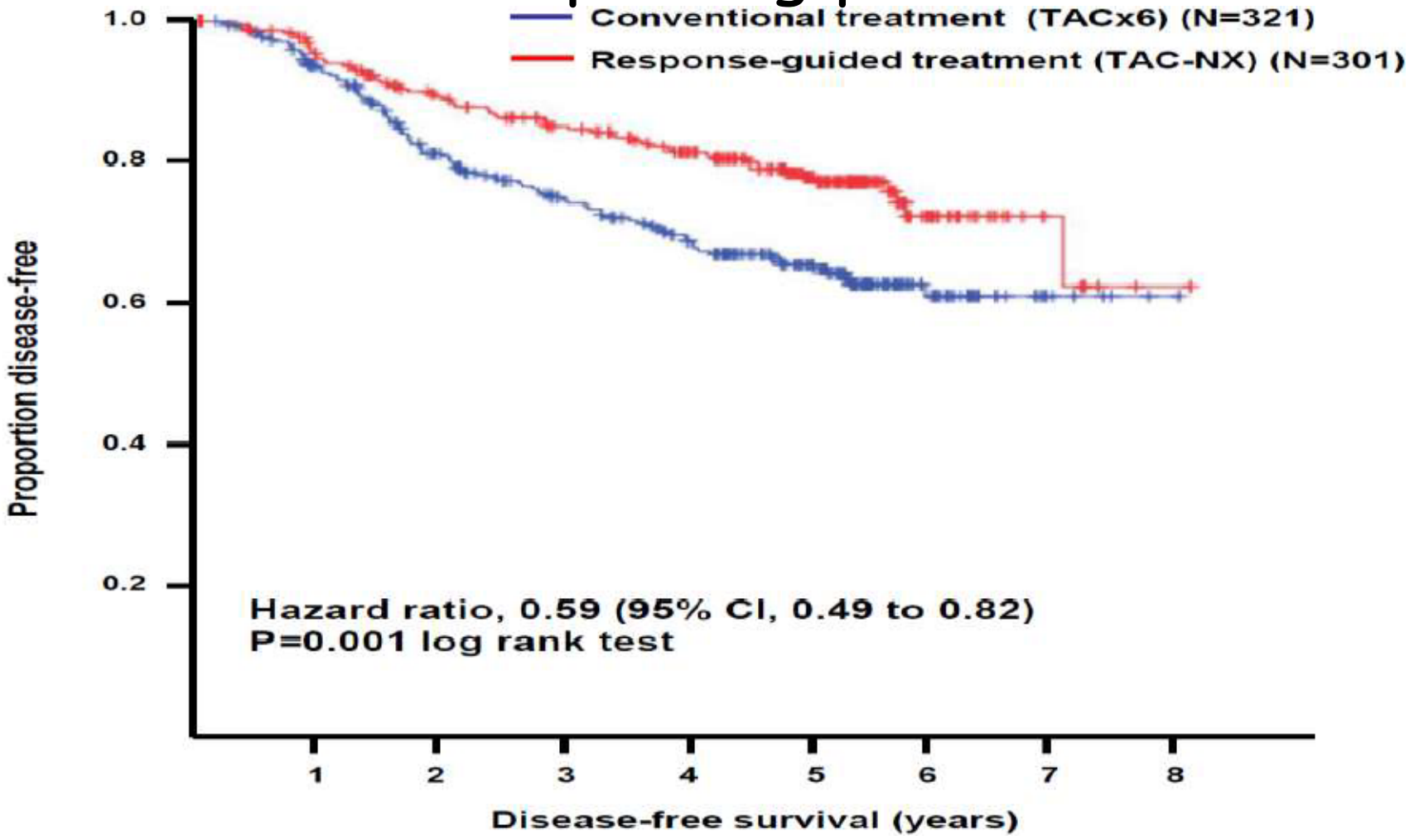
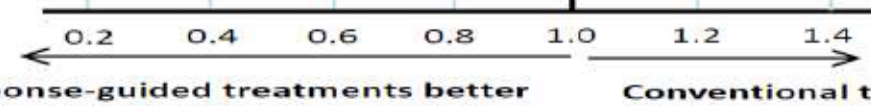
DFS after TACx6 vs TAC-NX in non-responding patients



Subgroup analysis comparing DFS after conventional vs response-guided treatment

Subgroup	N patients	Hazard ratio (95% CI)	Test for interaction
Overall	2012	0.74 (0.60-0.85)	
Age (years)			0.67
< 40	353	0.66 (0.42-1.03)	
≥ 40	1659	0.73 (0.60-0.88)	
cT-stage			0.66
cT1-3	1737	0.70 (0.56-0.85)	
cT4	267	0.79 (0.54-1.17)	
cT-size			0.22
<40 mm	775	0.62 (0.44-0.85)	
≥40 mm	1212	0.79 (0.63-0.98)	
cN status			0.19
Negative	894	0.84 (0.61-1.14)	
Positive		0.66 (0.53-0.82)	
Histological type			0.71
Ductal or other	1571	0.73 (0.60-0.88)	
Lobular	270	0.61 (0.37-1.03)	
Grade			0.25
1 or 2	1176	0.79 (0.61-1.01)	
3	725	0.65 (0.49-0.85)	
Hormone receptor status			0.008
Negative	717	0.94 (0.73-1.22)	
Positive	1295	0.56 (0.44-0.73)	
HER2 status			0.54
Negative	1145	0.63 (0.49-0.81)	
Positive	486	0.72 (0.51-1.04)	
Breast cancer phenotype			0.12
Luminal A	572	0.55 (0.37-0.82)	0.01*
Luminal B (HER2-)	211	0.40 (0.20-0.79)	
Luminal B (HER2+)	281	0.56 (0.33-0.96)	
HER2+ (non-luminal)	178	1.01 (0.61-1.67)	
Triple negative	362	0.87 (0.61-1.25)	



*comparing luminal vs non-luminal tumors
CI confidence interval

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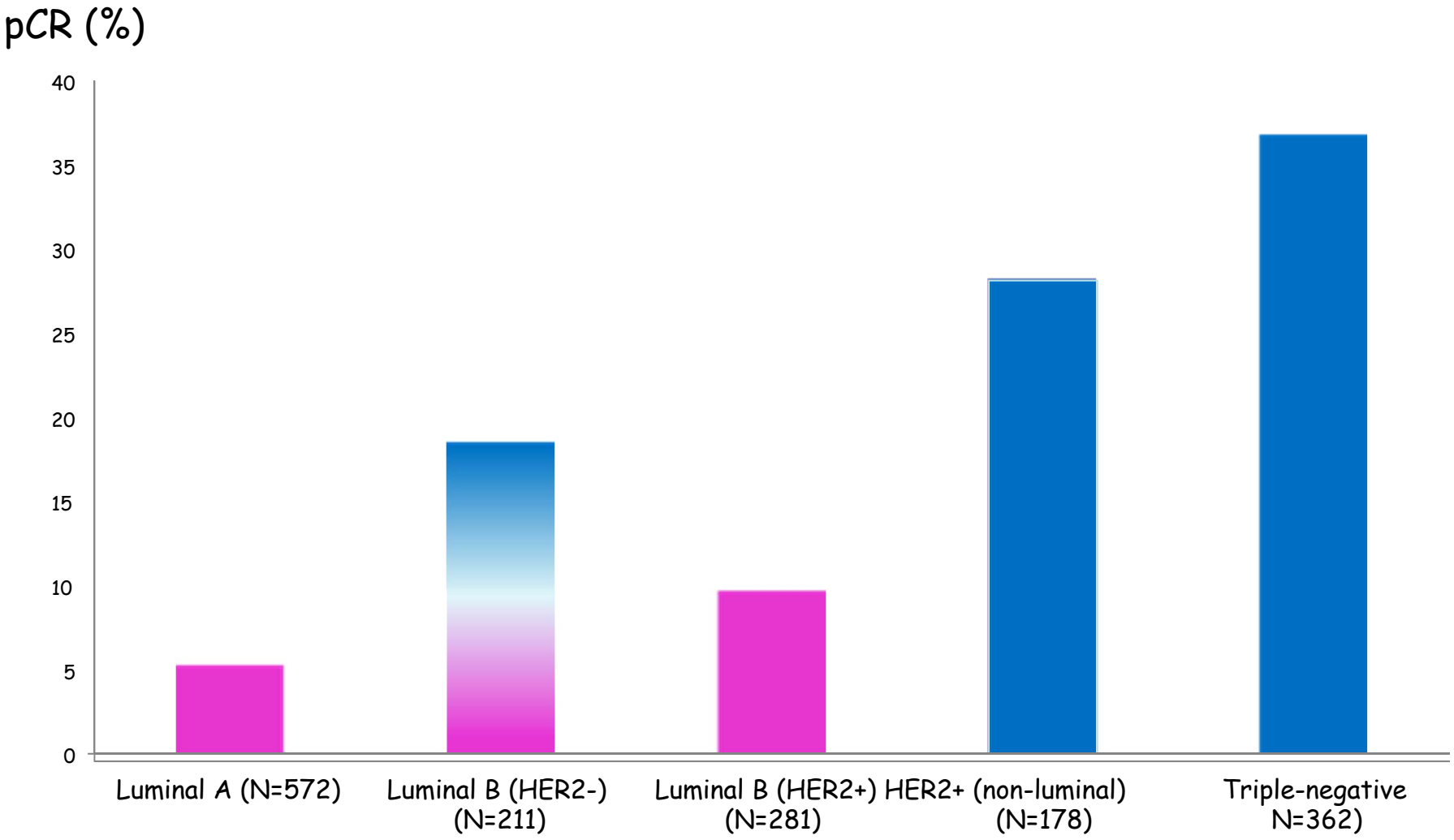
Breast Cancer phenotypes (St. Gallen definition*)

Phenotype	Definition	Conventional %	Response-guided %
Luminal A	HR+, HER2-, G1/2	34.4	37.1
Luminal B (HER2-)	HR+, HER2-, G3	13.5	12.8
Luminal B (HER2+)	HR+, HER2+	17.3	17.8
HER2+ (non-luminal)	HR-, HER2+	11.7	10.4
Triple-negative	HR-, HER2-	23.1	22.0
Missing		N=181	N=227

*Goldhirsch A, Ann Oncol 2011

pCR Rates by Subtype



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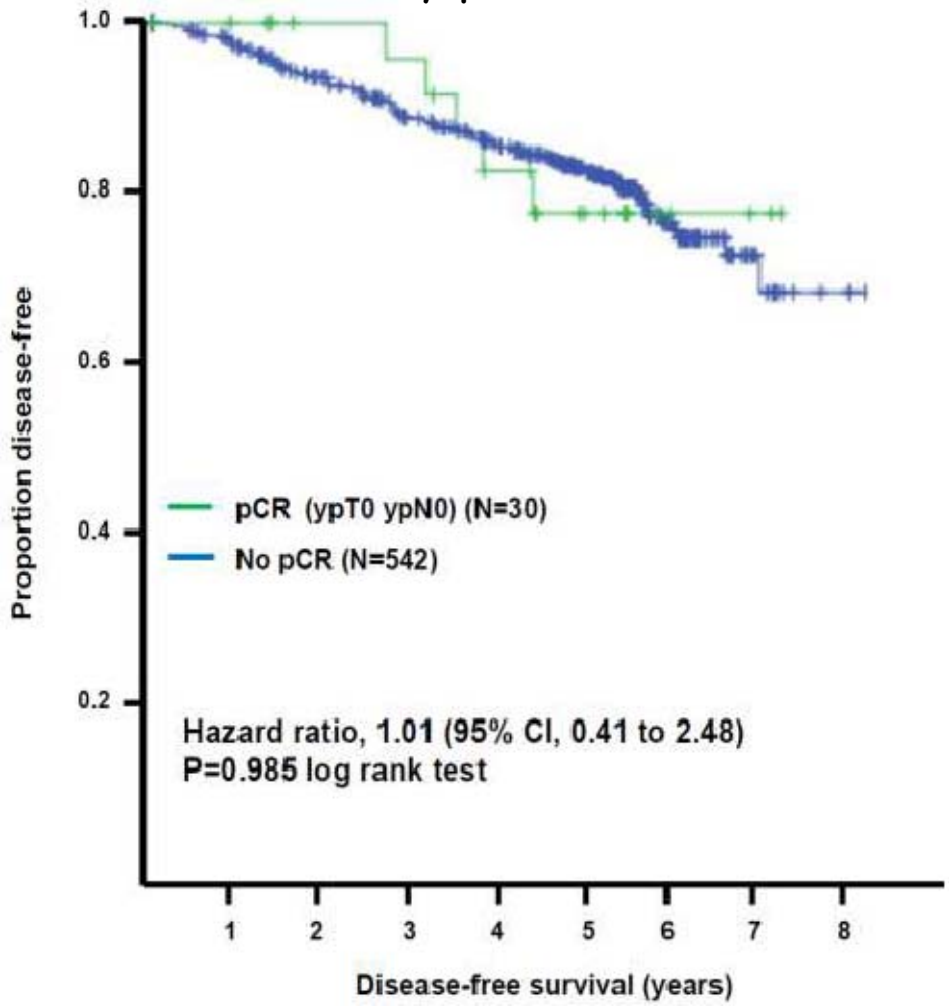
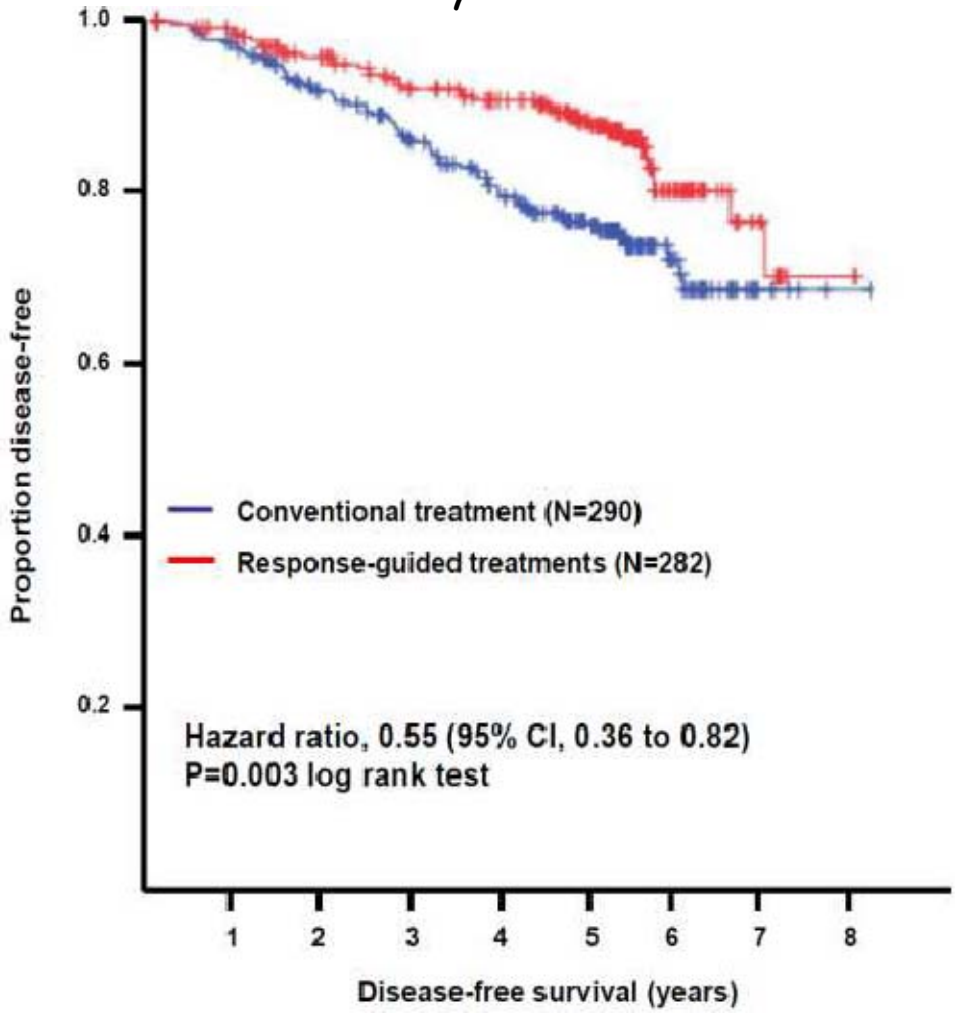
DFS in Luminal A tumors

by pCR



by treatment



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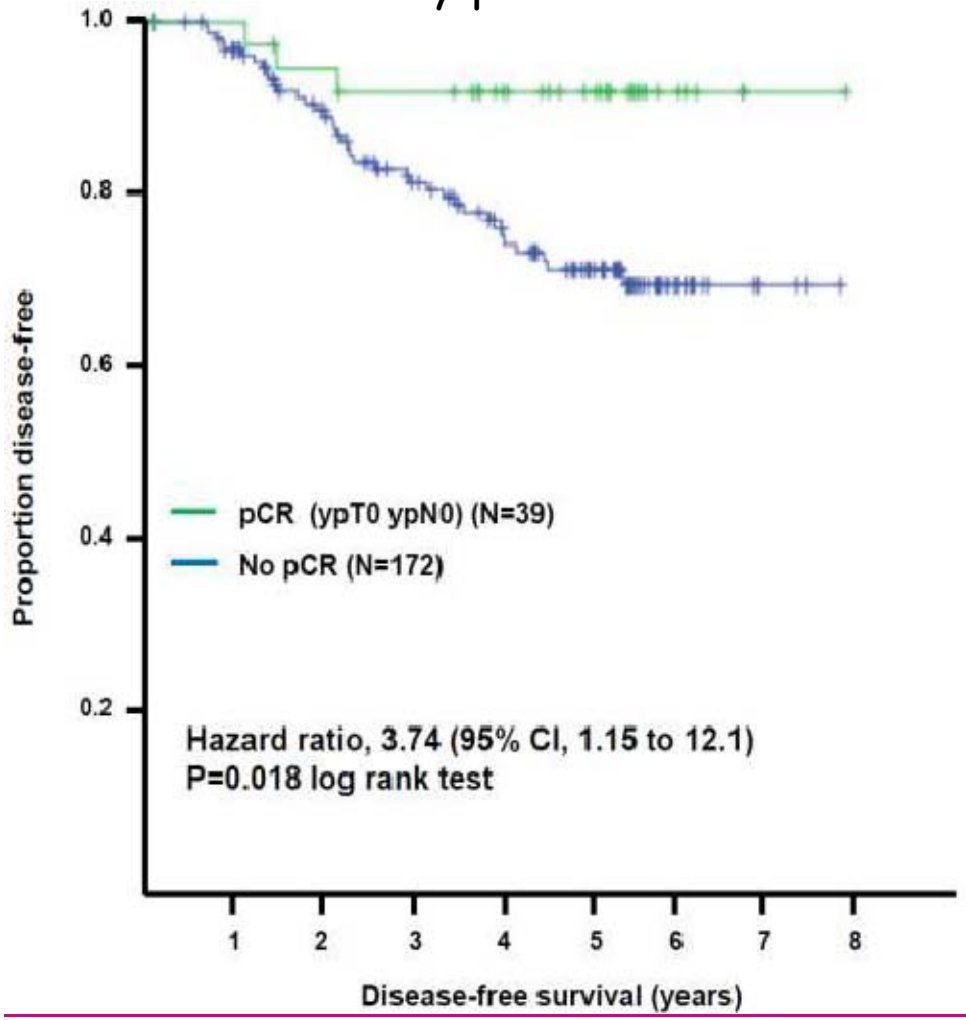
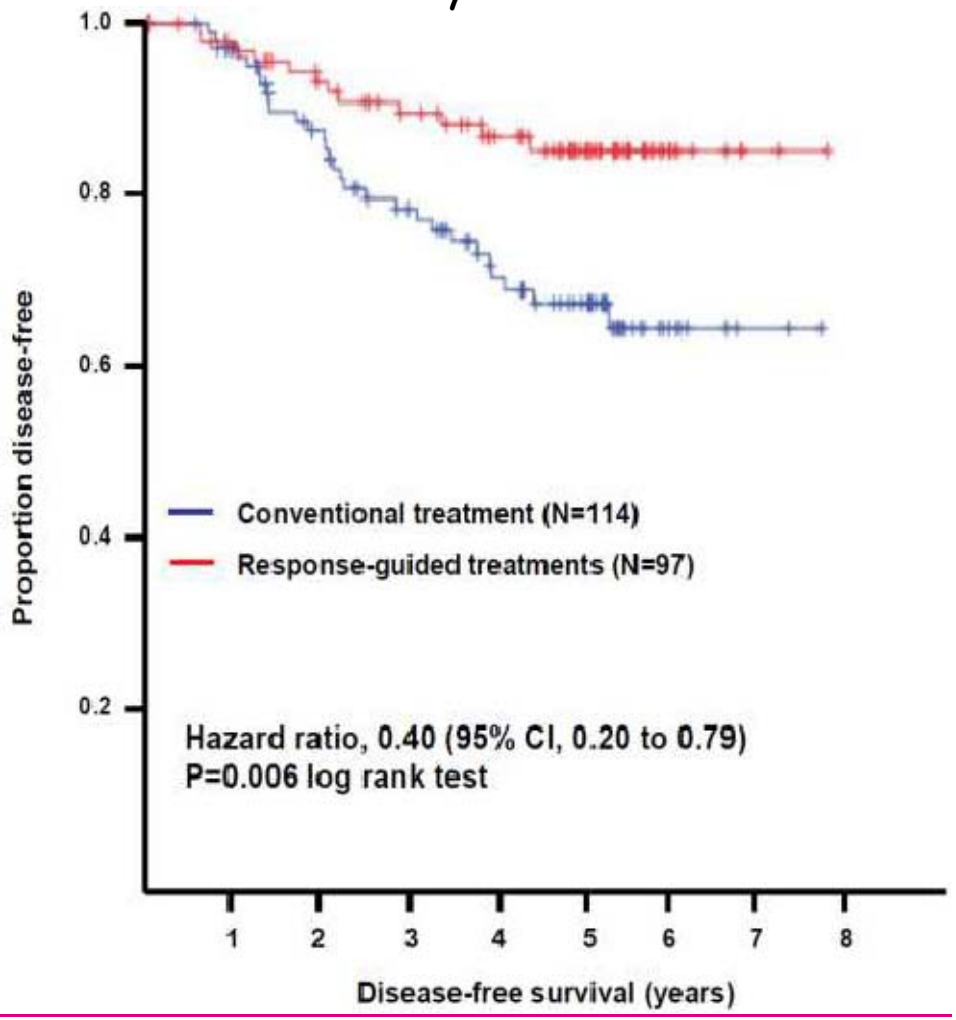
DFS in Luminal B (HER2-)

by pCR



by treatment



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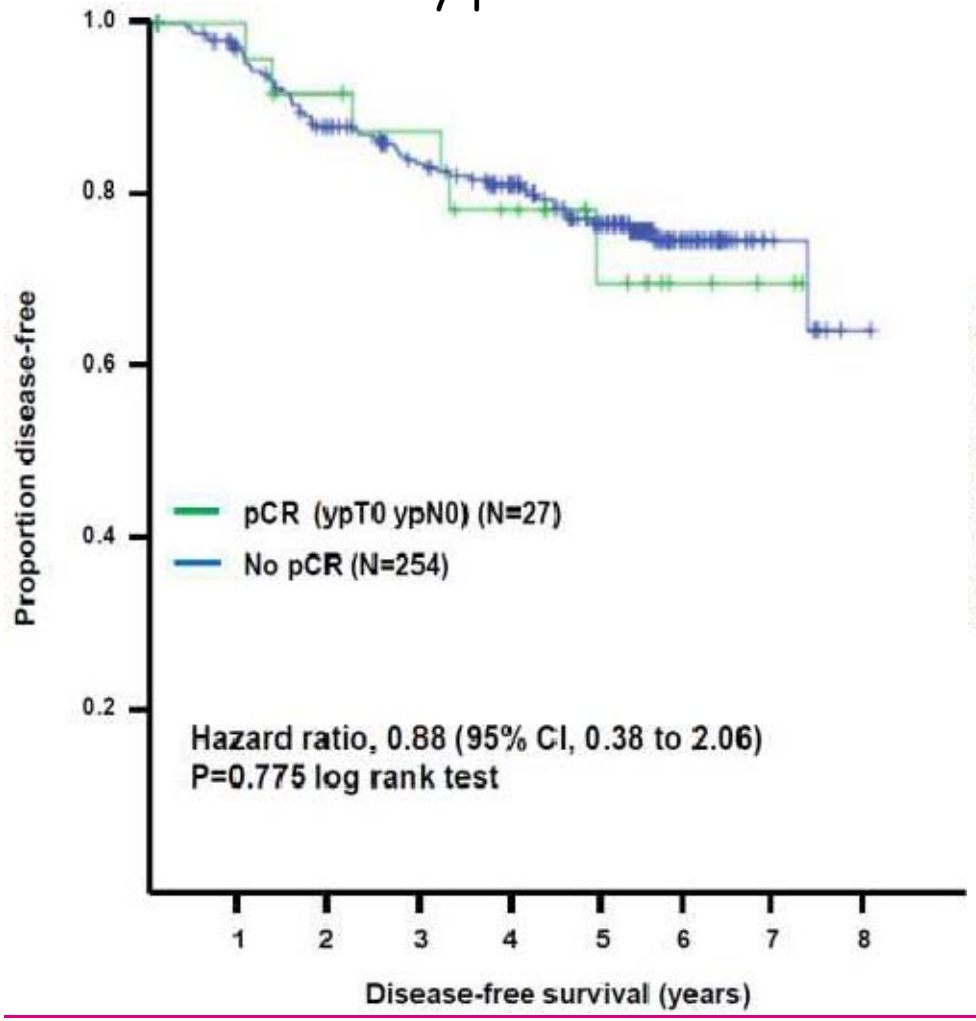
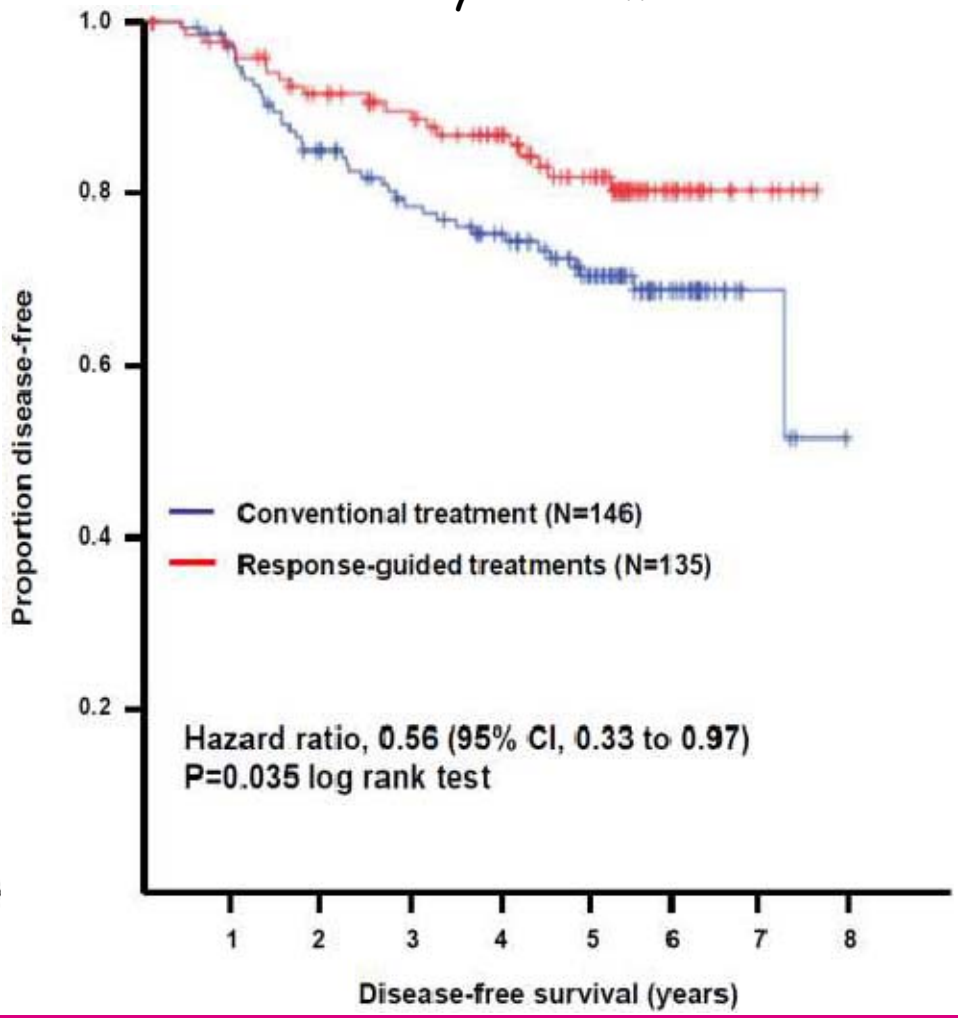
DFS in Luminal B (HER2+) tumors

by pCR



by treatment



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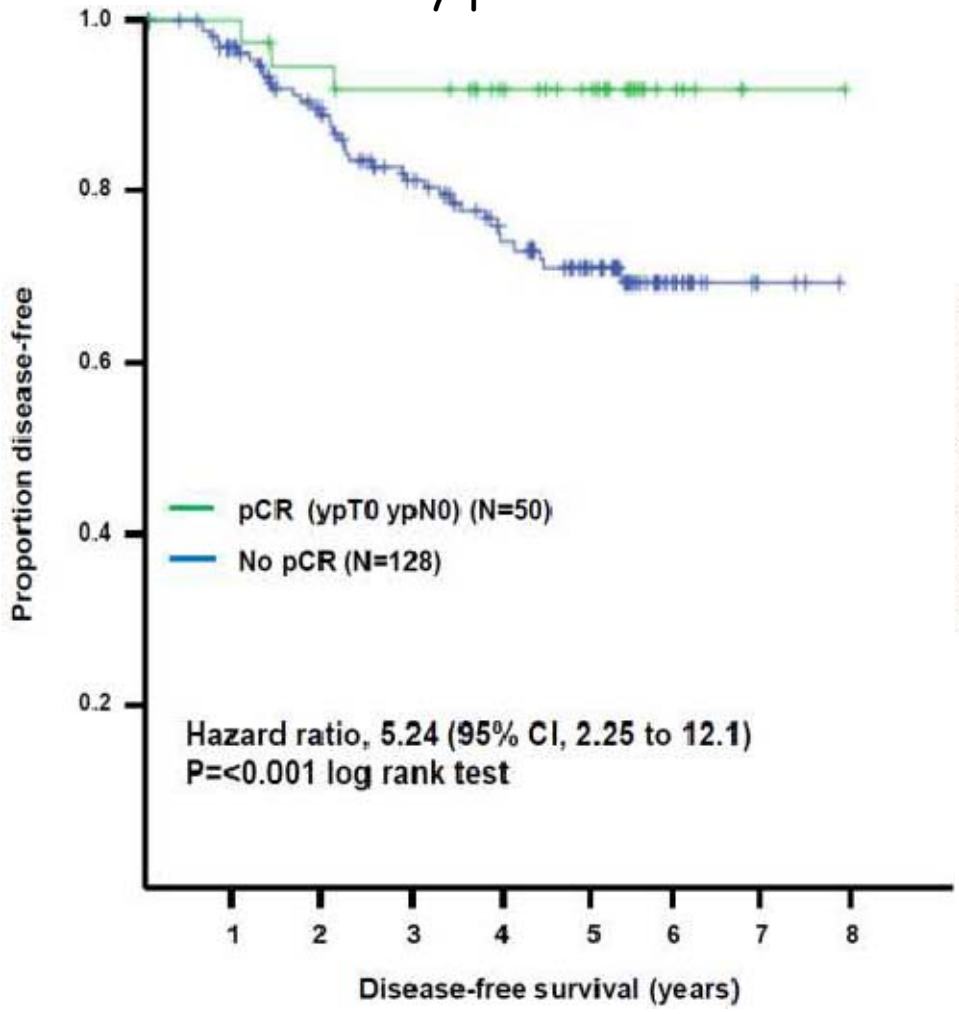
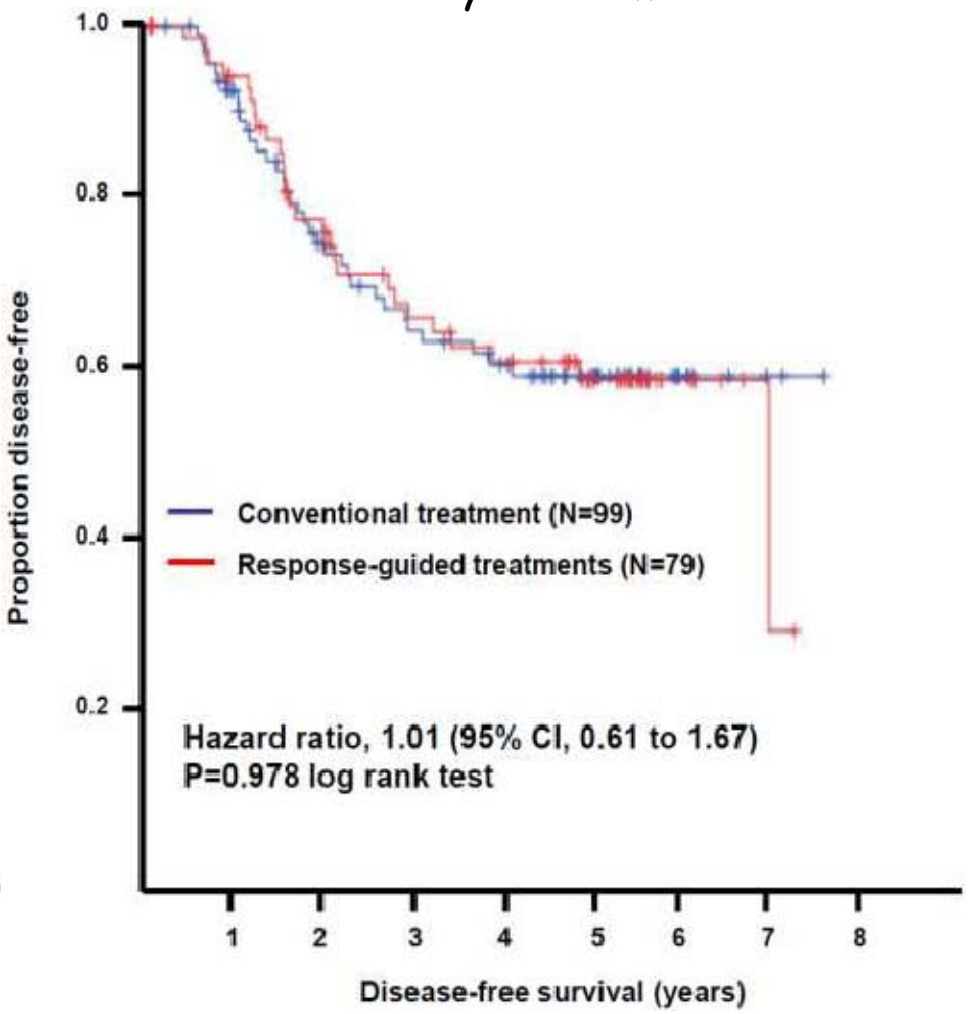
DFS in HER2+(non-luminal) tumors

by pCR



by treatment



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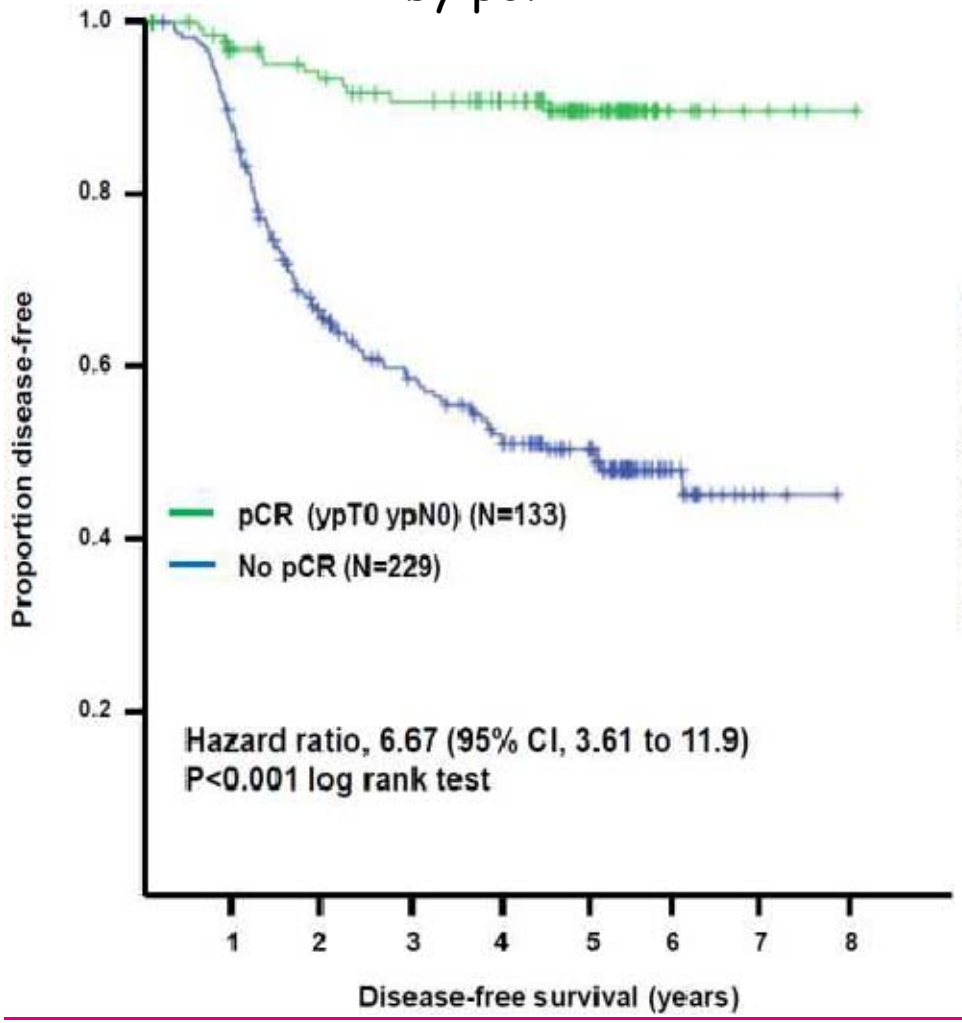
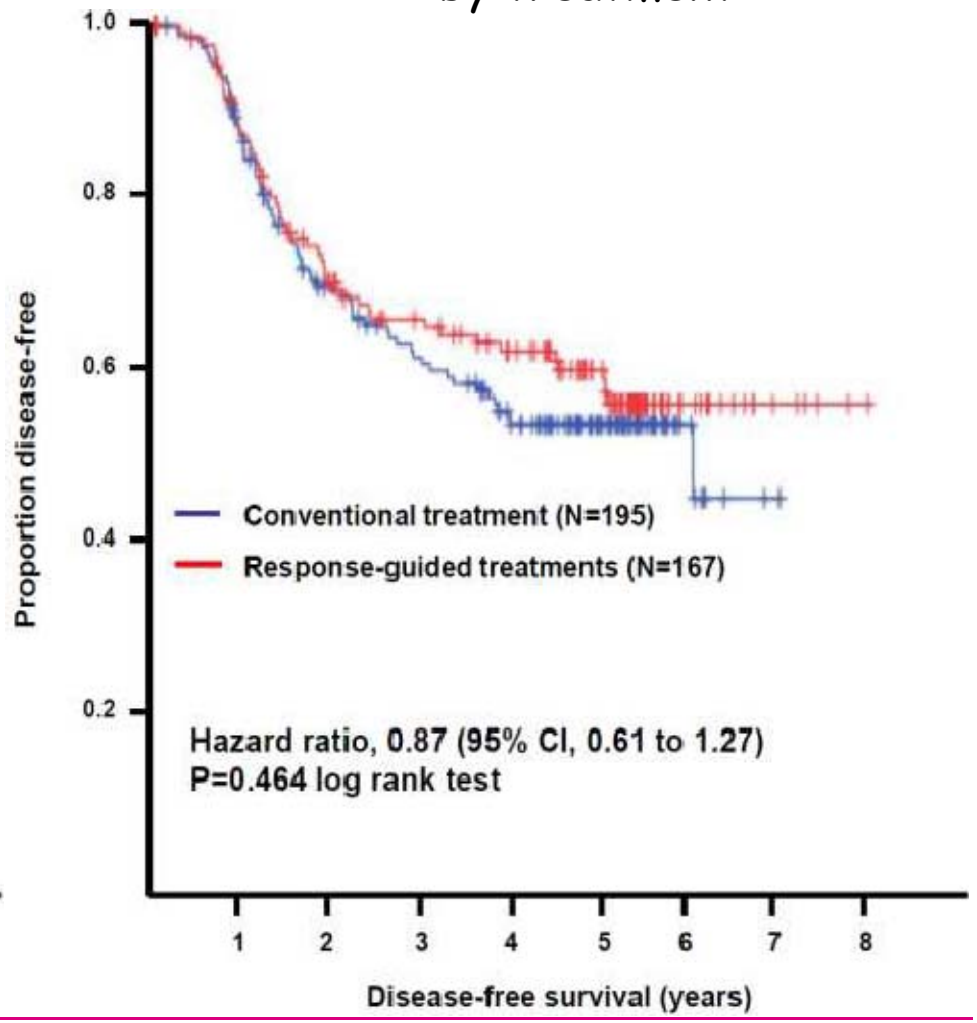
DFS in Triple Negative Tumors

by pCR



by treatment



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Conclusion

Interim response-guided (longer or sequential) neoadjuvant chemotherapy improved survival.

Treatment effects on survival derived from luminal-type tumors.

- This treatment effect could not be predicted by pCR as these tumors have lower pCR rates and their prognosis does not depend on pCR.

Patients with HER2+ or triple-negative tumors did not benefit from response-guided treatment.

- pCR is highly prognostic in these subgroups.
- Lack of treatment effect on pCR rate corresponds to lack of long term treatment.

NEOADJUVANT CHEMOTHERAPY OF PACLITAXEL WITH OR WITHOUT RAD001 - RESULTS OF THE NON-RESPONDER PART OF THE GEPARQUINTO STUDY (GBG 44)

Huober et al

Abstract 3-6

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GBG
GERMAN
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GEPAR quinto
HER2-
Non-Responder

Introduction

The oral signal transduction inhibitor everolimus (RAD001 = Rad), binds selectively to mTOR (mammalian target of rapamycin)

mTOR is an intracellular protein kinase controlling cellular proliferation of activated T-lymphocytes and neoplastic cells.

In vitro synergistic reactions with Rad and several chemotherapeutic drugs including paclitaxel were observed1

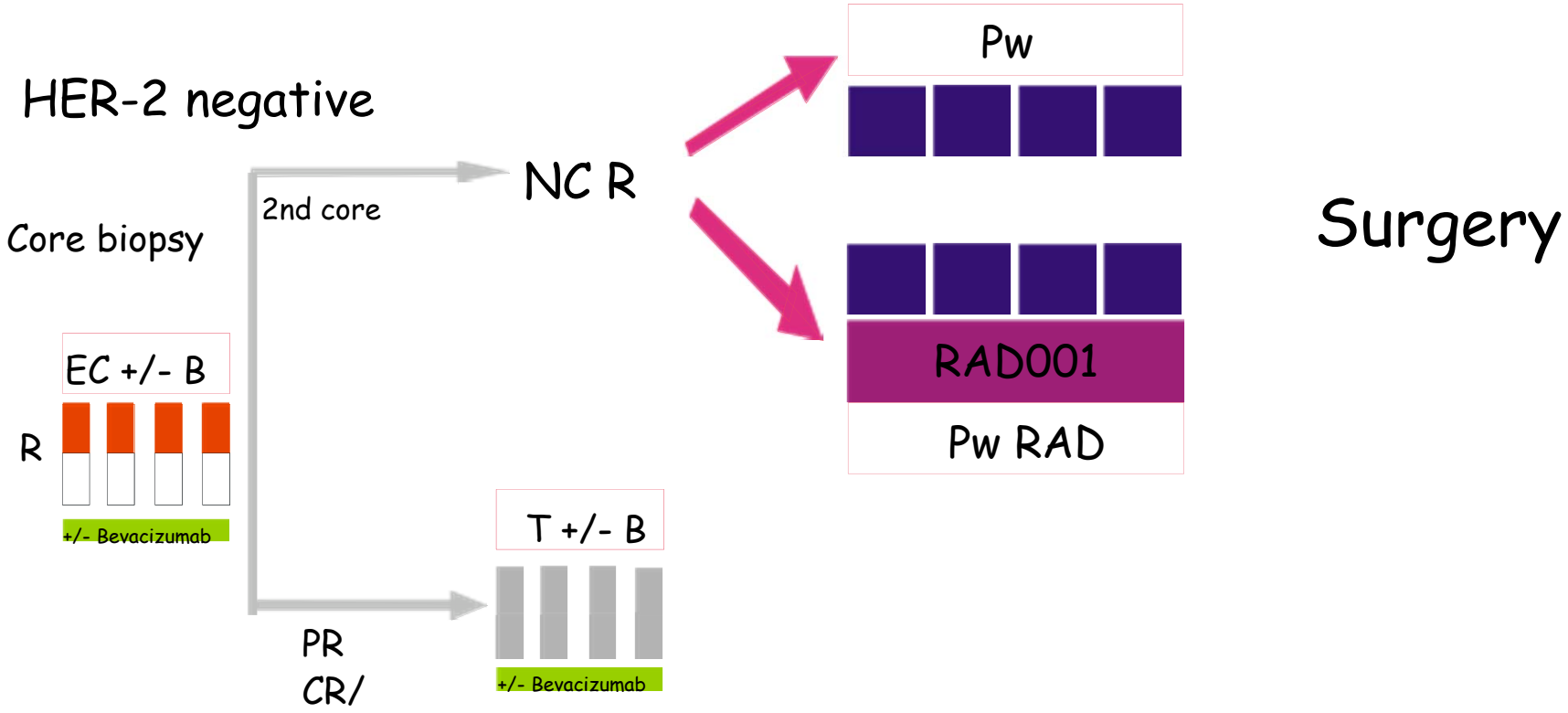
Additional neoadjuvant treatment strategies are needed for patients without early clinical response

[1] O`Reilly T et al. Anti-Cancer Drugs 2011

GEPAR quinto

HER2-
Non-Responder

Study Design



E = Epirubicin
C = Cyclophosphamide
T = Docetaxel
B = Bevacizumab

Pw = Paclitaxel, weekly (80 mg/m2: day 1 q day 8 - 12 weeks)
R = RAD001 (5 mg / day from day 13 after a dose escalation starting from 2.5 mg every other day to 5mg every day)

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GEPAR quinto
HER2-
Non-Responder

Patients & Tumor Characteristics

	Pw N=198	Pw+Rad N=197
age (median yrs)	51	50
Age < 40 years (%)	13.1	9.1
palpable T-size (median mm)	40	40
	%	%
cT 4 (a-c)	8.6	8.1
inflammatory	8.1	9.1
cN +	55.7	59.1
lobular type	11.1	10.2
hormone receptor positive	71.2	73.1
grade 3	35.5	33.7

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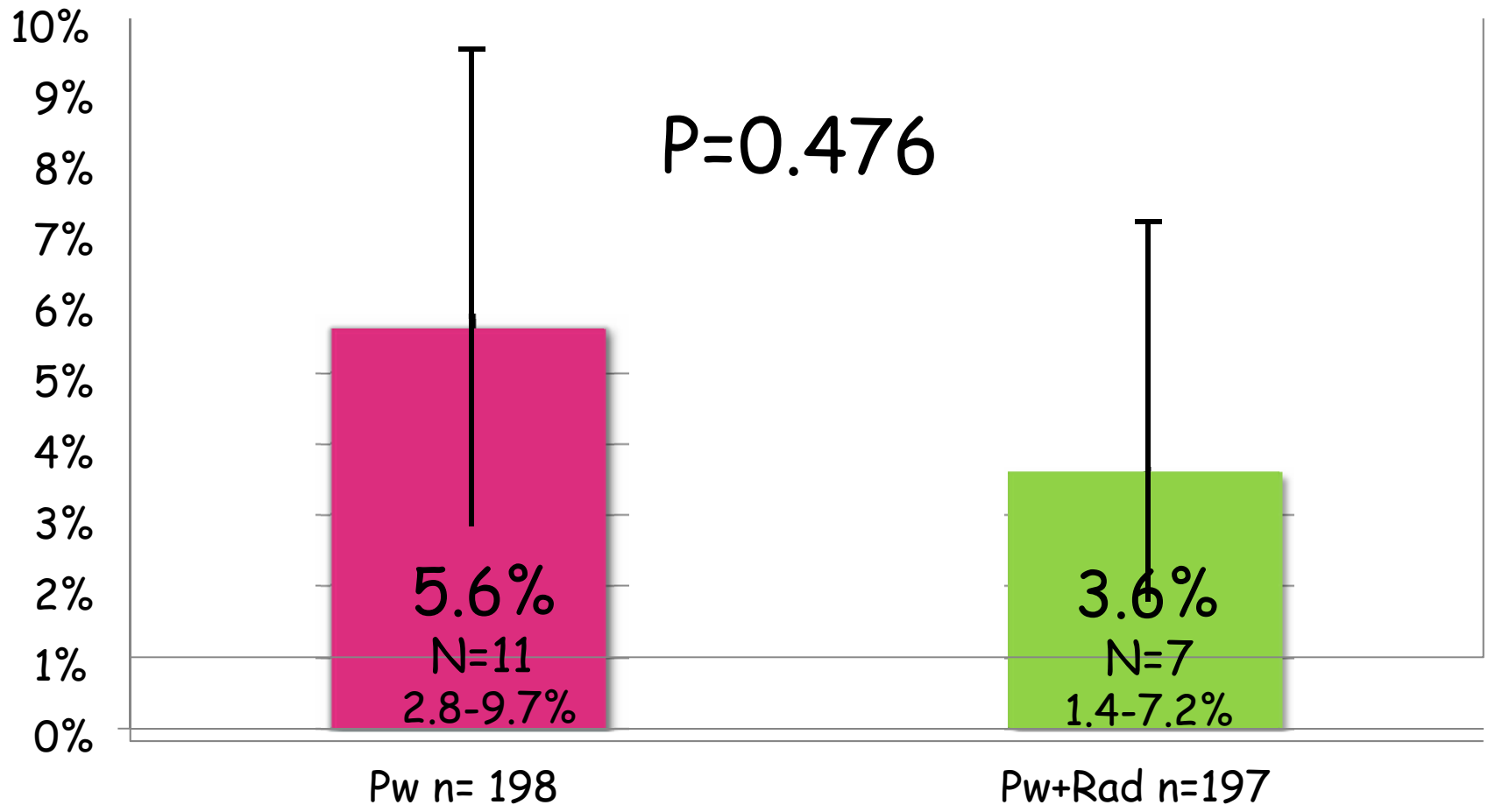
GEPAR quinto

HER2-
Non-Responder

pCR

(no invasive & no non-invasive residuals in breast & nodes
based on central pathology report review N=395)



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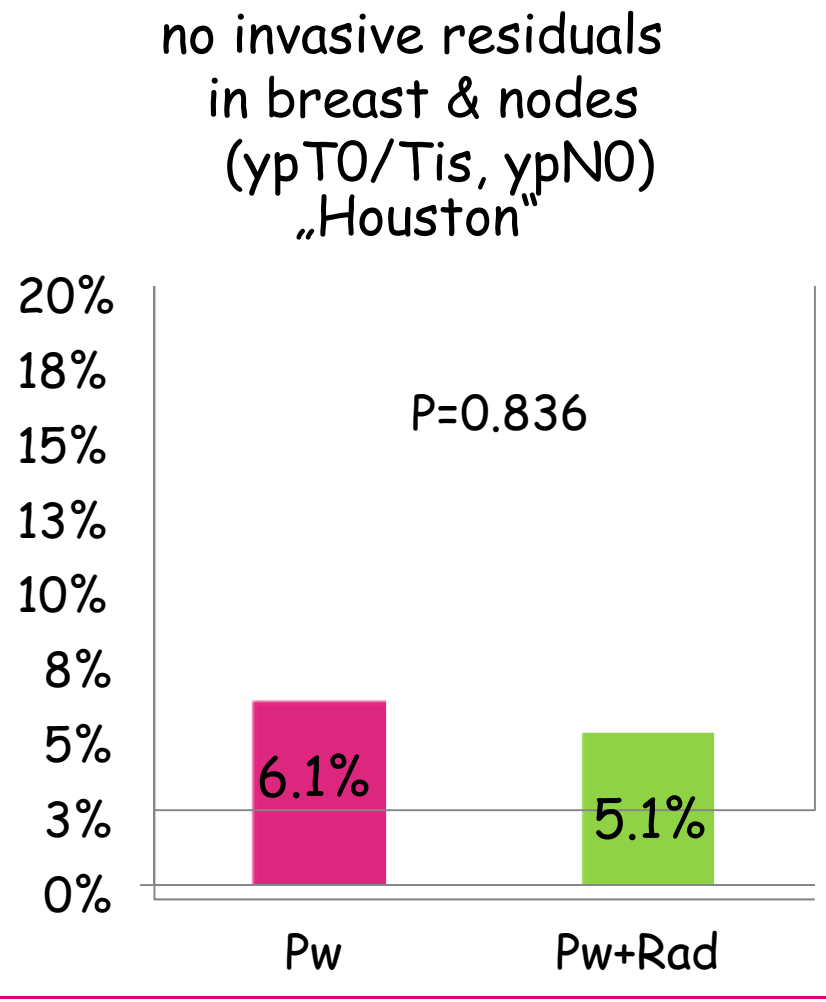
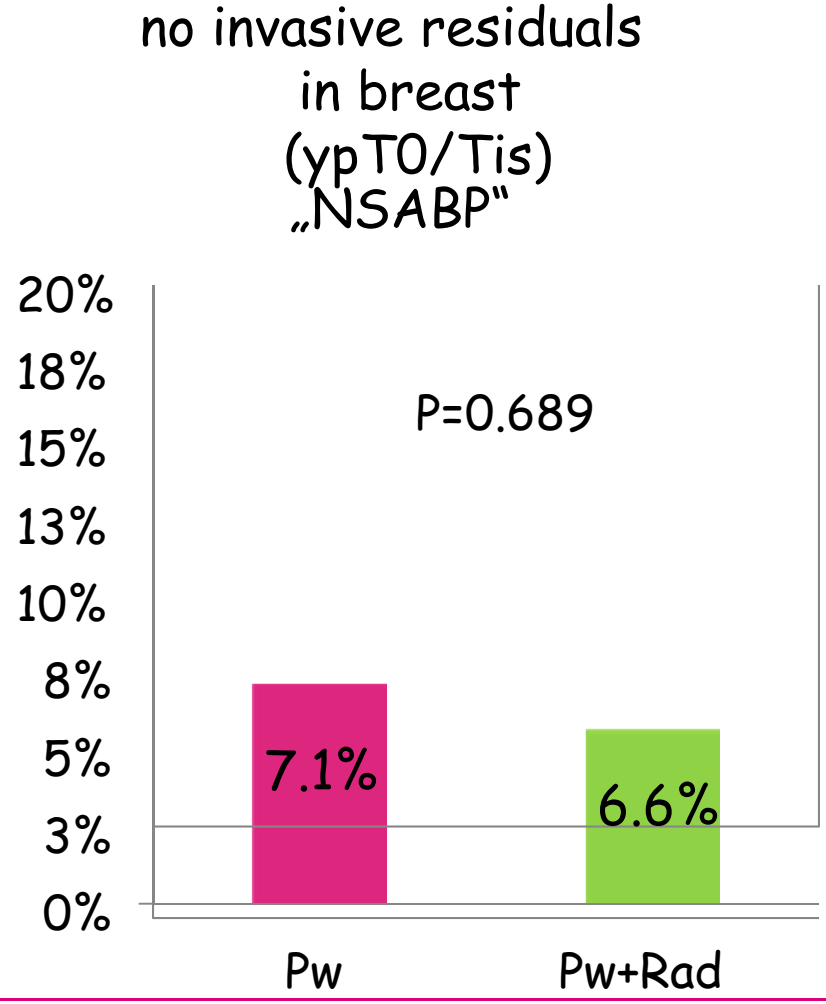
GEPAR quinto

HER2-
Non-Responder

pCR Rates According to Secondary Endpoint Definitions





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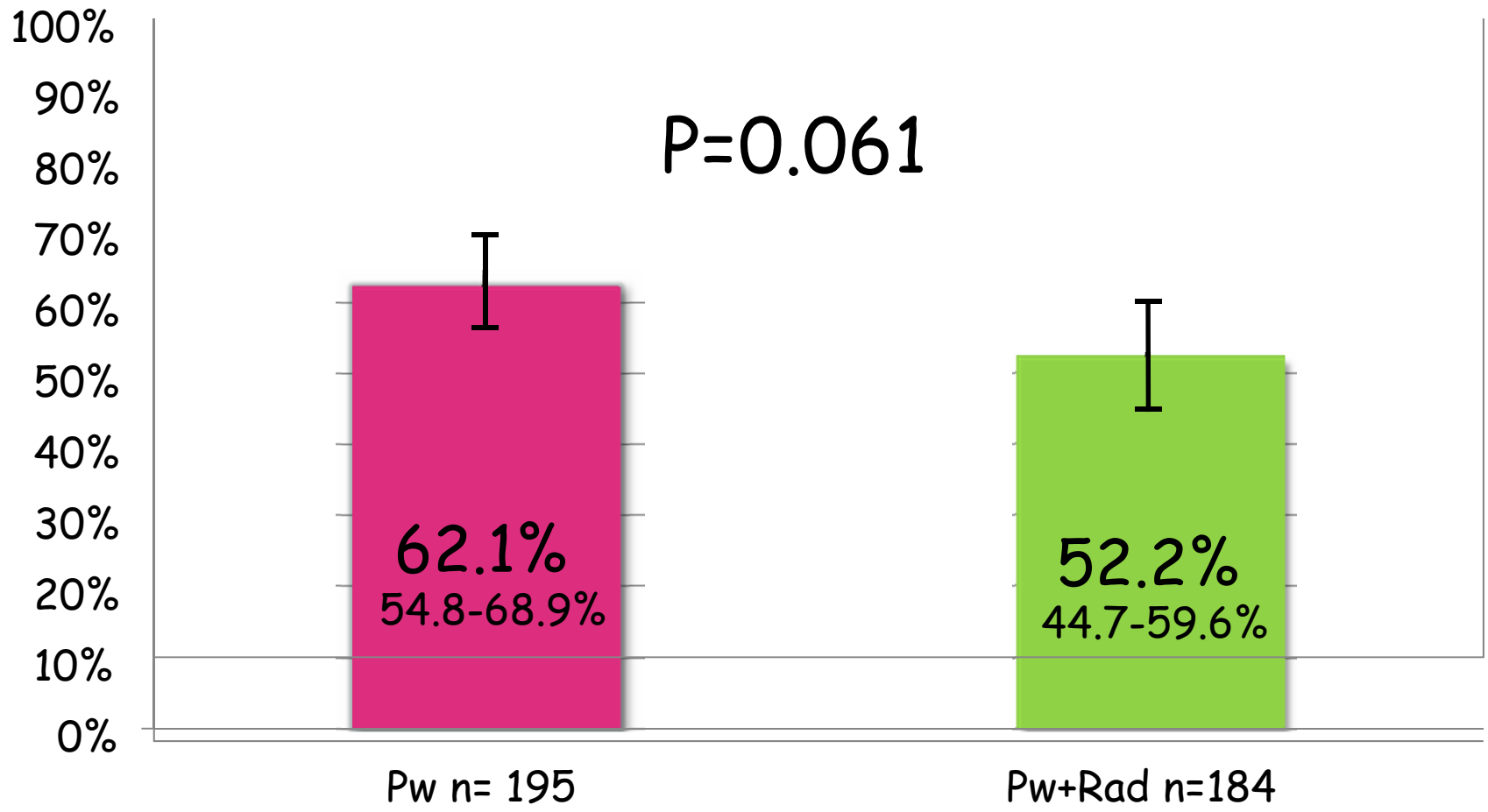
HER2-
Non-Responder

cCR+cPR

(clinical complete and partial response at surgery n=379)



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GEPAR quinto
HER2-
Non-Responder

Conclusions

pCR rate is low (4.6%) in patients not responding to the initial 4 cycles of neoadjuvant chemotherapy with or without Bev

Addition of Rad to 12 weeks paclitaxel did not improve pCR rate in these patients (Pw 5.6% vs. Pw+Rad 3.6%; P=0.476)

Toxicity was higher in the group treated with Rad

DFS and OS have to be awaited because pCR might not be the appropriate endpoint (high number HR+)

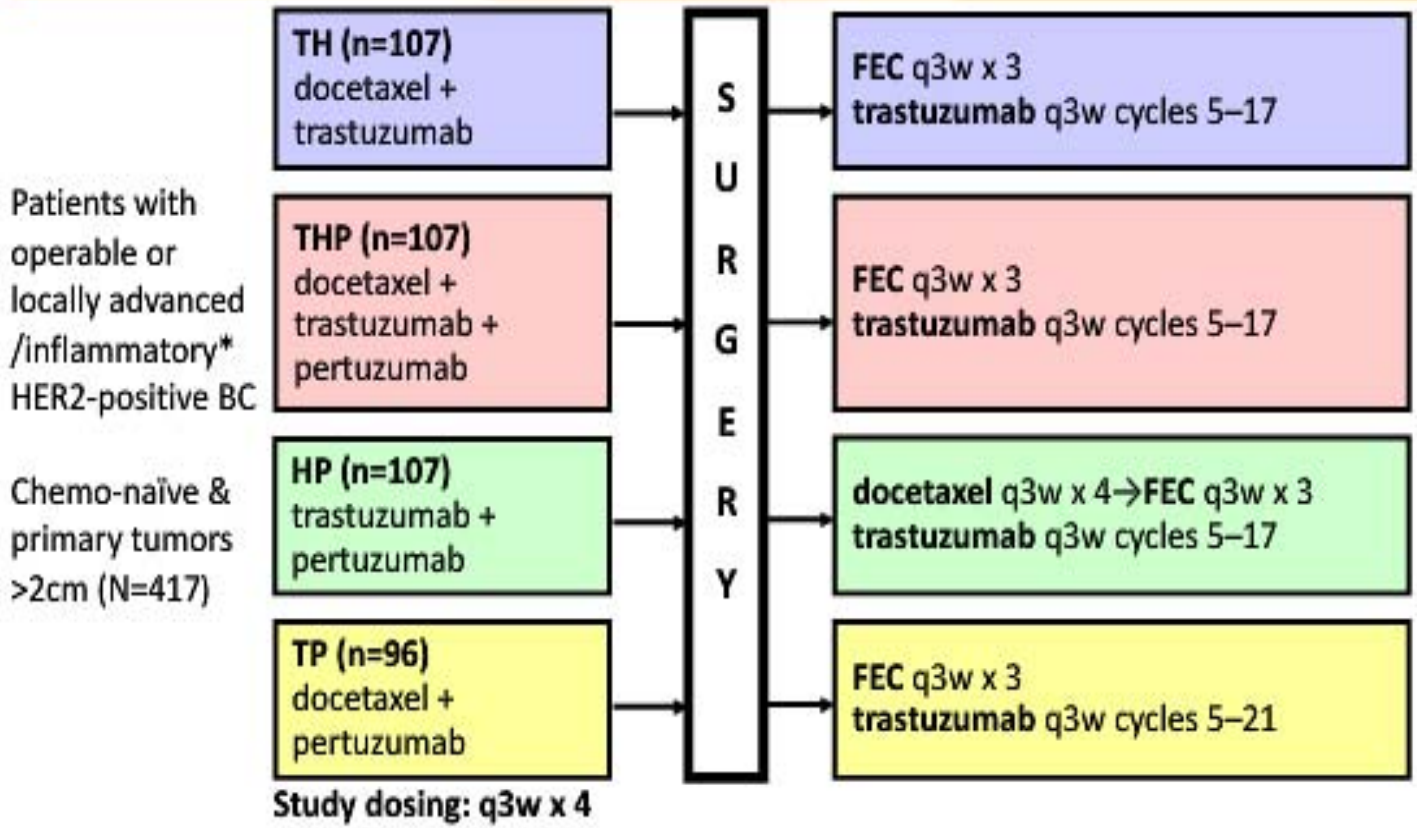
A large biomarker program is ongoing to identify predictive markers

Neo-adjuvant pertuzumab and trastuzumab: Biomarker analyses of a 4-arm randomized phase 2 trial (NeoSphere) in patients with HER2-positive breast cancer

Gianni et al

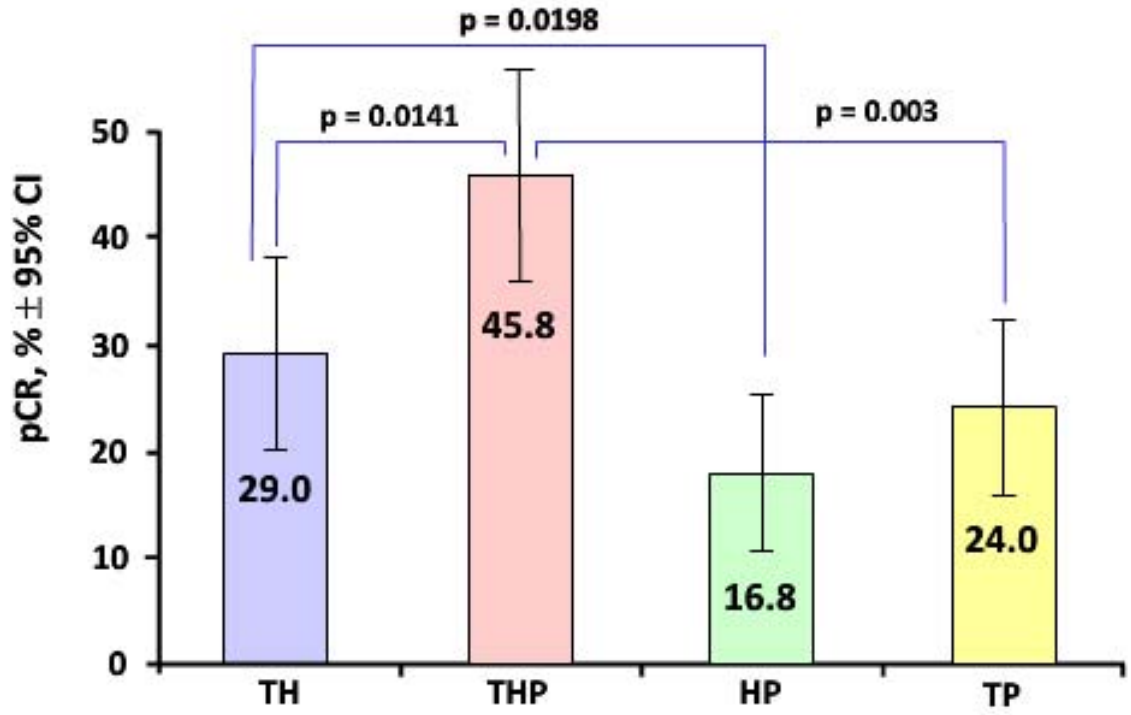
Abstract S5-1

NeoSphere: study design



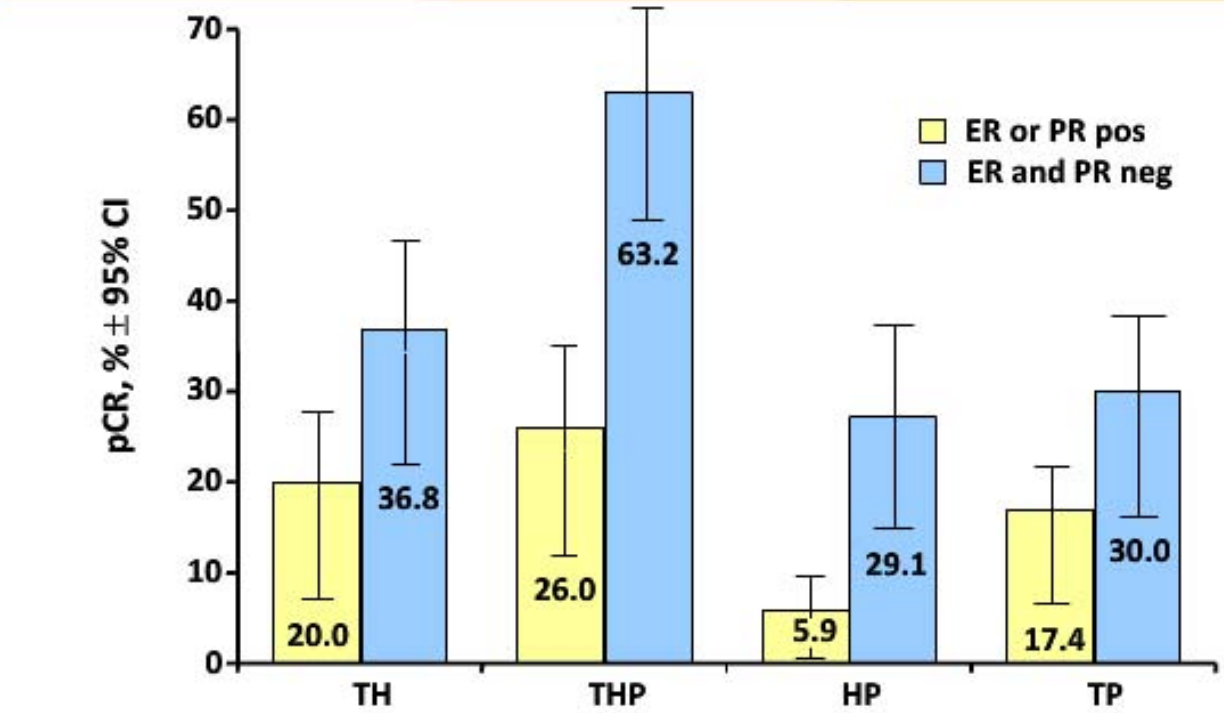
BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide
*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
H, trastuzumab; P, pertuzumab; T, docetaxel

NeoSphere pCR rates: ITT population summary



H, trastuzumab; P, pertuzumab; T, docetaxel

NeoSphere: pCR and hormone receptors status



H, trastuzumab; P, pertuzumab; T, docetaxel

NeoSphere: Correlative results

- PI3-kinase mutations were not associated with rate of PCR
- No role for truncated forms of HER2, including $p95^{HER2}$ in predicting PCR
- IGF1R, HER3, PTEN and EGFR were higher in ER-positive cancers, while HER2 was higher in ER-negative breast cancers

Practice changing?

- Potentially important:
  - Late recurrences in HER2-positive breast cancers
- Confirmatory:
  - Decreased incidence (and importance) of PCR in HR-positive, HER2-positive breast cancers
  - Equivalence of anthracycline and non-anthracycline containing regimens in HER2-positive breast cancers
  - Dual targeting of HER2 superior to single agents in pre-operative setting
- Depressing:
  - Poor outcome for patients with TNBC who do not obtain a PCR and…
  - Lack of improvement in PCR rate with non-resistant chemotherapeutics and novel agents