Instituto Goiano de Oncologia e Hematologia

QUIMIOTERAPIA NEOADJUVANTE

Princípios gerais e particularidades

Leandro Gonçalves Oliveira- CRM 16266

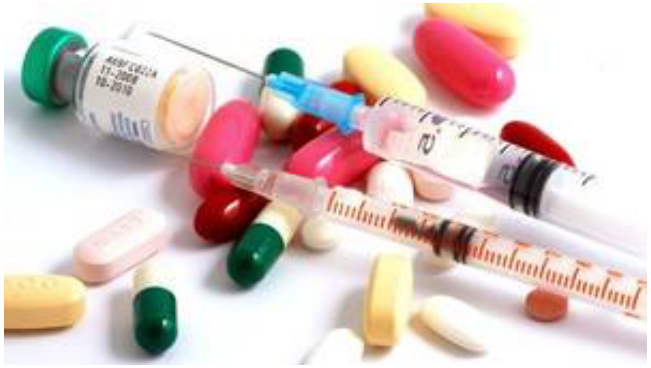
Goiânia, 15/08/17

TEMPO LIMITADO

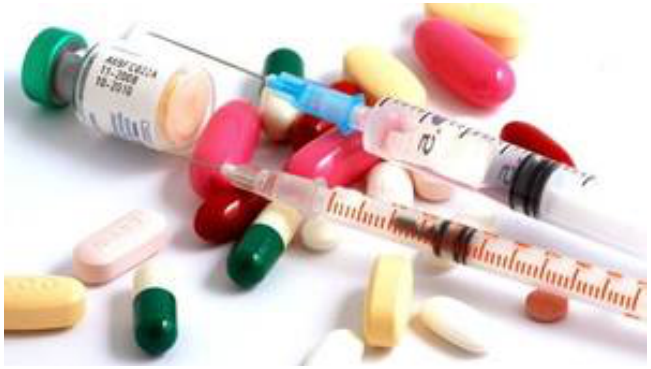
Objetivos

Nos 20 min de apresentação espero transmitir:

- Conceitos gerais sobre tratamento neoadjuvante
- Avaliação pré-tratamento e seleção dos pacientes
- Importância da resposta patológica completa
- TERAPIAS-PADRÃO PARA HER 2+ E HER 2 NEG
- Existe papel da platina no tratamento neoadjuvante do câncer de mama triplo negativo?



QUIMIOTERAPIA ADJUVANTE

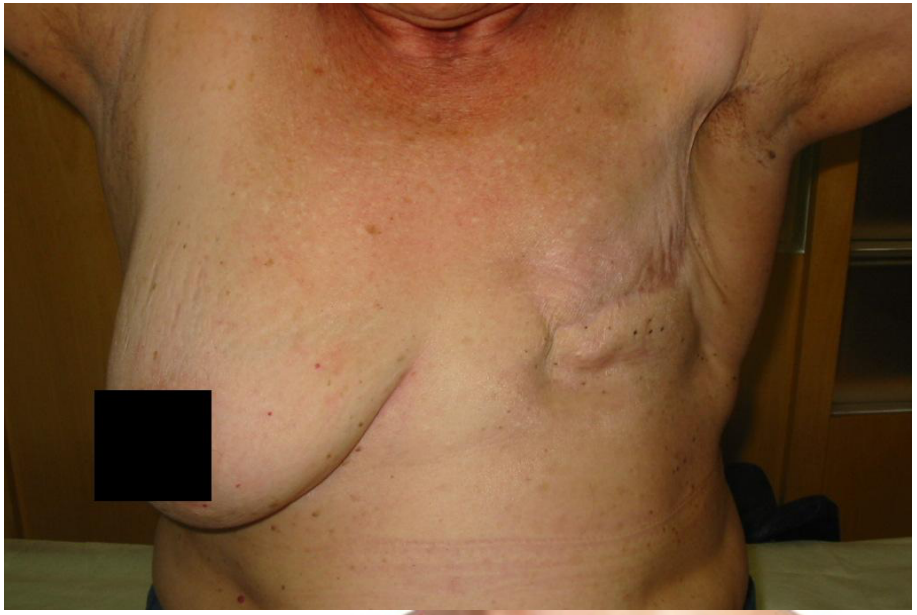


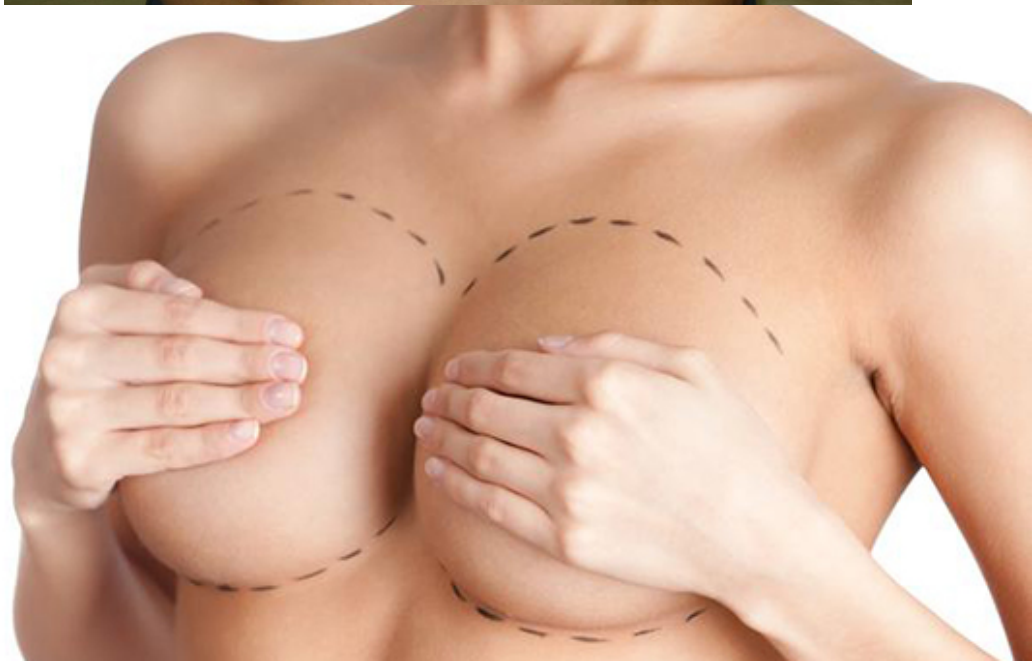
QUIMIOTERAPIA
NEOADJUVANTE

Conceitos gerais

- Objetivos:

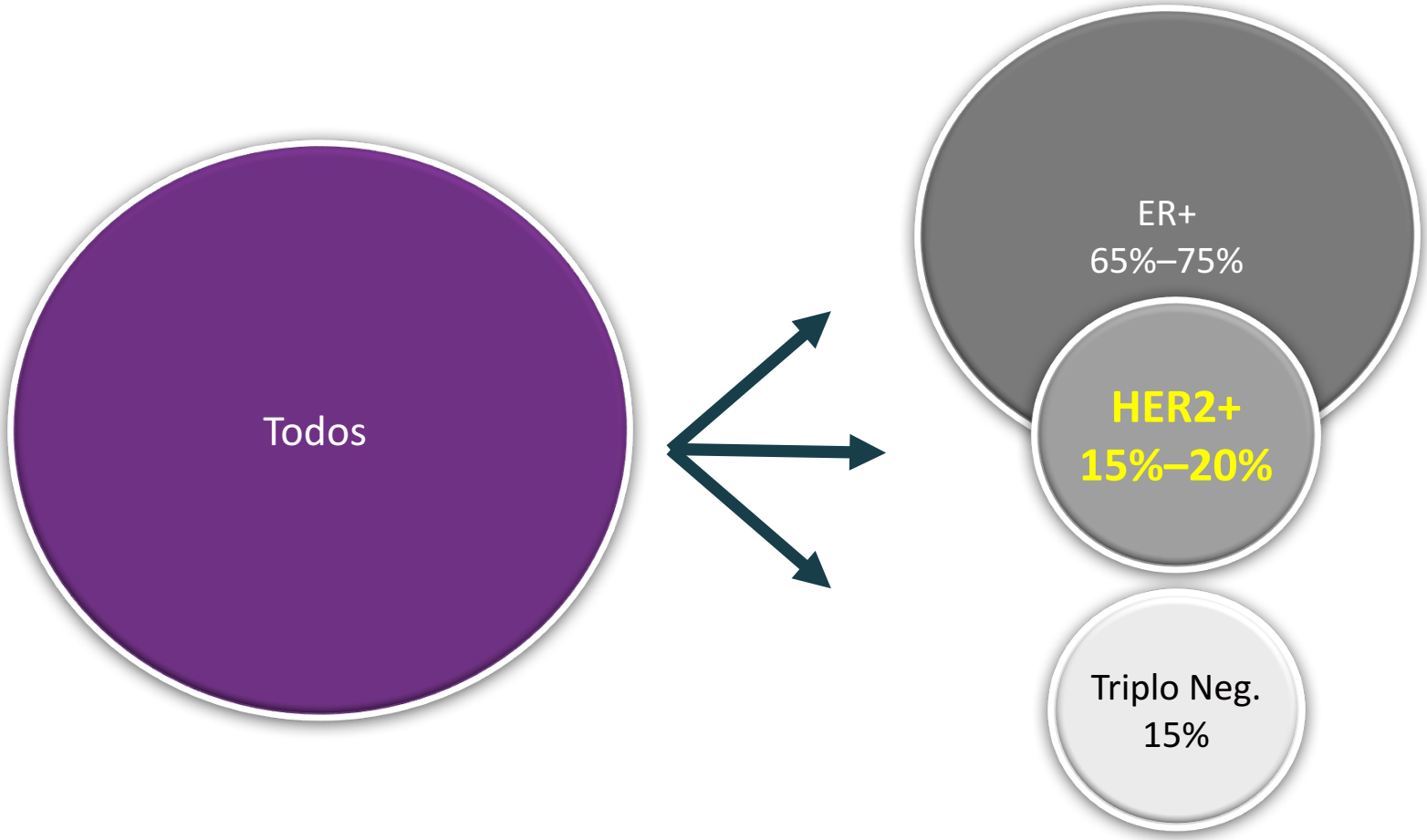
1. *Downstage*
2. Avaliação precoce da efetividade do tto sistêmico
3. Avaliação prognóstica
4. Tratamento precoce da doença micrometastática
5. Instrumento para aprovação mais rápida de novas drogas
6. Câncer de mama na gestação
7. Planejamento de terapia local (BRCA, dúvidas)
8. Acesso a Pertuzumabe (HER 2 +)





Fenótipos de câncer de mama

- Fenótipos de interesse por terem implicações terapêuticas claras.



Avaliação pré-tratamento

- História clínica
- Estadiamento sistêmico (sobretudo para estadio III)
- Biópsia e IHQ. PAAF/biopsia axilar
- Laboratório com bioquímica básica
- ECO
- Marcação tumoral/ axilar
- Avaliação genética

Neoadjuvante x Adjuvante

Systematic review

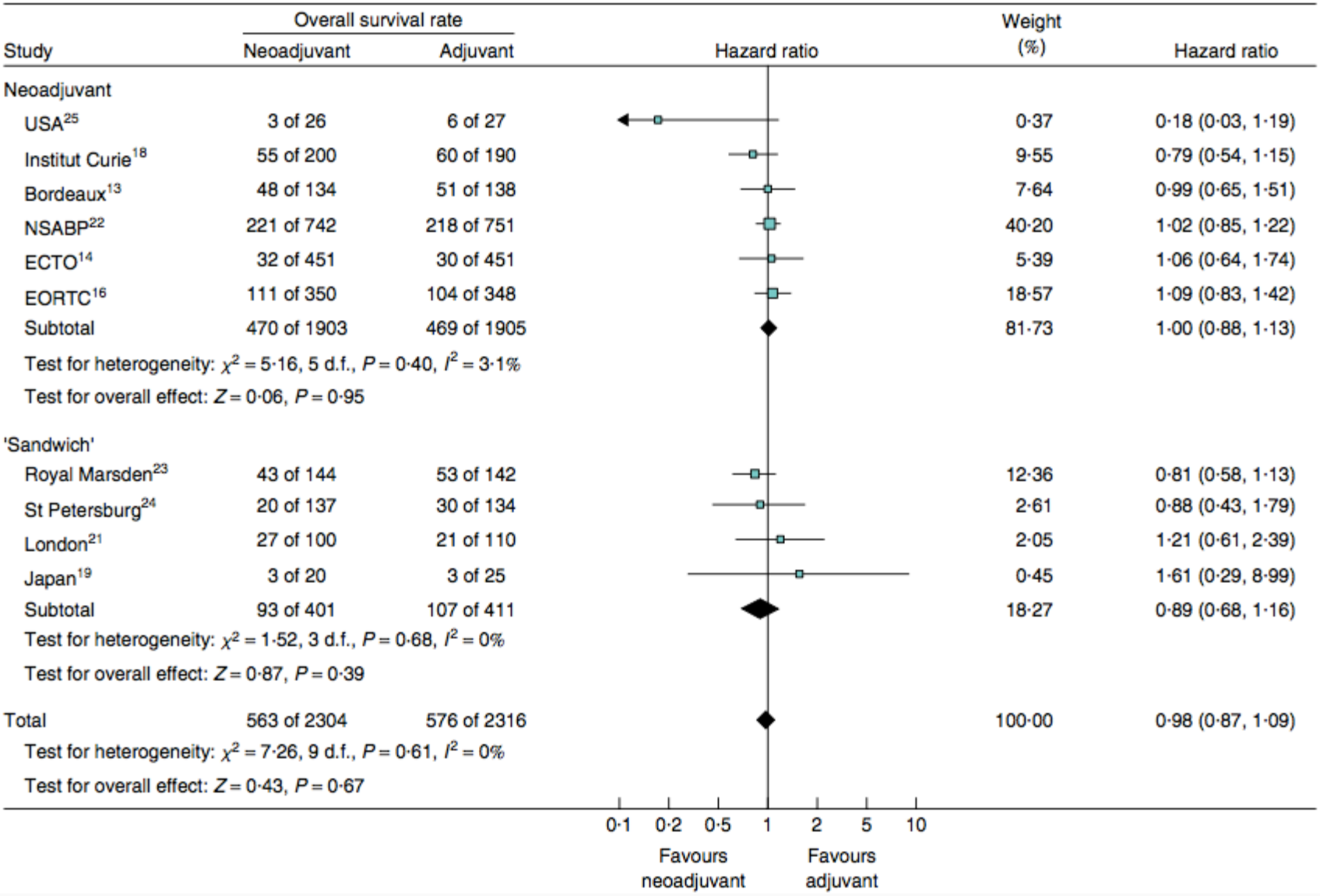
Neoadjuvant chemotherapy for operable breast cancer

J. S. D. Mieog, J. A. van der Hage and C. J. H. van de Velde

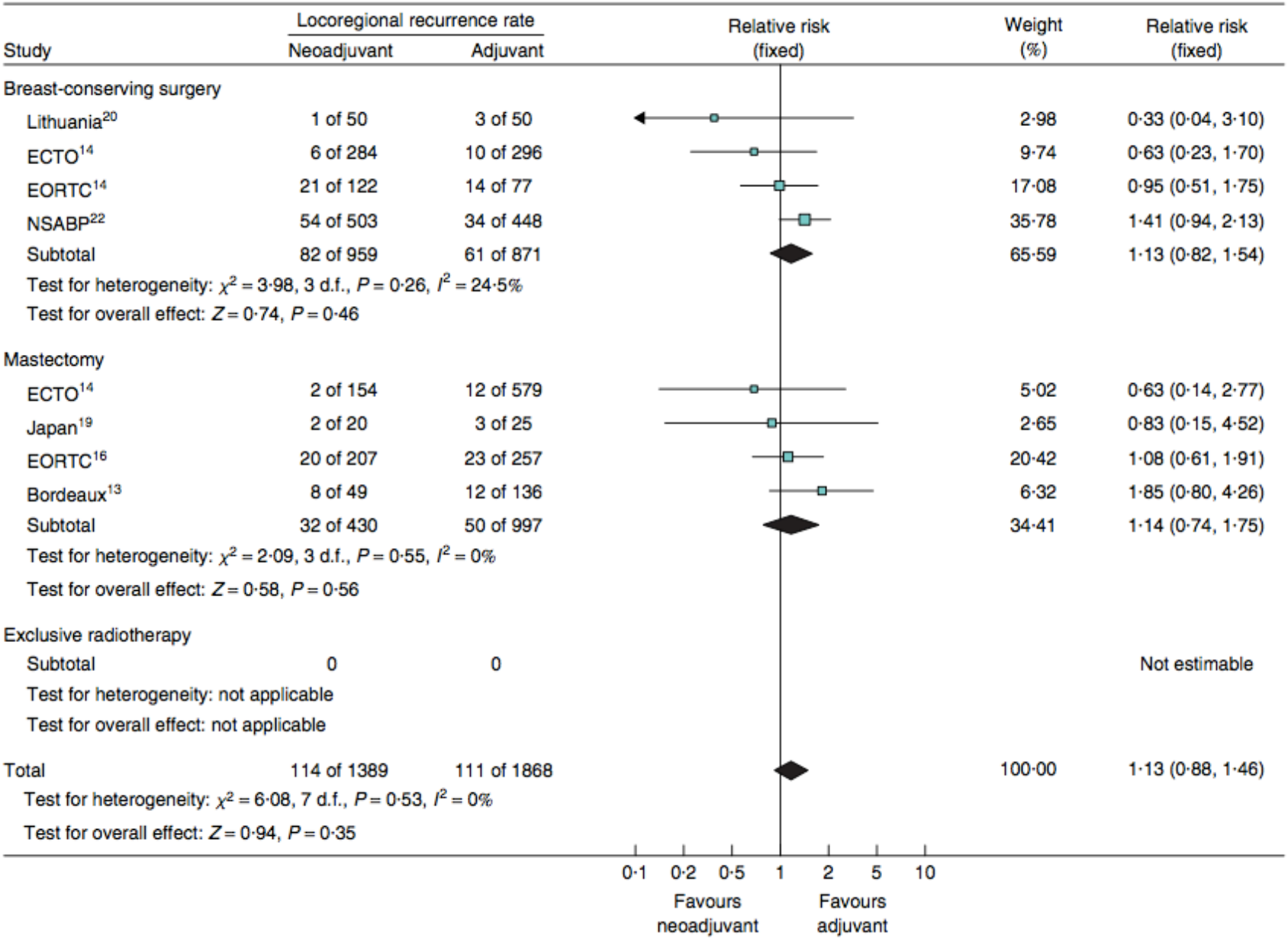
Department of Surgery, Leiden University Medical Centre, Albinusdreef 2, 2300 RC Leiden, The Netherlands
Correspondence to: Professor C. J. H. van de Velde (e-mail: C.J.H.van_de_Velde@lumc.nl)

British Journal of Surgery 2007; **94**: 1189–1200

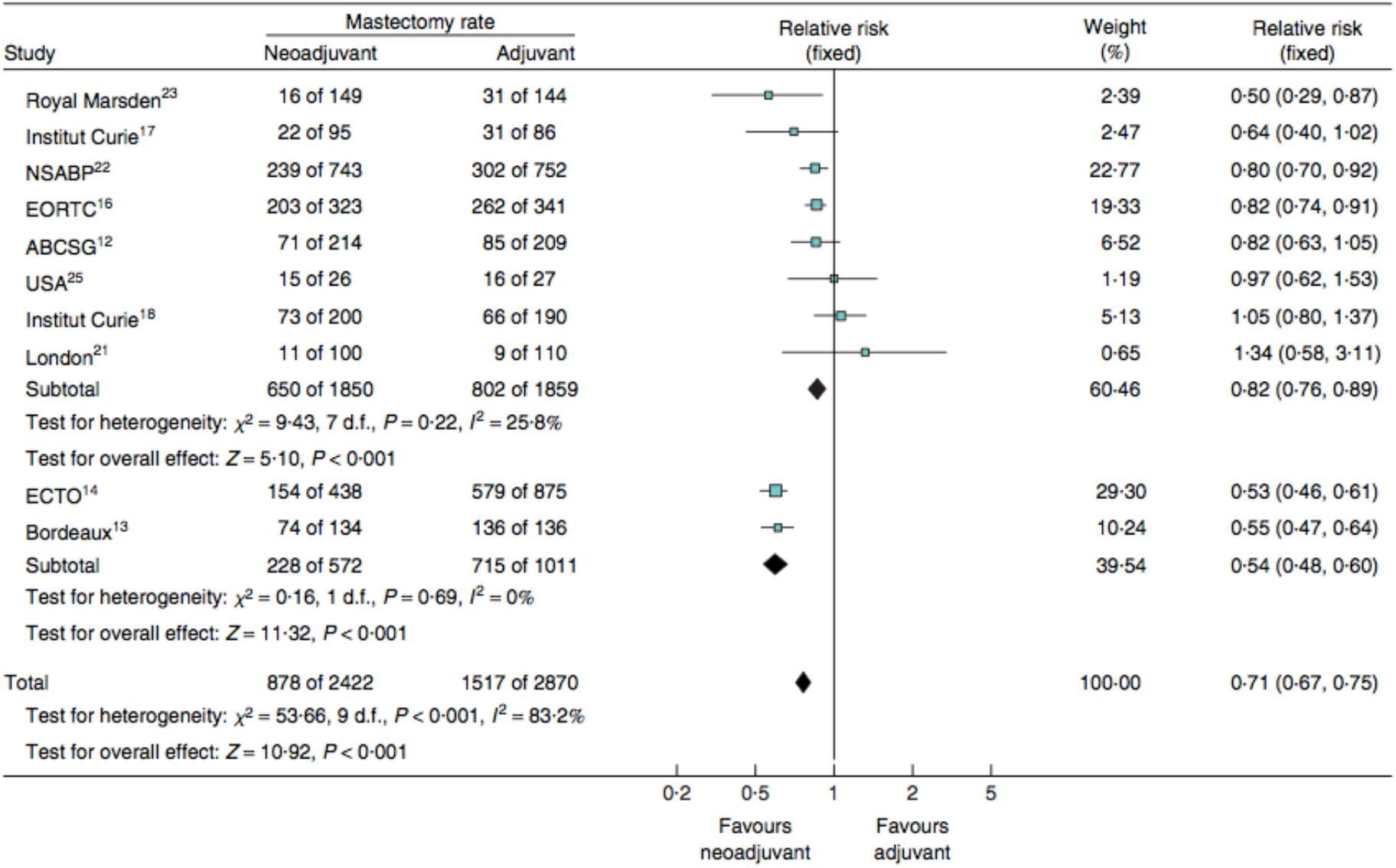
Sobrevida Global



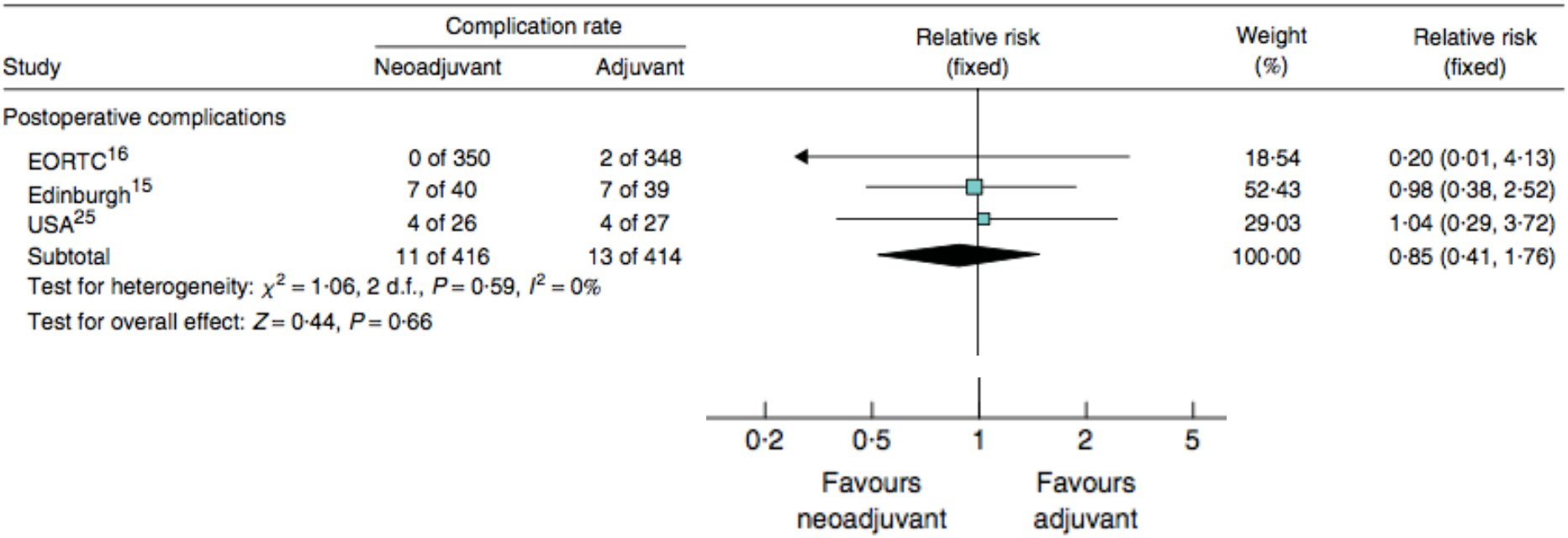
Recorrência local



Taxa de mastectomia



Taxa de complicações



pCR é amplamente definida como a ausência de células cancerosas após a ressecção tumoral

pCR é amplamente utilizada para avaliar a resposta à terapia neoadjuvante

A resposta é finalmente avaliada nas amostras de tumor ressecadas

Comumente denominada	**pCR mamária** (bpCR)	**pCR total** (tpCR)	**pCR do German Breast Group** (GBG)
Código TNM	**ypT0/is**	**ypT0/is N0**	**ypT0/N0**
Definição	Ausência de câncer invasivo na mama (independentemente de carcinoma ductal *in situ* ou envolvimento nodal)	Ausência de câncer invasivo na mama e linfonodos axilares (independentemente de carcinoma ductal *in situ*)	Ausência de câncer invasivo e *câncer in situ* na mama e linfonodos axilares

Ambas associadas a melhores resultados a longo prazo de eficácia em comparação à pCR mamária

Ogston, et al. The Breast 2003; Cortazar, et al. Lancet 2014; von Minckwitz, et al. J Clin Oncol 2012.

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

9440 included in the trial-level analysis

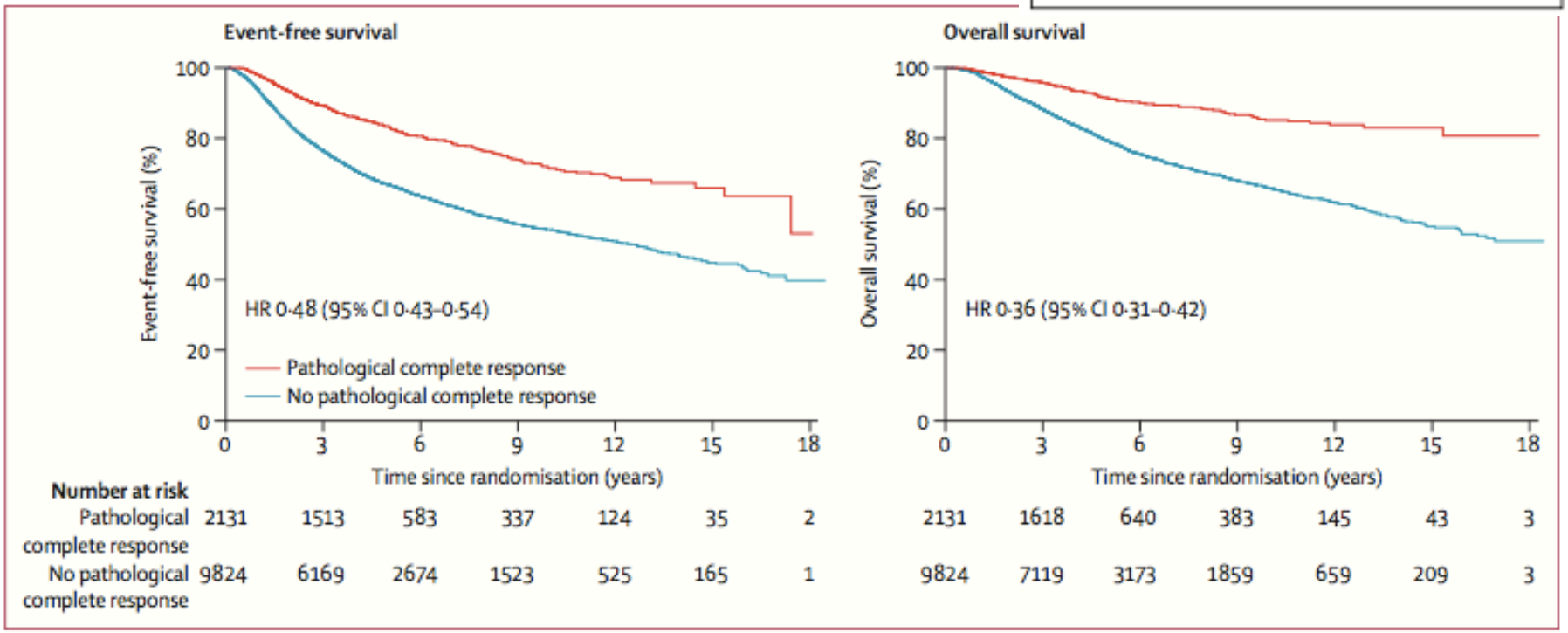


Figure 2: **Associations between pathological complete response and event-free survival and overall survival**
ypT0/is ypN0 definition of pathological complete response (ie, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ). HR=hazard ratio.

Published online February 14, 2014 http://dx.doi.org/10.1016/S0140-6736(13)62422-8

Definições de RPC

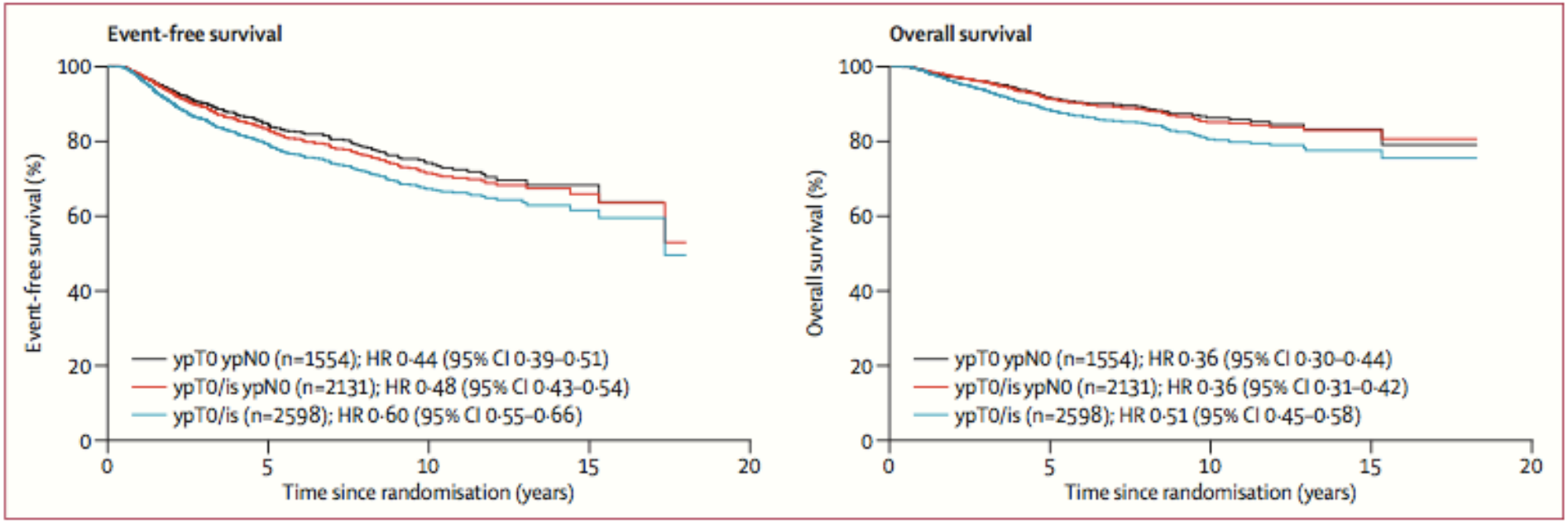
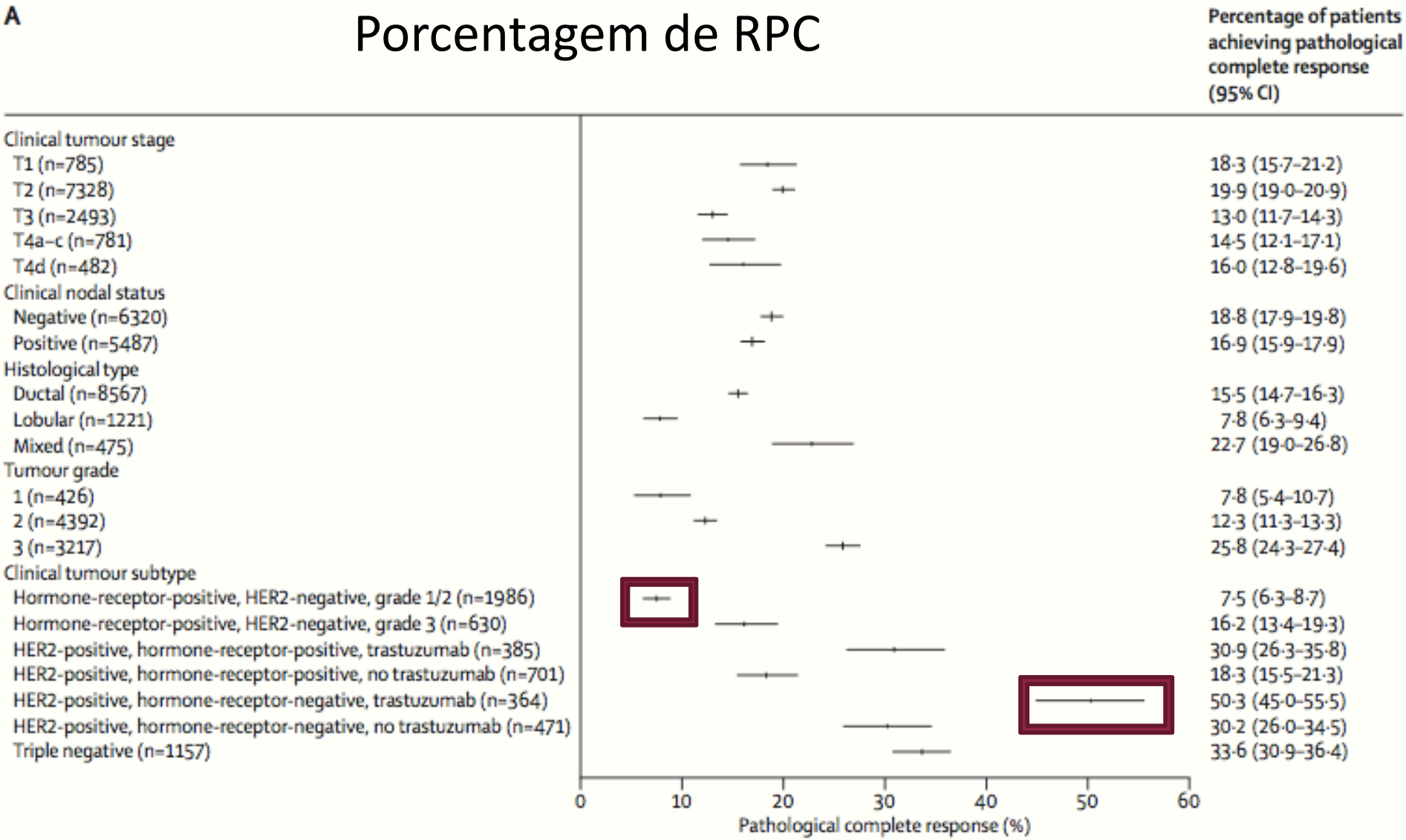
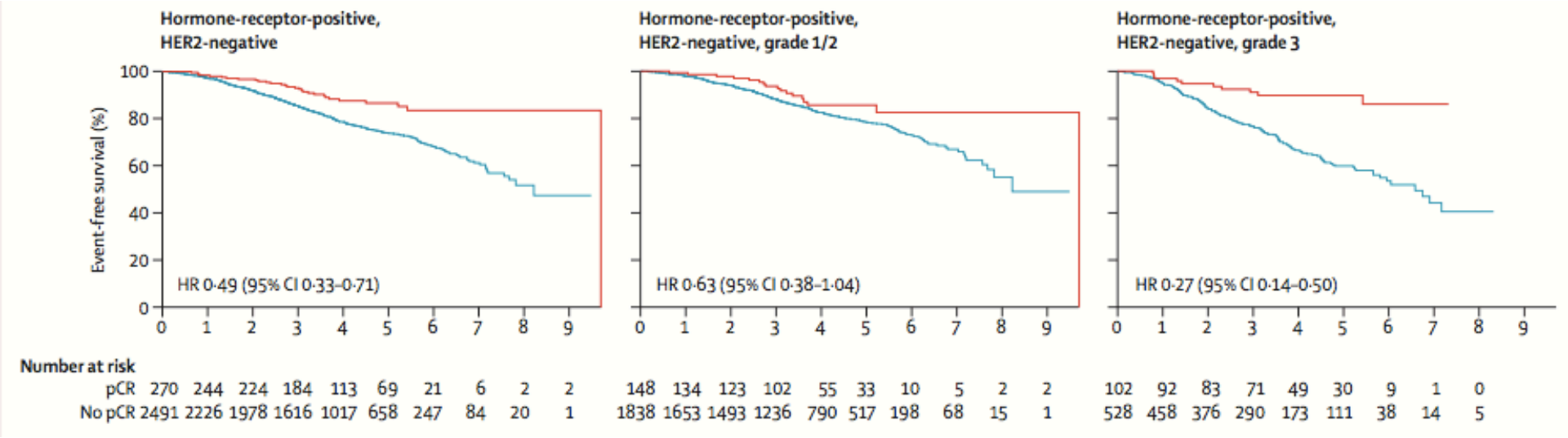


Figure 3: **Associations between three definitions of pathological complete response and event-free survival and overall survival**

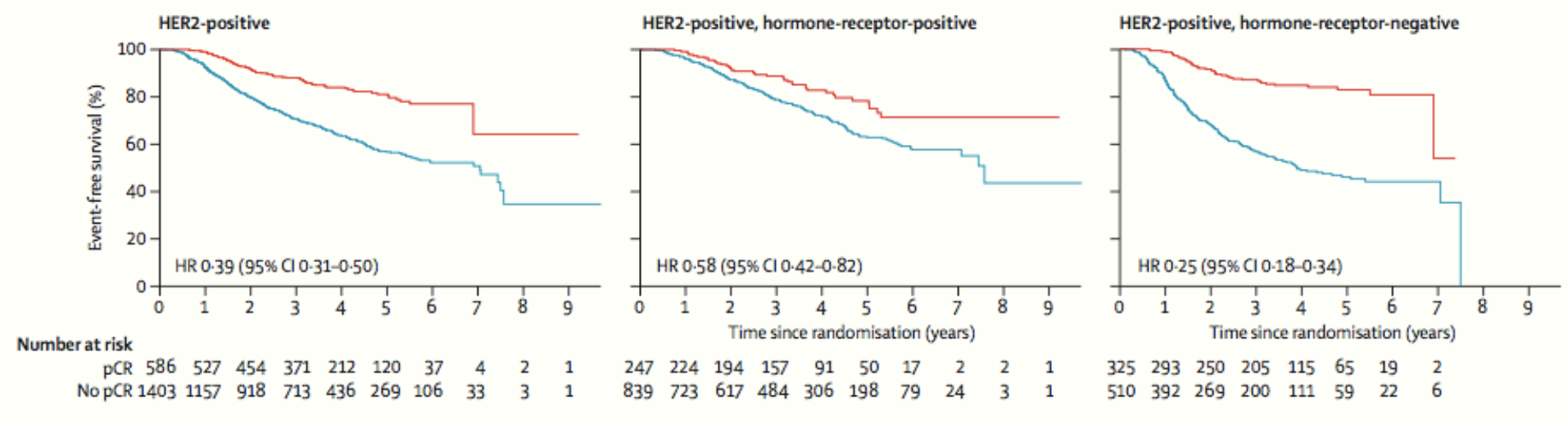
Porcentagem de RPC



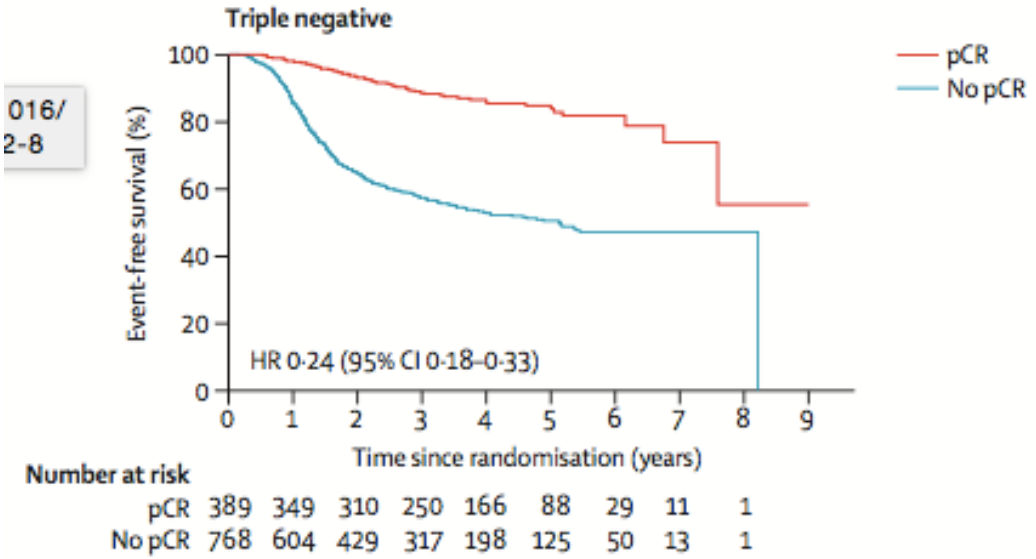
Rh+ HER 2 -


Hormone-receptor-positive, HER2-negative
Hormone-receptor-positive, HER2-negative, grade 1/2
Hormone-receptor-positive, HER2-negative, grade 3
Event-free survival (%)
100
80
60
40
20
0
HR 0·49 (95% CI 0·33–0·71)
HR 0·63 (95% CI 0·38–1·04)
HR 0·27 (95% CI 0·14–0·50)
0 1 2 3 4 5 6 7 8 9
Number at risk
pCR 270 244 224 184 113 69 21 6 2 2
No pCR 2491 2226 1978 1616 1017 658 247 84 20 1
pCR 148 134 123 102 55 33 10 5 2 2
No pCR 1838 1653 1493 1236 790 517 198 68 15 1
pCR 102 92 83 71 49 30 9 1 0
No pCR 528 458 376 290 173 111 38 14 5

HER 2 +



TRIPLO NEGATIVO



HER 2 POSITIVO

Estudo NOAH (MO16432):
Lancet 2010

Estudo NeoSphere
Lancet 2012
Lancet 2016

Estudo TRYPHAENA
Annals of Oncology 2013

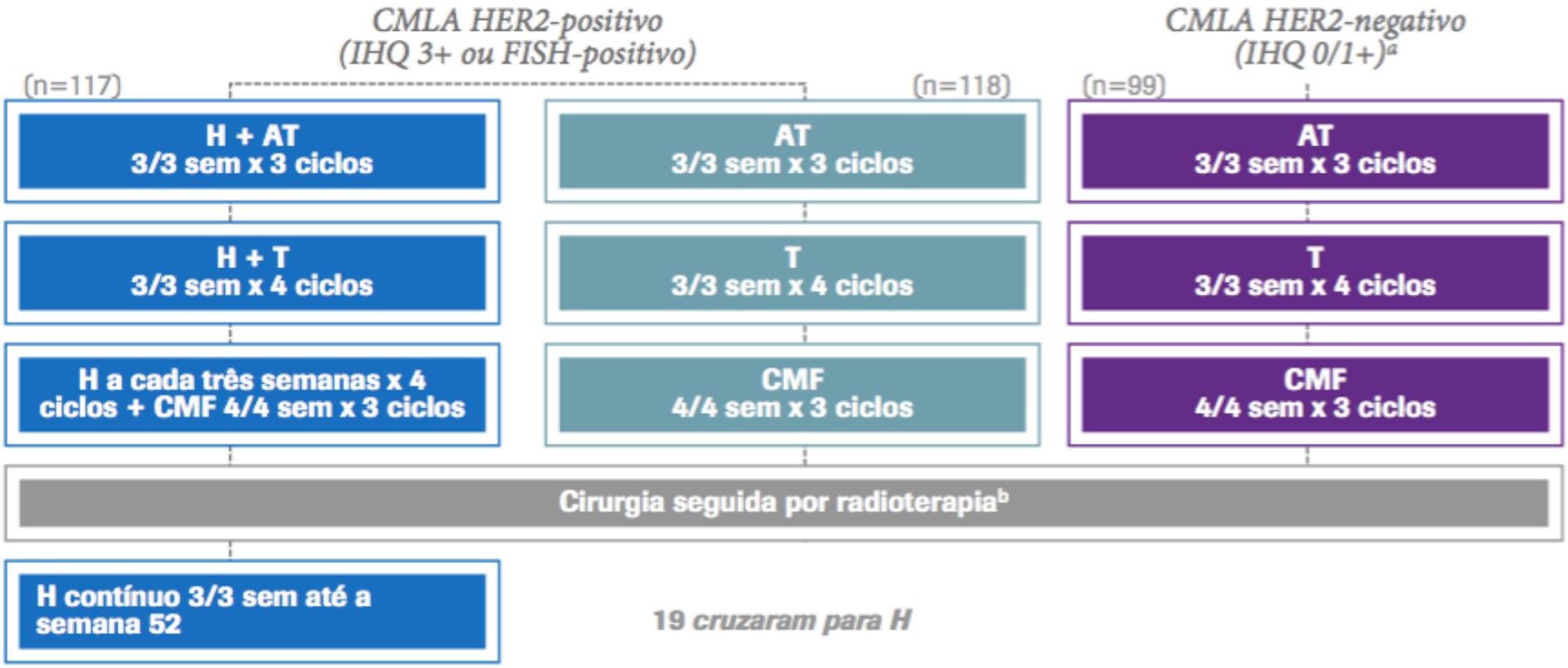
Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort

Luca Gianni, Wolfgang Eiermann, Vladimir Semiglazov, Alexey Manikhas, Ana Lluch, Sergey Tjulandin, Milvia Zambetti, Federico Vazquez, Mikhail Byakhow, Mikhail Lichinitser, Miguel Angel Climent, Eva Ciruelos, Belén Ojeda, Mauro Mansutti, Alla Bozhok, Roberta Baronio, Andrea Feyereislova, Claire Barton, Pinuccia Valagussa, Jose Baselga

Desenho do estudo

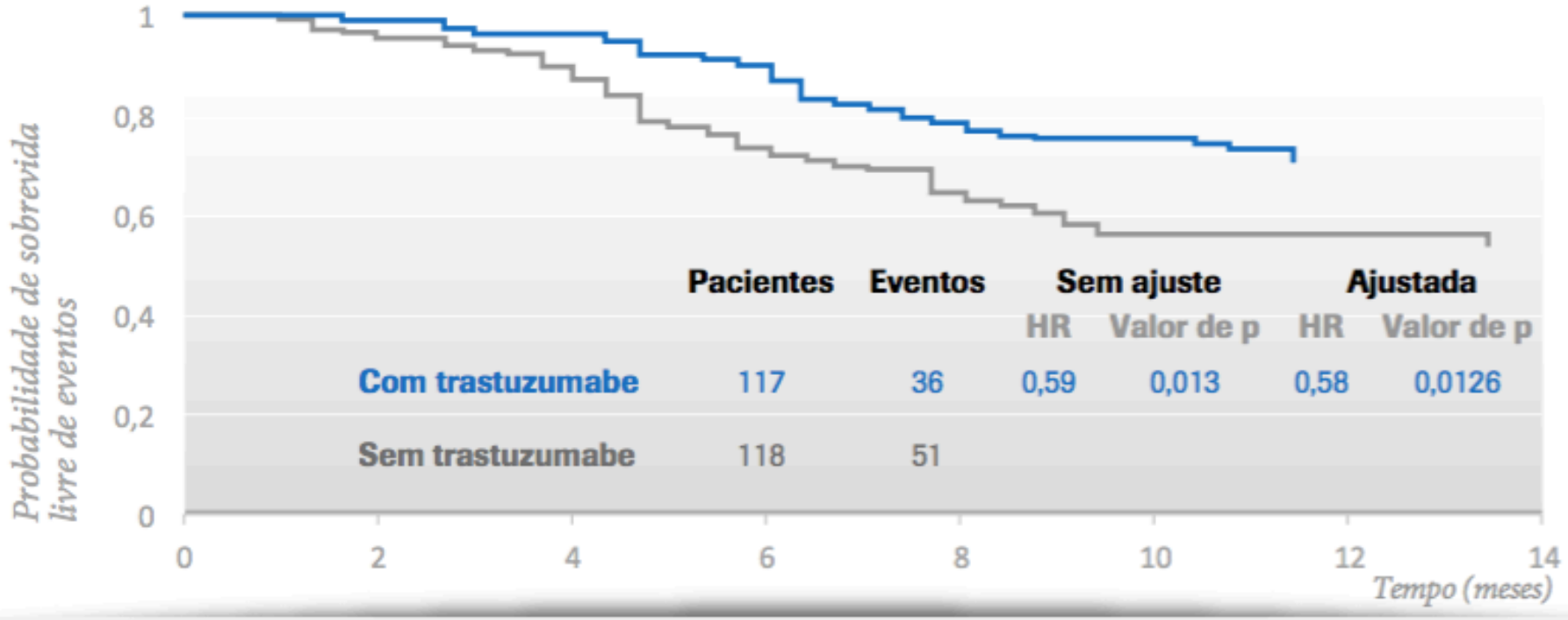
Estudo NOAH (MO16432): Lancet 2010

Um estudo internacional, aberto e fase III de trastuzumabe neoadjuvante–adjuvante em pacientes que apresentam câncer de mama localmente avançado ou inflamatório HER2- positivo



SLE na ITT HER2-positiva

Benefício significativo de SLE com adição de trastuzumabe à quimioterapia em pacientes HER2-positivas



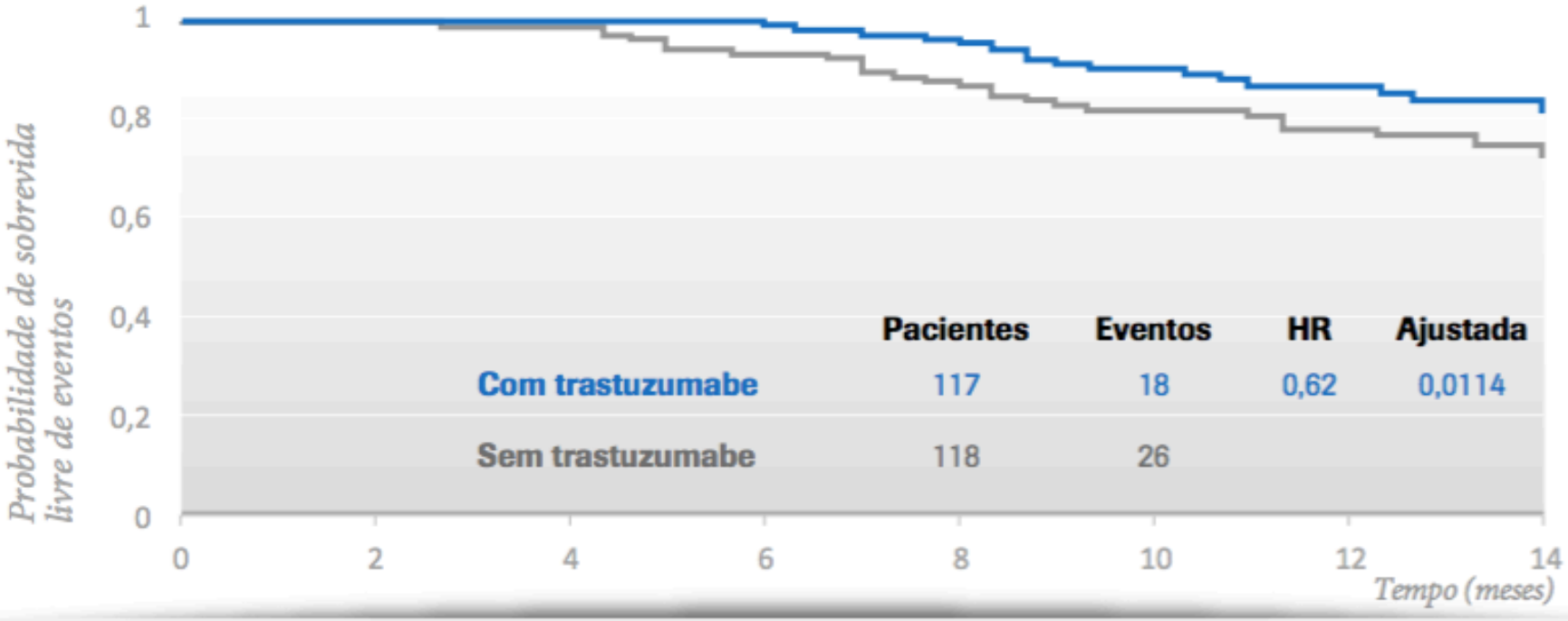
	Pacientes	Eventos	Sem ajuste		Ajustada	
			HR	Valor de p	HR	Valor de p
Com trastuzumabe	117	36	0,59	0,013	0,58	0,0126
Sem trastuzumabe	118	51				

Nº em risco

117	113	109	102	87	75	58	40
118	109	100	82	71	58	40	22

Sobrevida global na população ITT HER2-positiva

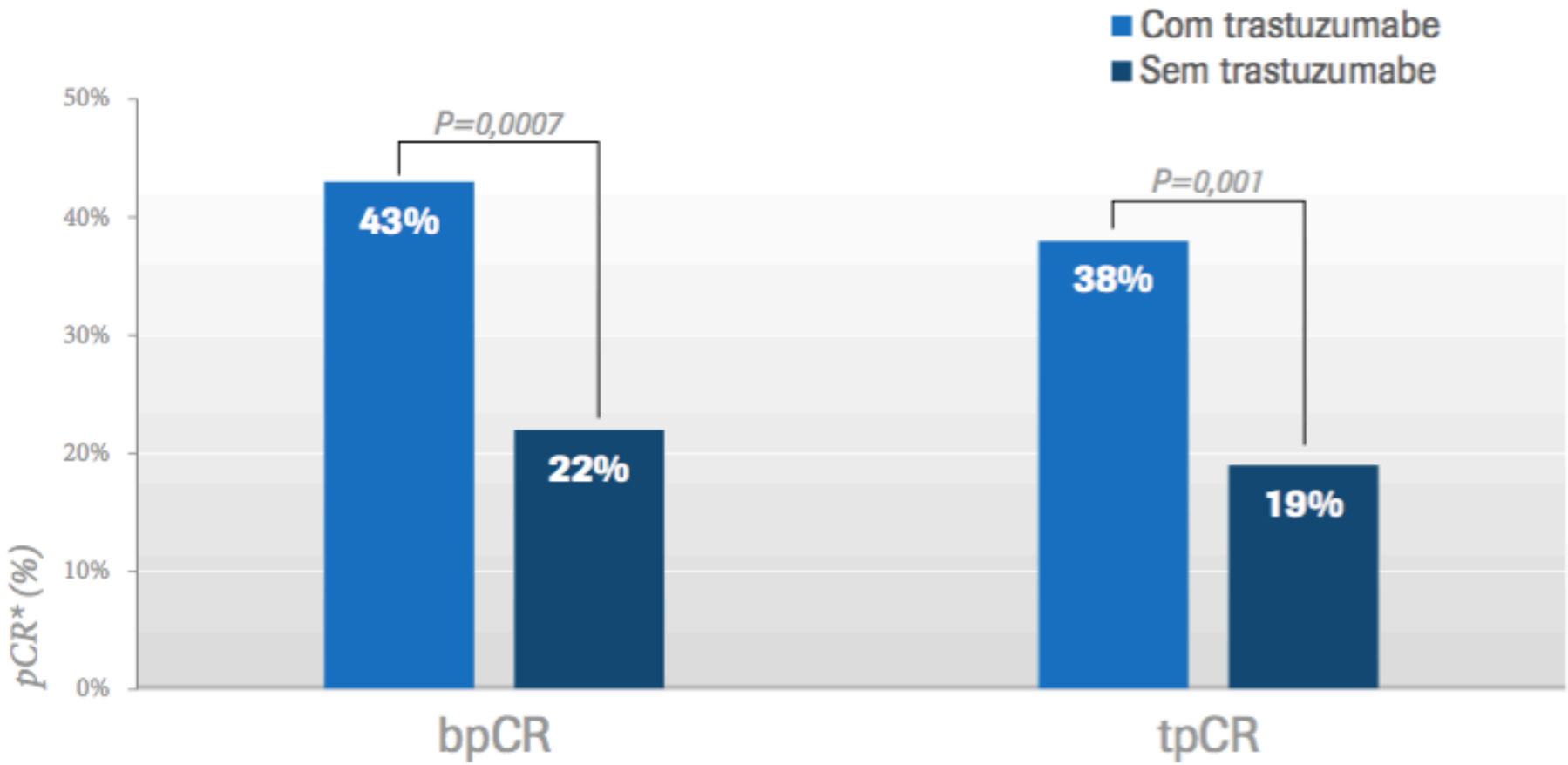
Tendência de benefício de sobrevida global com adição de trastuzumabe à quimioterapia em pacientes HER2-positivas



Nº em risco							
117	114	113	112	101	85	67	46
118	113	110	104	93	81	57	34

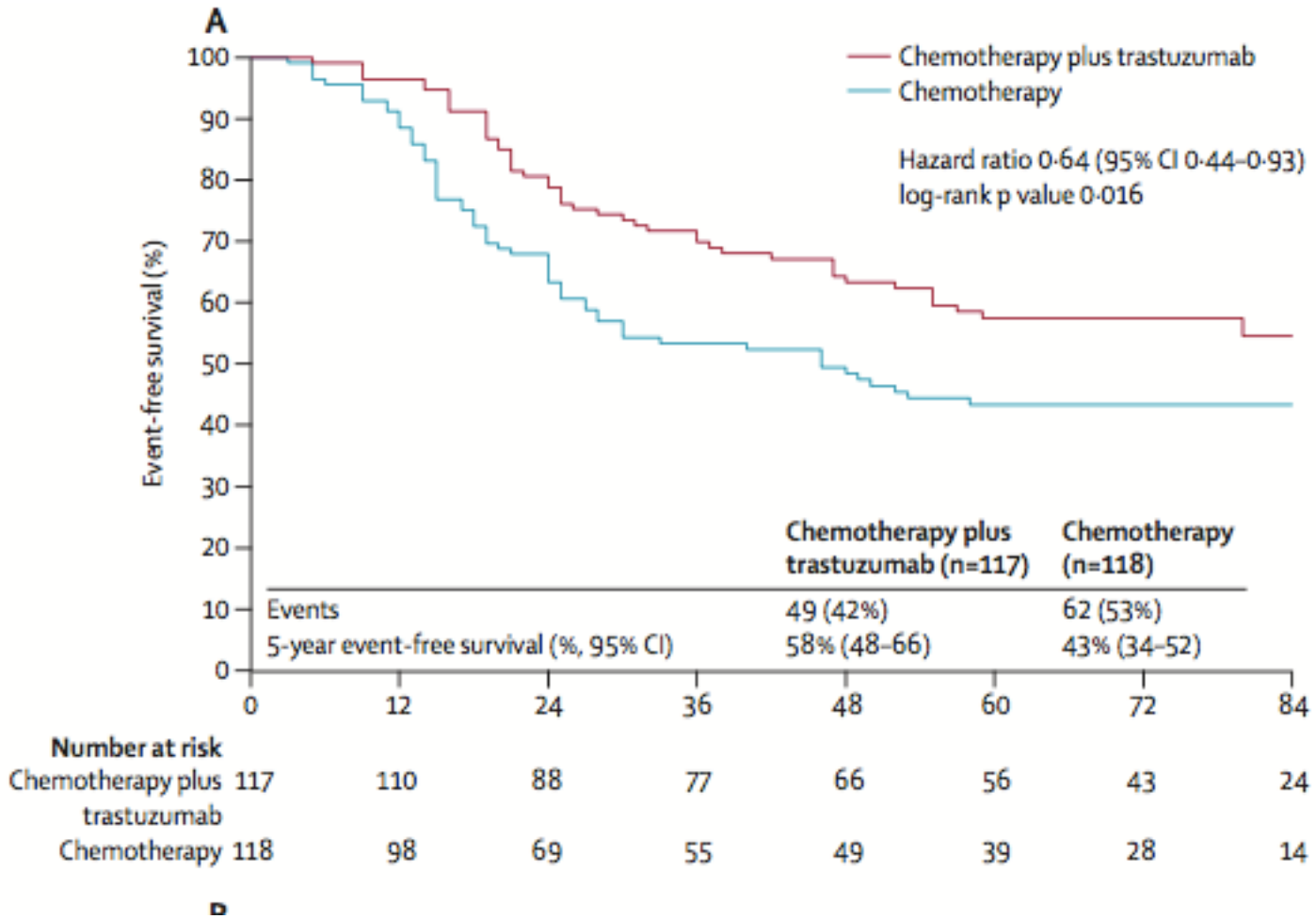
Taxas de pCR na população ITT

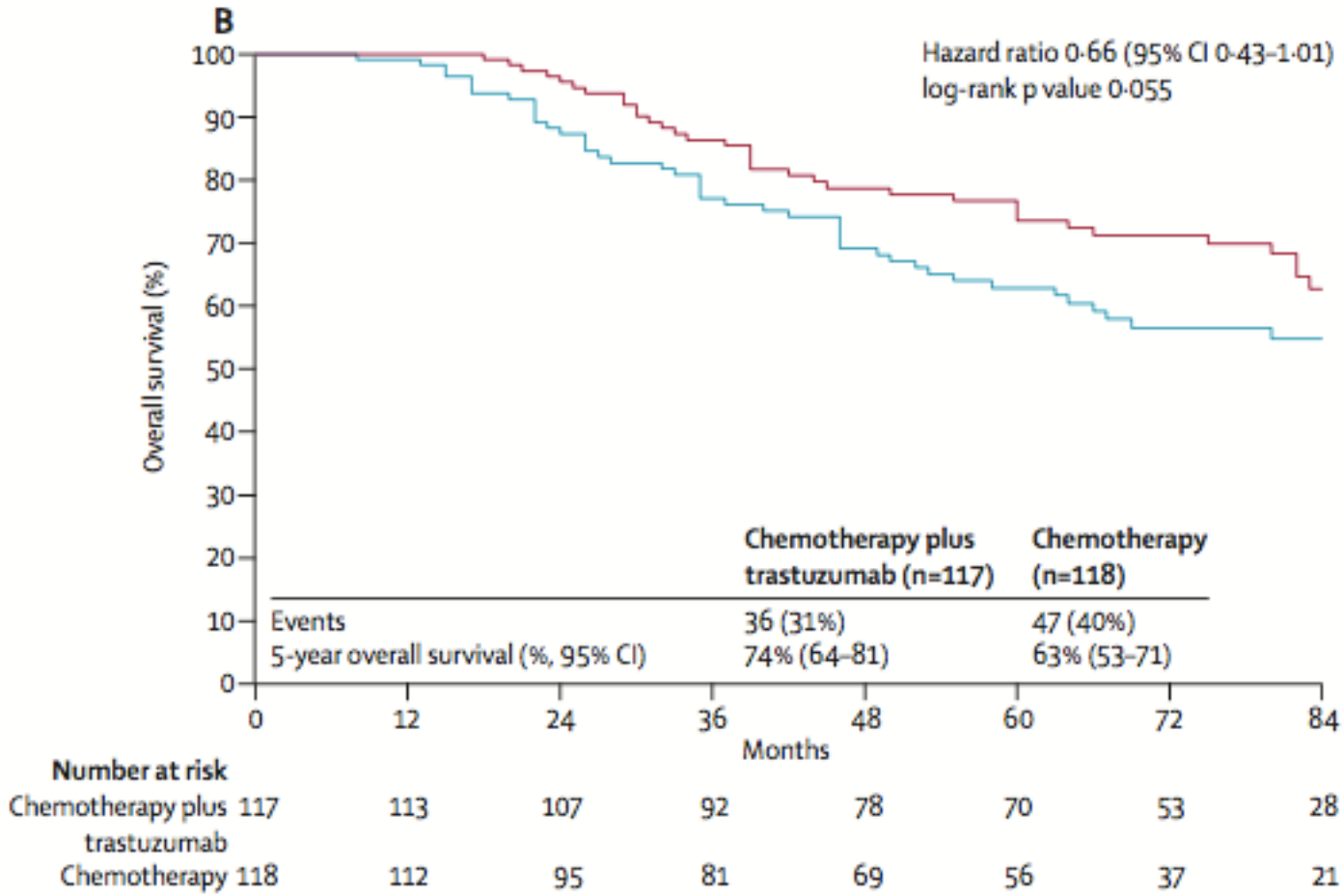
Melhora significativa em pCR com adição de trastuzumabe à quimioterapia nos grupos de tratamento HER2-positivos



Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort

Luca Gianni, Wolfgang Eiermann, Vladimir Semiglazov, Ana Lluch, Sergei Tjulandin, Milvia Zambetti, Angela Moliterni, Federico Vazquez, Mikhail J Byakhov, Mikhail Lichinitser, Miguel Angel Climent, Eva Ciruelos, Belen Ojeda, Mauro Mansutti, Alla Bozhok, Domenico Magazzù, Dominik Heinzmann, Jutta Steinseifer, Pinuccia Valagussa, Jose Baselga


A
Chemotherapy plus trastuzumab
Chemotherapy
Hazard ratio 0·64 (95% CI 0·44–0·93)
log-rank p value 0·016
Event-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
Chemotherapy plus trastuzumab (n=117)
Chemotherapy (n=118)
Events
49 (42%)
62 (53%)
5-year event-free survival (%, 95% CI)
58% (48–66)
43% (34–52)
0
12
24
36
48
60
72
84
Number at risk
Chemotherapy plus trastuzumab 117 110 88 77 66 56 43 24
Chemotherapy 118 98 69 55 49 39 28 14
B


B
Hazard ratio 0·66 (95% CI 0·43–1·01)
log-rank p value 0·055
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Chemotherapy plus trastuzumab (n=117)
Chemotherapy (n=118)
Events
36 (31%)
47 (40%)
5-year overall survival (%, 95% CI)
74% (64–81)
63% (53–71)
0
12
24
36
48
60
72
84
Months
Number at risk
Chemotherapy plus trastuzumab 117 113 107 92 78 70 53 28
Chemotherapy 118 112 95 81 69 56 37 21

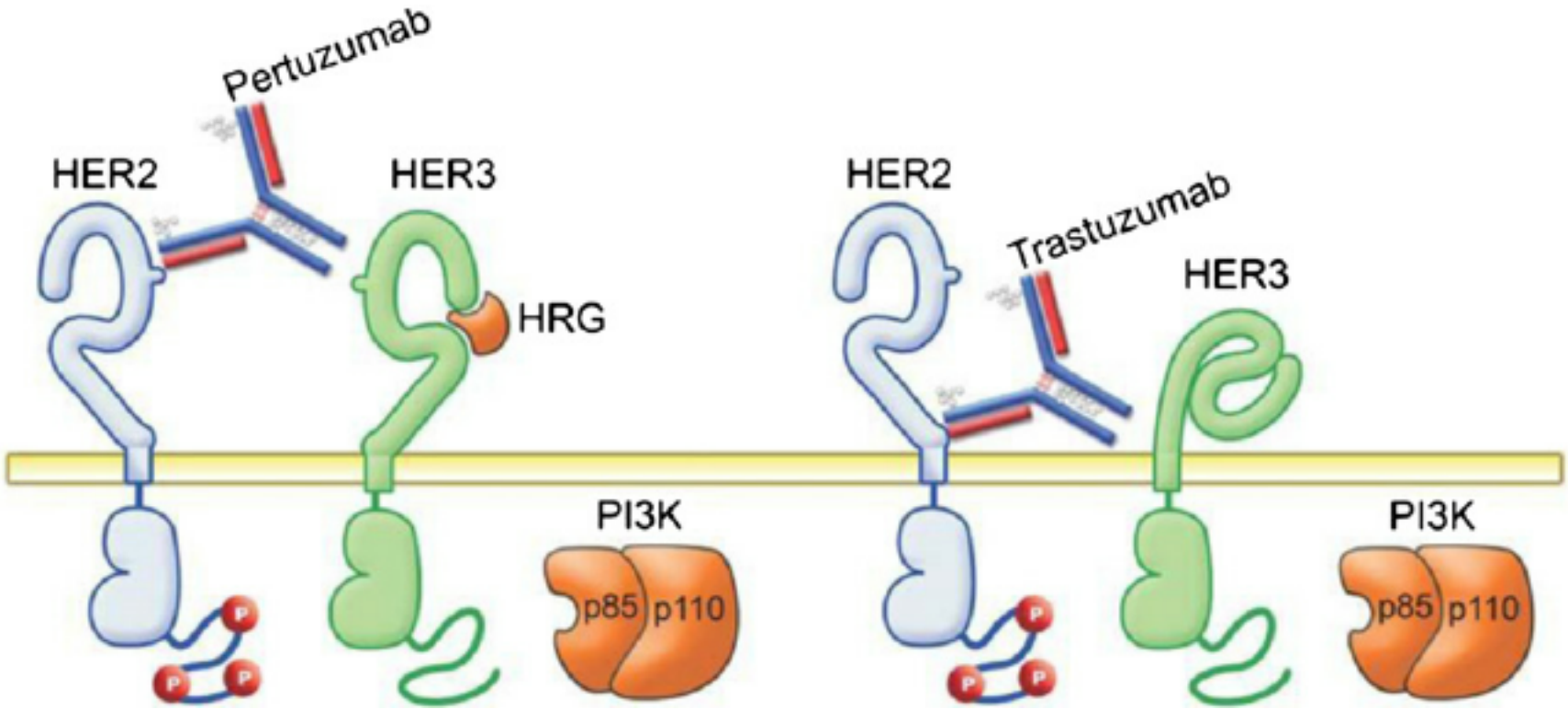
Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa

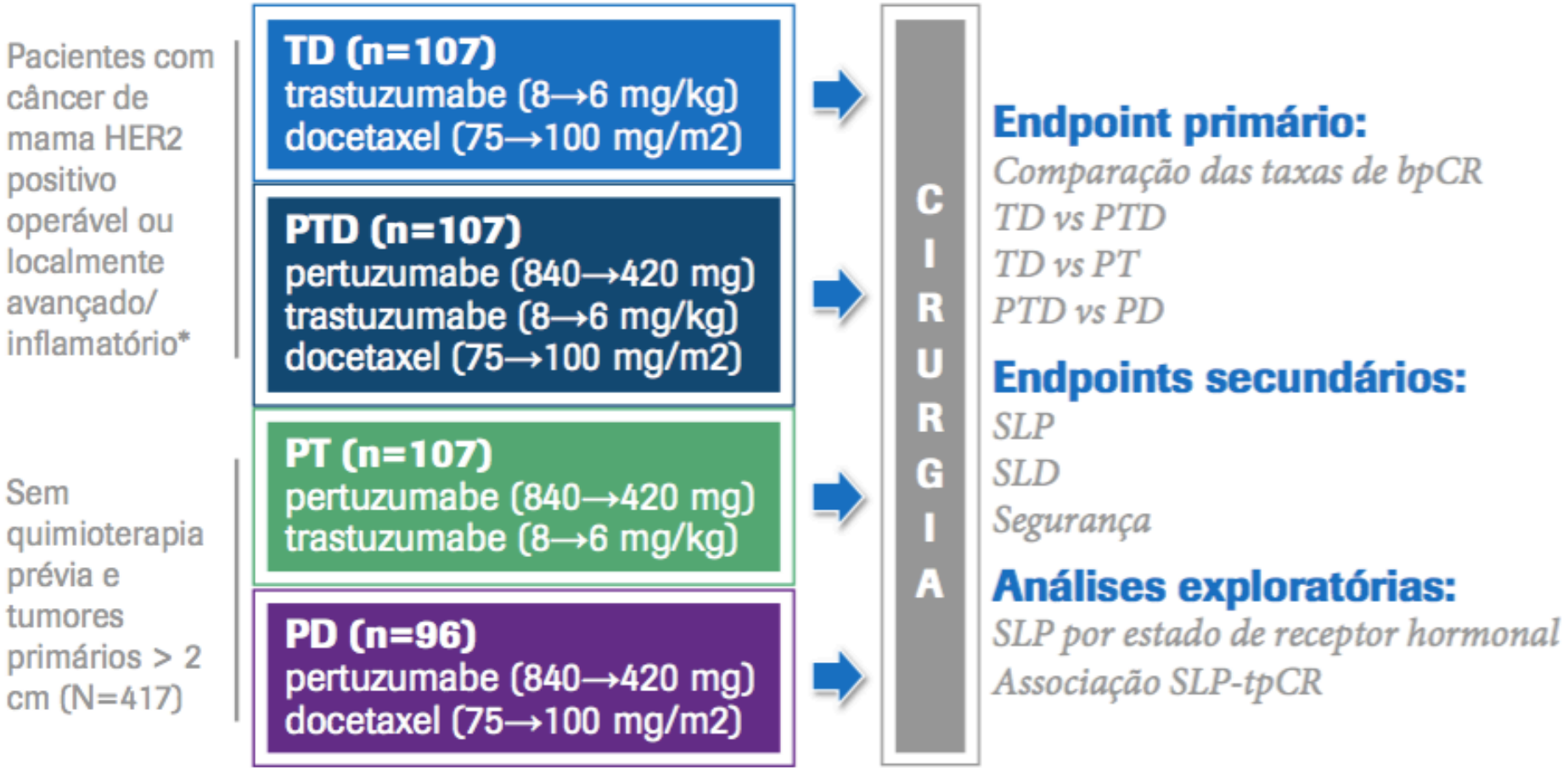
Estudo NeoSphere
Lancet 2012
Lancet 2016

5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial

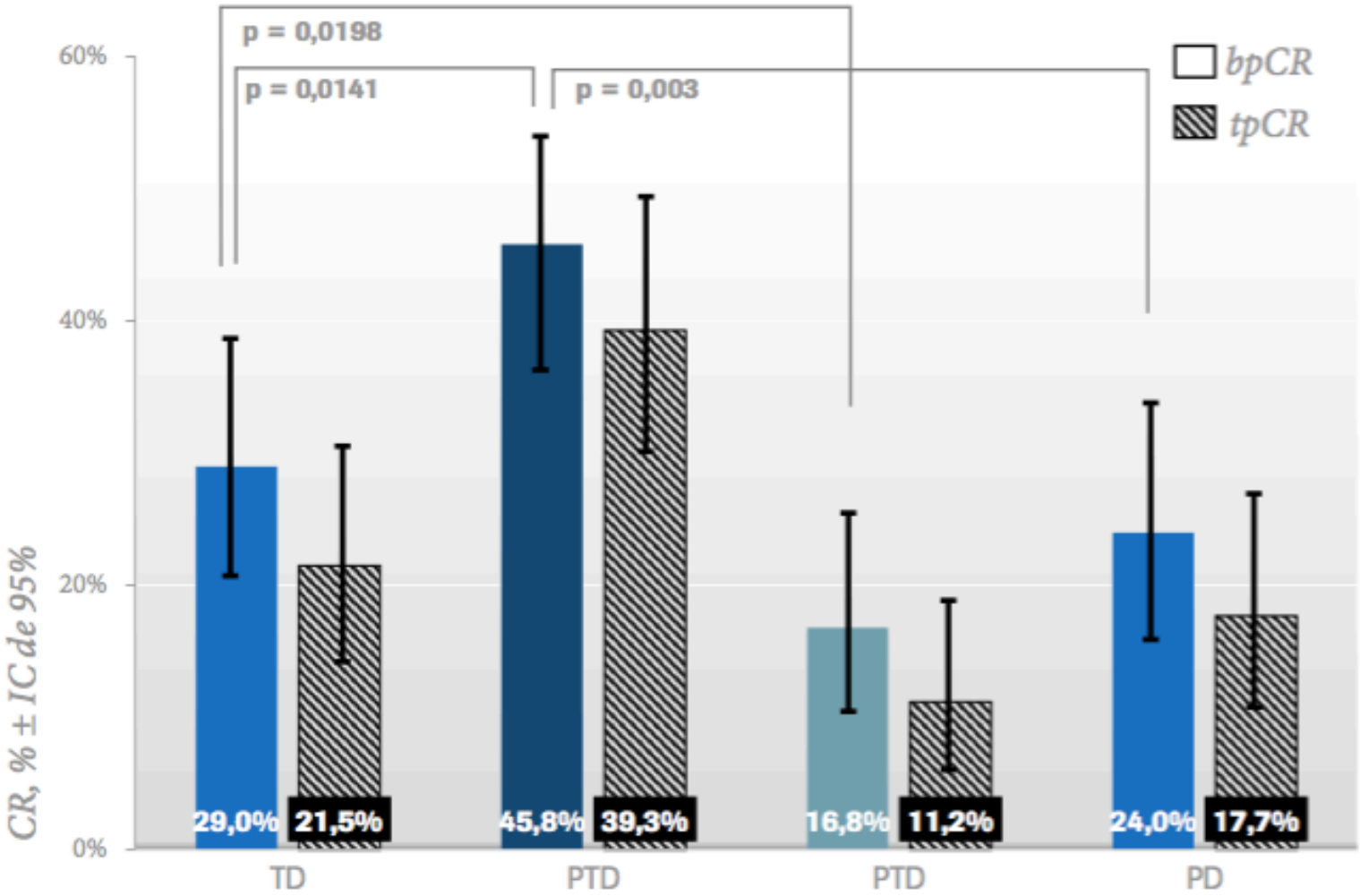
Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Starosławska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Valeria Bianchi, Domenico Magazzù, Virginia McNally, Hannah Douthwaite, Graham Ross, Pinuccia Valagussa


Pertuzumab
HER2
HER3
HRG
PI3K
p85
p110
HER2
Trastuzumab
HER3
PI3K
p85
p110

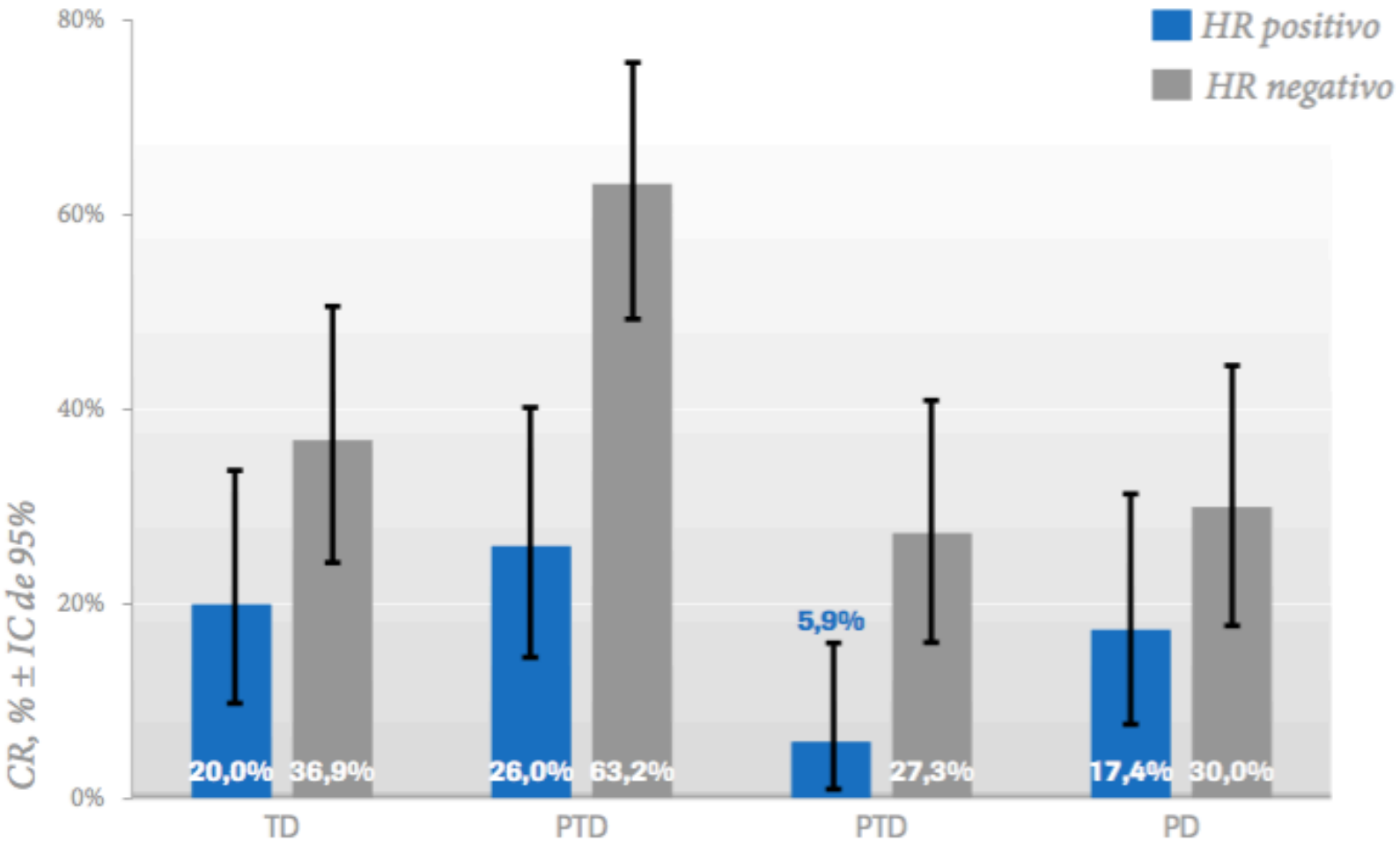
NeoSphere: desenho e objetivos do estudo



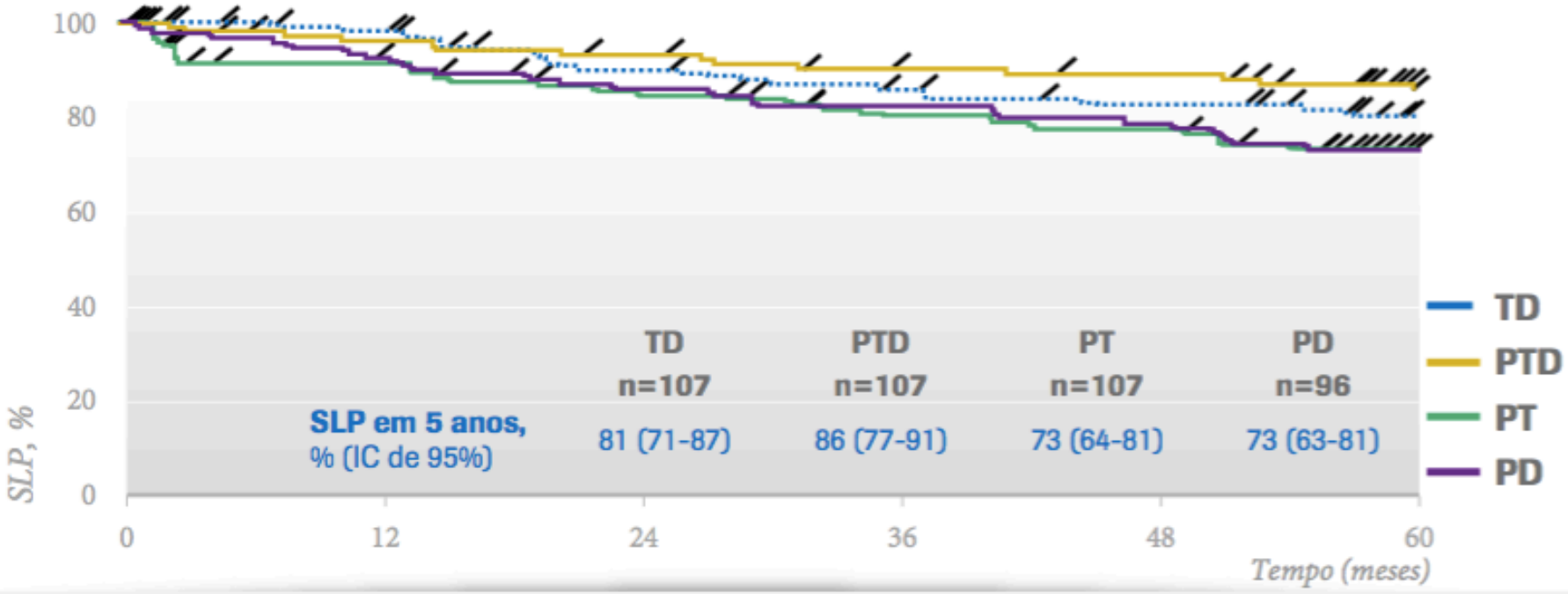
Resultados pCR



Resultados bpCR

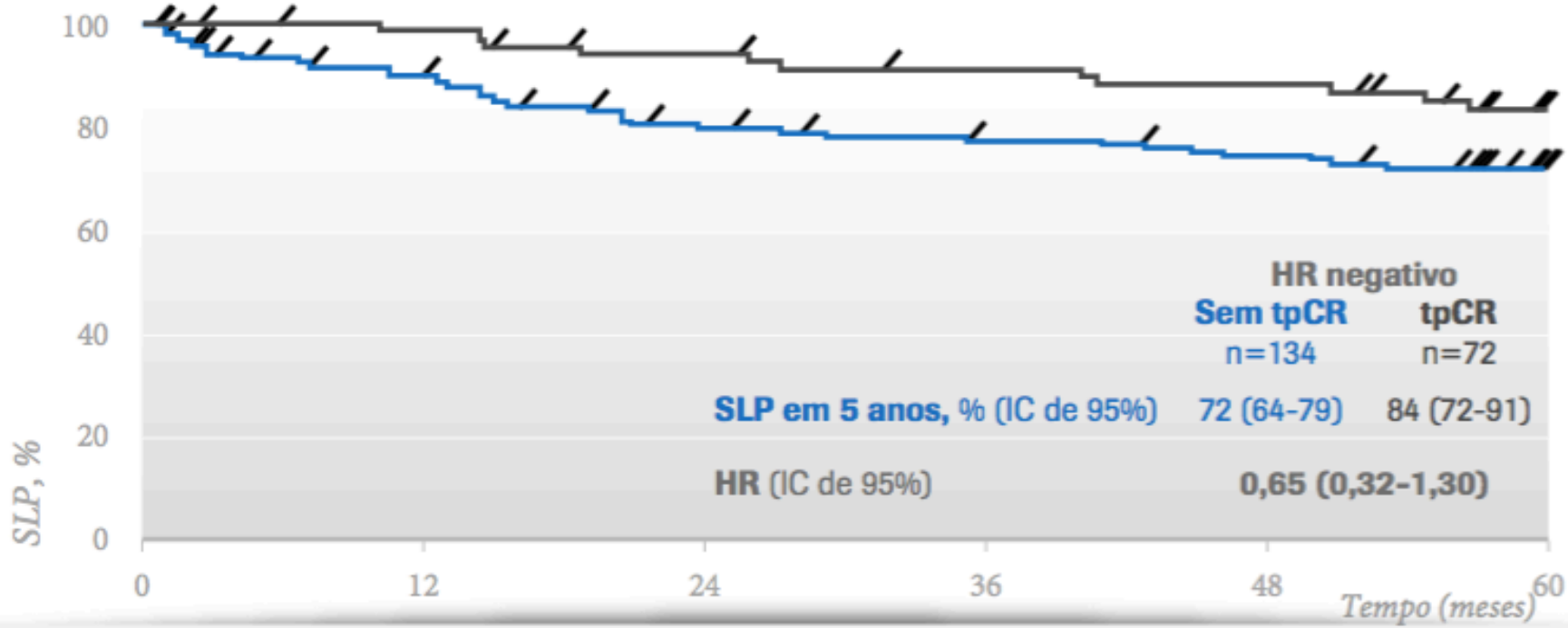


SLP: todos os braços de terapia, população ITT



Nº em risco						
TD	107	101	89	83	78	58
PTD	107	99	94	88	86	63
PT	107	93	86	80	77	55
PD	96	85	76	72	69	57

SLP para tpCR e sem tpCR por estado de receptor hormonal, População ITT – tumores HR negativos



	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=108)	Pertuzumab plus docetaxel (group D; n=94)
Alopecia	70 (65%)	68 (64%)	1 (1%)	63 (67%)
Neutropenia	67 (63%)	54 (50%)	1 (1%)	59 (63%)
Diarrhoea	36 (34%)	49 (46%)	30 (28%)	51 (54%)
Nausea	39 (36%)	41 (38%)	15 (14%)	34 (36%)
Fatigue	29 (27%)	28 (26%)	13 (12%)	24 (26%)
Rash	23 (21%)	28 (26%)	12 (11%)	27 (29%)
Mucosal inflammation	23 (21%)	28 (26%)	3 (3%)	24 (26%)
Myalgia	24 (22%)	24 (22%)	10 (9%)	19 (20%)
Asthenia	19 (18%)	22 (21%)	3 (3%)	15 (16%)
Headache	12 (11%)	12 (11%)	15 (14%)	12 (13%)

Data are n (%).

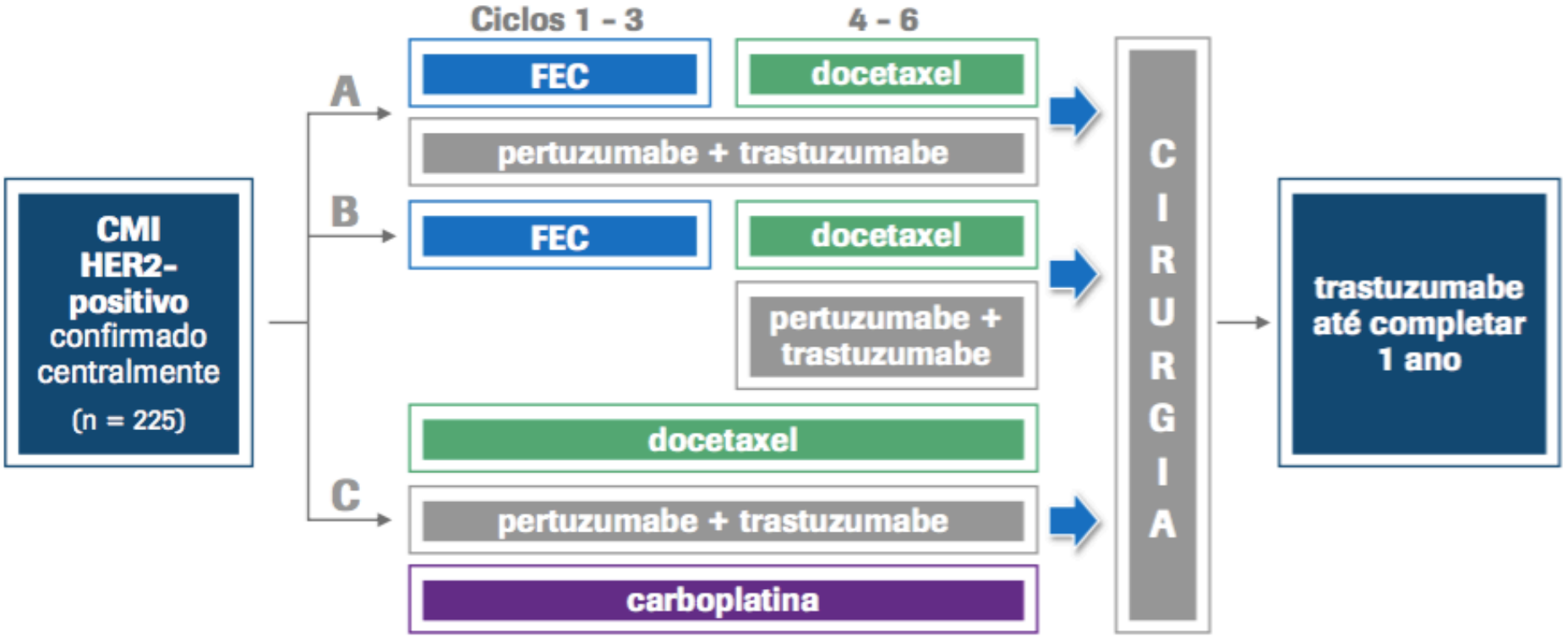
Table 4: Summary of the ten most common adverse events (any grade)

Annals of Oncology 24: 2278–2284, 2013
doi:10.1093/annonc/mdt182
Published online 22 May 2013

Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA)

A. Schneeweiss[1*], S. Chia[2], T. Hickish[3], V. Harvey[4], A. Eniu[5], R. Hegg[6], C. Tausch[7], J. H. Seo[8], Y.-F. Tsai[9], J. Ratnayake[10], V. McNally[10], G. Ross[10] & J. Cortés[11]

[1]National Center for Tumor Diseases, University Hospital, Heidelberg, Germany; [2]British Columbia Cancer Agency – Vancouver Centre, University of British Columbia, Vancouver, Canada; [3]Royal Bournemouth Hospital, Bournemouth University, Bournemouth, UK; [4]Regional Cancer and Blood Centre, Auckland City Hospital, Auckland, New Zealand; [5]Cancer Institute "I Chiricuta", Cluj-Napoca, Romania; [6]Hospital Pérola Byington and FMUSP, São Paulo, Brazil; [7]Breast Center, Zürich, Switzerland; [8]Division of Medical Oncology, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea; [9]Taipei-Veterans General Hospital, Taipei, Taiwan; [10]Roche Products Limited, Welwyn, UK; [11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain



Todos os 3 braços foram experimentais

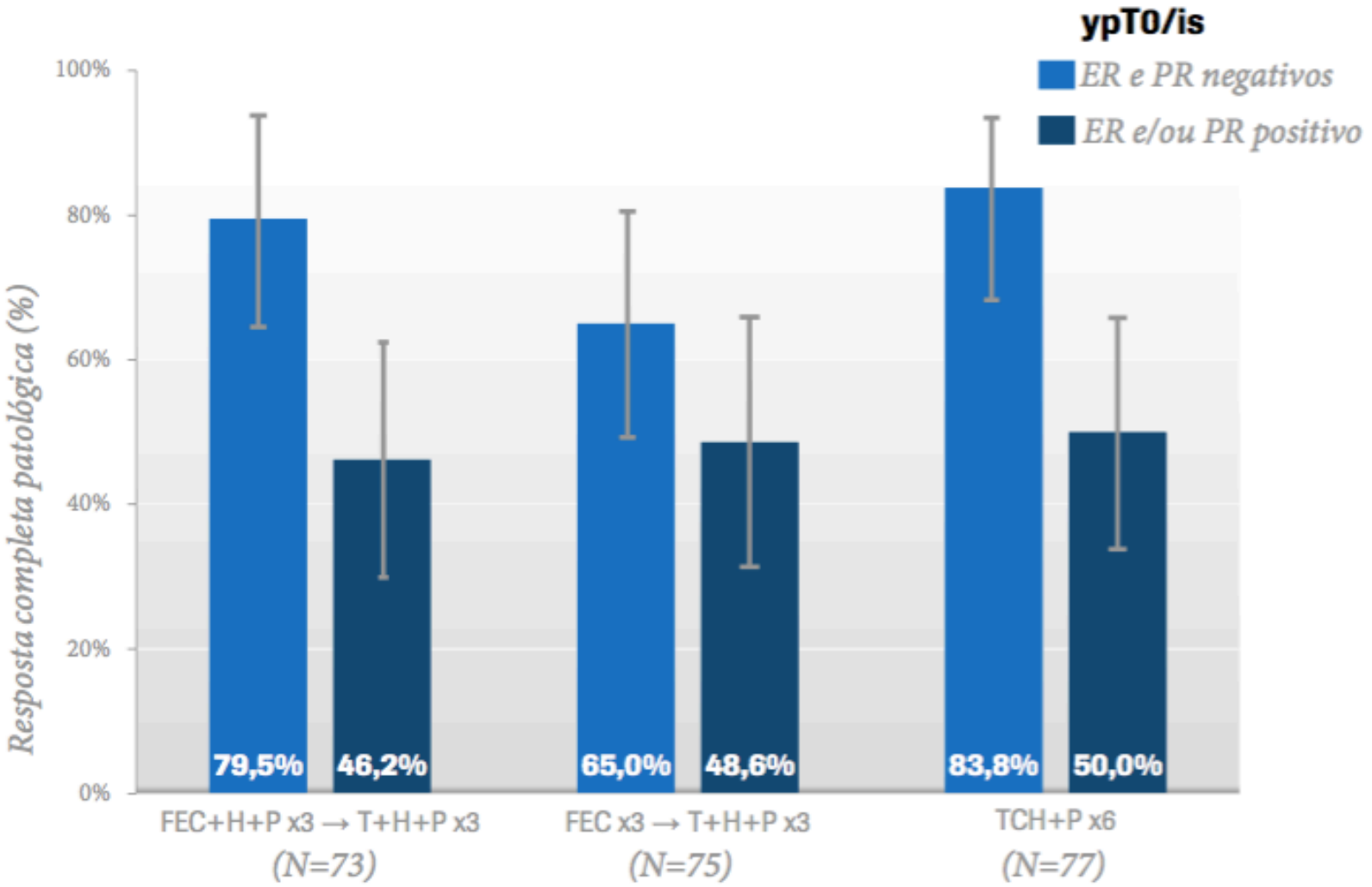
Administração do estudo a cada três semanas:

FEC: 500 mg/m², 100 mg/m², 600 mg/m²
Carboplatina: AUC 6
Trastuzumabe: Dose de ataque de 8 mg/kg, dose de manutenção de 6 mg/kg
Pertuzumabe: Dose de ataque de 840 mg, 420 mg de manutenção
Docetaxel: 75 mg/m² (com aumento para 100 mg/m², se tolerado, apenas nos braços A e B)

Eventos cardíacos durante o tratamento neoadjuvante

	FEC+H+P x3 → T+H+P x3 (n = 72)	FEC x3 → T+H+P x3 (n = 75)	TCH+P x6 (n=76)
DVSE sintomática (grau ≥3), n (%)	0 (0,0)	2 (2,7)	0 (0,0)
DVSE (todos os graus), n (%)	4 (5,6)	3 (4,0)	2 (2,6)
Declínio de FEVE ≥ 10 pontos percentuais para menos de 50%, n (%)	3 (4,2)	4 (5,3)	3 (3,9)

Resposta completa patológica



HER 2 NEGATIVOS

- RH+:

- TRIPLO NEGATIVOS:

HER 2 NEGATIVOS

- RH+:
- Candidato a quimioterapia neoadjuvante?
- Mudança de conduta em caso de *downstage*?

- TRIPLO NEGATIVOS:
- Incorporar platina?

PRIMEIROS ESTUDOS

Study (year)	N° Pts	Regimen	cCR	cRP
Swain SM (1987)	76	CAMFx (2-11)	49%	**44%**
Perloff M (1988)	113	CAFVPx 3	22%	**55%**
Hortobagyi GN (1988)	174	CAFx 3	17%	**70%**
Jacquillant CL (1988)	98	VbTMFAPx (2-4)	23%	**68%**
Valagussa P (1990)	277	AVx (3-4)	7%	**55%**
Pierce LJ (1992)	107	CAMF	-	-
Schwartz GF (1994)	189	CMF or CAFx (3-11)	NA	**85%**
Zambetti M (1999)	88	E or A x 3	3%	**67%**

ESCOLHA DA QUIMIOTERAPIA

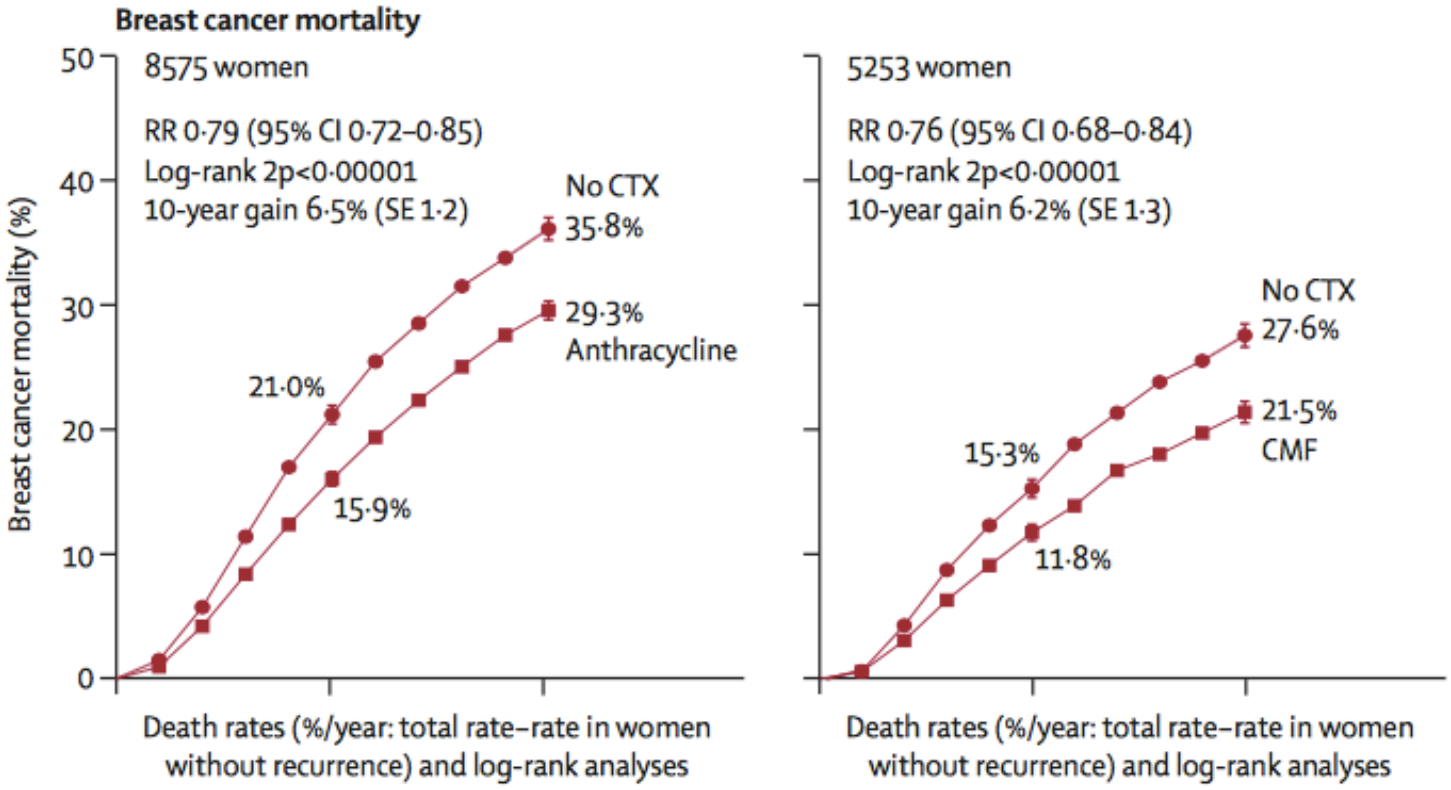
- Esquemas de quimioterapia conforme adjuvância:

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

www.thelancet.com Vol 379 February 4, 2012

QT x Não-QT

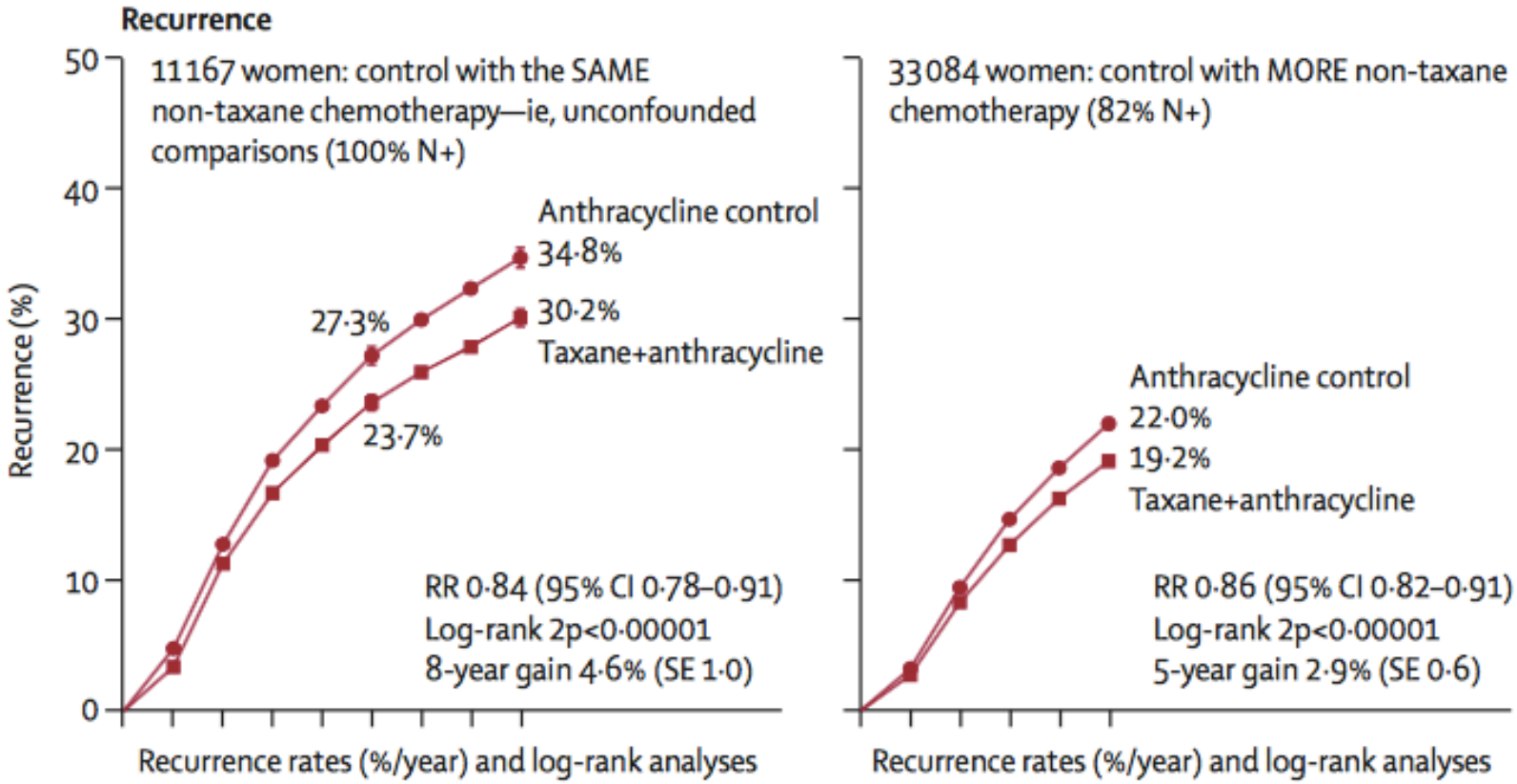


Allocation	Years 0–4	Years 5–9	Year 10+
CTX	3·38 SE 0·13	3·57 SE 0·16	2·83 SE 0·19
No CTX	4·77 SE 0·17	4·31 SE 0·21	2·98 SE 0·22
Rate ratio	0·73 SE 0·05	0·83 SE 0·07	0·92 SE 0·11
(O–E)/V	−97·5/307·0	−35·9/193·2	−6·7/81·0

Years 0–4	Years 5–9	Year 10+
2·51 SE 0·14	2·42 SE 0·16	1·80 SE 0·16
3·23 SE 0·17	3·14 SE 0·19	2·10 SE 0·18
0·75 SE 0·07	0·74 SE 0·08	0·82 SE 0·12
−43·5/151·3	−33·7/109·6	−11·9/59·1

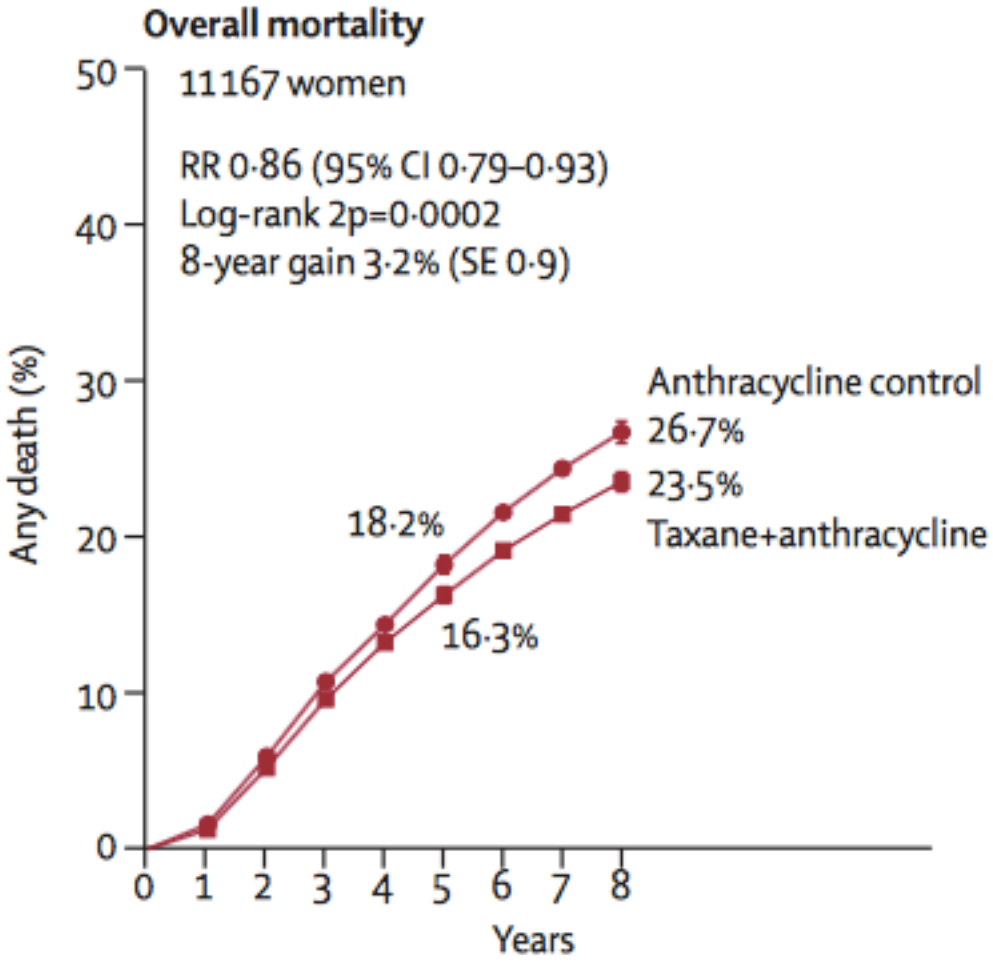
Overall mortality

BENEFICIO DO TAXANE



Allocation	Years 0–4	Year 5+	Years 0–4	Year 5+
Tax+anth	5·51 (1280/23 249)	3·10 (413/13 343)	4·37 (2607/59 665)	3·01 (153/5082)
Control	6·43 (1239/19 259)	3·62 (381/10 534)	5·02 (2586/51 508)	2·69 (127/4727)
Rate ratio	0·84 SE 0·04	0·85 SE 0·07	0·85 SE 0·03	1·03 SE 0·13
(O–E)/V	–95·5/557·3	–30·5/182·8	–181·4/1153·8	1·9/63·6

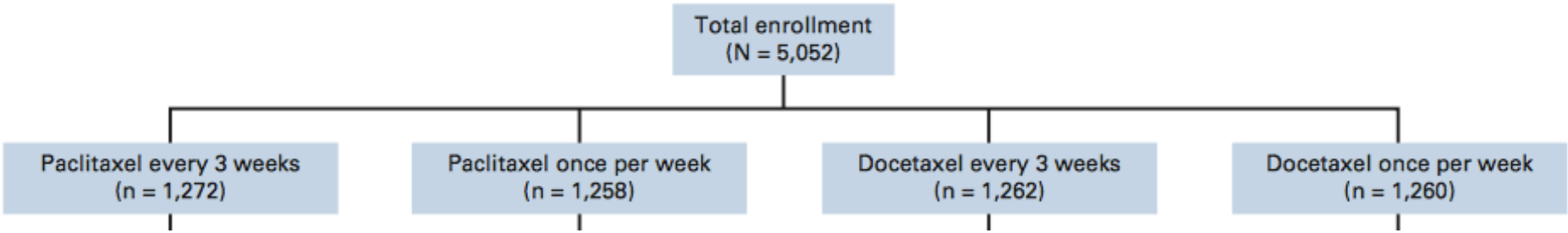
BENEFICIO DO TAXANE

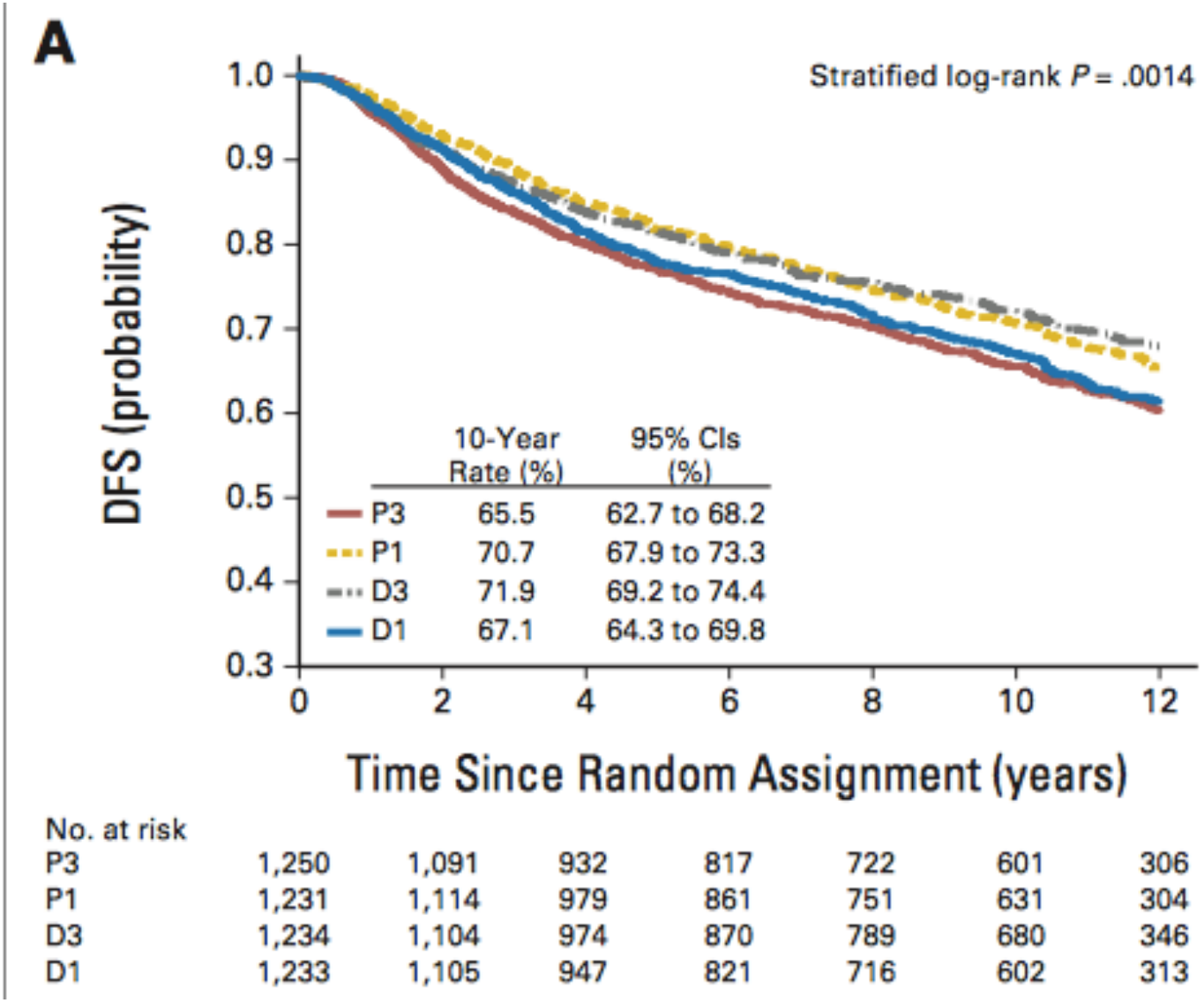


Escolha do taxane

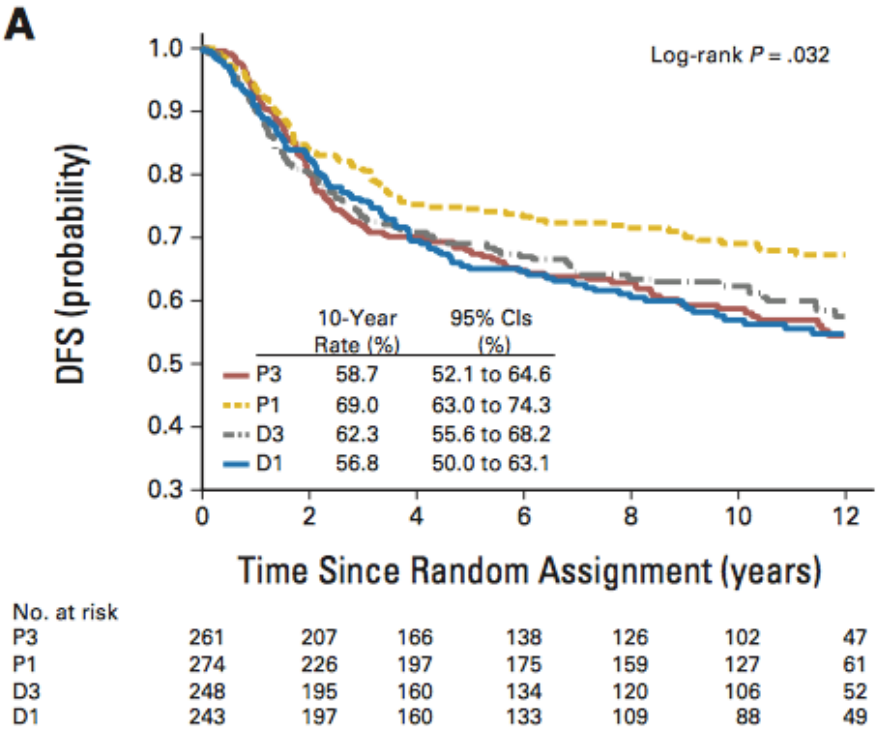
VOLUME 33 · NUMBER 21 · JULY 20 2015

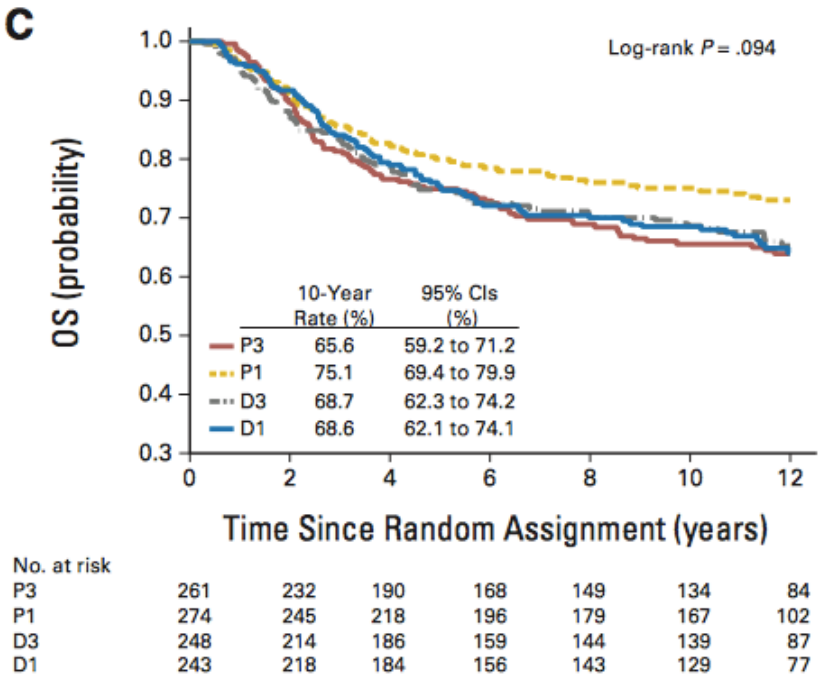
JOURNAL OF CLINICAL ONCOLOGY




A
Stratified log-rank P = .0014
DFS (probability)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
10-Year Rate (%)
95% CIs (%)
P3 65.5 62.7 to 68.2
P1 70.7 67.9 to 73.3
D3 71.9 69.2 to 74.4
D1 67.1 64.3 to 69.8
0 2 4 6 8 10 12
Time Since Random Assignment (years)
No. at risk
P3 1,250 1,091 932 817 722 601 306
P1 1,231 1,114 979 861 751 631 304
D3 1,234 1,104 974 870 789 680 346
D1 1,233 1,105 947 821 716 602 313

Triplo negativo

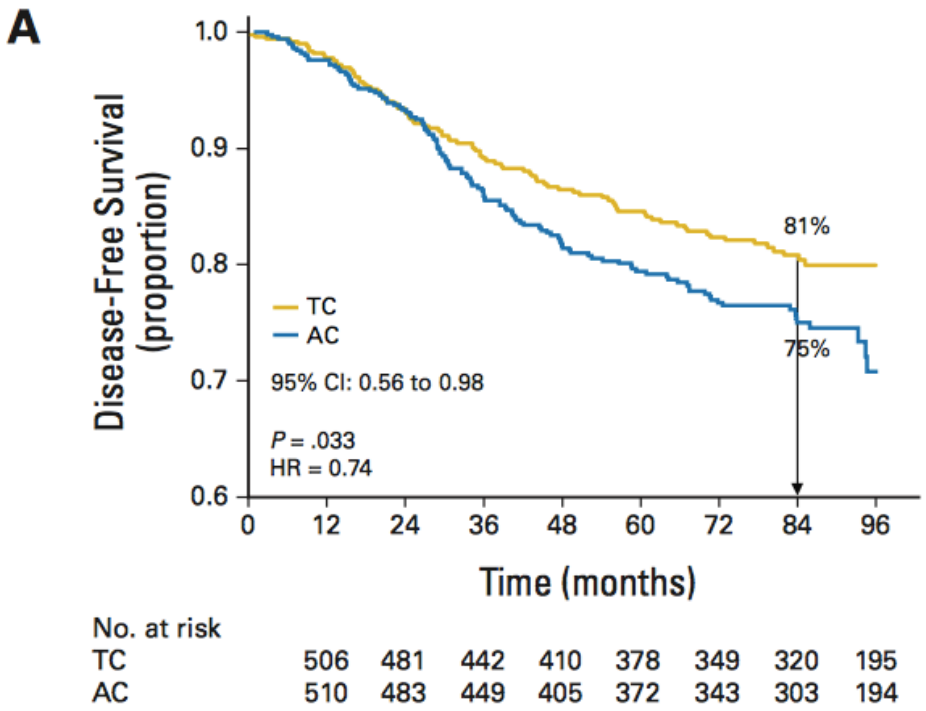


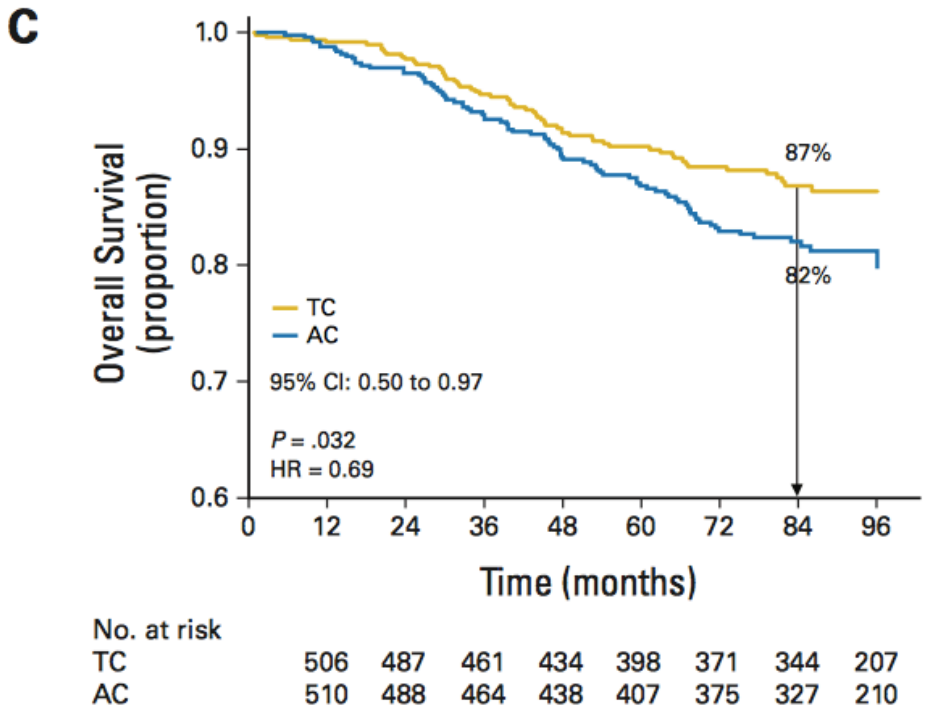


TC X AC

VOLUME 27 · NUMBER 8 · MARCH 10 2009

JOURNAL OF CLINICAL ONCOLOGY





Dose-Dense Chemotherapy in Nonmetastatic Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Luisa Bonilla, Irit Ben-Aharon, Liat Vidal, Anat Gafter-Gvili, Leonard Leibovici, Salomon M. Stemmer

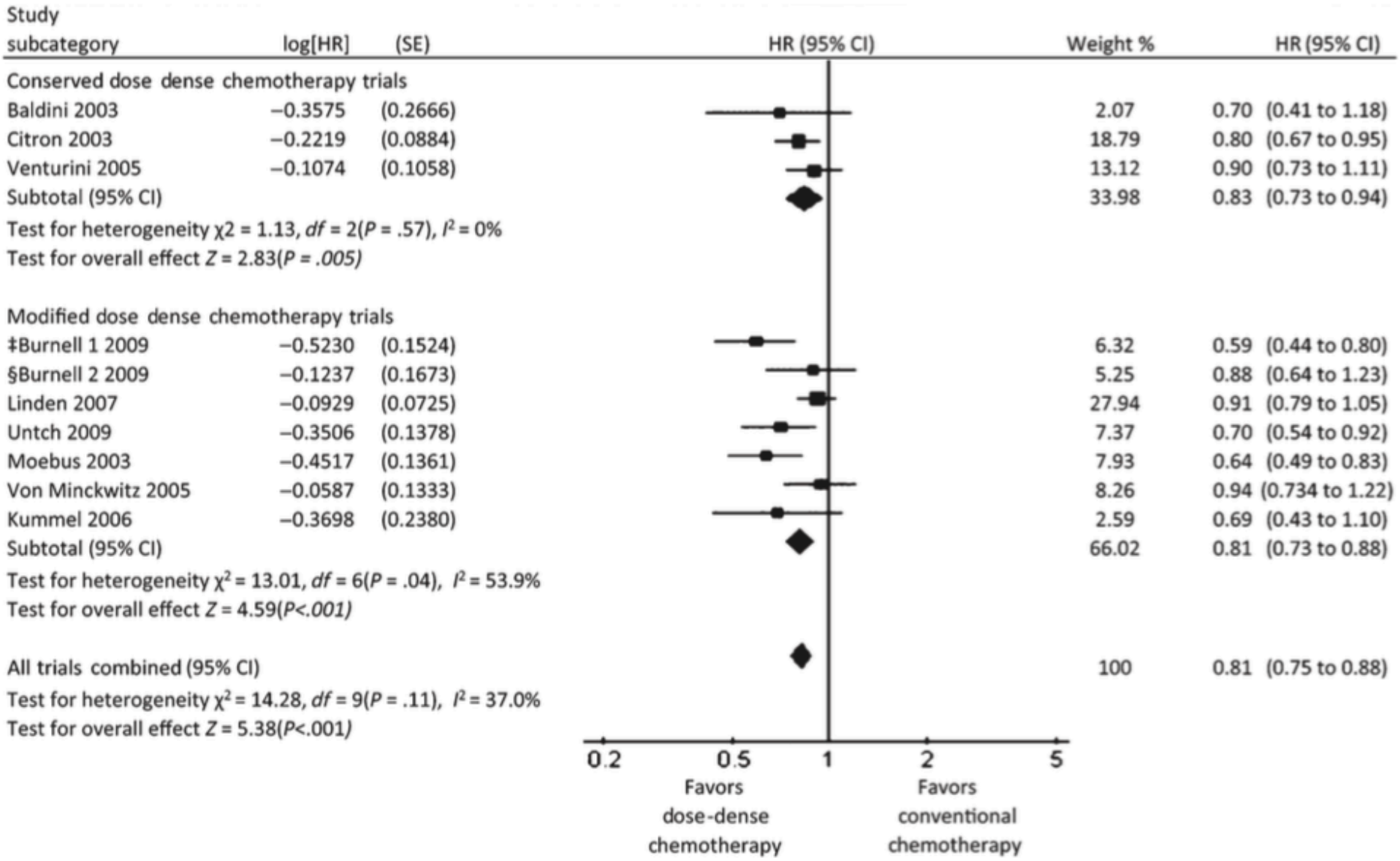
Manuscript received April 11, 2010; revised September 3, 2010; accepted September 17, 2010.

Correspondence to: Salomon M. Stemmer, MD, Institute of Oncology, Davidoff Center, Rabin Medical Center, Petah Tikva, Israel (e-mail: shtemers@clalit.org.il).

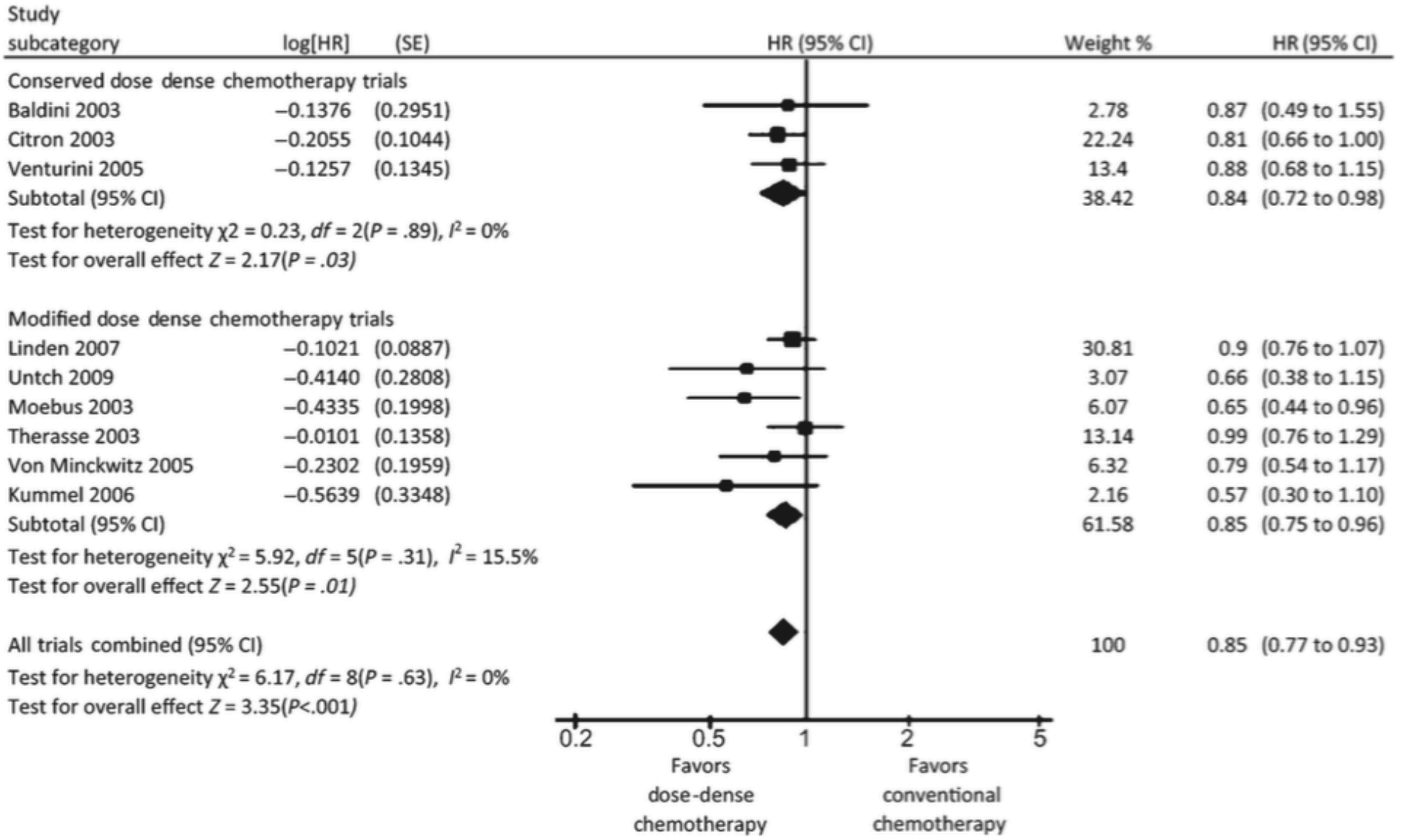
J Natl Cancer Inst 2010;102:1845–1854

10 ESTUDOS HETEROGÊNEOS

SOBREVIDA LIVRE DE RECORRÊNCIA

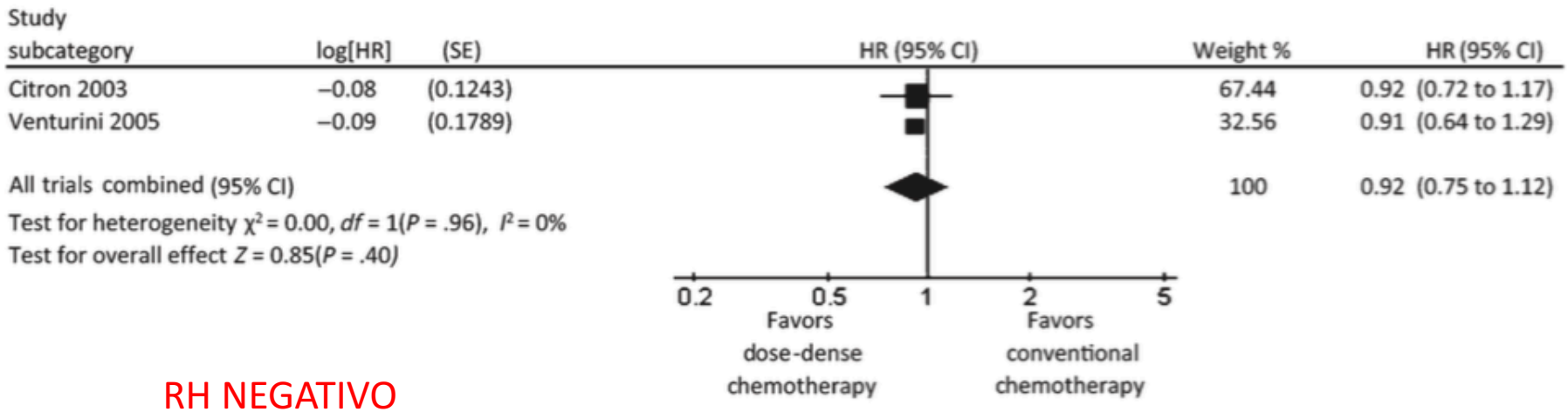


SOBREVIDA GLOBAL



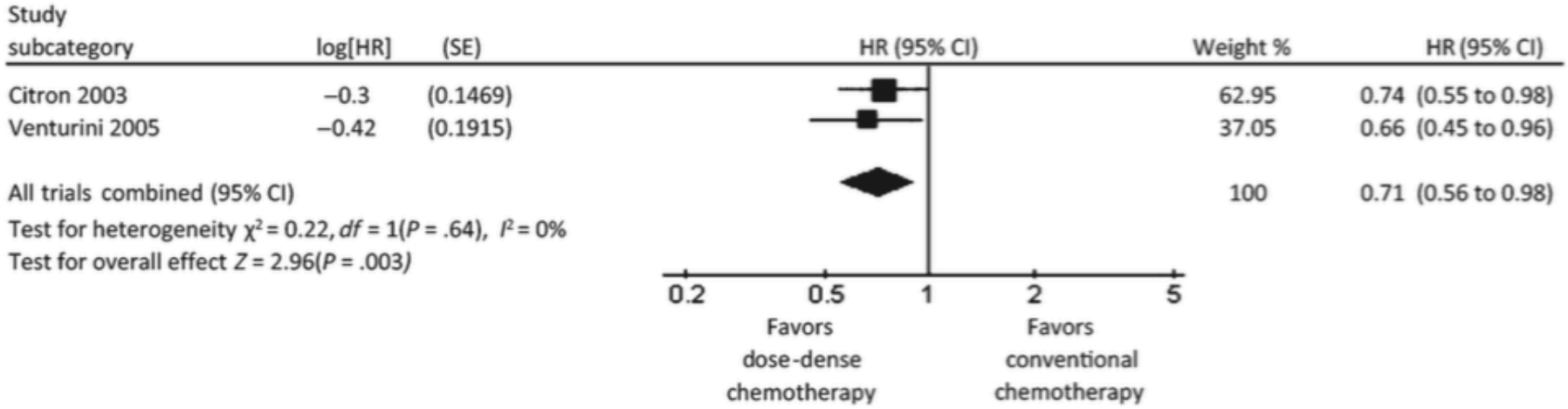
RH POSITIVO

A



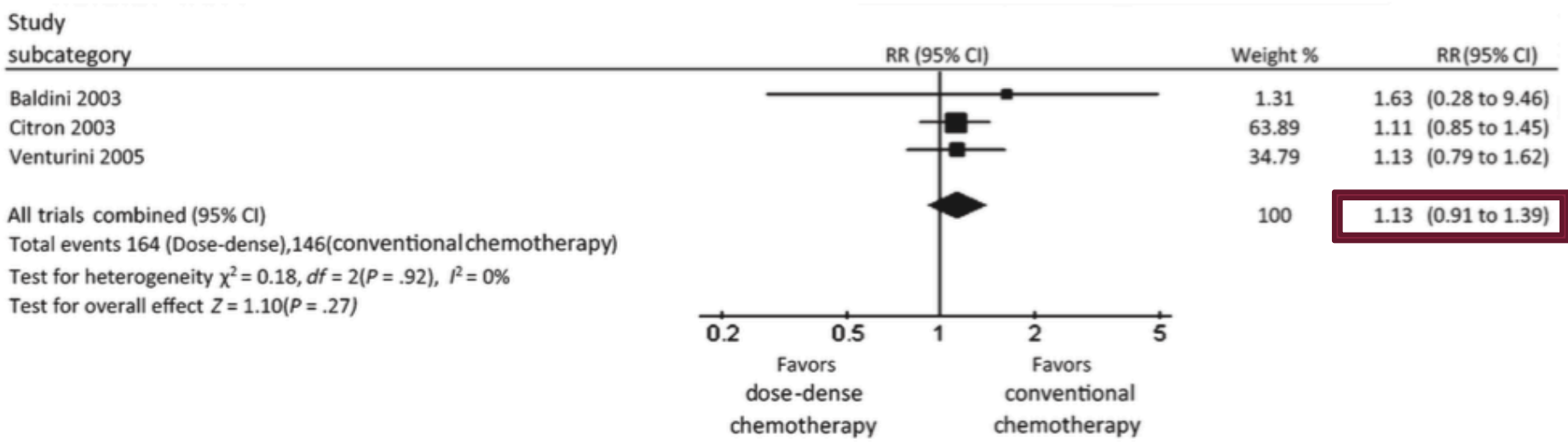
RH NEGATIVO

B



TAXA DE COMPLICAÇÕES

A



E a platina??

SAN ANTONIO BREAST CANCER SYMPOSIUM®

2015

UT Medicine CTRC Health Science Center San Antonio

AACR American Association for Cancer Research

Baylor College of Medicine

S2-04

Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto)

Dr. von Minckwitz institution received research funding from Roche, Teva and GSK.

GBG GERMAN BREAST GROUP

Introduction

- Carboplatin added to anthracycline/taxane-based neoadjuvant chemotherapy significantly improved pathological complete response (pCR) rates in patients with triple-negative breast cancer (TNBC) in two large phase II b studies (GeparSixto, CALGB 40603).[1,2]
- In GeparSixto, carboplatin improved the pCR rate from 36.9 to 53.2% (+17.4%; p=0.005) in patients with TNBC only.[1]
- Germline *(g)BRCA* status was a significant predictor of pCR; but results were non conclusive for predicting the effect of carboplatin.[3]
- Here we report disease-free survival (DFS) for GeparSixto after median 35 months of observation.

[1]von Minckwitz G et al. Lancet Oncol 2014, [2]Sikov et al. J Clin Oncol 2015
[3]von Minckwitz G et al. ASCO 2014

GBG GERMAN BREAST GROUP

Design for Patients with TNBC

N=315 patients with centrally confirmed TNBC

R

PM

PMCb

cT2, cT3, or cT4a-d
or
cT1 and cN+ or
pN_{SLN}+

Surgery

Paclitaxel (P) 80 mg/m² q1w

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

Carboplatin (Cb) q1w
Dose of AUC 2 was reduced to AUC 1.5 after enrolment of 330 patients

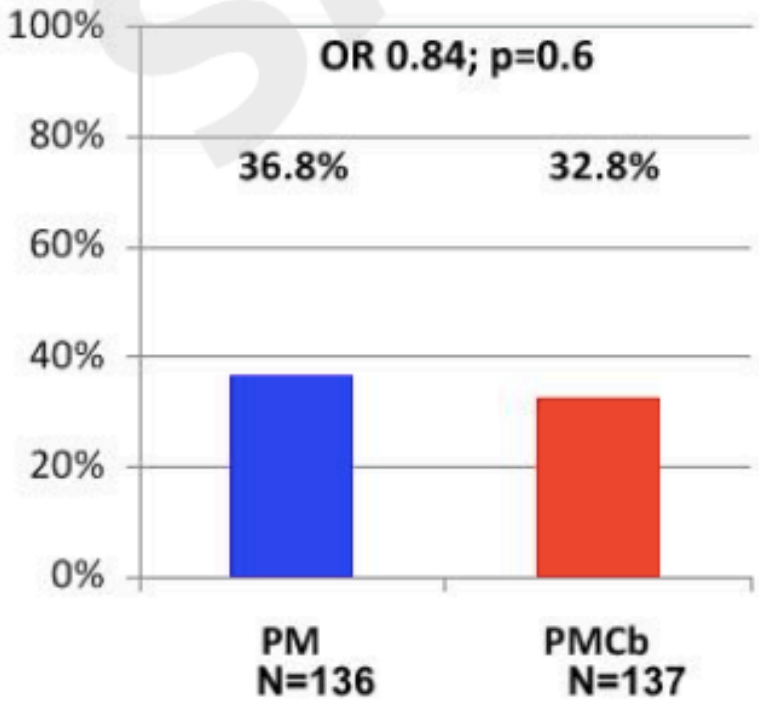
Bevacizumab 15 mg/kg q3w

GBG GERMAN BREAST GROUP

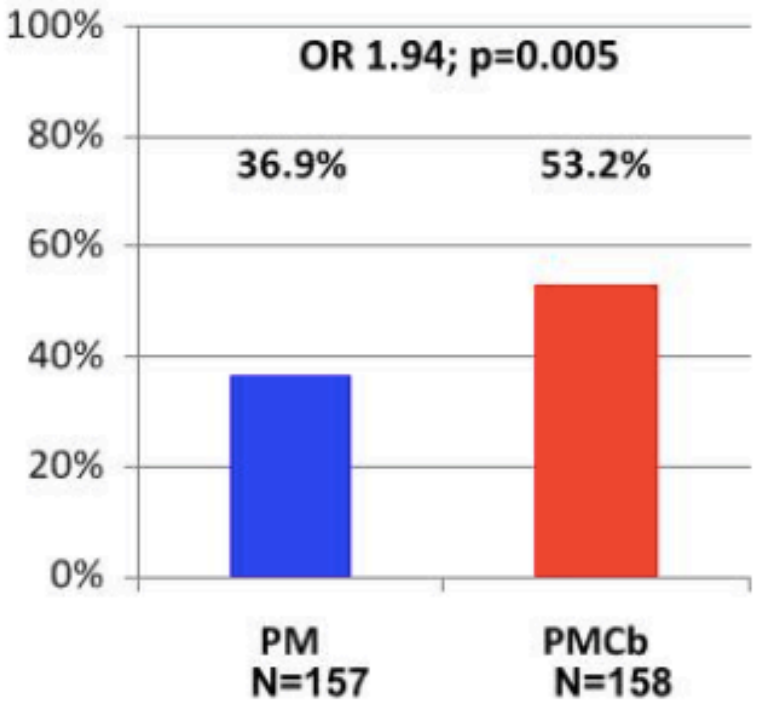
pCR Rates by Subtype

ypT0 ypN0

HER2-pos. BC



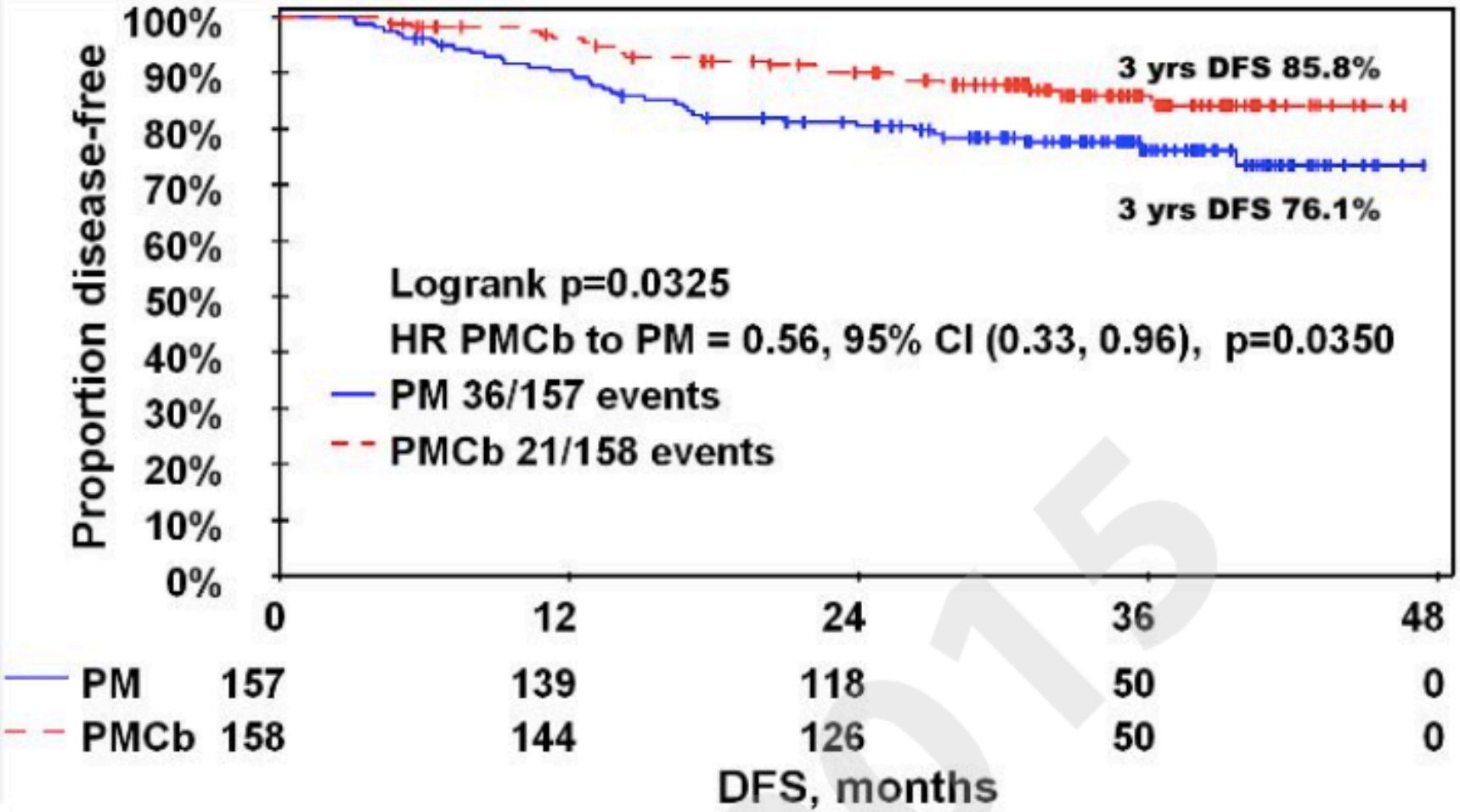
TNBC



Test for interaction p=0.015

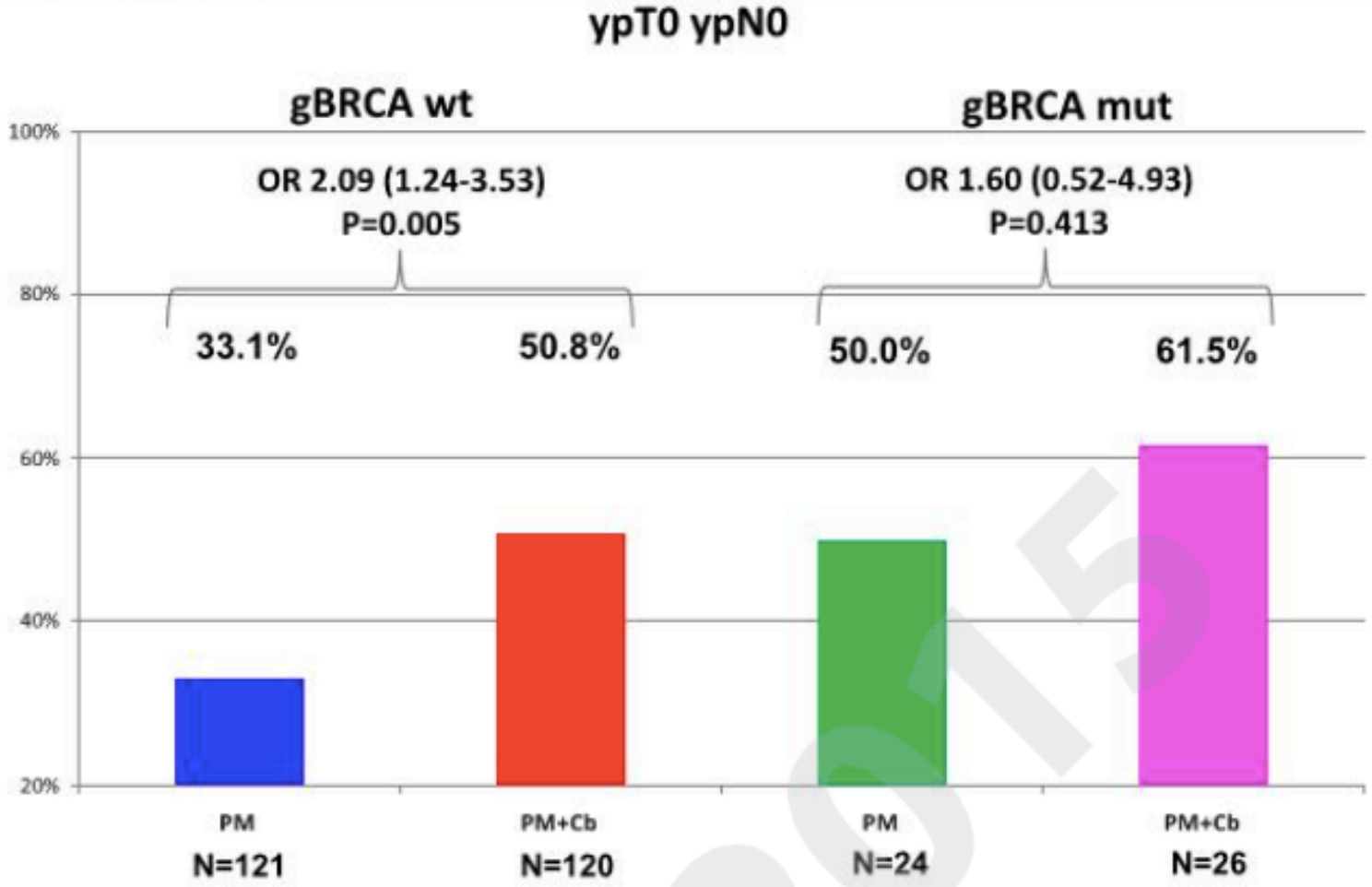
GBG GERMAN BREAST GROUP

DFS: Effect of Carboplatin in TNBC



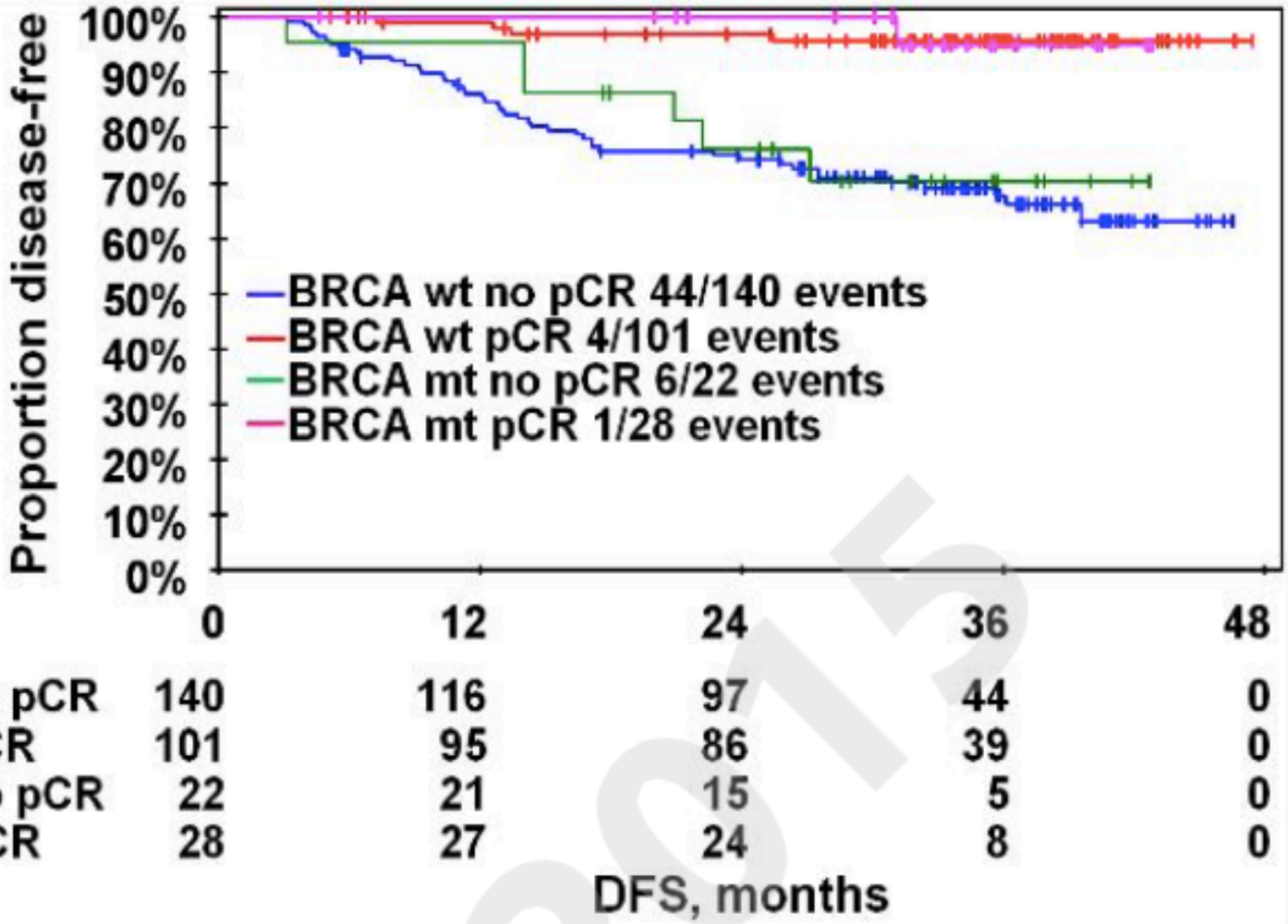
GBG GERMAN BREAST GROUP

pCR Rates by *gBRCA* Status and Carboplatin in TNBC



GBG GERMAN BREAST GROUP

DFS by g*BRCA* Status and pCR in TNBC

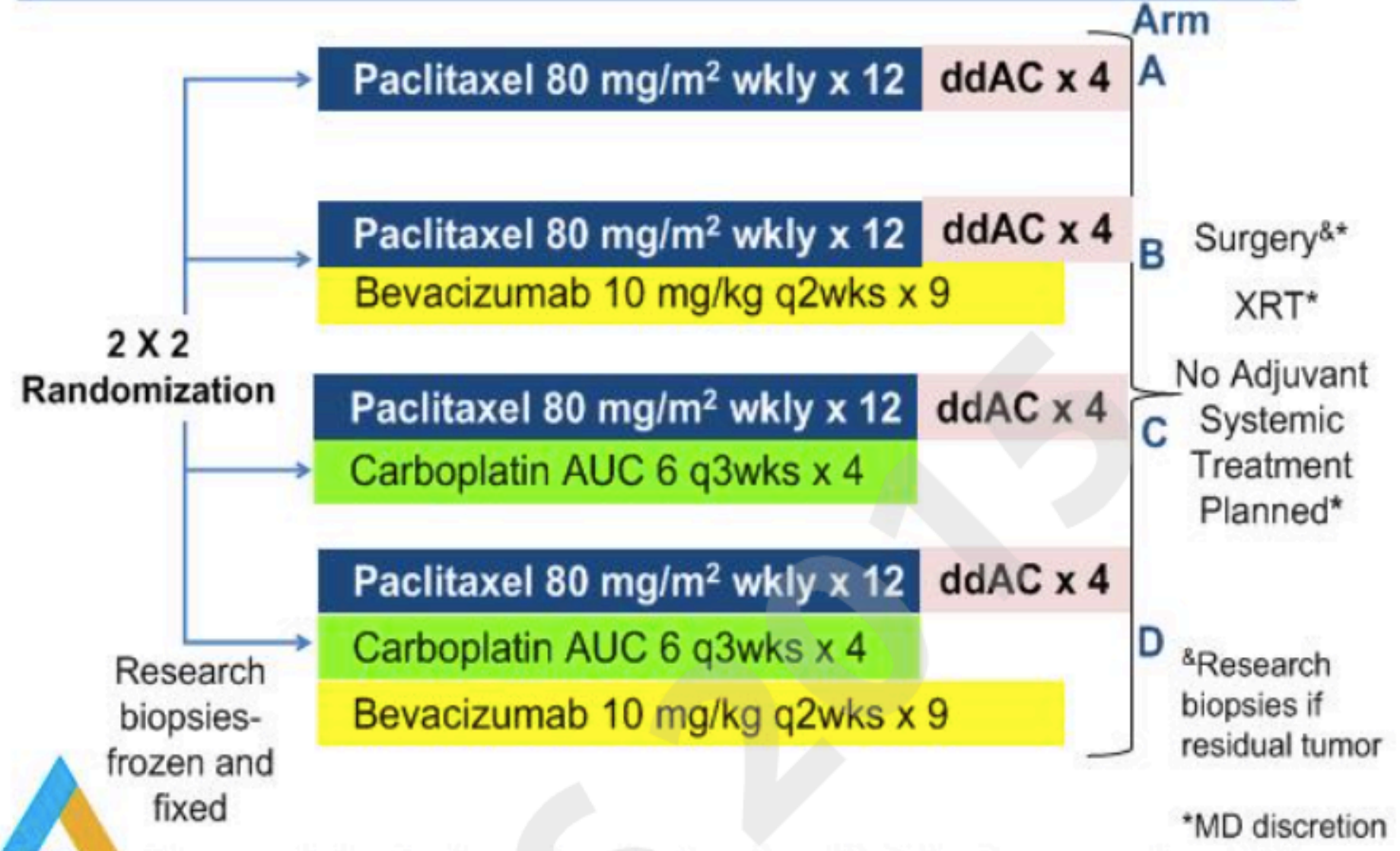


S2-05

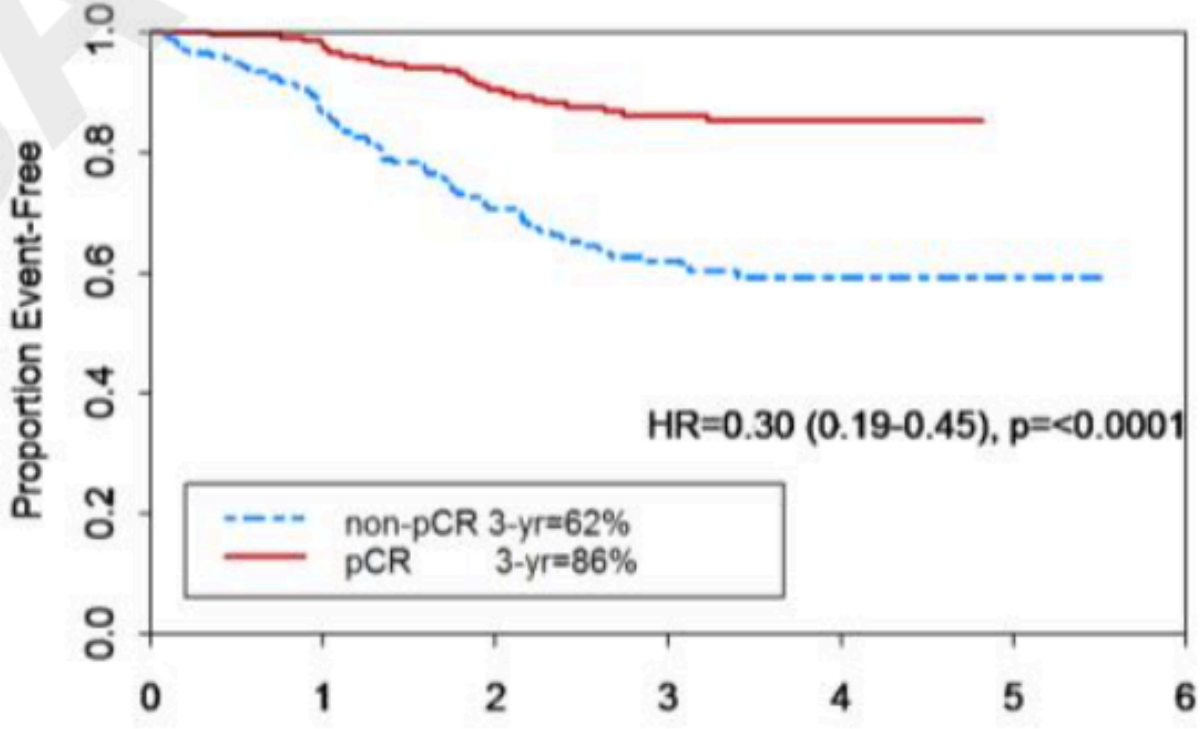
Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: outcomes from CALGB 40603 (Alliance)

Dr. Sikov: speaker for Eisai. He has also disclosed that he has a contract with AbbVie. He has disclosed unpaid participation on advisory boards for Celgene and AbbVie.

CALGB 40603: Schema – Randomized Phase II

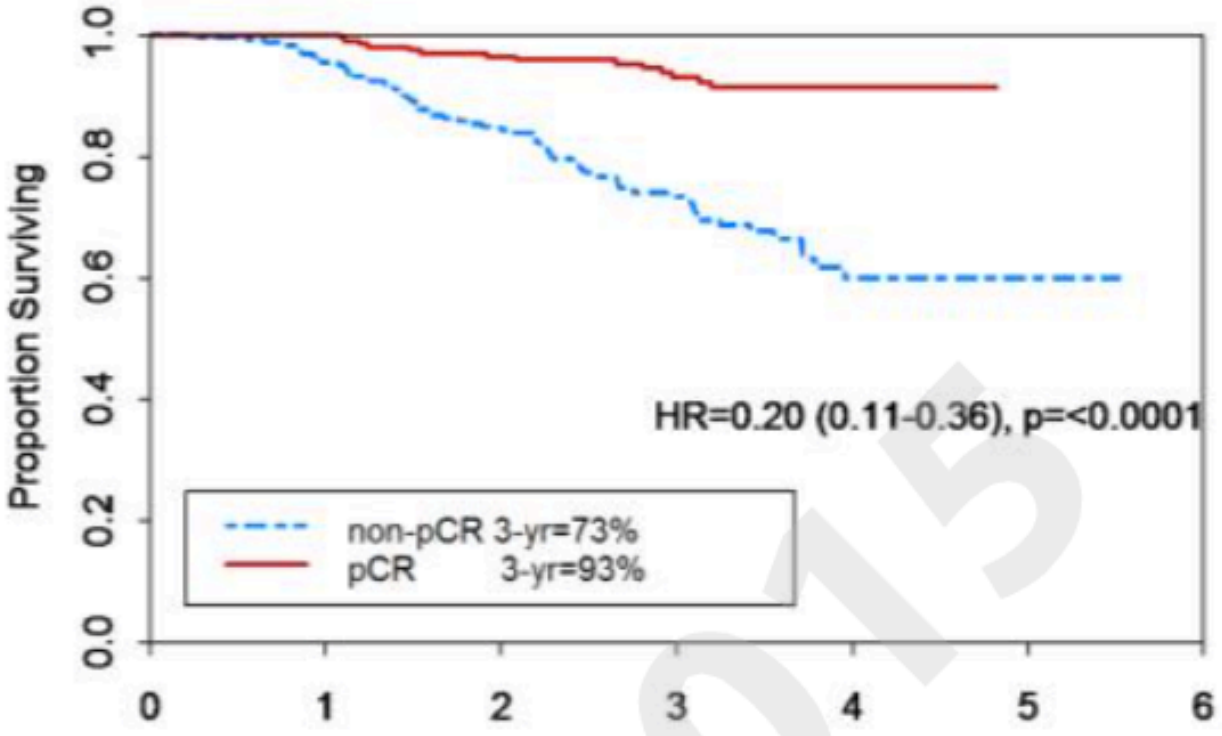


CALGB 40603 – EFS by pCR Breast/Axilla



Number at Risk							
non-pCR	236	189	141	81	32	4	0
pCR	207	198	166	114	36	0	0

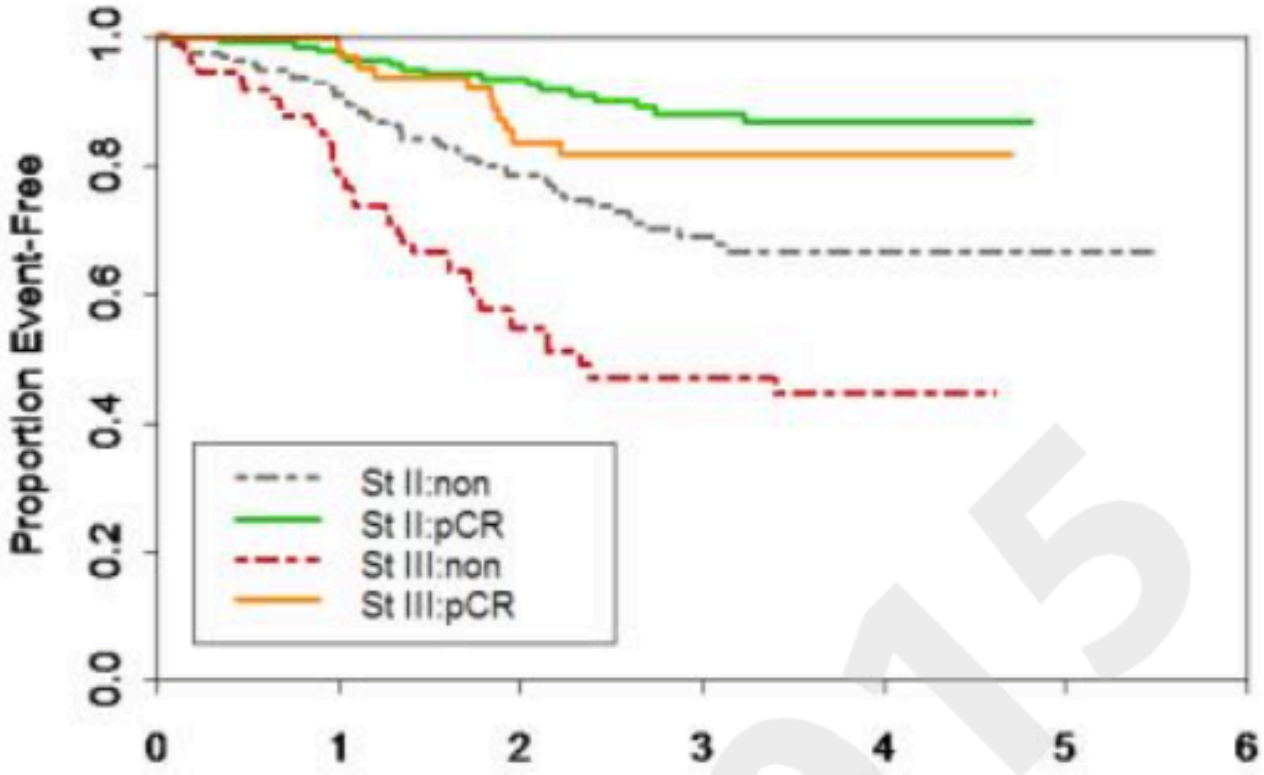
CALGB 40603 – OS by pCR Breast/Axilla



Number at Risk

non-pCR	236	210	170	99	33	4	0
pCR	207	202	178	122	37	0	0

CALGB 40603 – EFS by Clinical Stage/Response

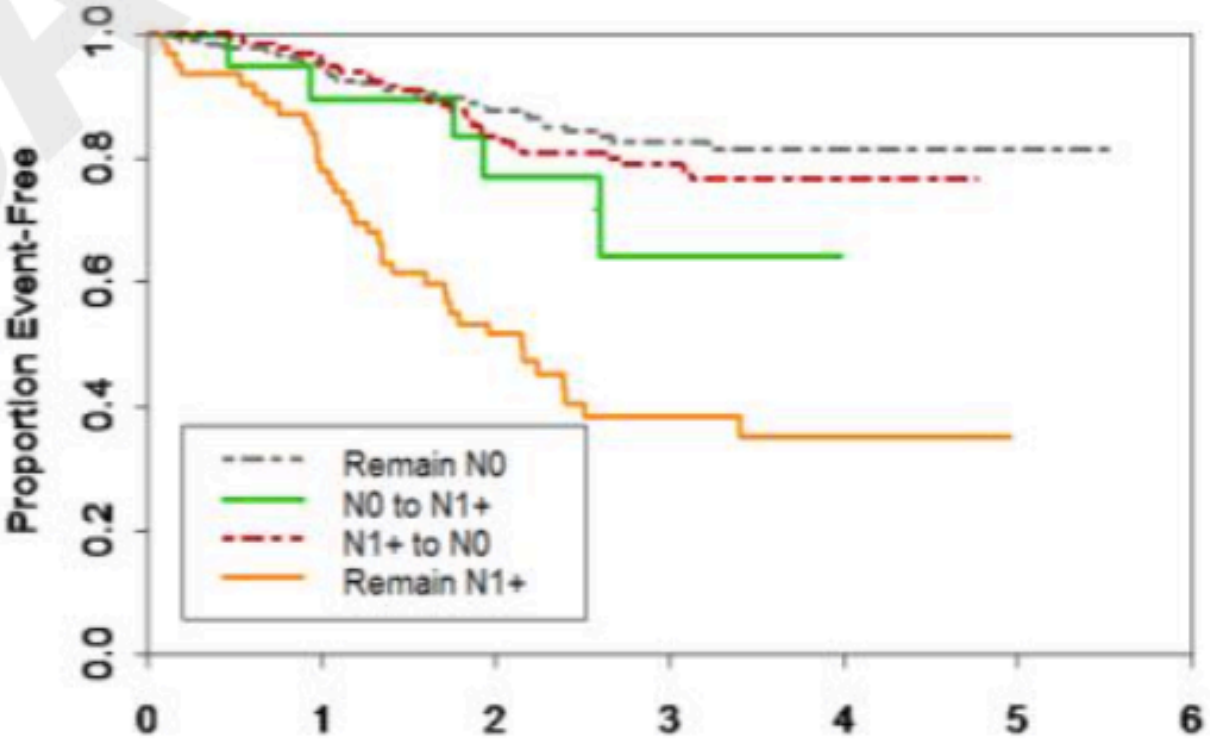


Number at Risk

St II:non	158	134	105	61	25	4	0
St II:pCR	142	135	119	80	23	0	0
St III:non	78	55	36	20	7	0	0
St III:pCR	65	63	47	34	13	0	0

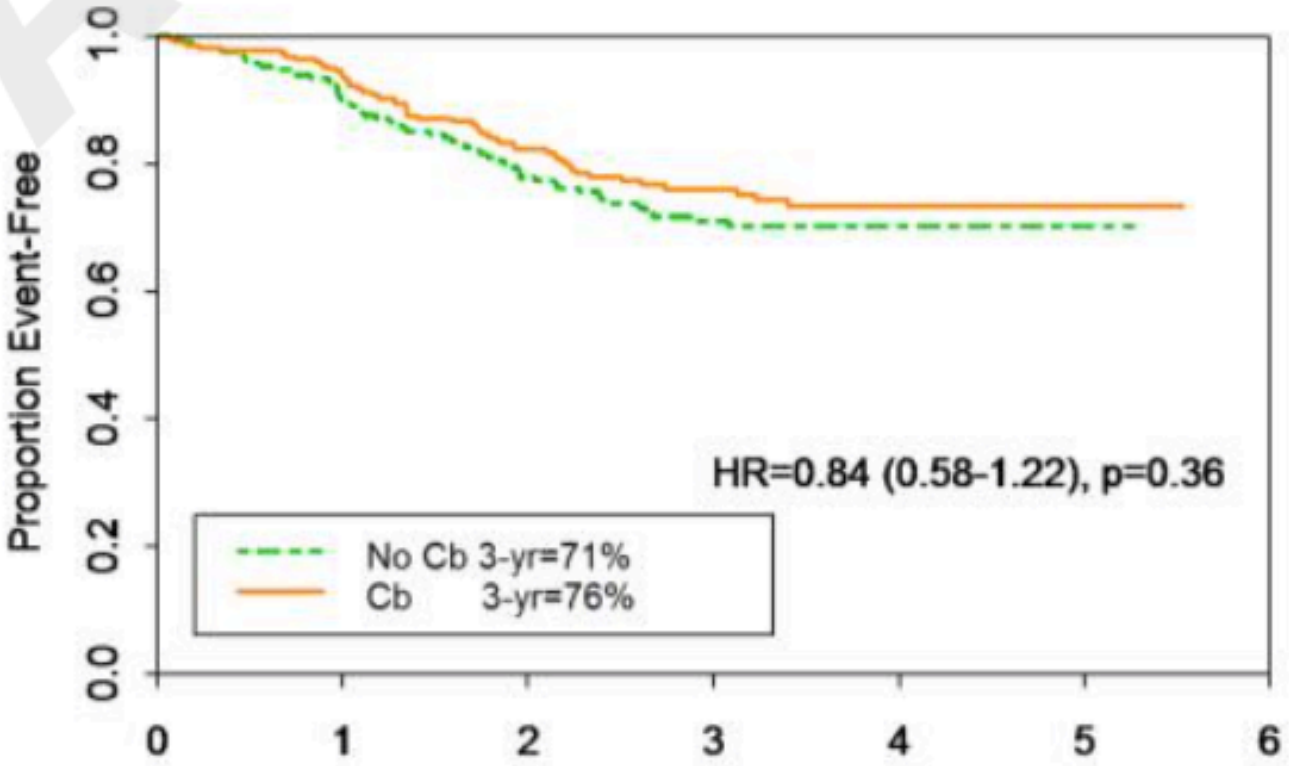
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 40603 – EFS by Nodal Status/Response



Number at Risk							
Remain N0	177	162	135	83	31	4	0
N0 to N1+	20	17	12	4	0	0	0
N1+ to N0	133	126	99	72	23	0	0
Remain N1+	63	48	30	14	4	0	0

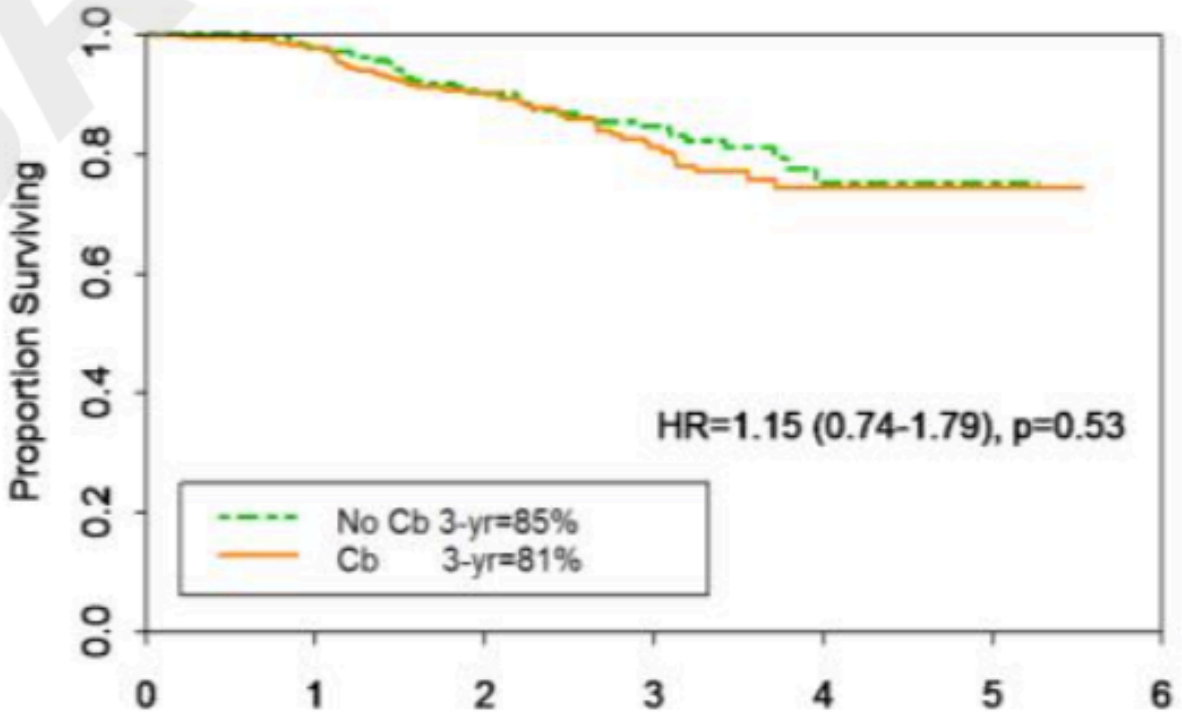
CALGB 40603 – EFS for carboplatin vs. not



Number at Risk

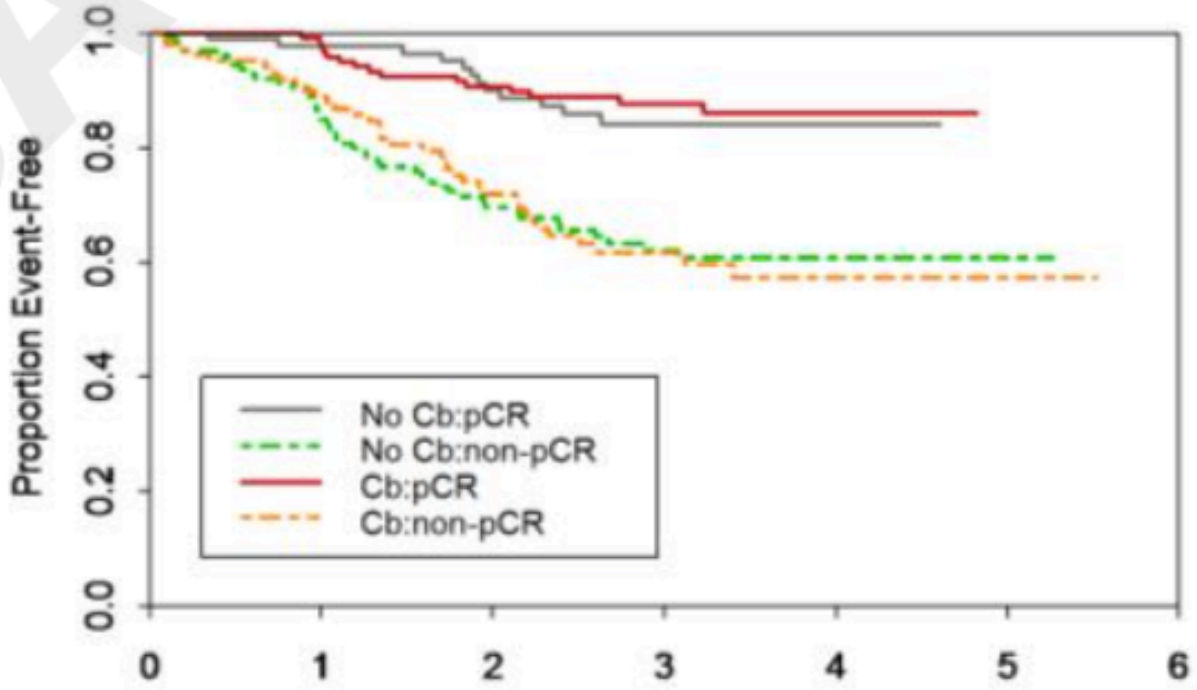
No Cb	218	185	145	94	31	2	0
Cb	225	202	162	101	37	2	0

CALGB 40603 – OS for carboplatin vs. not



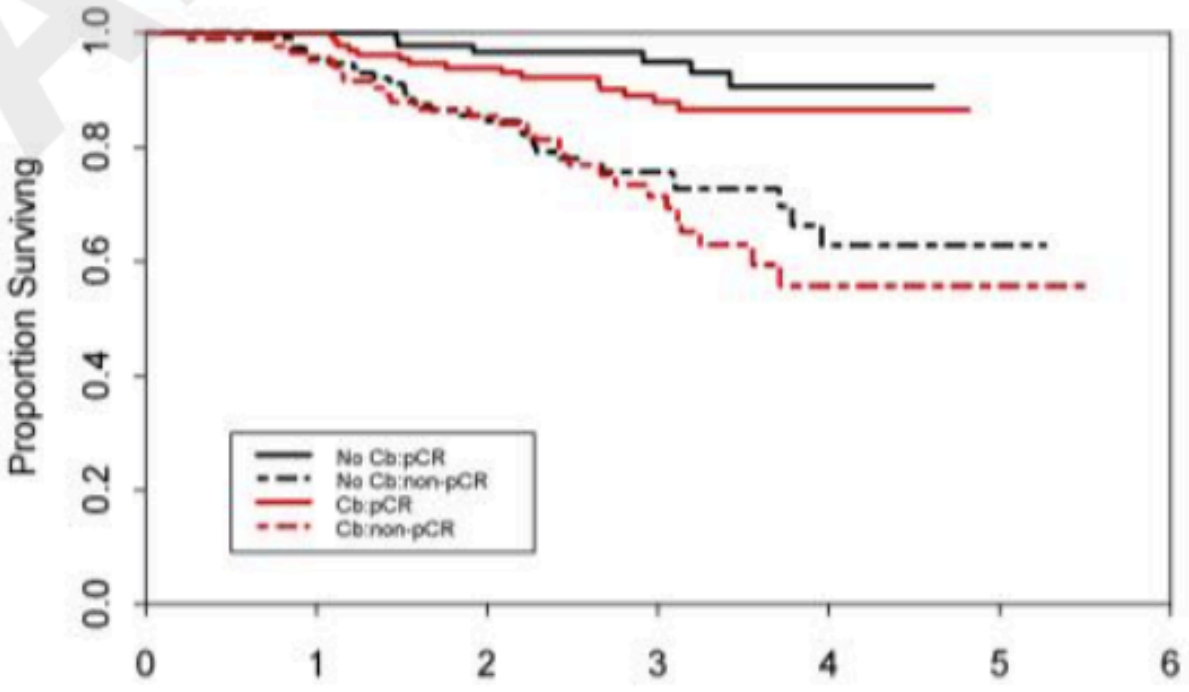
Number at Risk							
No Cb	218	202	169	111	31	2	0
Cb	225	210	179	110	39	2	0

CALGB 40603 – EFS by Factor and Response



Number at Risk							
No Cb:pCR	87	81	69	45	11	0	0
No Cb:non-pCR	131	104	76	49	20	2	0
Cb:pCR	120	117	97	69	25	0	0
Cb:non-pCR	105	85	65	32	12	2	0

CALGB 40603 – OS by Factor and Response



Number at Risk							
No Cb:pCR	98	93	83	56	12	0	0
No Cb:non-pCR	114	107	85	54	18	2	0
Cb:pCR	133	132	113	75	28	0	0
Cb:non-pCR	88	78	66	35	11	2	0

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PREOPERATIVE/ADJUVANT THERAPY REGIMENS [1,2,3,4]

Regimens for HER2-negative disease[5,6]

Preferred regimens:

- **Dose-dense AC** (doxorubicin/cyclophosphamide) **followed by paclitaxel every 2 weeks**
- **Dose-dense AC** (doxorubicin/cyclophosphamide) **followed by weekly paclitaxel**
- **TC** (docetaxel and cyclophosphamide)

Other regimens:

- **Dose-dense AC** (doxorubicin/cyclophosphamide)
- **AC** (doxorubicin/cyclophosphamide) **every 3 weeks** (category 2B)
- **CMF** (cyclophosphamide/methotrexate/fluorouracil)
- **AC followed by docetaxel every 3 weeks**
- **AC followed by weekly paclitaxel**
- **EC** (epirubicin/cyclophosphamide)
- **TAC** (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8,9]

Preferred regimens:

- **AC followed by T + trastuzumab ± pertuzumab**[10] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- **TCH** (docetaxel/carboplatin/trastuzumab) **± pertuzumab**

Other regimens:

- **AC followed by docetaxel + trastuzumab ± pertuzumab**[10]
- **Docetaxel + cyclophosphamide + trastuzumab**
- **FEC** (fluorouracil/epirubicin/cyclophosphamide) **followed by docetaxel + trastuzumab + pertuzumab**[10]
- **FEC followed by paclitaxel + trastuzumab + pertuzumab**[10]
- **Paclitaxel + trastuzumab**[11]
- **Pertuzumab + trastuzumab + docetaxel followed by FEC**[10]
- **Pertuzumab + trastuzumab + paclitaxel followed by FEC**[10]

Take home message

- Quimioterapia realizada previamente à cirurgia, ou neoadjuvante, apresenta similar sobrevida livre de progressao e global em relação à quimioterapia adjuvante.
- Um dos principais objetivos é o *downstage* tumoral
- A resposta patológica completa (RPC)é fator prognóstico importante.
- Para tumores HER-2 positivos, recomenda-se incorporar trastuzumabe (e se possível, pertuzumabe).
- Para tumores HER-2 negativos, os protocolos de quimioterapia se baseiam nos protocolos da adjuvância
- A incorporação da carboplatina na neoadjuvância para triplo negativos aumenta a taxa de RPC. Pacientes com resposta completa parecem possuir prognostico semelhante, independente do uso de carboplatina e do status BRCA.