Prospettive per l'adiuvante nel Triple Negative

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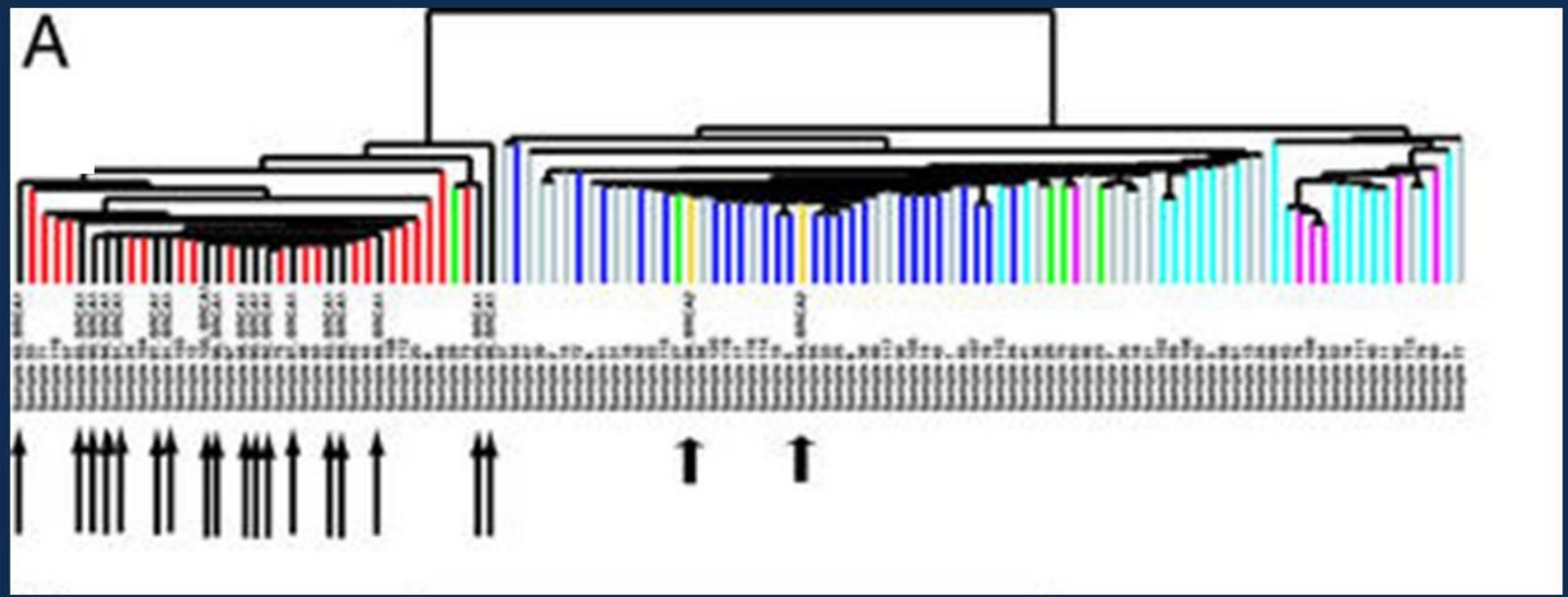
TNBC- Epidemiology

- Triple negative breast cancer (TNBC) definition:
  - – lack of expression of estrogen receptor and progesterone receptor
  - HER2 not overexpressed/amplified
- 10-20% of all breast cancers
- TNBC includes rare histologies
    - Metaplastic, medullary, adenoid cystic carcinoma
- High cell proliferation, poor cellular differentiation, many recurrent copy number imbalances, and mutations in the TP53

Associations between TNBC and g*BRCA*



BRCA1 ***BRCA2***

Most *BRCA1* carriers get basal-like breast cancer

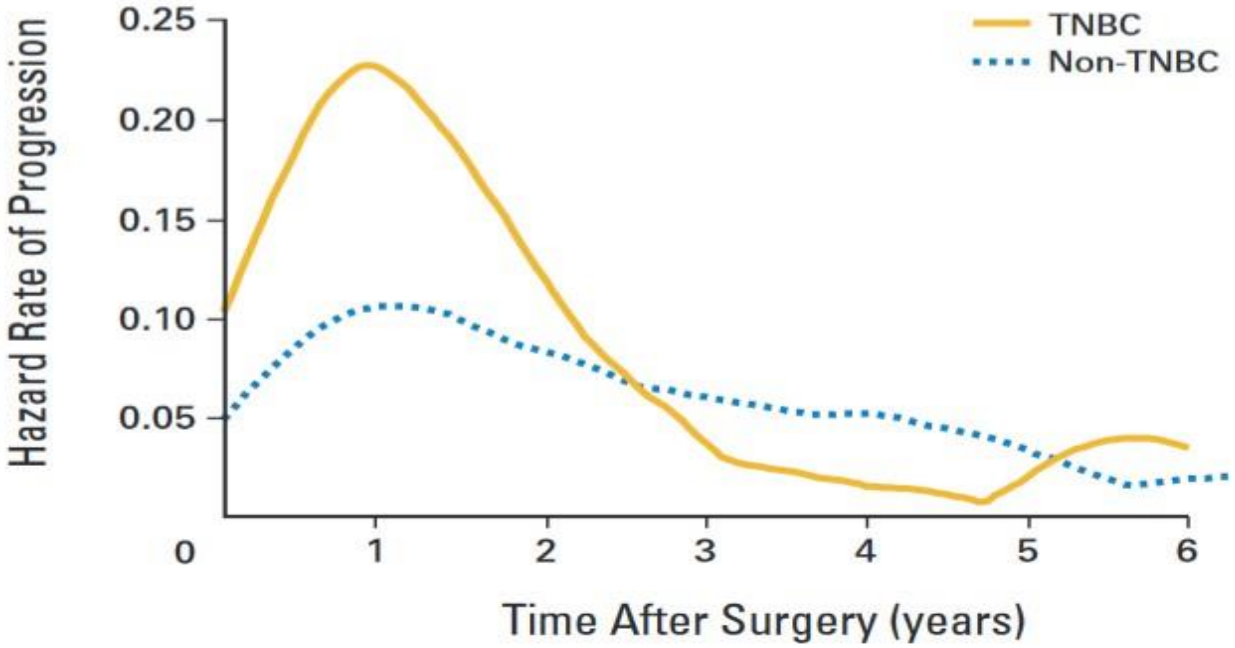
but

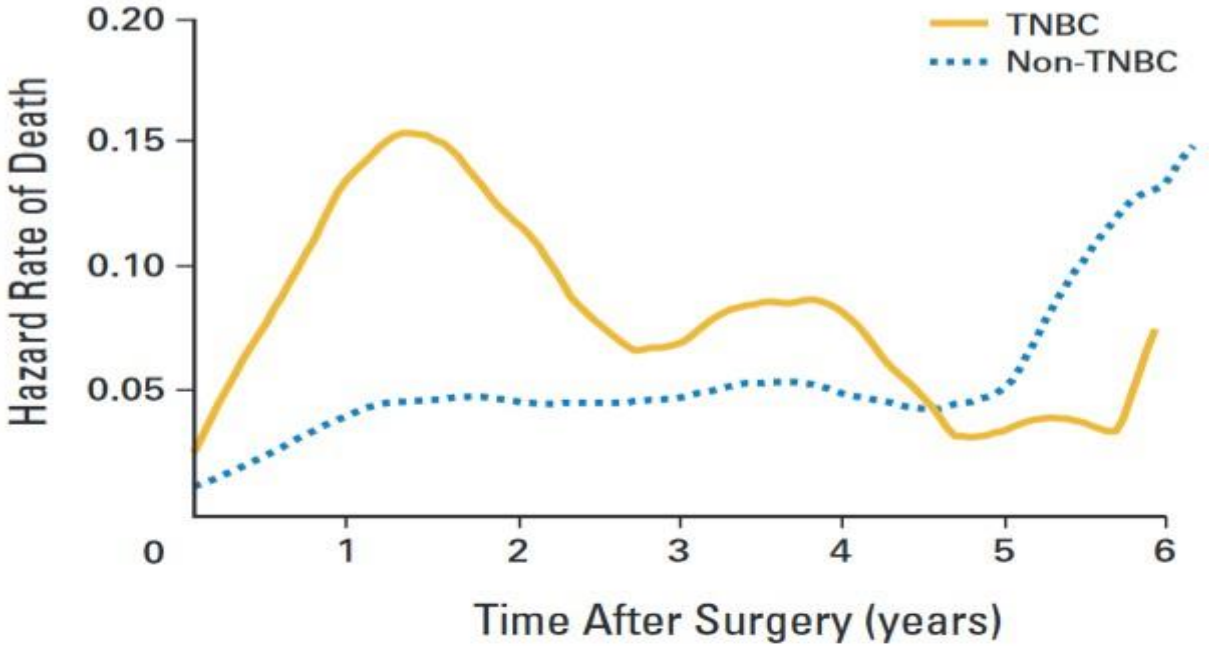
Most basal-like breast cancers are NOT in *BRCA1* carriers…

~20% of genomic instability in TNBC is explained by BRCA1/2 inactivation

Is the BRCA1 pathway abnormal in sporadic basal-like breast cancer?

Hazard rates of progression and death: TNBC vs. Others



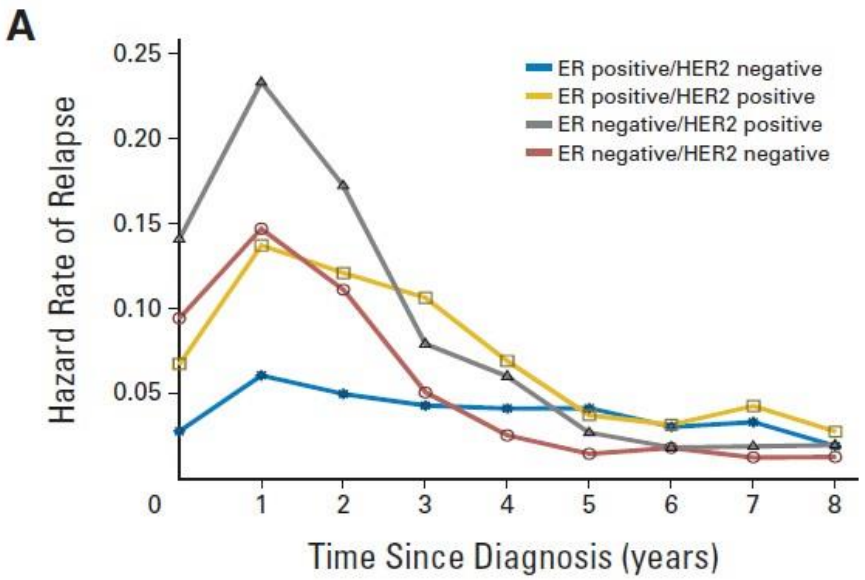


Liedtke C, *et al.*, J Clin Oncol 2008;26;1275–81.

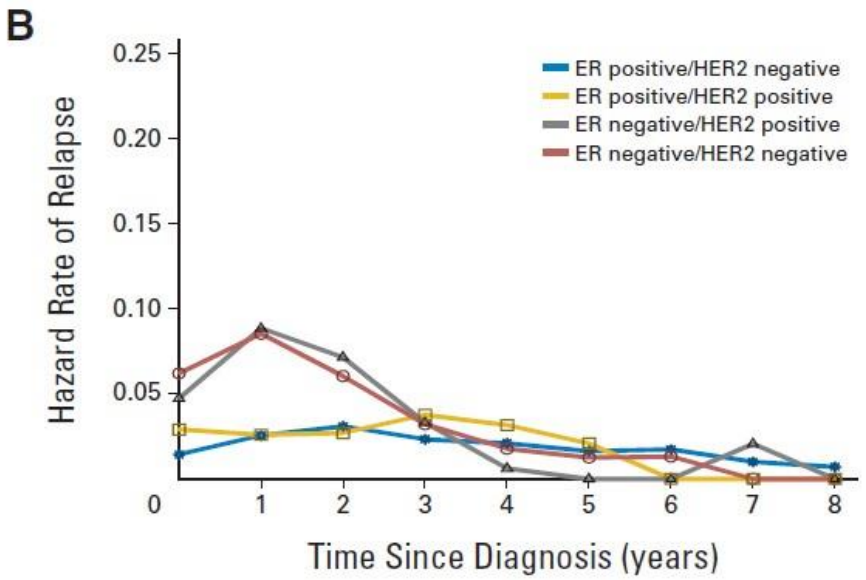
PROGRESS IN ADJUVANT CT: EFFECT FOR TNBC

British Columbia Cancer Agency stage I-III BC (7,178 patients)
→1,132 (15.8%) patients with ER neg and HER2 neg BC

Cohort 1: 1986 - 1992



Cohort 2: 2004 - 2008

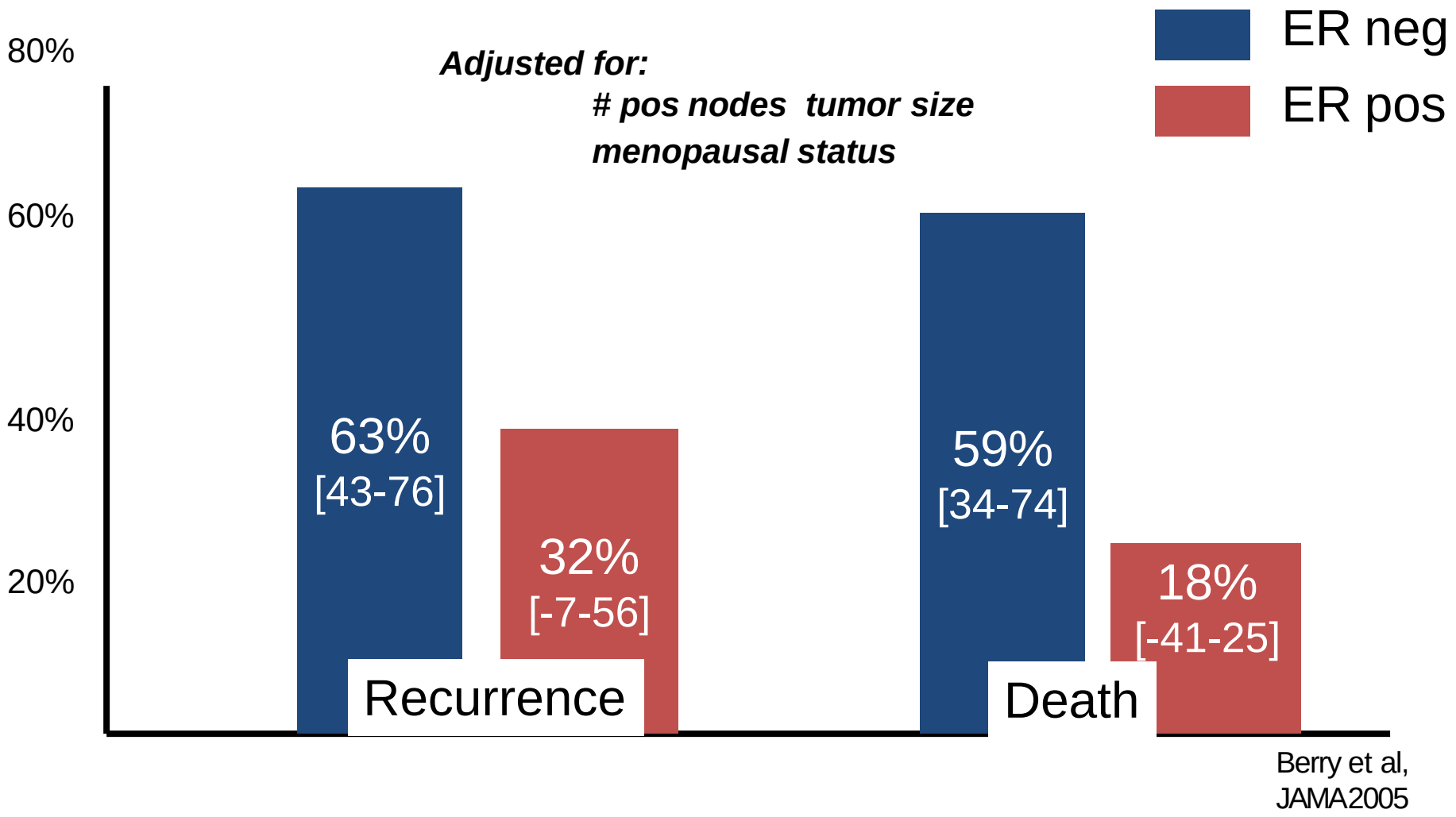


Cossetti RJD, *et al.*, J Clin Oncol 2015;33:65–73.

Adjuvant therapy in TNBC- Outline

- Small Tumor
- Addition of Taxanes
- High Dose Chemotherapy
- PARPi: narrowing target population to BRCA+
- Timing of chemotherapy

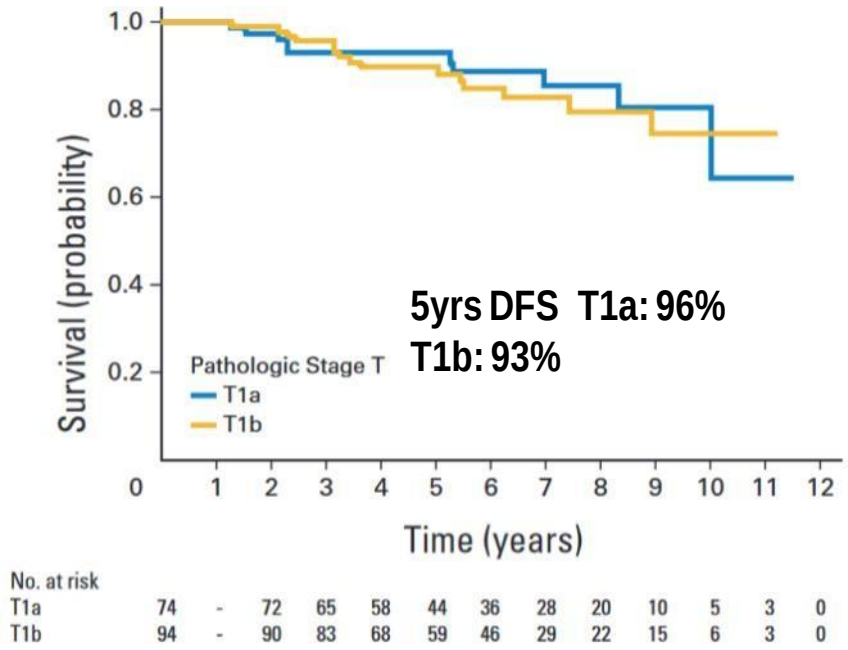
Benefit from CT in TNBC



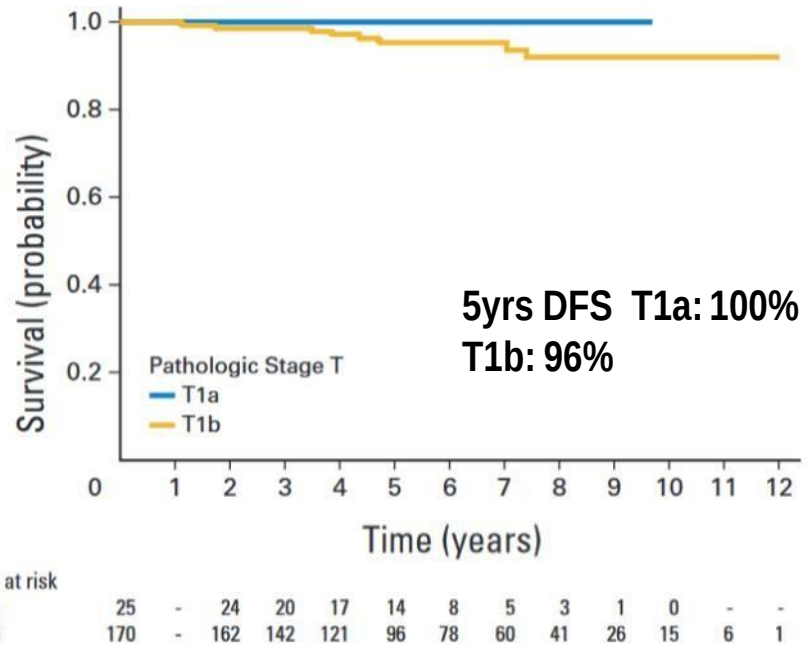
Berry et al,
JAMA2005

ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH SMALL TNBC

No chemotherapy



Chemotherapy



Vaz-Luis I, *et al.*, J Clin Oncol 2014;32:2142–50.

Options for Stage I Disease

- Chemotherapy treatment options for low risk disease:
  - 1) simple regimen (AC, TC, CMF)
  - 2) sequential anthracycline/taxane

	Enthusiasm for Chemotherapy	Possible Regimens
Microinvasion only	Virtually none	---
T1a	Low to moderate	Simple
T1b	Moderate to high	Simple
T1c	High	Simple or selectively sequential approach

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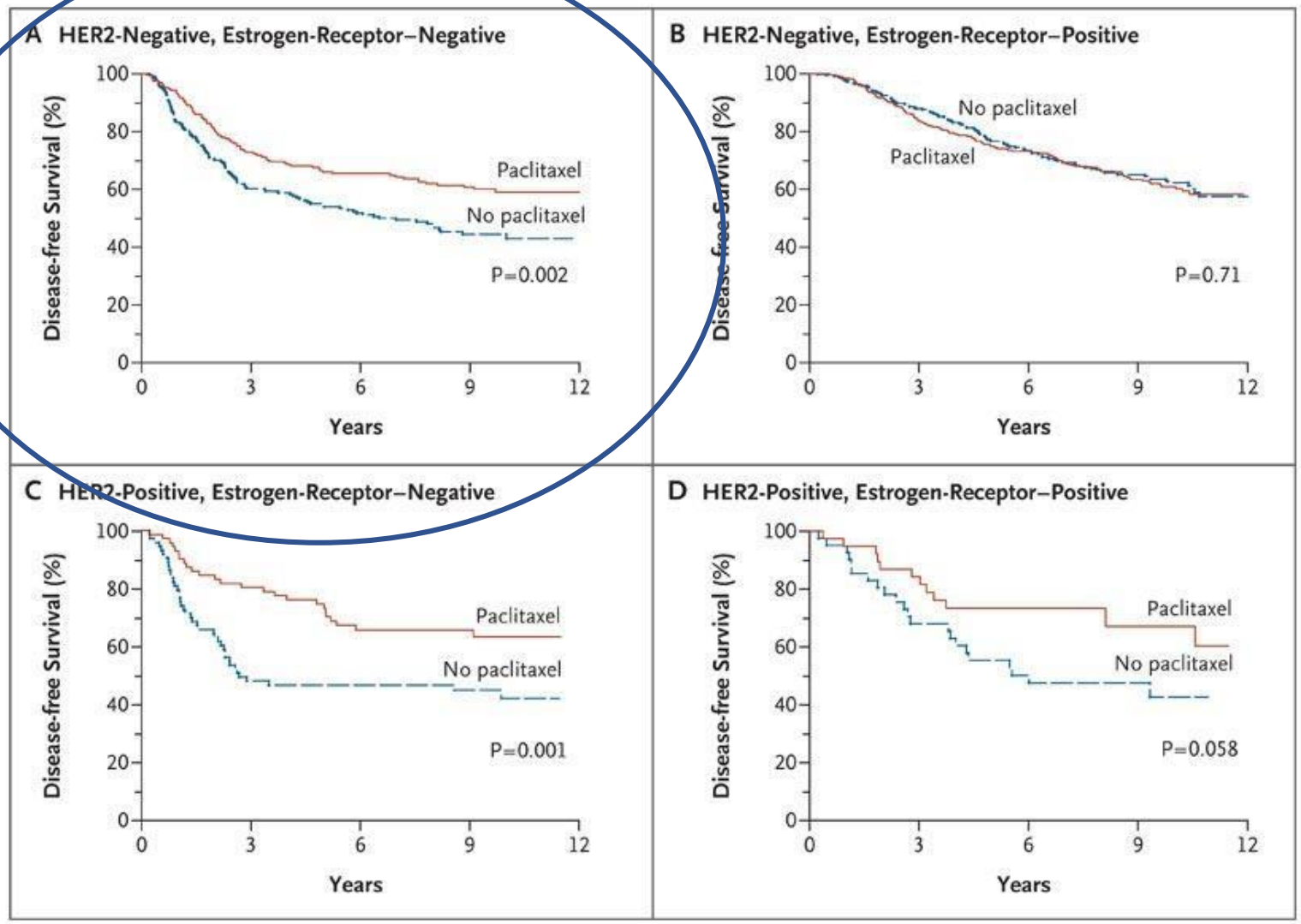
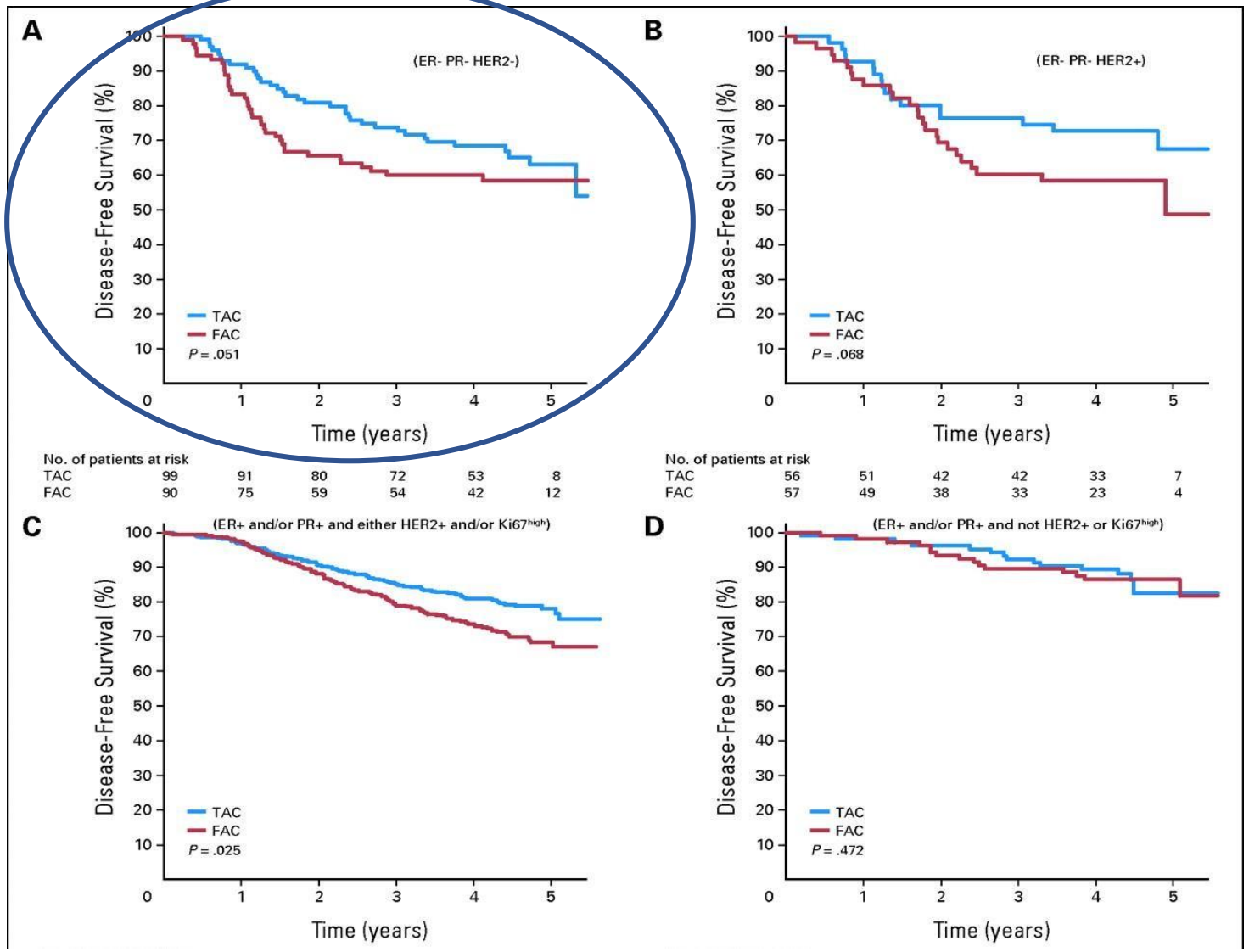
CALGB9344: ACx 4 ± Paclitaxel x 4 Outcomes for Subtypes



Hayes D et al. N Engl J Med 2007;357:1496-1506

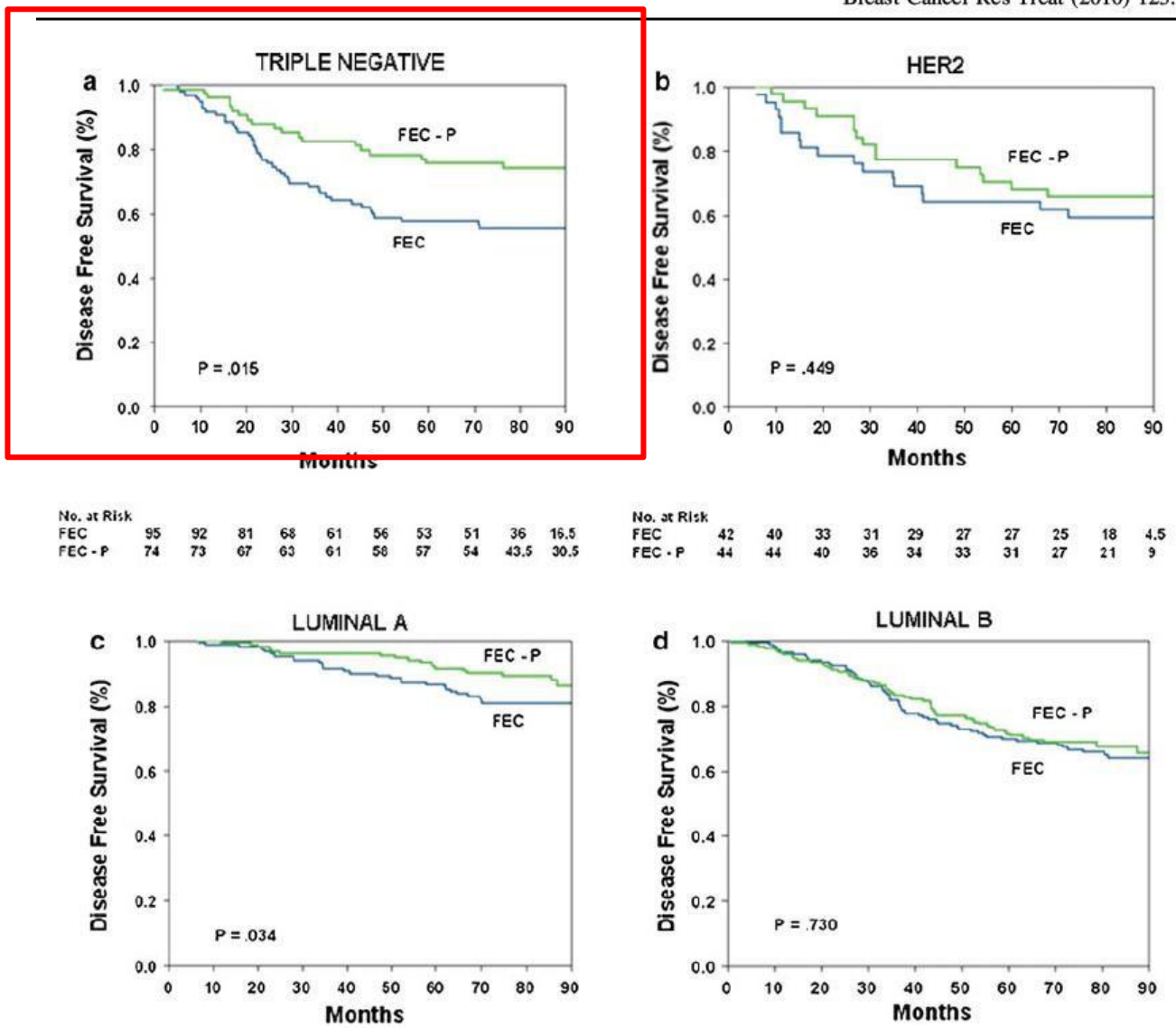
BCIRG 001: TAC vs FAC
Outcome for Subtypes



Hugh J et al. JCO 2009;27:1168-1176

GEICAM 9906: FEC vs FEC/P Outcomes by Subtypes

Breast Cancer Res Treat (2010) 123:149–157



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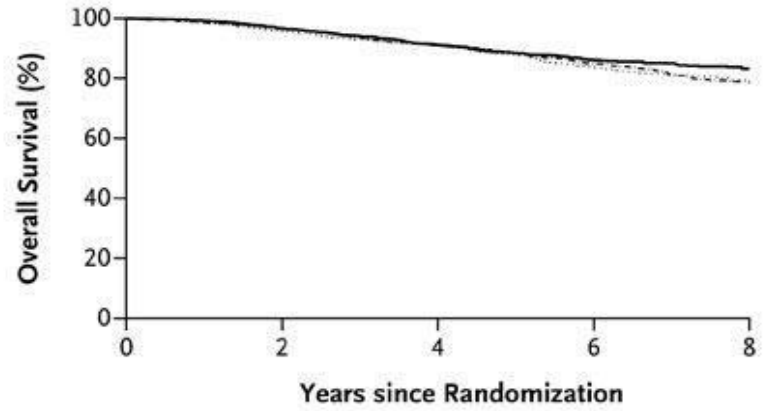
NSABP B-30. AC_4-T_4 vs TAC_4 vs AT_4 Overall Survival and Disease-free Survival.

A

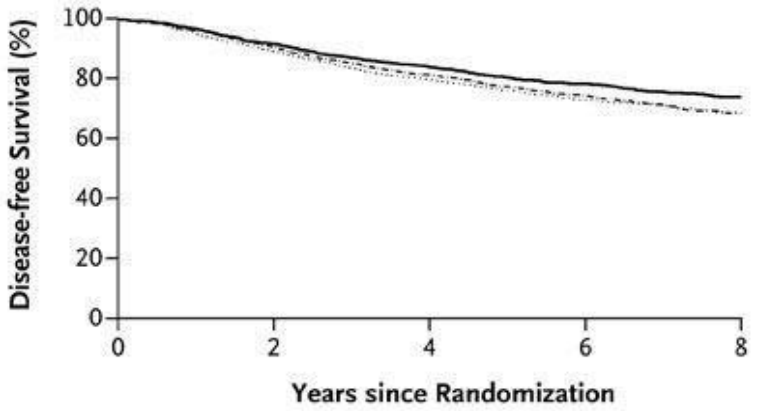
	No. of Patients	No. of Events	Hazard Ratio	P Value
Sequential ACT	1753	240	0.86 vs. concurrent ACT	0.09
			0.83 vs. doxorubicin–docetaxel	0.03
Doxorubicin–docetaxel	1753	285		
Concurrent ACT	1758	278	0.96 vs. doxorubicin–docetaxel	0.67



No. at Risk					
Total	5264	5042	4620	2300	779
Sequential ACT	1753	1685	1533	775	271
Doxorubicin–docetaxel	1753	1668	1531	752	253
Concurrent ACT	1758	1689	1556	773	255

B

	No. of Patients	No. of Events	Hazard Ratio	P Value
Sequential ACT	1753	388	0.83 vs. concurrent ACT	0.01
			0.80 vs. doxorubicin–docetaxel	0.001
Doxorubicin–docetaxel	1753	468		
Concurrent ACT	1758	457	0.96 vs. doxorubicin–docetaxel	0.58

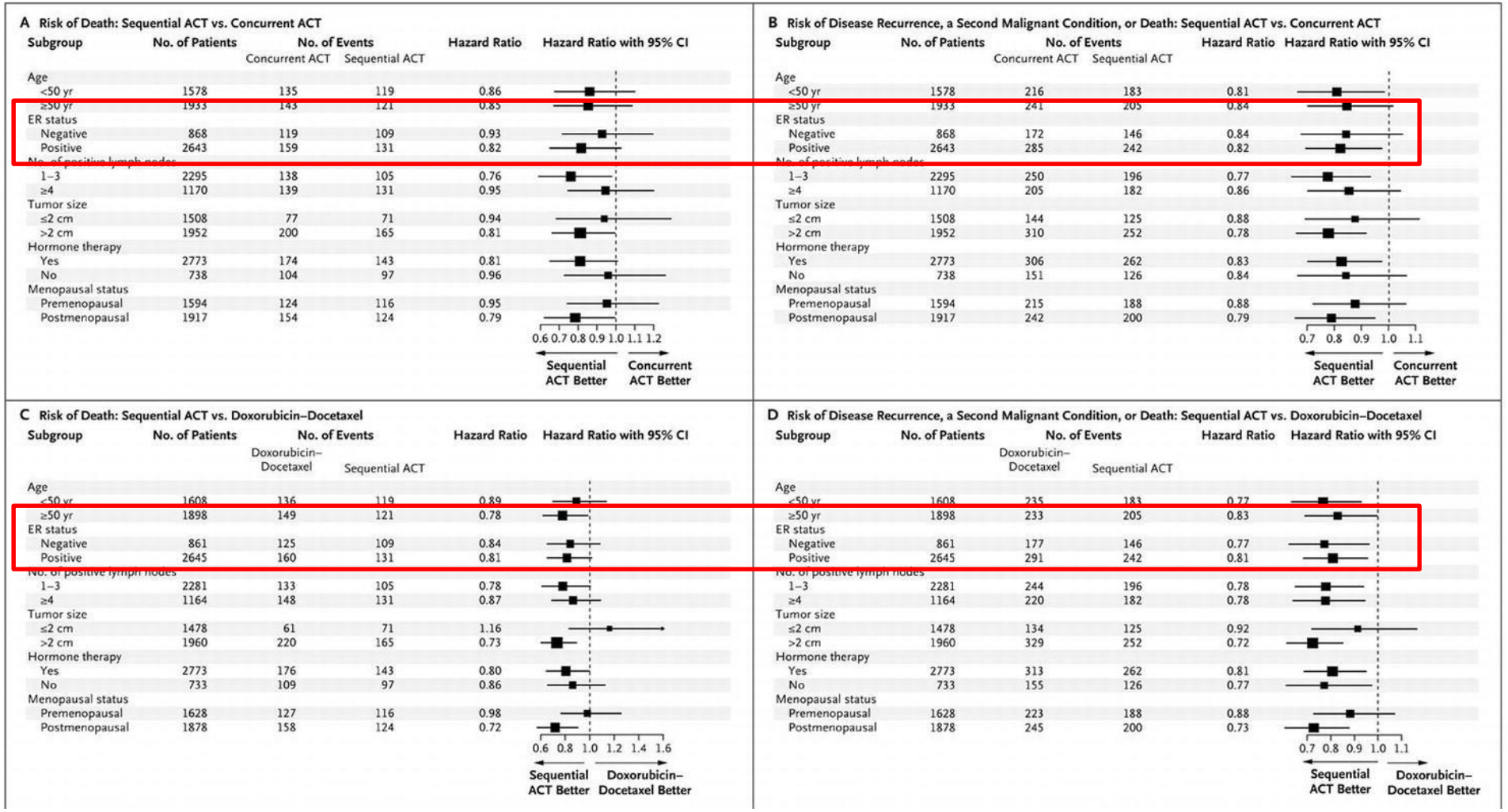


No. at Risk					
Total	5264	4743	4158	2021	679
Sequential ACT	1753	1600	1414	709	242
Doxorubicin–docetaxel	1753	1557	1349	652	222
Concurrent ACT	1758	1586	1395	660	215

Swain SM et al. N Engl J Med 2010;362:2053-2065.

NSABP B-30. AC_4-T_4 vs TAC_4 vs AT_4 TNBC subgroup

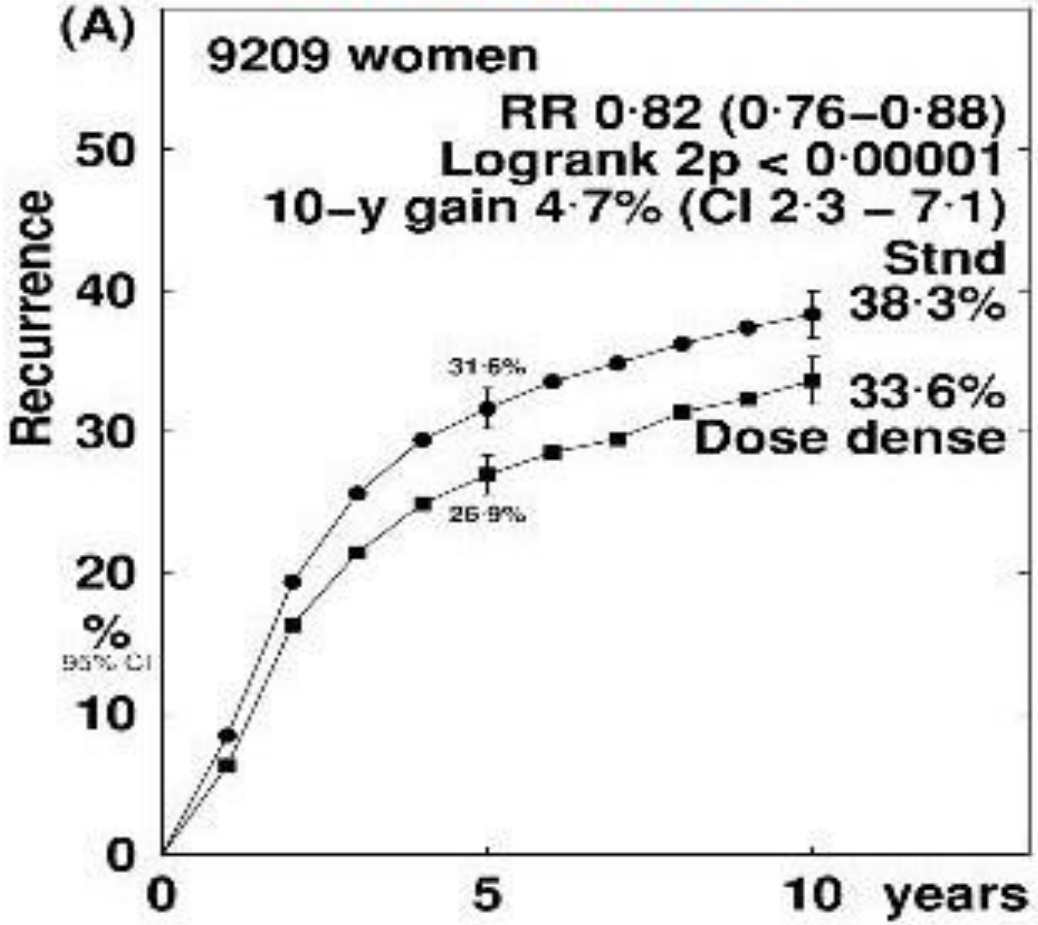
OS DFS



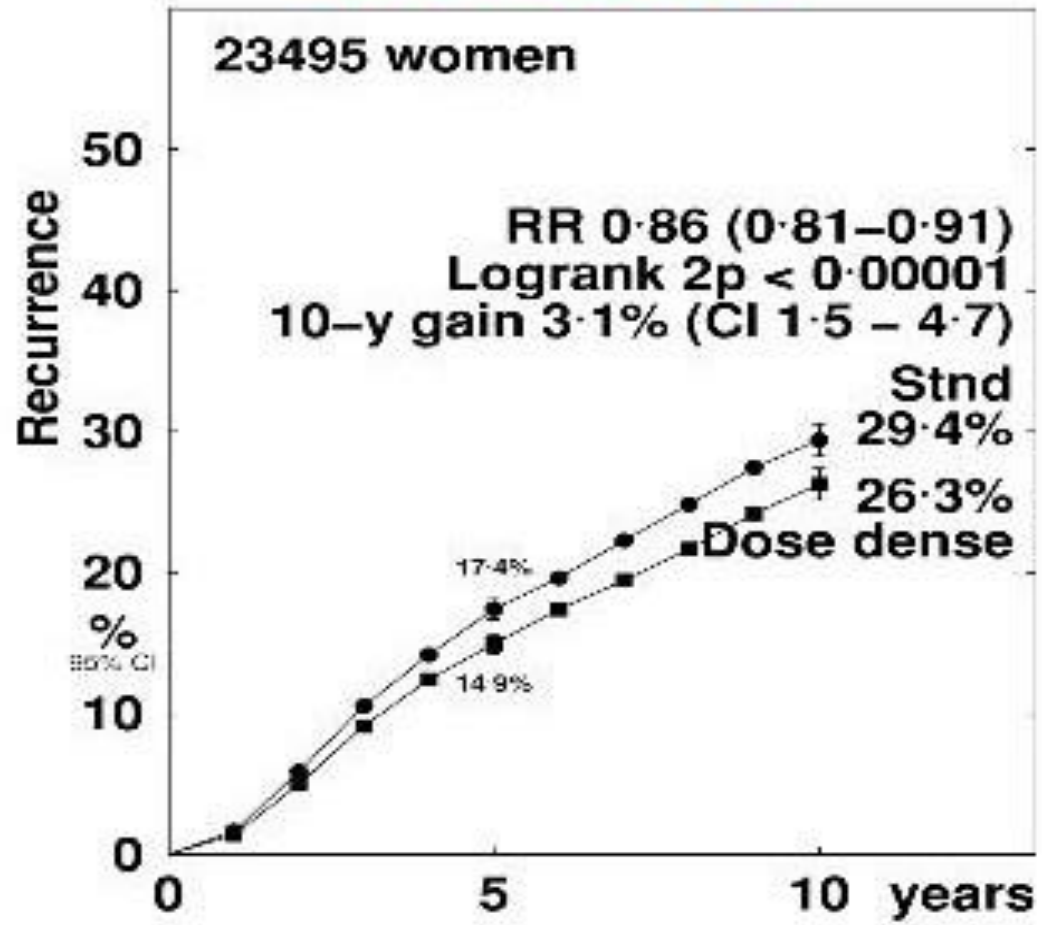
Swain SM et al. N Engl JMed 2010;362:2053-2065.

Pooled Analysis: recurrence by ER status

ER- Negative

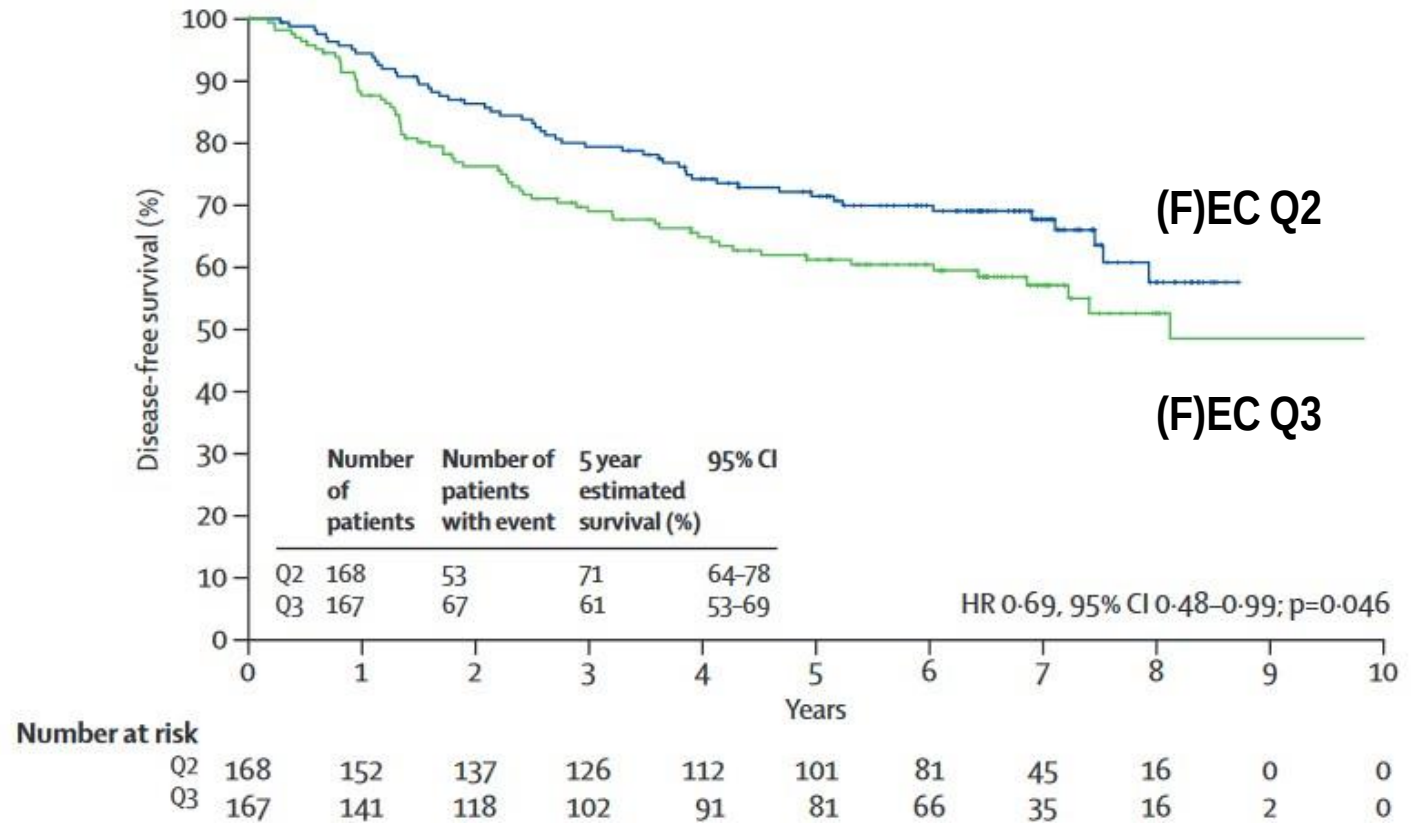


ER - Positive



GIM-2: ADJUVANT DOSE-DENSE CHEMOTHERAPY FOR N+ BC PTS

(F)EC Q2 *vs.* (F)EC Q3: Disease-free survival
N=335 HR-



Adjuvant therapy in TNBC- Outline

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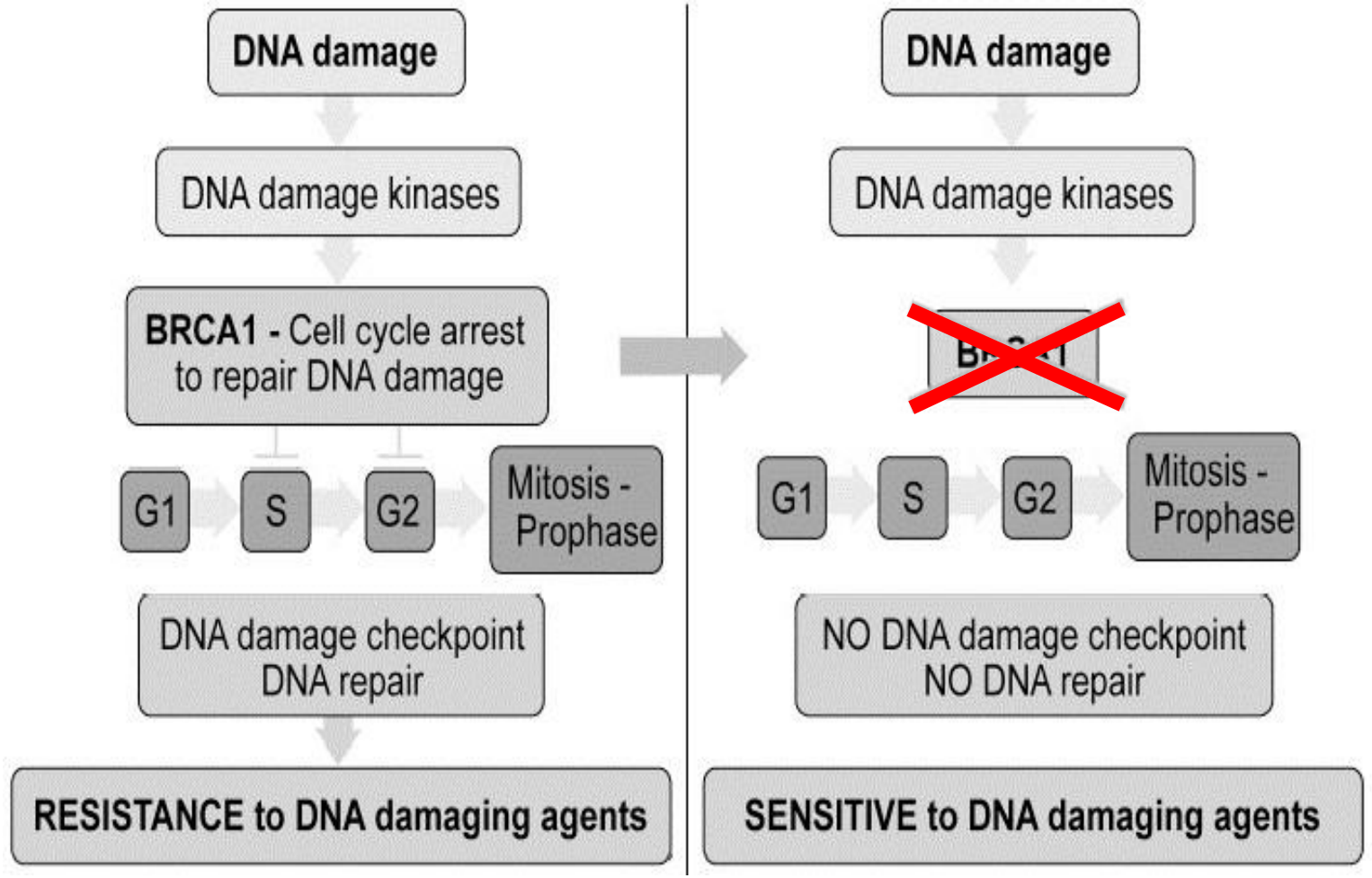
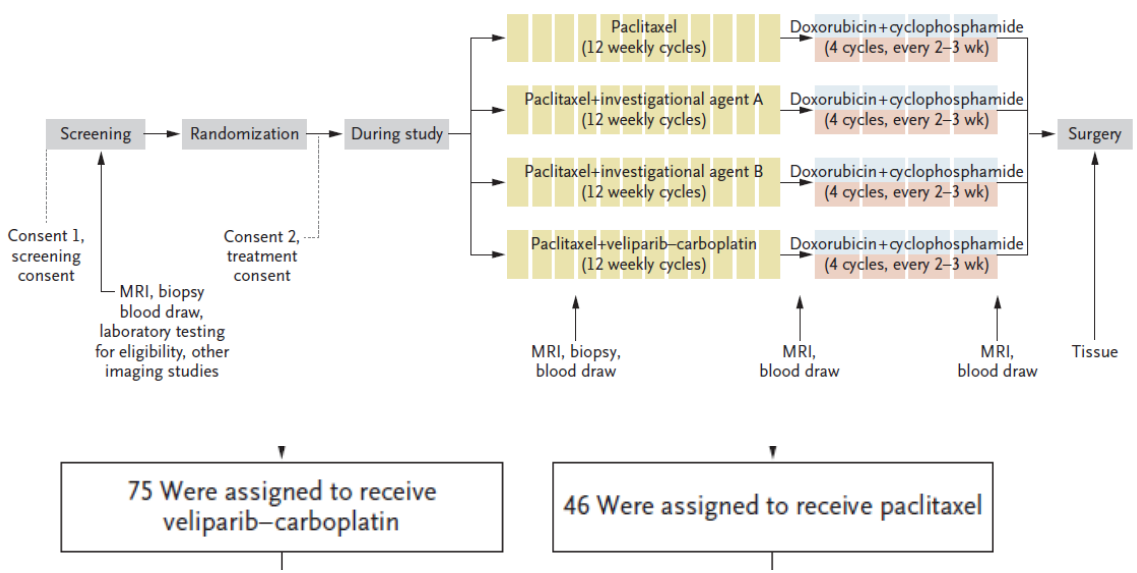
DRUG-SPECIFIC CHEMOTHERAPY FOR TNBC?

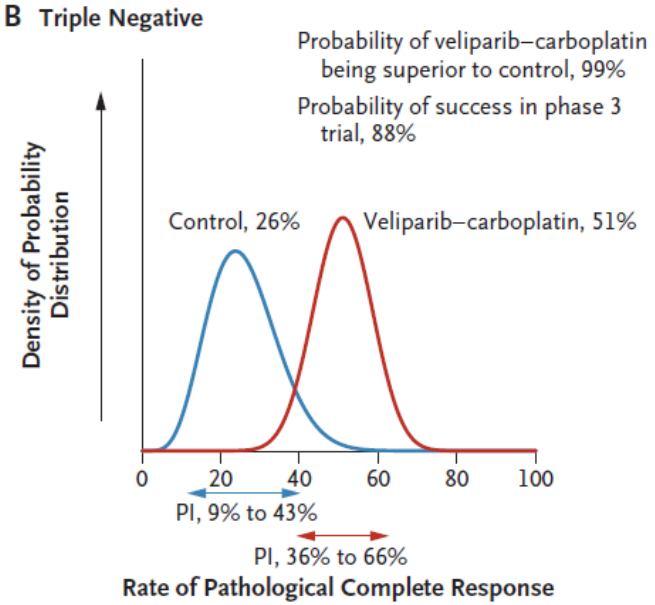


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

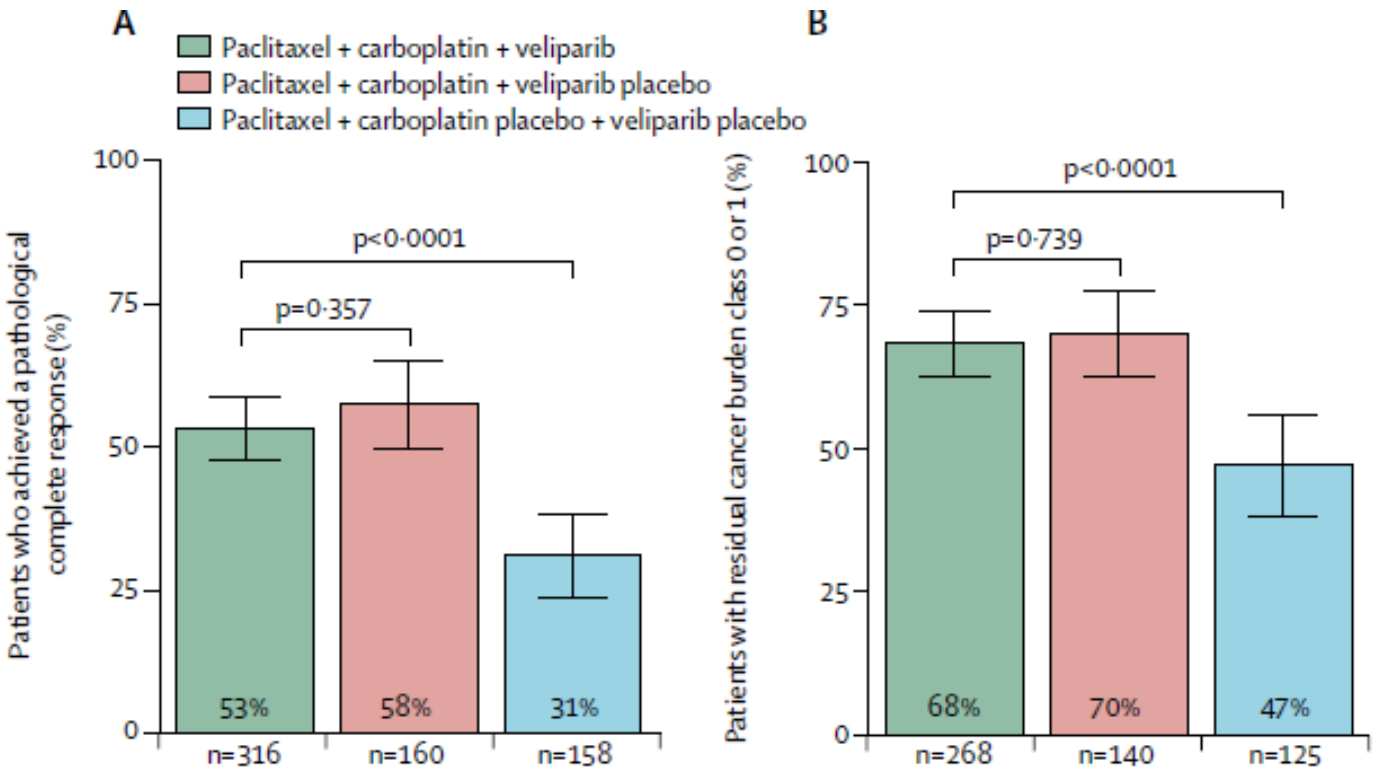
Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer





Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial

Sibylle Loibl, Joyce O'Shaughnessy, Michael Untch, William M Sikov, Hope S Rugo, Mark D McKee, Jens Huober, Mehra Golshan, Gunter von Minckwitz, David Maag, Danielle Sullivan, Norman Wolmark, Kristi McIntyre, Jose J Ponce Lorenzo, Otto Metzger Filho, Priya Rastogi, W Fraser Symmans, Xuan Liu, Charles E Geyer Jr



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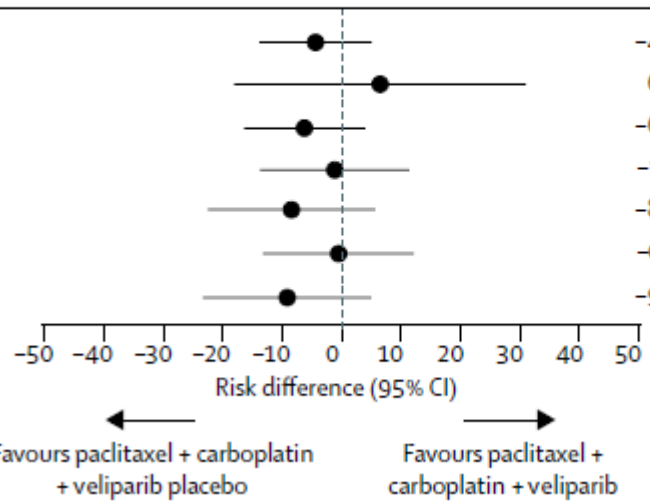
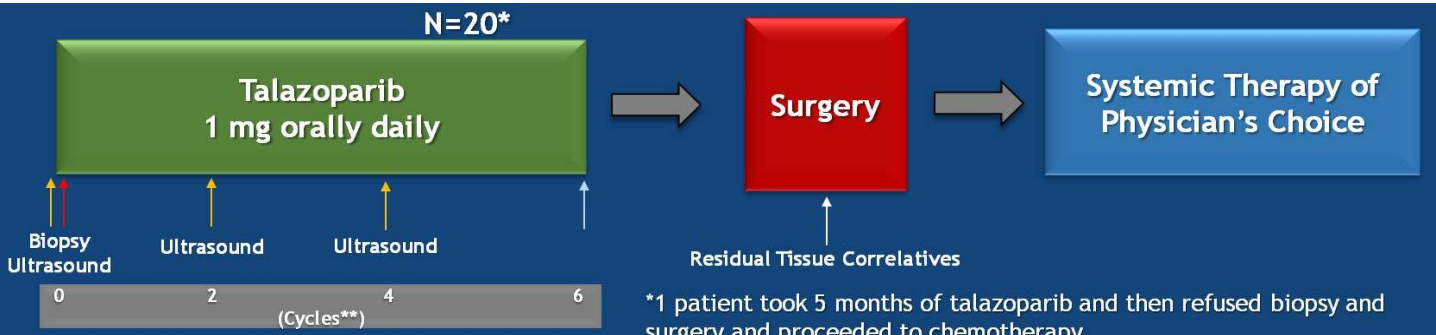
Lancet Oncol 2018; 19: 497–509

A

	n/N (%)		Risk difference (95% CI)
	Paclitaxel + carboplatin + veliparib placebo	Paclitaxel + carboplatin + veliparib	
All patients	92/160 (58%)	168/316 (53%)	−4·3 (−13·8 to 5·1)
BRCA1 or *BRCA2* mutation, or both	12/24 (50%)	26/46 (57%)	6·5 (−18·1 to 31·1)
No mutation in *BRCA1* or *BRCA2*	80/136 (59%)	142/270 (53%)	−6·2 (−16·4 to 4·0)
Lymph node stage N0	54/87 (62%)	106/174 (61%)	−1·2 (−13·7 to 11·4)
Lymph node stage N1–2	38/73 (52%)	62/142 (44%)	−8·4 (−22·5 to 5·7)
AC dose every 2 weeks	50/89 (56%)	98/176 (56%)	−0·5 (−13·2 to 12·2)
AC dose every 3 weeks	42/71 (59%)	70/140 (50%)	−9·2 (−23·3 to 5·0)



Neoadjuvant talazoparib for BRCA mut



*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy
** 1 cycle=28 days

Eligibility

- Tumors > 1 cm
- Clinical Stage I-III
- Germline BRCA mutation
- No previous therapy for invasive breast cancer

Exclusion

- HER2 positive

Primary Objectives

- pCR (ypT0/is ypN0)
- RCB-0 + RCB-I

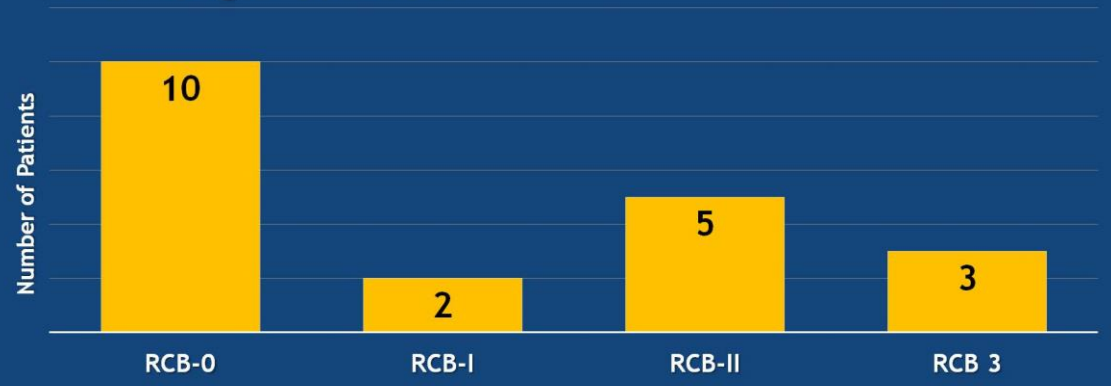
Secondary Objective

- Evaluate toxicity

Characteristics		Number of Patients
BRCA mutation	1	17
	2	3
Tissue Receptor Subtype	TNBC (<10% ER or PR)	15
	Hormone Receptor positive (≥10%)	5

Neoadjuvant talazoparib for BRCA mut

Pathologic Results

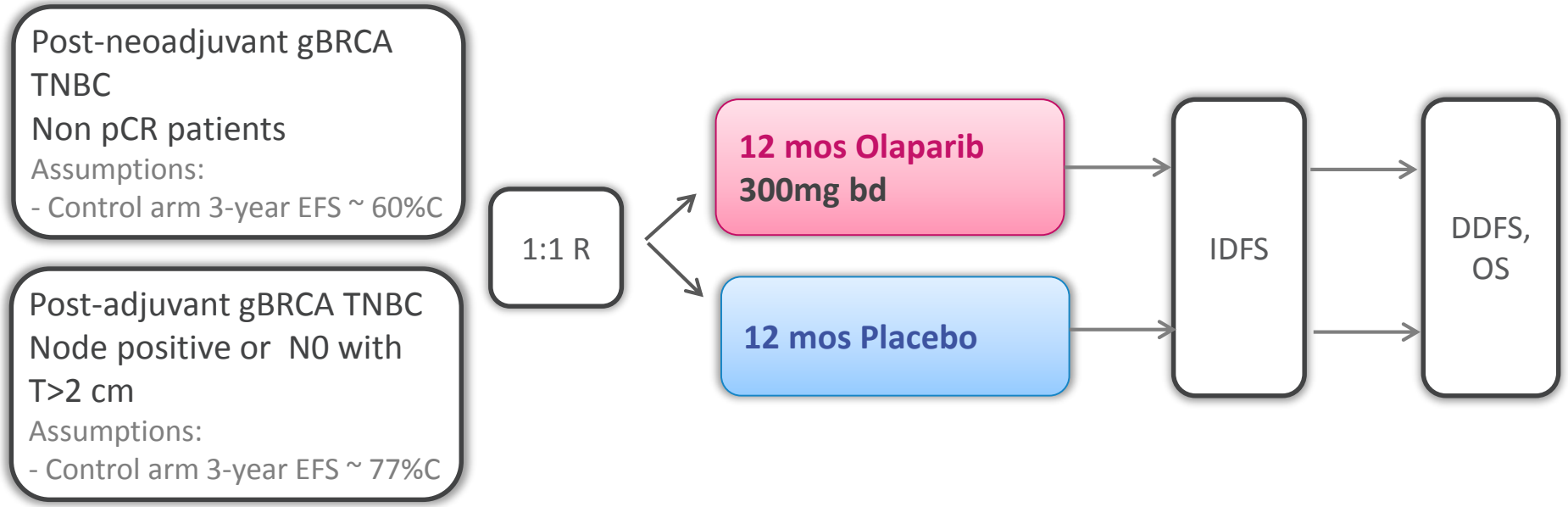


pCR (RCB-0): 10/19 = 53%, 95% CI = 32%, 73%

RCB-0+I: 12/19 = 63%, 95% CI = 41%, 81%

Variable	RCB-0	RCB-I	RCB-II	RCB-III
BRCA1 (n=16)	8	1	5	2
BRCA2 (n=3)	2	1	0	0
TNBC (n=14)	7	1	4	2
HR+ (n=5)	3	1	1	0
Stage 1 (n=5)	4	0	1	0
Stage 2 (n=12)	5	2	4	1
Stage 3 (n=2)	1	0	0	1

OlympiA



N=1,320

- **Study to start recruiting patients with TNBC; plan to add ER/PR+ patients once data available from PK/PD interactions (expected Mid 2014)**
- **Primary endpoint: IDFS (invasive disease-free survival; STEEP approach)**
  - **HR=0.7 (CV=0.81), 90% power, 5% significance level, approx 330 events required**
    - **Assumes consistent treatment effect (HR=0.7) across patient groups**
    - **N=1320 (25% maturity), assuming 4 years recruitment, IDFS analysis estimated approx. 5.5–6 years from FSI**

Adjuvant therapy in TNBC- Outline

- Small Tumor
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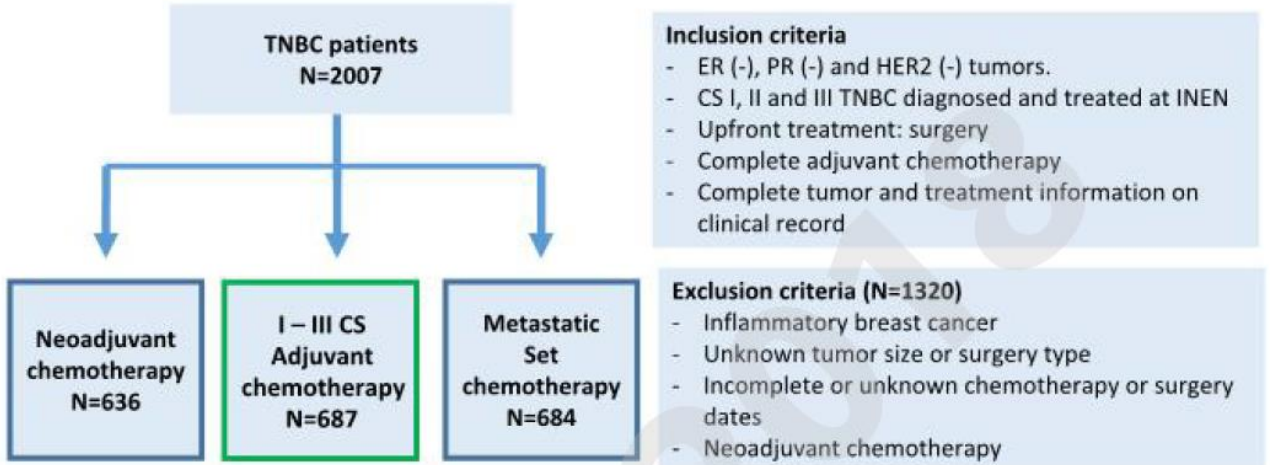
- High Dose Chemotherapy
- PARPi: narrowing target population to BRCA+
- Timing of chemotherapy

Impact of the delayed initiation of adjuvant CT in TNBC

Objectives

We evaluated the influence of time to adjuvant chemotherapy (TTC) on the survival (OS – DFS - DRFS) of TNBC patients diagnosed at the Instituto Nacional de Enfermedades Neoplasicas (Lima, Peru) between 2000 to 2014.

Methods: study population (1)



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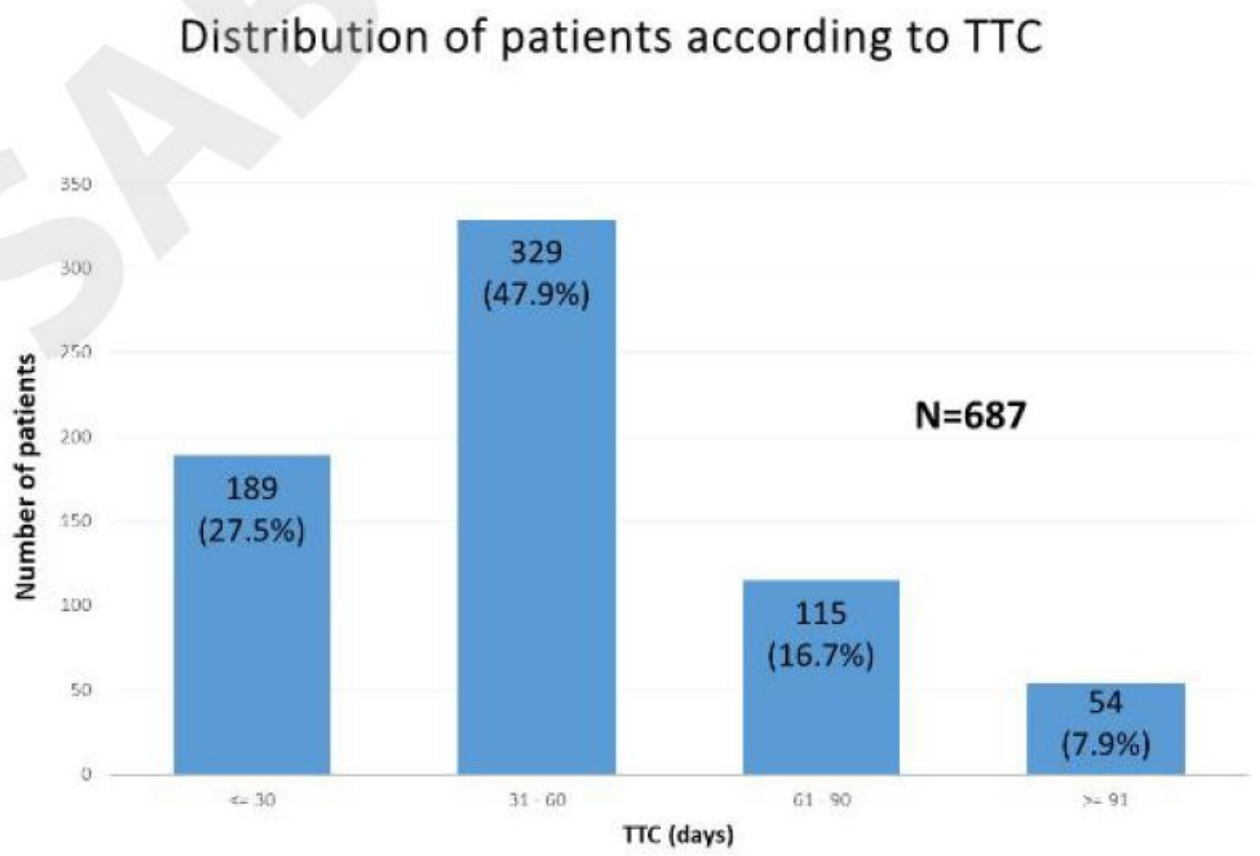
Impact of the delayed initiation of adjuvant CT in TNBC



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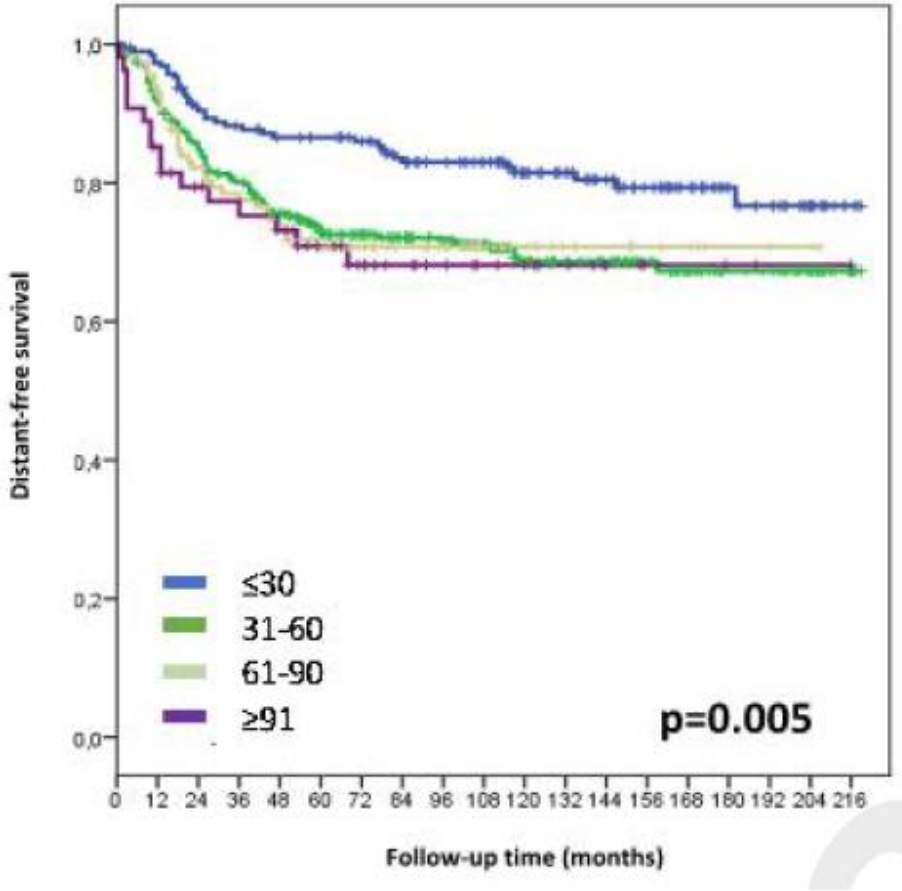
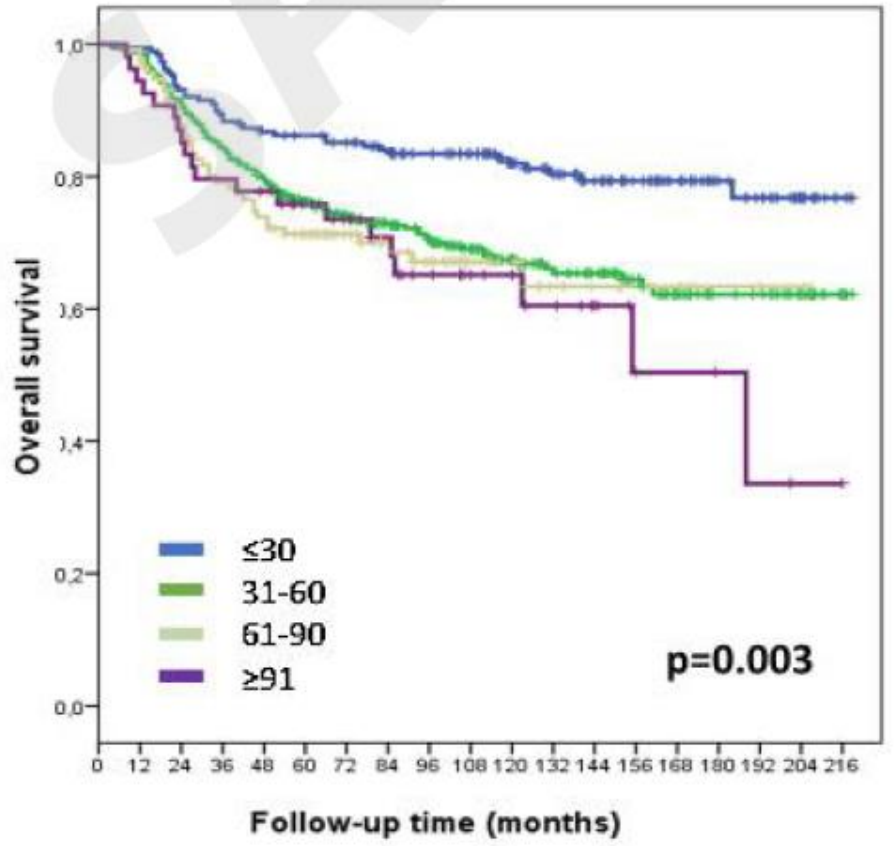
Impact of the delayed initiation of adjuvant CT in TNBC

TTC

Variables	Total (n=687) (%)	Time to chemotherapy (days) ≤30	31-60	61-90	≥91	p Value
Age, years						**0.007**
Median/Range	48/[21-89]	46/[23-77]	48/[21-89]	50/[28-82]	49/[30-76]	
Diagnosis period						**<0.001**
2000 - 2004	195 (28.4)	77 (40.7)	92 (28.0)	17 (14.8)	9 (16.7)	
2005 -2009	287 (41.8)	91 (48.1)	129 (39.2)	42 (36.5)	25 (46.3)	
2010 - 2014	205 (29.8)	21 (11.1)	108 (32.8)	56 (48.7)	20 (37.0)	
Clinical Stage						0.439
I	72 (10.5)	19 (10.1)	30 (9.1)	18 (15.7)	5 (9.3)	
II	413 (60.1)	117 (61.9)	200 (60.8)	67 (58.3)	29 (53.7)	
III	202 (29.4)	53 (28.0)	99 (30.1)	30 (26.1)	20 (37.0)	
Surgery type						**0.028**
Conservative	255 (37.1)	62 (32.8)	114 (34.7)	54 (47.0)	25 (46.3)	
Mastectomy	432 (62.9)	127 (67.2)	215 (65.3)	61 (53.0)	29 (53.7)	
Resection margin (n=255)						**0.018**
Yes	112 (43.9)	19 (17.0)	48 (42.9)	31 (27.7)	14 (12.5)	
No	143 (56.1)	43 (30.1)	66 (46.2)	23 (16.1)	11 (7.7)	
Type of adjuvant chemotherapy						**0.014**
Anthracycline-based	285 (41.5)	97 (51.3)	130 (39.5)	34 (29.6)	24 (44.4)	
Anthracycline + Taxane-based	375 (54.6)	84 (44.4)	188 (57.1)	75 (65.2)	28 (51.9)	
Others	27 (3.9)	8 (4.2)	11 (3.3)	6 (5.2)	2 (3.7)	

Impact of the delayed initiation of adjuvant CT in TNBC





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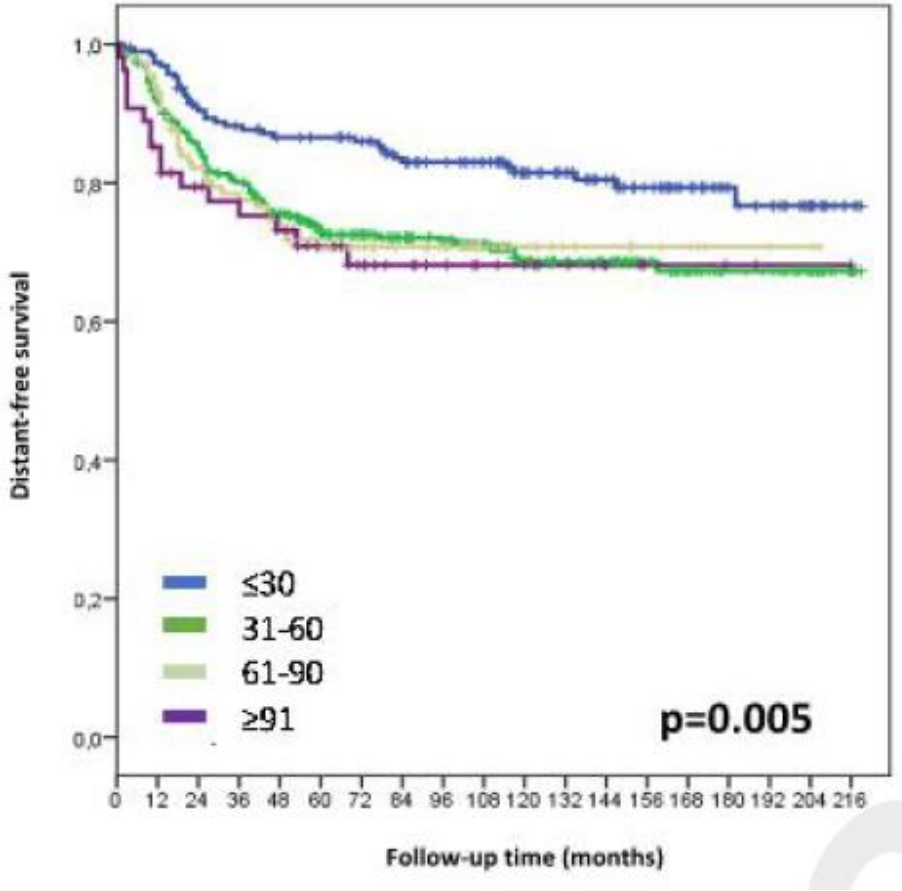
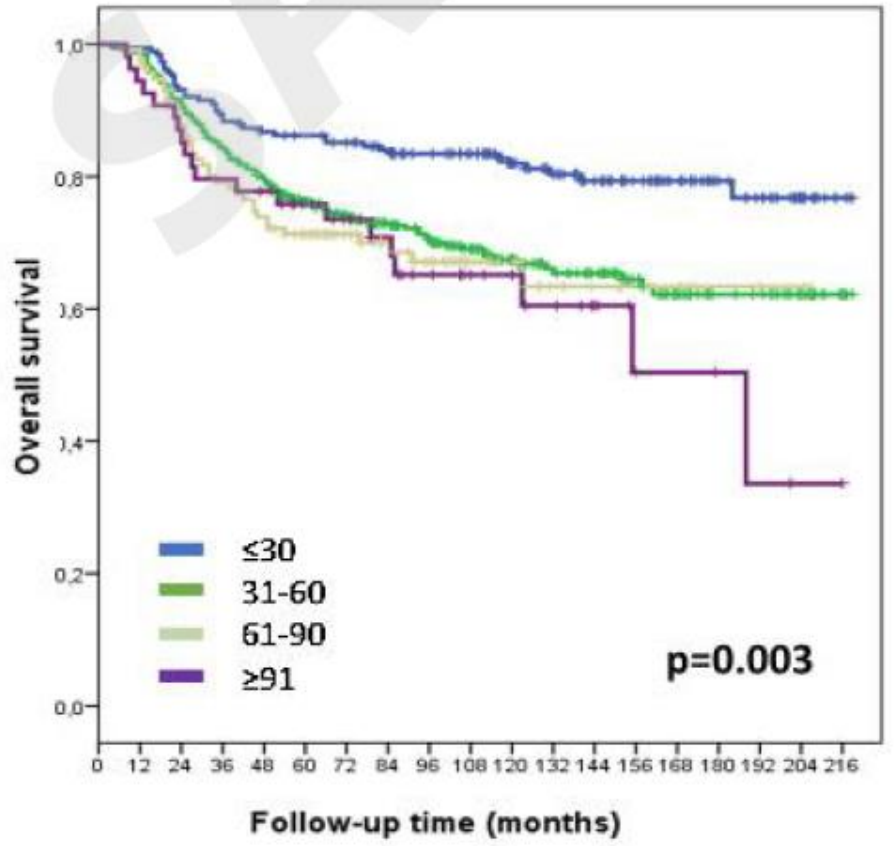
Impact of the delayed initiation of adjuvant CT in TNBC





Morante Z, et al. SABCS 2018

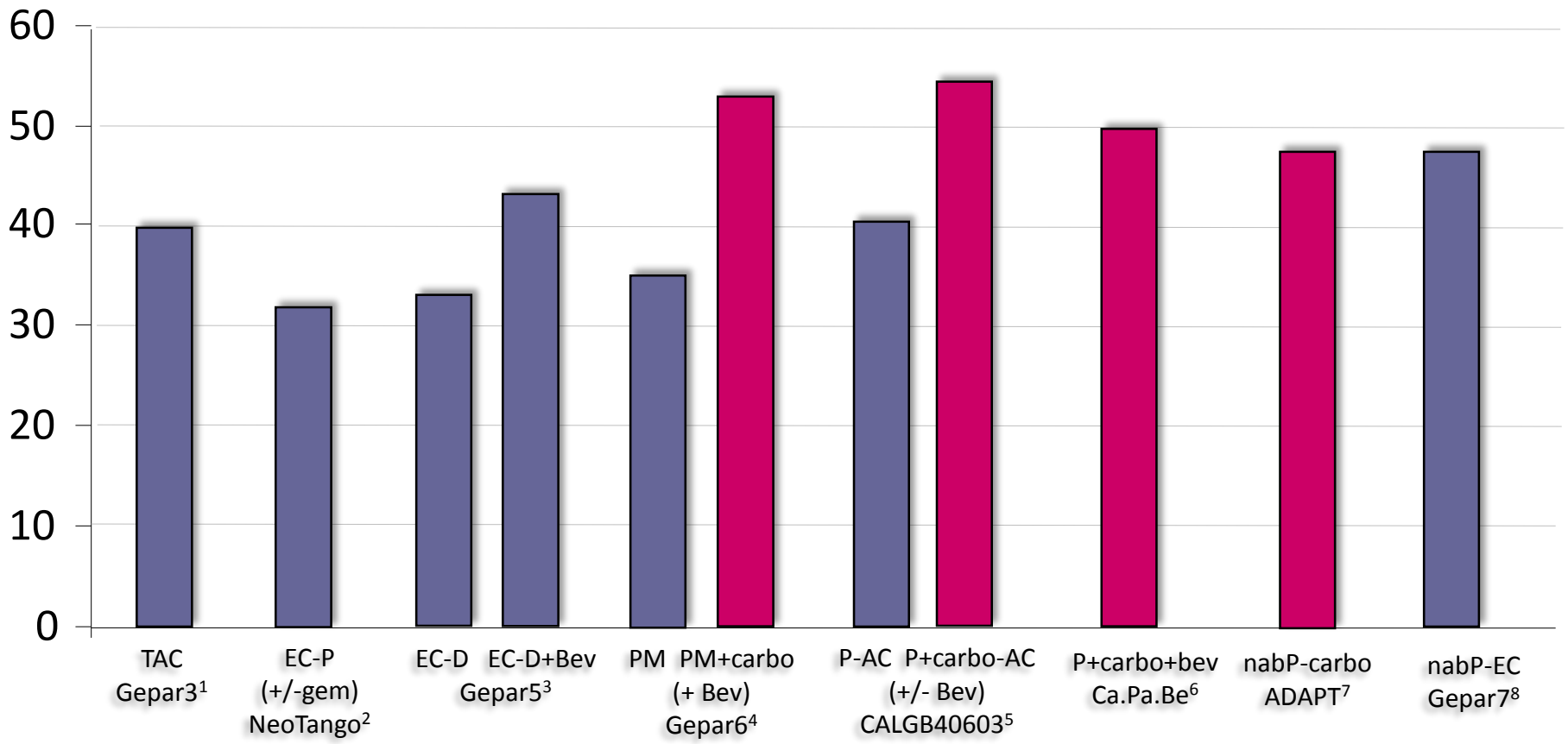
Adjuvant therapy in TN

- Low thresholds for adjuvant chemotherapy treatment for TNBC (~ 0.5 cm, node- negative)
- Standard chemotherapy agents are effective adjuvant therapy
- Enhancements to adjuvant chemotherapy (addition of taxanes, sequential therapy, dose dense schedule) should be considered
- Alternative regimens
  - Preferred regimen without anthracyclines: TC
  - Preferred regimen without taxanes: AC or CMF
- PARP inhibitors hold great promises for BRCA-mut patients
- Timing of adjuvant treatment matters!

(Neo)Adjuvant therapy in TNBC-Outline

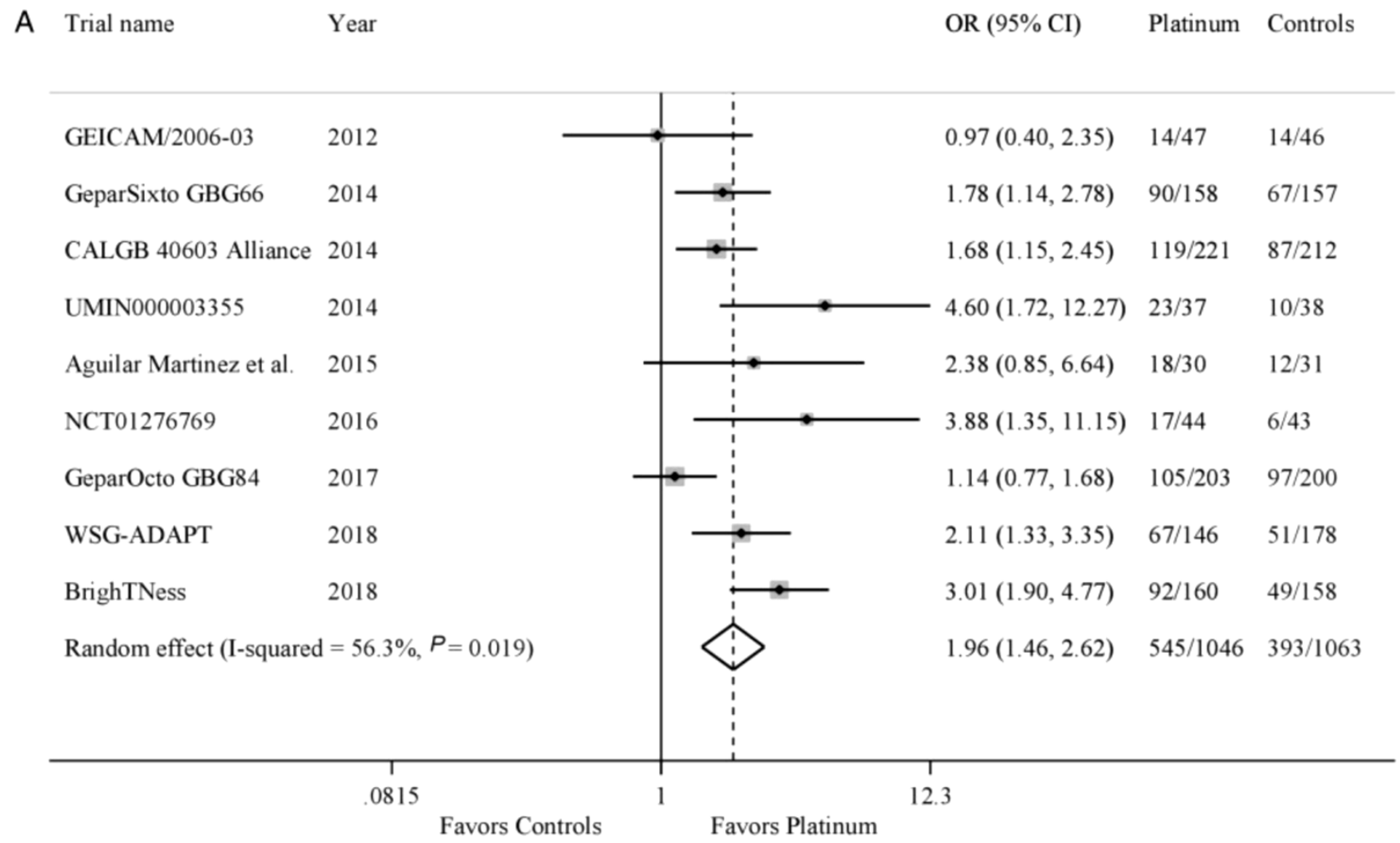
- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

pCR rates (breast/axilla) in TNBC



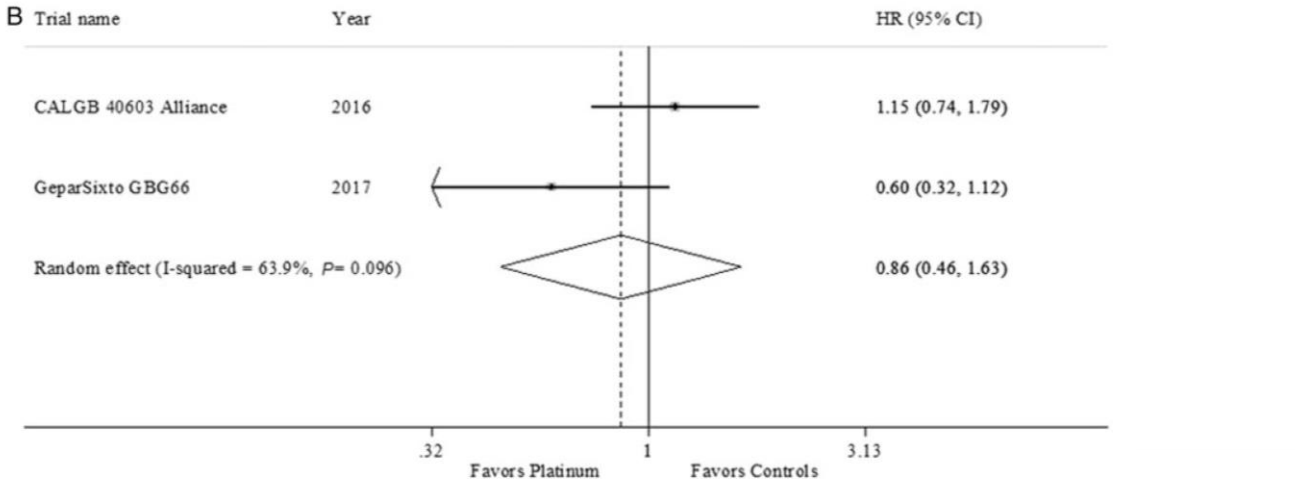
1. Huober J, BCRT 2010; 2. Earl HM, Lancet Oncol 2014; 3. von Minckwitz, NEJM 2012; 4. von Minckwitz, Lancet Oncol 2014; 5. Sikov, J Clin Oncol 2015; 6. Guarneri V, Ann Surg Oncol 2015; 7. Gluz O, SABCS 2015; 8. Untch M, SABCS 2014

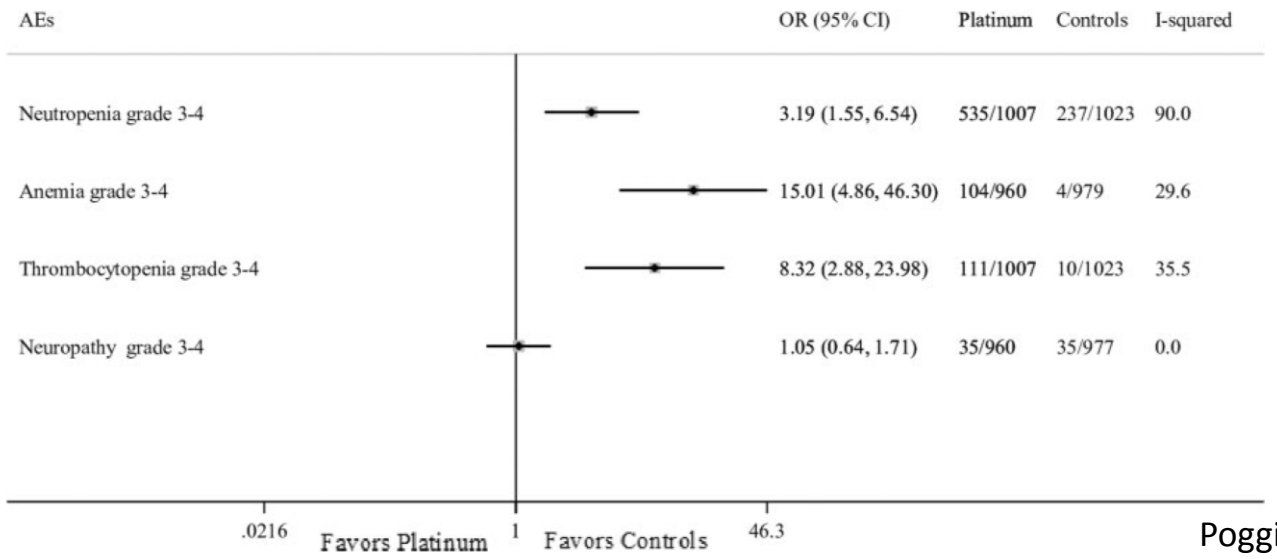
Adding platinum to neoadj CT increases pCR



Poggio F. et al. Ann Oncol 2018

Survival benefit is uncertain and adding platinum is more toxic



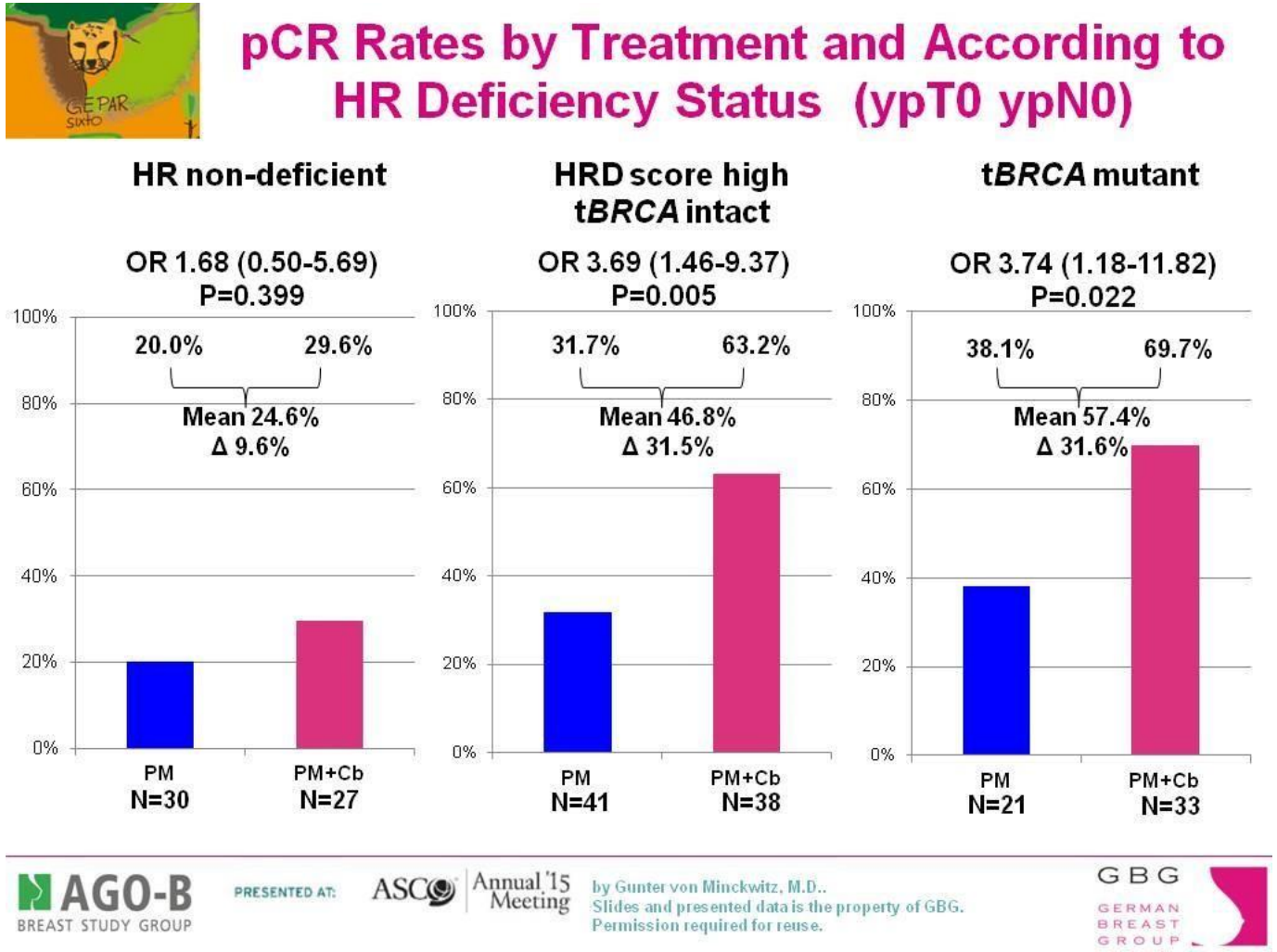


Hazard-ratios for overall survival

Safety profile

Poggio F. et al. Ann Oncol 2018

pCR RATES BY TREATMENT AND ACCORDING TO HR DEFICIENCY STATUS (ypT0 ypN0)



Presented By Von Minckwitz G, at 2015 ASCO Annual Meeting.

QUESITO GRADE n.5:
Platino nella terapia neoadiuvante per TNBC

Roma 2018

QUESITO CLINICO N. 14 (RIFERIRSI AL quesito GRADE n. 5) (Figura n. 9)

Nelle donne con carcinoma mammario TRIPLO NEGATIVO (recettori ormonali negativi ed HER2-negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, è raccomandabile l'aggiunta del platino ad uno schema standard con antracicline e taxani rispetto alla sola chemioterapia a base di antracicline e taxani?

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne con carcinoma mammario triplo negativo (recettori ormonali negativi ed HER2 negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, l'aggiunta del platino ad uno schema standard con antracicline e taxani può essere preso in considerazione.	**Positiva debole**

Leggere capitolo 14- Raccomandazioni prodotte secondo metodologia GRADE

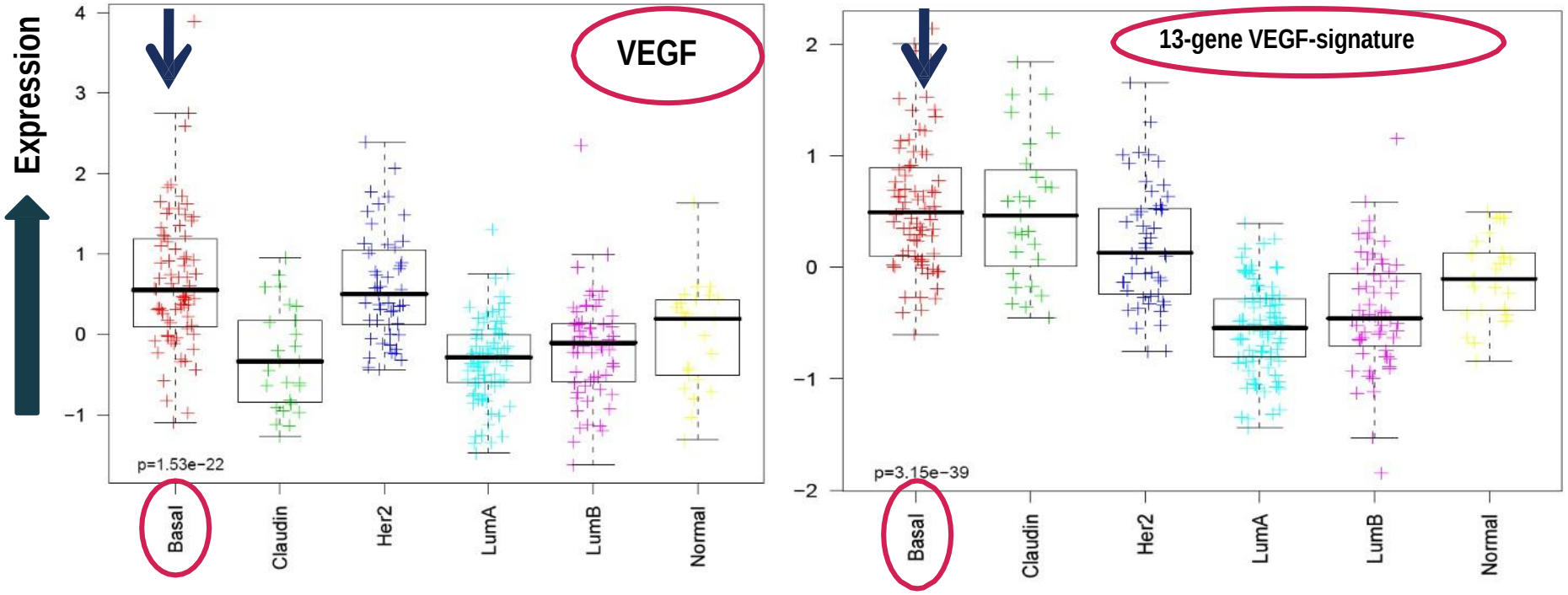
- Framework Evidence to Decision (EtD) utilizzato per supportare lo sviluppo della raccomandazione (allegato).
- Importanza degli effetti di beneficio: «MODERATE»
- Importanza degli effetti di danno: «SMALL»
- Qualità delle evidenze: «MODERATE»
- Valutazione rapporto beneficio/danno: «Incerto: favorevole» (10/11)

MV Dieci, AIOM 2018

(Neo)Adjuvant therapy in TNBC-Outline

- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

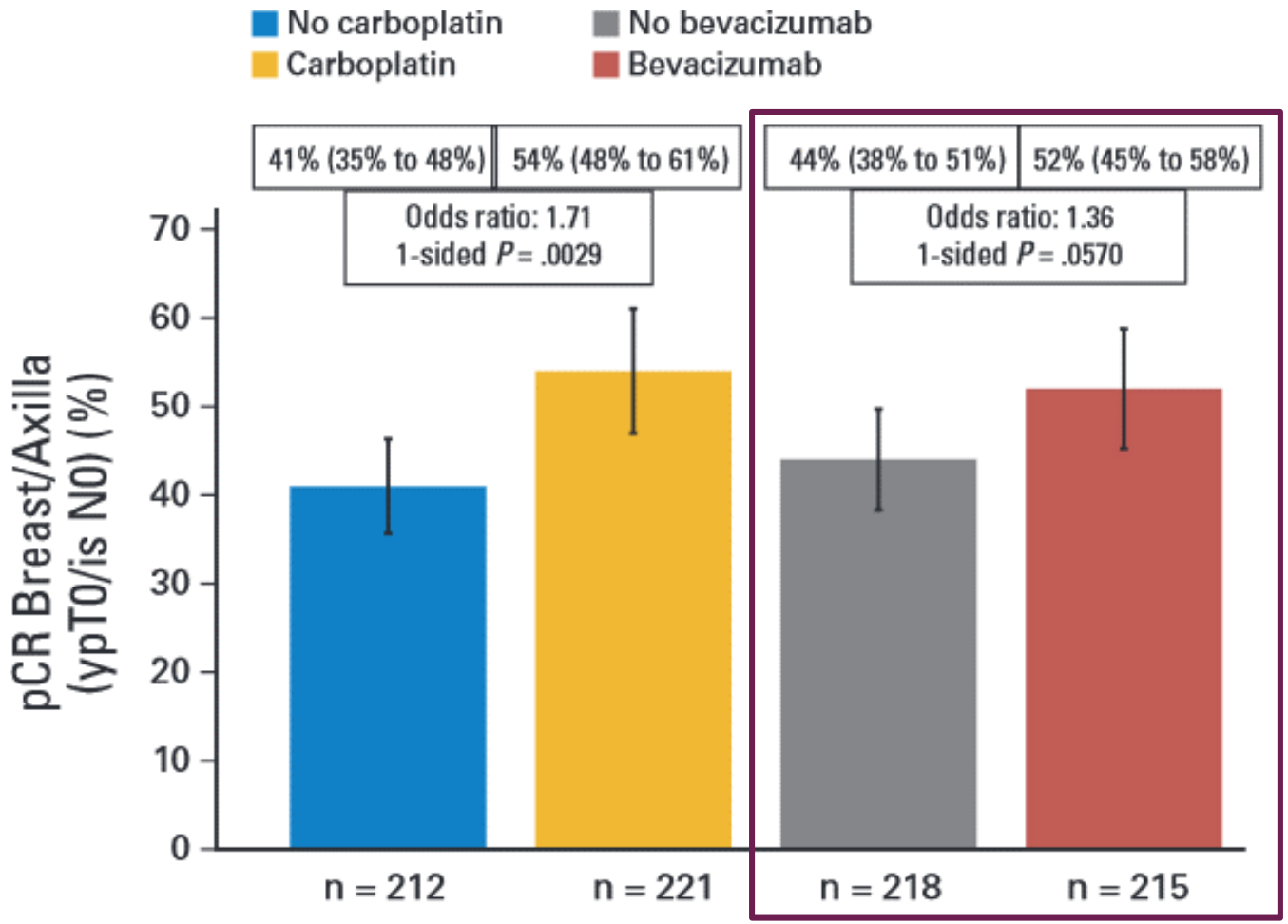
Hypoxia-related features and basal like tumours



Antiangiogenic approaches work in TNBC at least as well as other subtype, possibly more

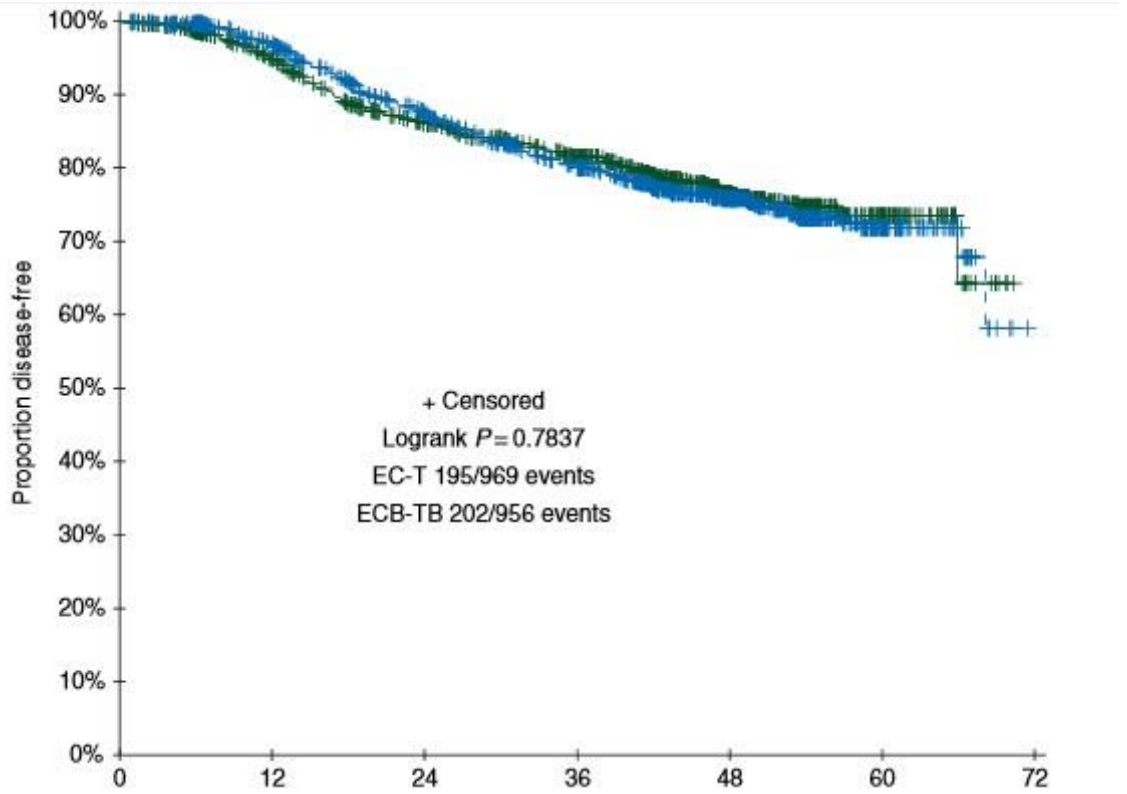
Perou CM, The Oncologist 2010; 15(5):39-48.

CALGB 40603: RESULTS BEV/NO BEV



Sikov WM, *et al.*, J Clin Oncol 2014;33:13–21

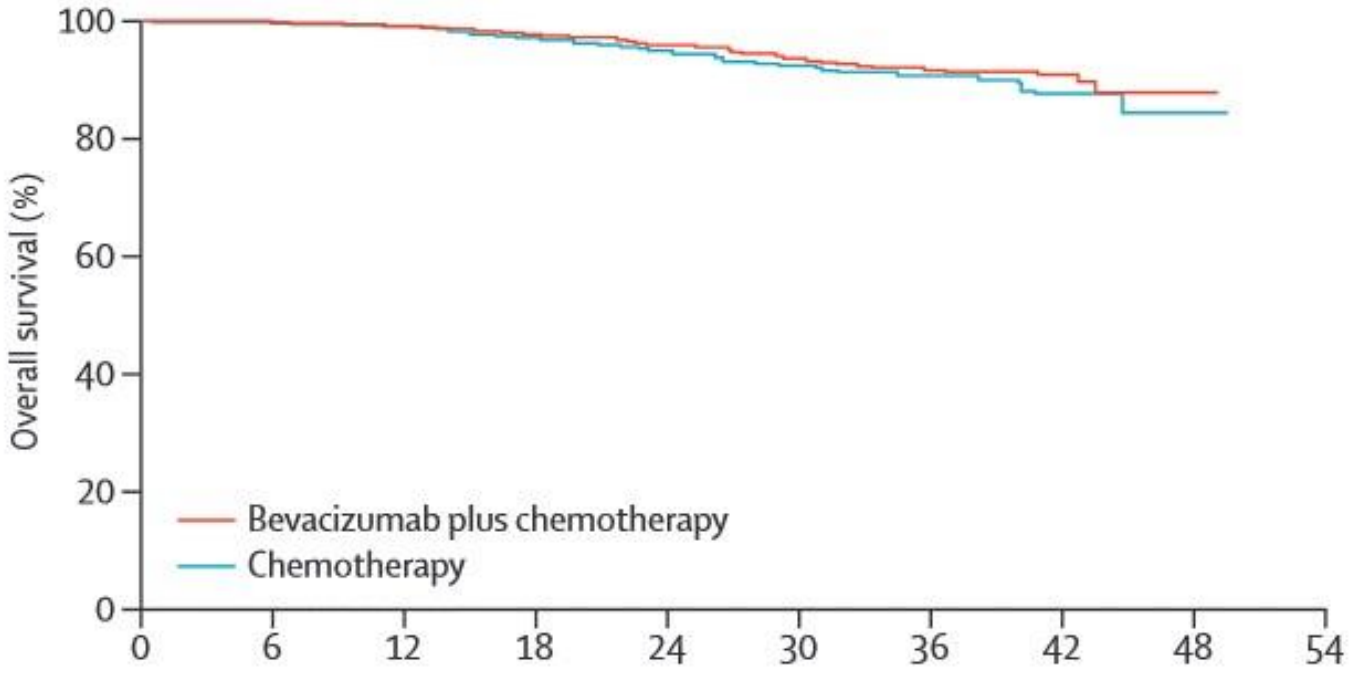
GEPARQUINTO: NEOADJUVANT BEVACIZUMAB AND SURVIVAL



Receptor status			.610
ER and/or PgR positive	1262	1.10 (.821, 1.47)	.527
ER and PgR negative	663	.990 (.757, 1.29)	.941

von Minckwitz G, *et al.*, Ann Oncol 2014;25:2363-72.

BEATRICE PHASE III ADJUVANT TRIAL



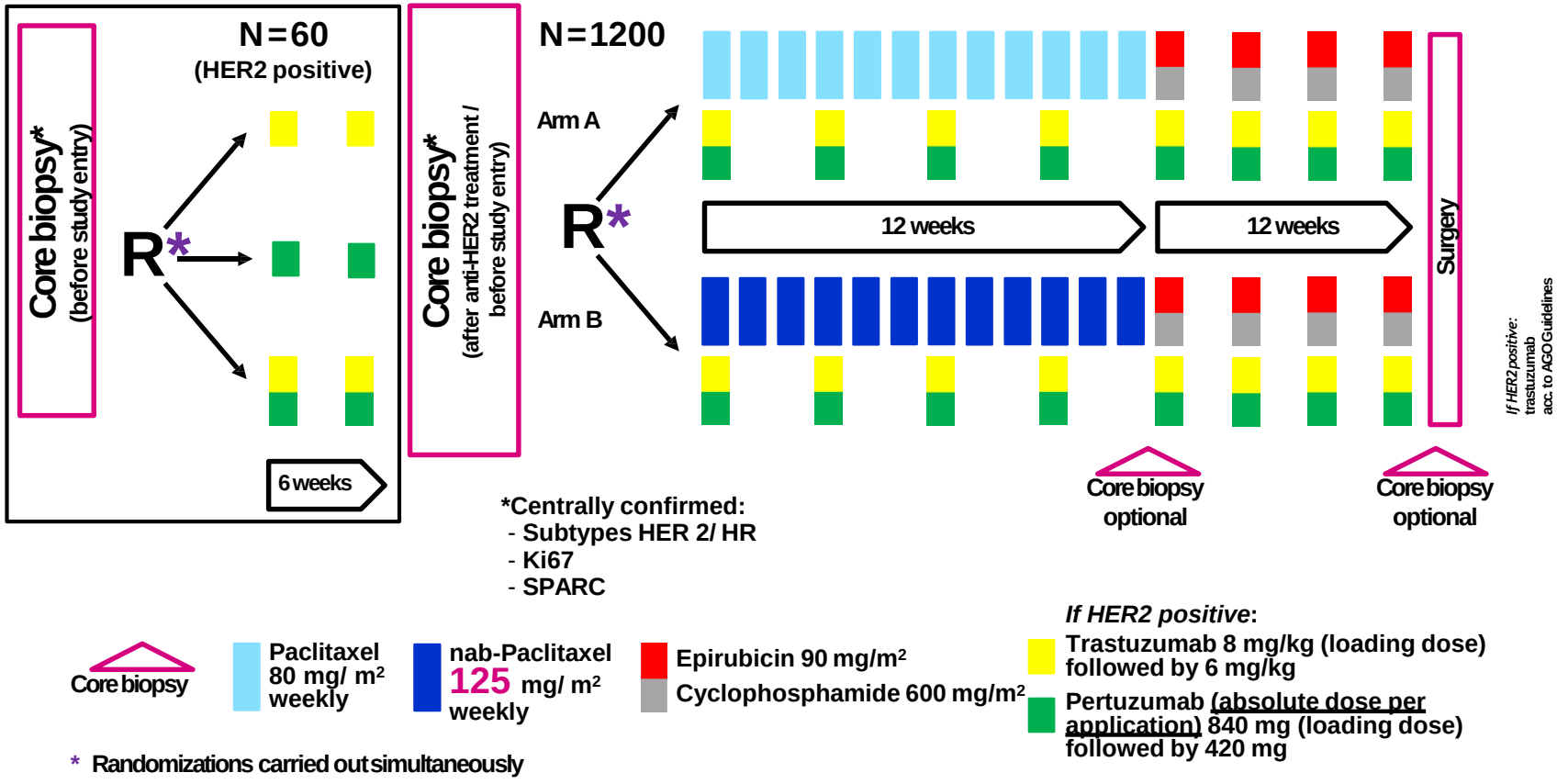
Number at risk										
Bevacizumab plus chemotherapy	1301	1264	1234	1196	1130	863	443	128	4	0
Chemotherapy	1290	1248	1215	1169	1087	831	424	113	4	0

Reprinted from Cameron D, Lancet 2013;14:933–42.

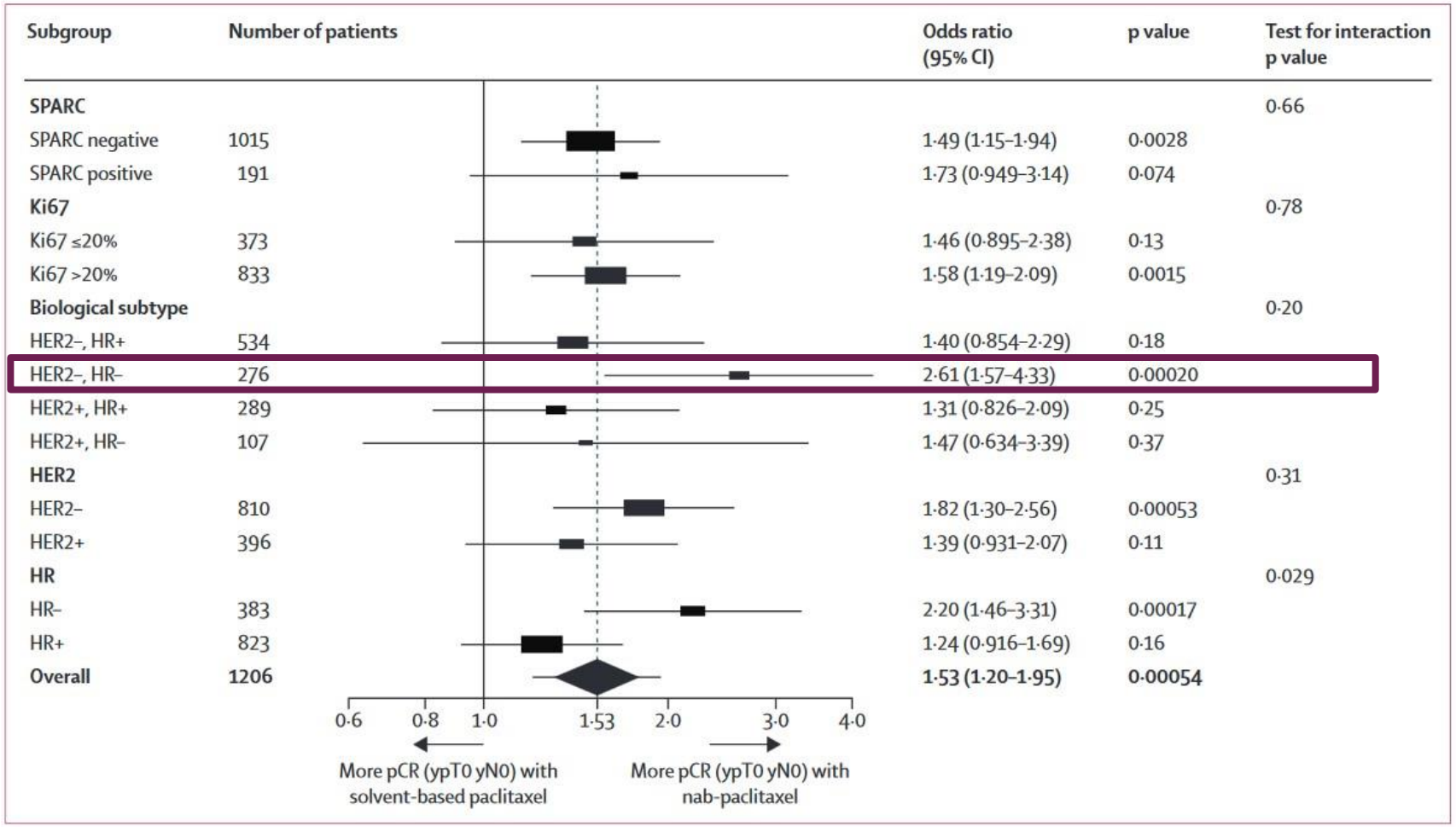
(Neo)Adjuvant therapy in TNBC-Outline

- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

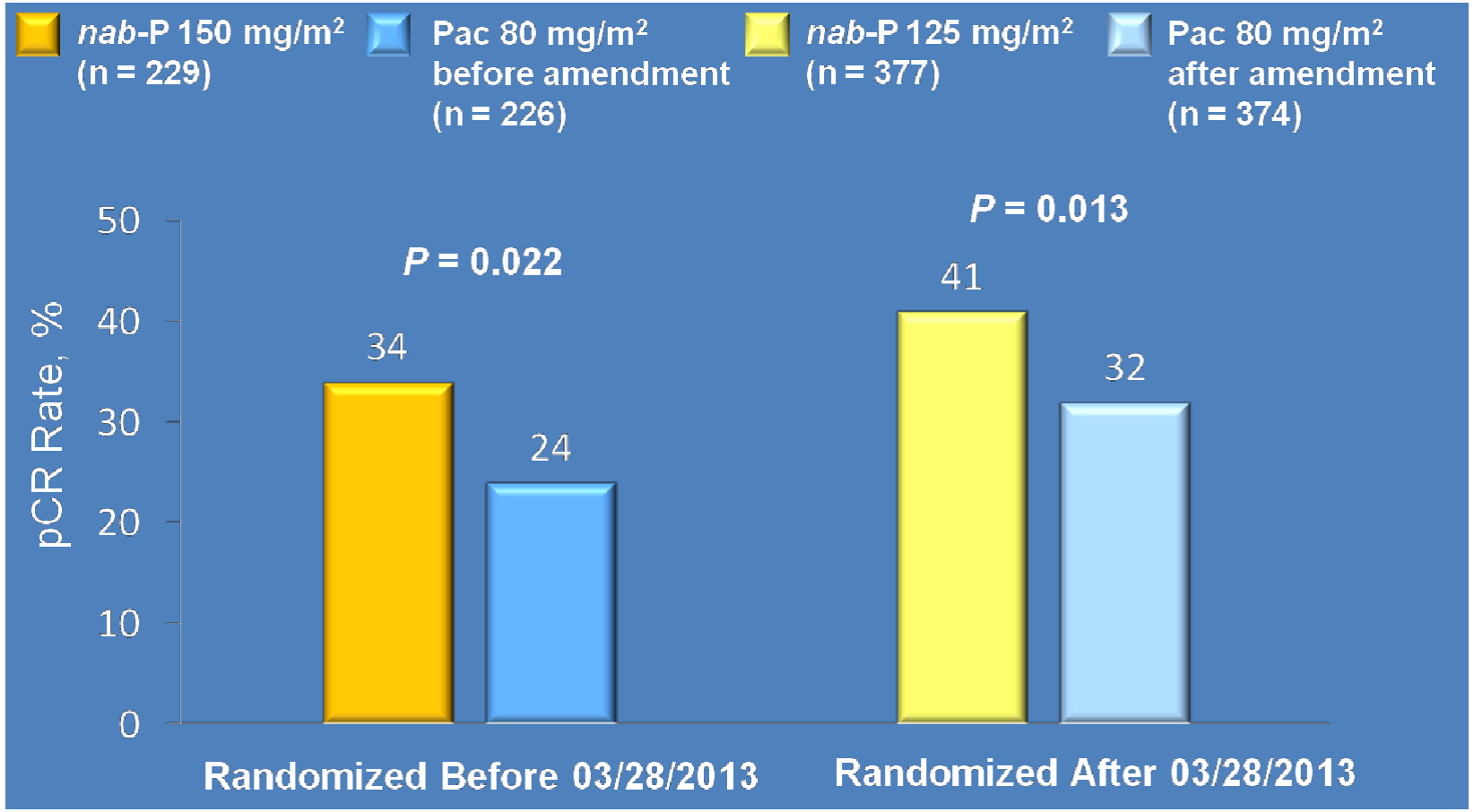
Neoadjuvant nabpaclitaxel for triple-negative breast cancer Geparsepto



GEPAR7: SUBGROUP ANALYSIS



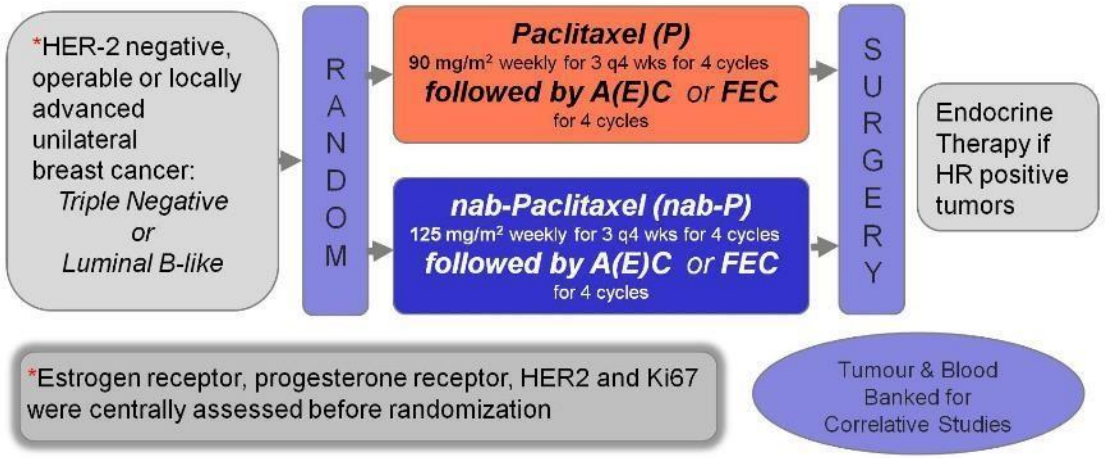
Neoadjuvant nabpaclitaxel for triple-negative breast cancer Geparsepto



Untch M, et al. Lancet Oncol. 2016. Epub ahead of print.

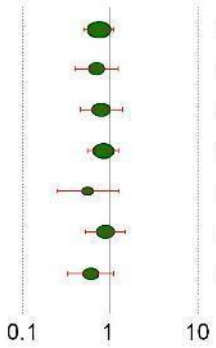
PHASE III RANDOMISED ETNA TRIAL

Scheme of the Phase III randomized ETNA trial



Subgroup Analysis: pCR rate

Category	Subgroup	*nab*-P %	P %	OR (95% CI)
	All	22.5	18.6	0.77 (0.52 - 1.13)
Tumor subtype	Luminal B-like	13.9	10.0	0.69 (0.39 - 1.21)
	Triple negative	41.3	37.3	0.85 (0.49 - 1.45)
Stage	Non-locally advanced	23.1	20.7	0.87 (0.57 - 1.31)
	Locally advanced	20.7	12.5	0.55 (0.24 - 1.25)
Age	<=50	22.0	20.7	0.90 (0.53 - 1.51)
	>50	23.1	16.1	0.63 (0.35 - 1.14)

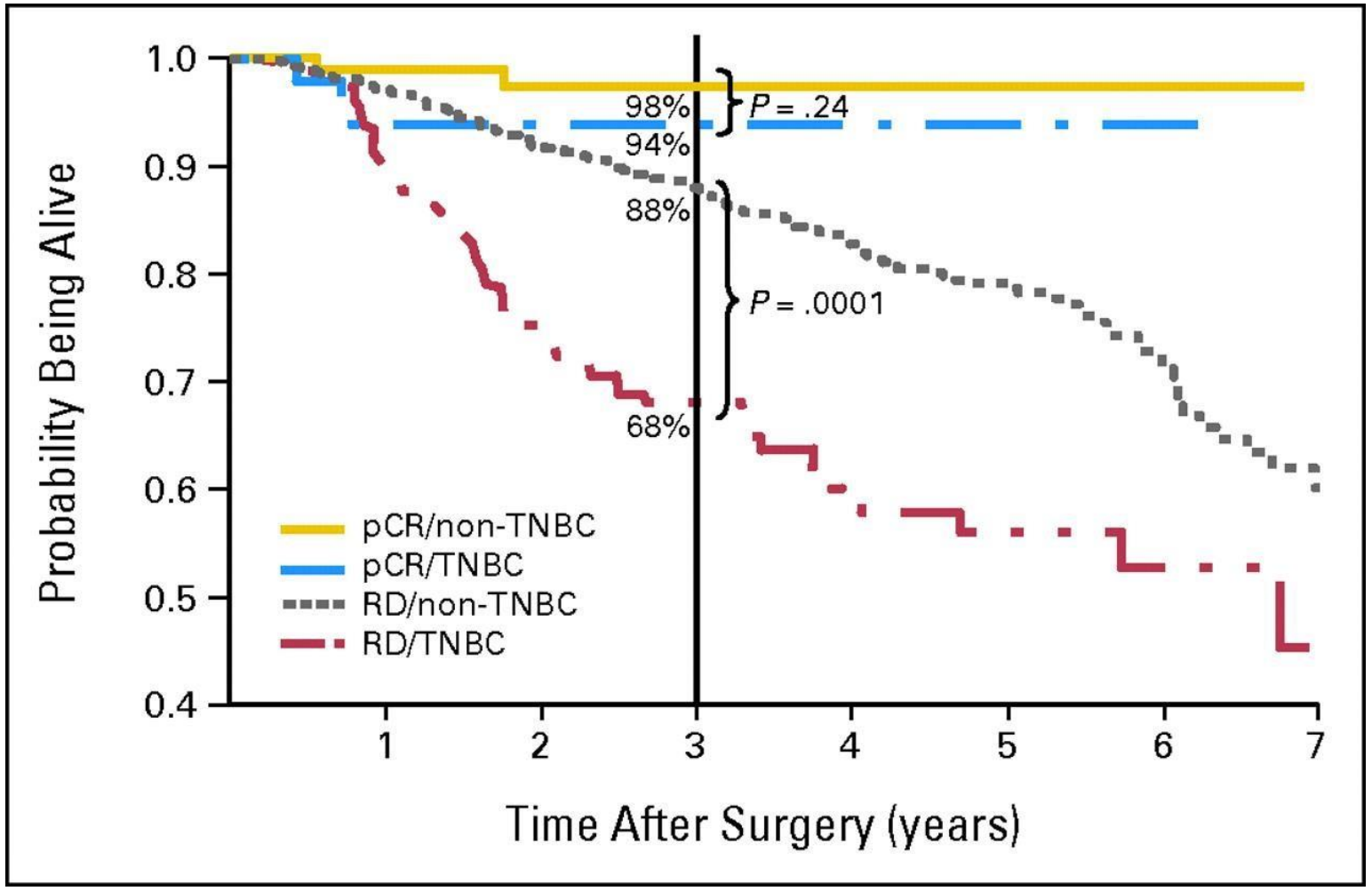


Gianni L, at 2016 ASCO Annual Meeting.

(Neo)Adjuvant therapy in TNBC-Outline

- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

Post-Neoadjuvant setting

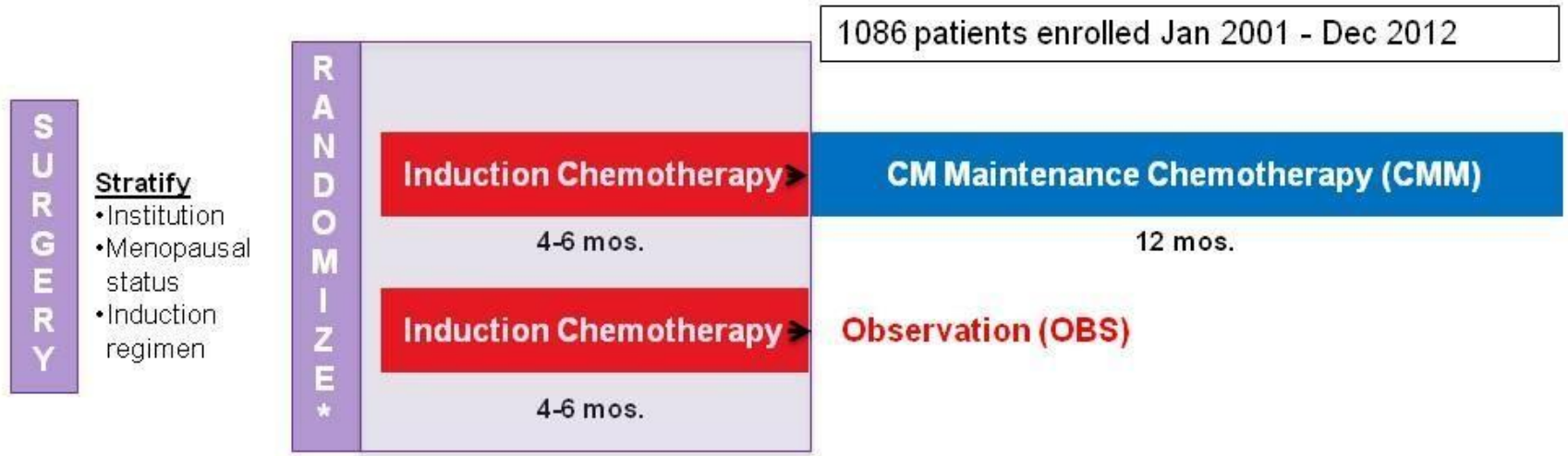


C. Liedtke JCO, 26, 8, 2008: pp. 1275-1281

CMM MAINTENANCE AFTER ADJUVANT CHEMOTHERAPY

IBCSG Trial 22-00 (CM Maintenance)

Hormone receptor negative (< 10% positive cells by IHC) by locally-determined ER and PgR



*Any time from start of induction to within 8 weeks after first day of last course of induction

1081 patients in ITT population; Median follow-up 6.9 years

75% TNBC

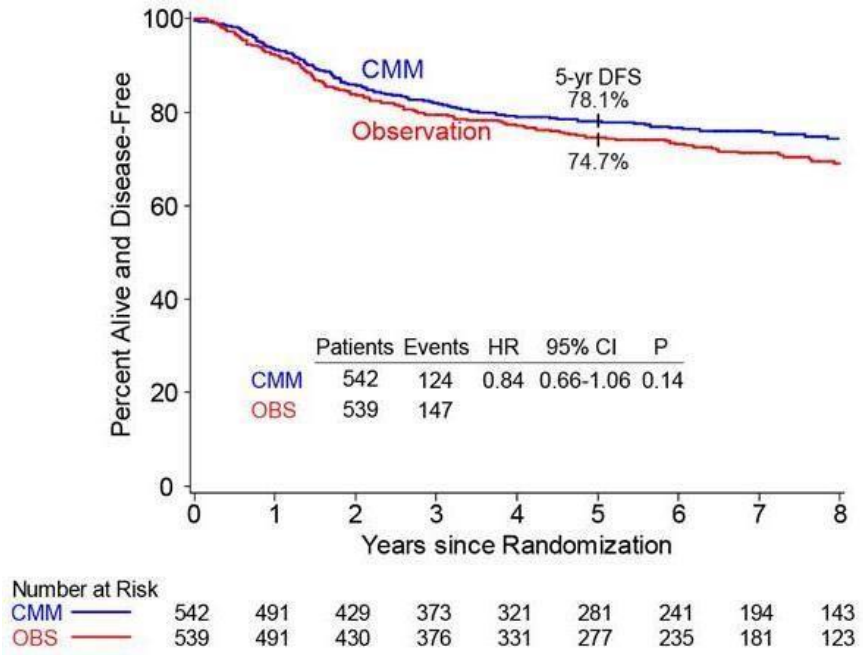
IBCSG

PRESENTED AT: ASCO Annual '15 Meeting

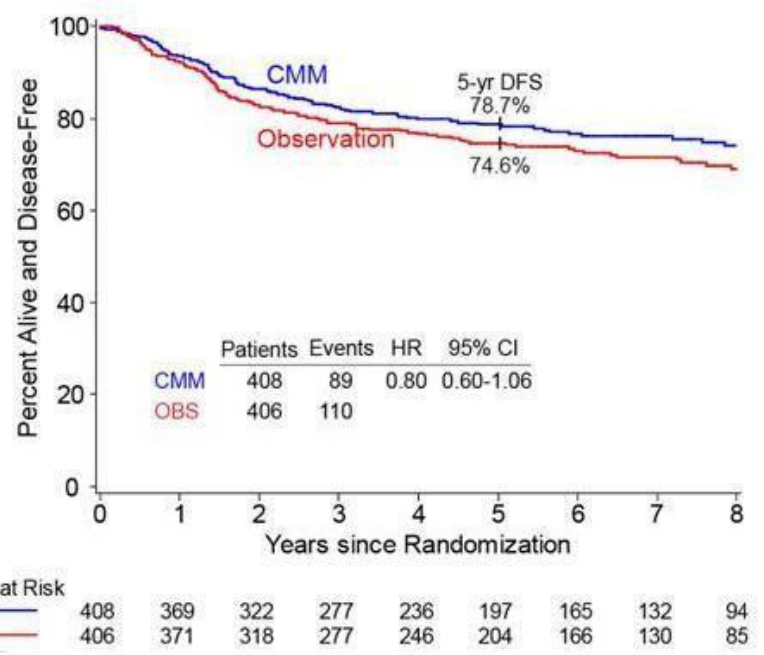
Colleoni M, at 2015 ASCO Annual Meeting.

CMM MAINTENANCE AFTER ADJUVANT CHEMOTHERAPY

All patients

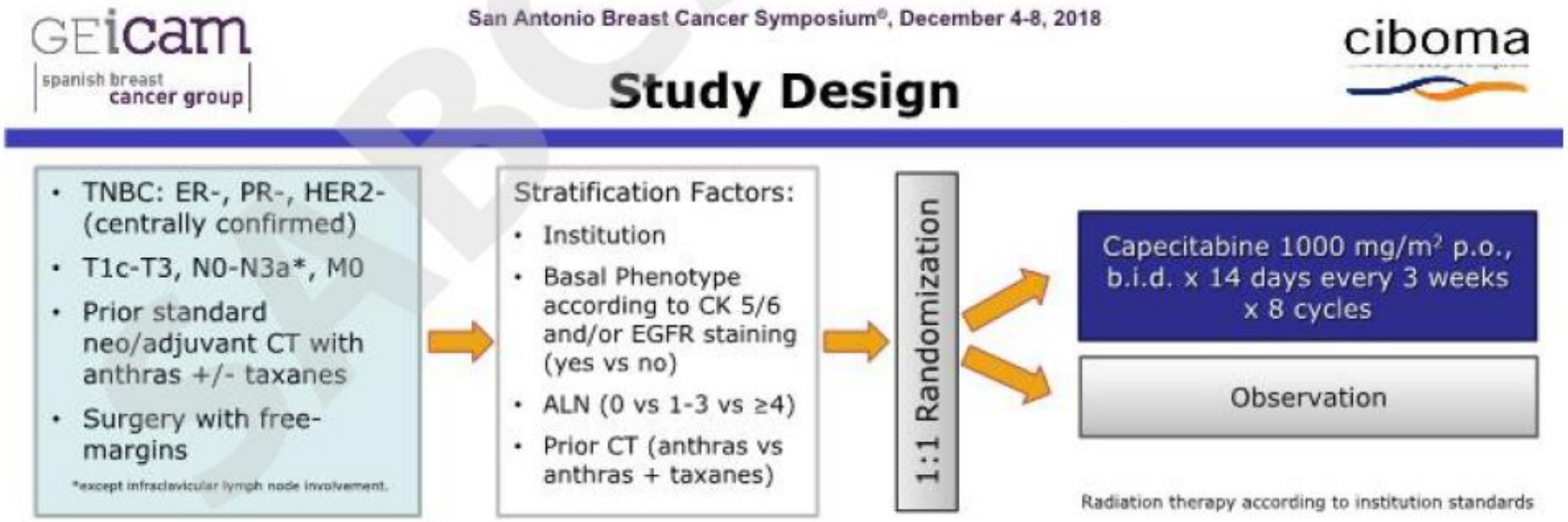


TN patients



Colleoni M, at 2015 ASCO Annual Meeting

GEICAM/CIBOMA randomized phase III trial



- 6 cy. of standard CT mandatory except for N0 tumors (4 cy. of AC admitted).
- Primary endpoint: Disease-Free Survival (DFS).
- Secondary endpoints: Overall Survival (OS), subgroup analyses, safety, biomarkers.

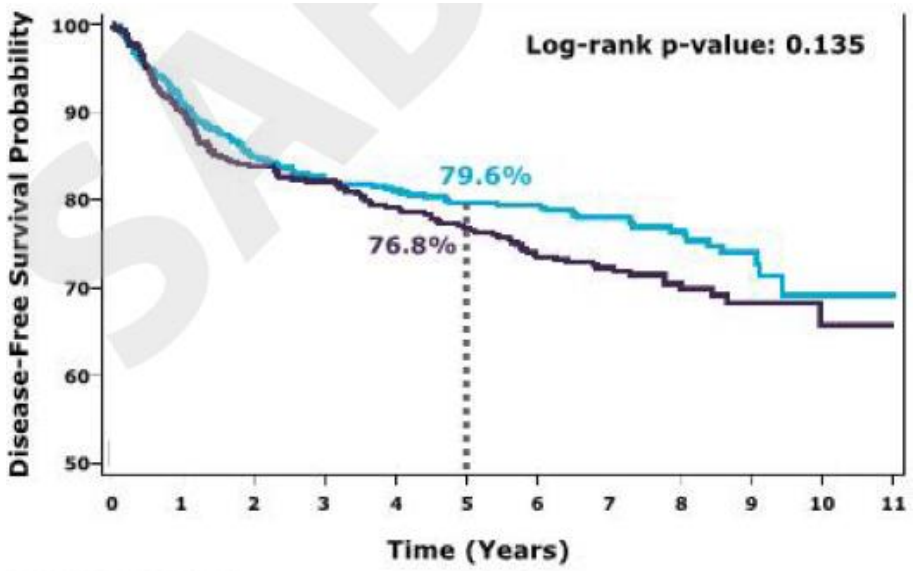
M. Martin, SABCS 2018

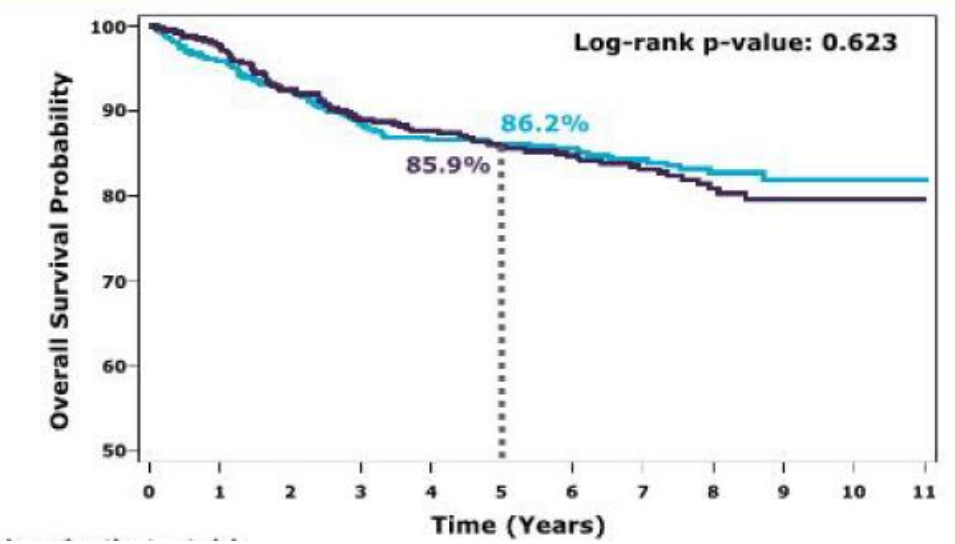
GEICAM/CIBOMA randomized phase III trial: patient characteristics

	Capecitabine (n=448)	Observation (n=428)
Median age, years (range)	50 (20-79)	49 (23-82)
Region, n (%)		
• Spain	272 (60.7)	260 (60.7)
• Latin America (LA)	176 (39.3)	168 (39.3)
Menopausal status at diagnosis, n (%)		
• Premenopausal	136 (30.4)	140 (32.7)
• Postmenopausal	312 (69.6)	288 (67.3)
Stage at diagnosis, n (%)		
• I	62 (13.8)	74 (17.3)
• II	270 (60.3)	271 (63.3)
• III	106 (23.7)	80 (18.7)
• Not available	10 (2.2)	3 (0.7)
Nodal status, n (%)		
• Negative	244 (54.5)	242 (56.5)
• 1–3 positive nodes	121 (27.0)	124 (29.0)
• ≥4 positive nodes	77 (17.2)	61 (14.3)
• Not available	6 (1.3)	1 (0.2)
Type of CT, n (%)		
• Adjuvant (only)	353 (78.8)	352 (82.2)
• Neoadjuvant (+/- adjuvant)	89 (19.9)	75 (17.5)
• Missing data	6 (1.3)	1 (0.2)
pCR in patients with neoadjuvant CT*, n (%)	22 (24.7)	19 (25.3)
CT regimens, n (%)		
• Anthracyclines-based	147 (32.8)	138 (32.2)
• Anthracyclines and Taxanes-based	301 (67.2)	290 (67.8)

M. Martin, SABCS 2018

GEICAM/CIBOMA randomized phase III trial: DFS and OS in ITT population





Median follow-up: 7.34 years

Group	Events
Capecitabine	105
Observation	120
HR: 0.82 (95% CI: 0.63, 1.06, p=0.136)	
Adjusted HR*: 0.79 (95% CI: 0.61, 1.03, p=0.082)	

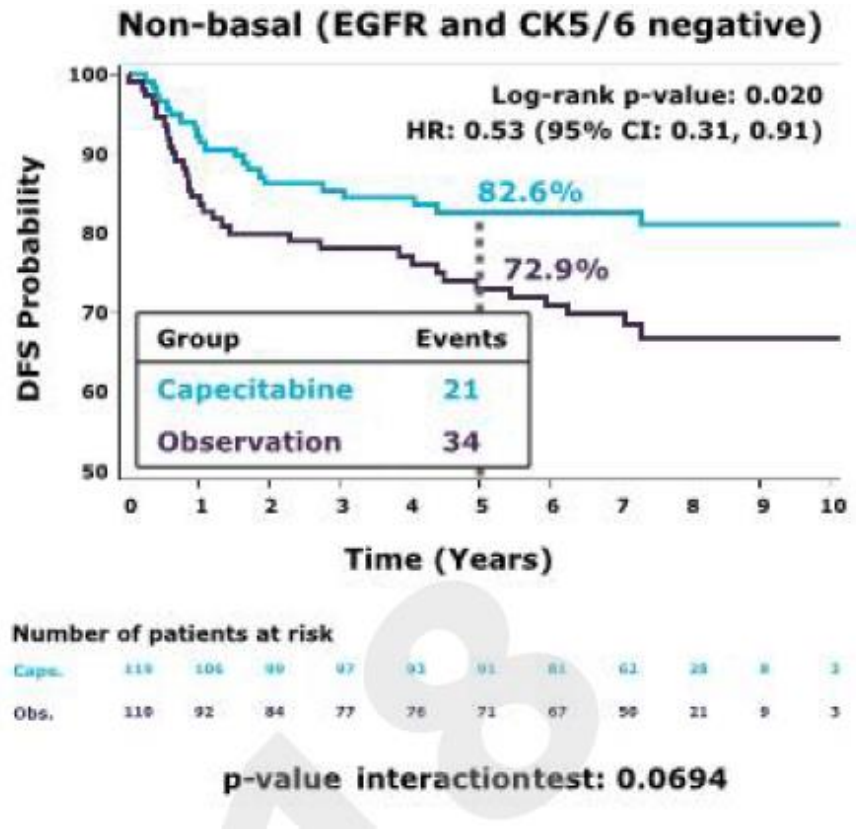
*Adjusted HR for stratification variables: Spain vs. LA, previous neo/adjuvant treatment (anthracyclines vs. anthracyclines and taxanes), number of involved nodes (0 vs. 1-3 vs. ≥4) and TN phenotype by IHC (basal vs. non-basal).

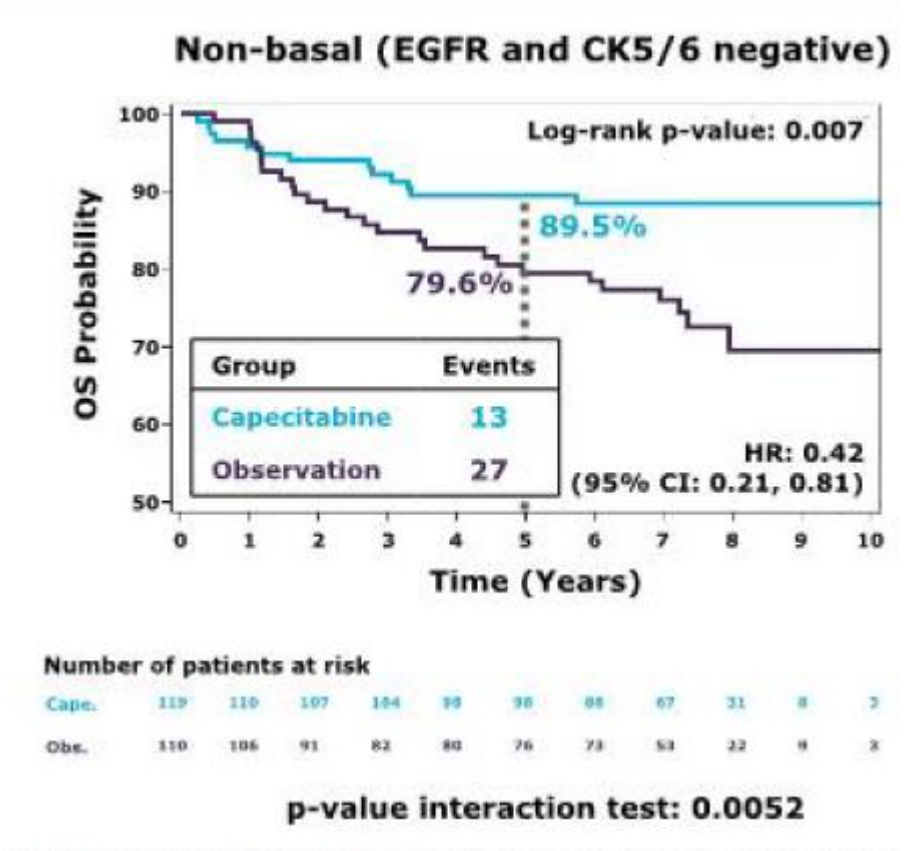
Median follow-up: 7.34 years

Group	Events
Capecitabine	71
Observation	73
HR: 0.92 (95% CI: 0.66, 1.28)	

M. Martin, SABCS 2018

GEICAM/CIBOMA randomized phase III trial: DFS and OS basal vs non basal





M. Martin, SABCS 2018

RCTs of Capecitabine in EBC

Study	Patients	RFS/DFS in TN	OS in TN
FinXX	1500 (202 TN)	**HR 0.53 (95%CI 0.31-0.92)**	**HR 0.55 (95%CI 0.31-0.96)**
GEICAM/2003-10	1384 N+(166 TN)	HR 1.19 (95%CI 0.70-2.04)	NR
GAIN	2994 N+ (421 TN)	HR 0.971 (95%CI 0.682-1.38)	NR
NCT00089479	2611 (780 TN)	HR 0.81 (95%CI 0.57-1.15)	**HR 0.62 (95%CI 0.41-0.94)**
Create-X	910 (286 TN) (post-neoadj)	**HR 0.58 (95%CI 0.39-0.87)**	**HR 0.52 (95%CI 0.30-0.90)**

Joensuu H et al, J Clin Oncol 2012 & JAMA Oncol 2018; Martin M et al, J Clin Oncol 2015; Mobus V et al, Ann Oncol 2017; O'Shaughnessy CCR 2015; NEJM 2017

(Neo)Adjuvant therapy in TNBC

Chemotherapy is the mainstay of treatment:

- Anthracycline+taxanes: first choice in the (neo)adjuvant setting
- BRCA-mut (or BRCAwt with BRCAness features?): chance for tailored- chemotherapy with platinum salts
- No role for bevacizumab-encouraging data for nab-paclitaxel
- If no pCR post neoadjuvant therapy may be a feasible and effective option