Terapia medica neoadiuvante

Unit of Investigative Clinical Oncology (INCO)
Fondazione del Piemonte per l'Oncologia
Candiolo Cancer Institute (IRCCs)

Question number 1

- Chemotherapy before or after surgery: any difference in outcomes?

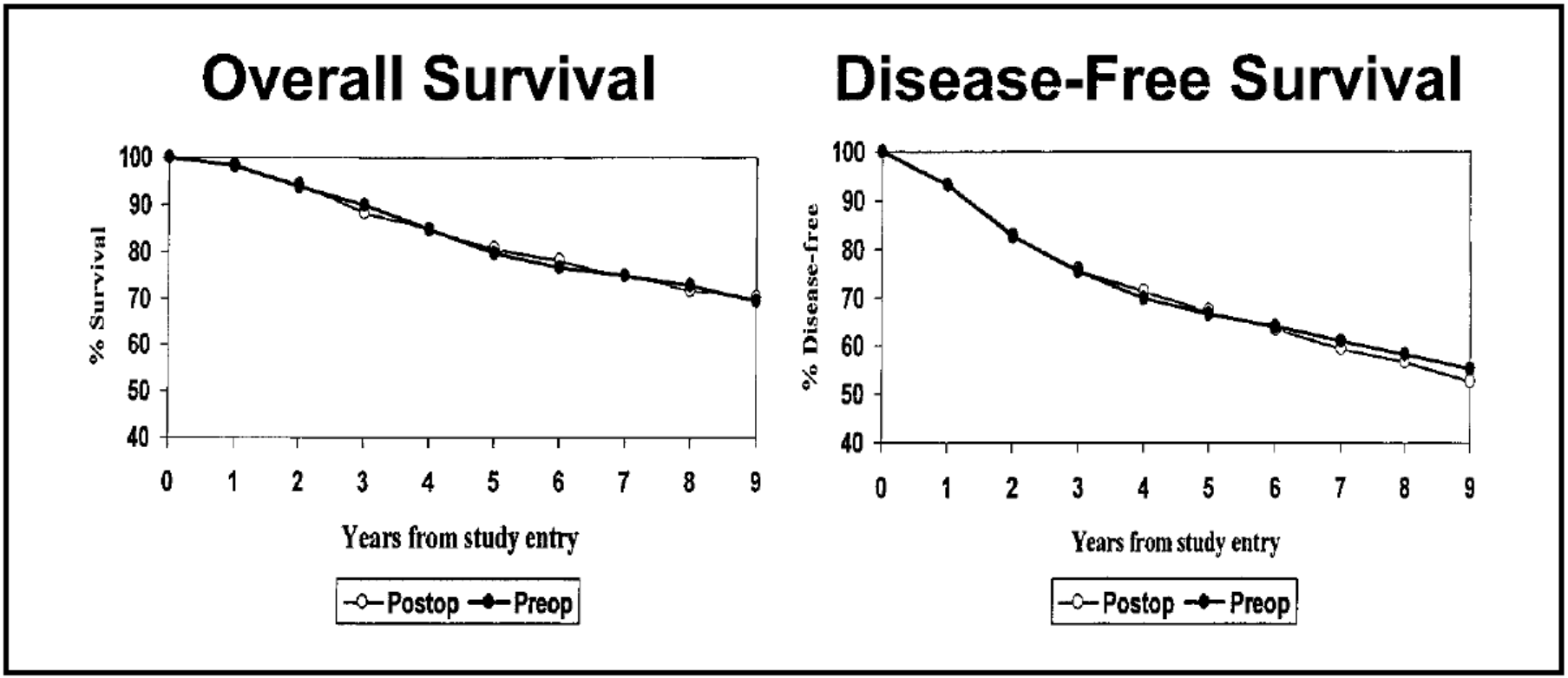
AC X 4 before or after surgery in patients with operable breast cancer: NSABP B-18

Table 1. Characteristics of Eligible Patients

Eligibility and Characteristics at Randomization	Treatment Group	
	Postoperative	Preoperative
Eligibility (no.)		
Randomized	763	760
Eligible	759	747
Characteristics (%)		
Age, years		
≤ 49	52	51
≥ 50	48	49
Nodal status (clinical)		
Negative	74	74
Positive	26	26
Breast cancer (clinical size, cm)		
≤ 2.0	27	29
2.1-5.0	59	58
≥ 5.1	13	13
Not reported	< 1	0

Fisher et al., J Clin Oncol 15; 2483, 1997

9-year follow-up of the NSABP B-18 study



Wolmark et al, J Natl Cancer Inst Monogr 30;96, 2001

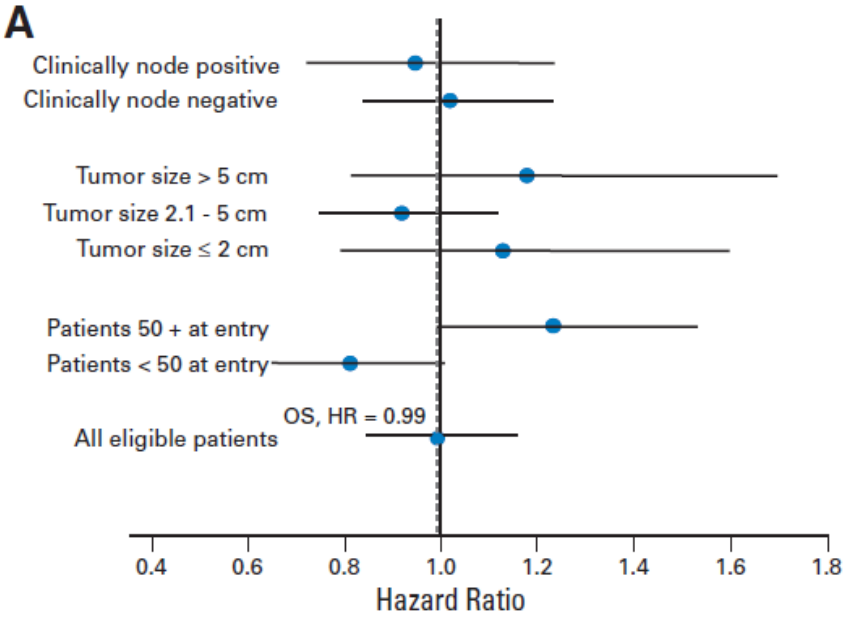
Ipsilateral Breast Cancer Recurrence according to treatment and co-variates

Clinical factor	Treatment group		
	Postoperative AC, % of patients with IBTR	Preoperative AC, % of patients with IBTR	Total, % of patients with IBTR
Age, y			
≤49	10.7	15.2	13.1
≥50	4.2	6.1	5.2
Clinical tumor size			
<3 cm	6.6	11.6	9.3
≥3 cm	8.3	10.1	9.3
Clinical and pathologic tumor response			
cCR*	N/A	9.8	
pCR	N/A	6.7	
pINV	N/A	11.5	
cPR	N/A	11.8	
cNR (cSD and cPD)	N/A	13.0	
Procedure after preoperative chemotherapy			
Lumpectomy vs. planned mastectomy	N/A	15.9	
Lumpectomy as planned	N/A	9.9	

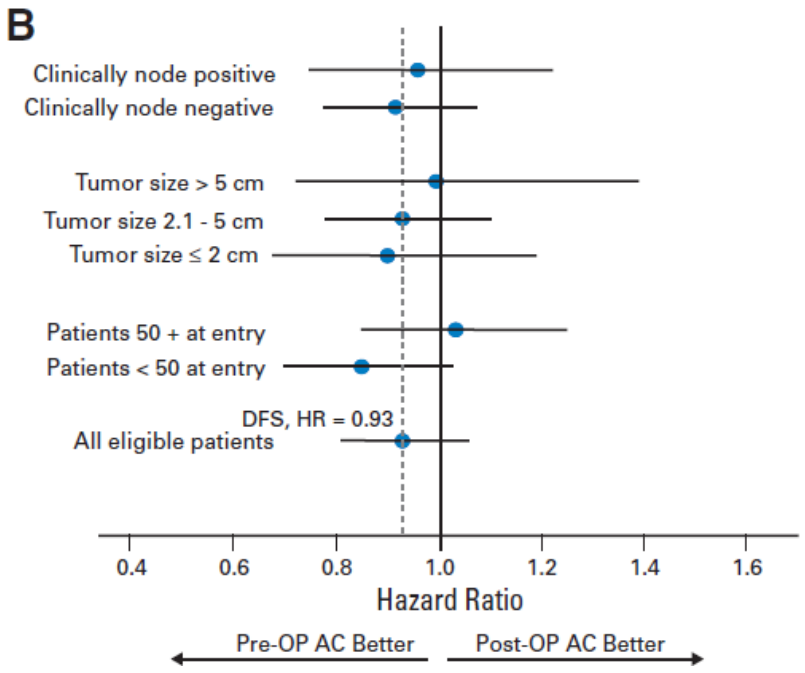
Wolmark et al, J Natl Cancer Inst Monogr 30;96, 2001

Further update in 2008

OS



DFS

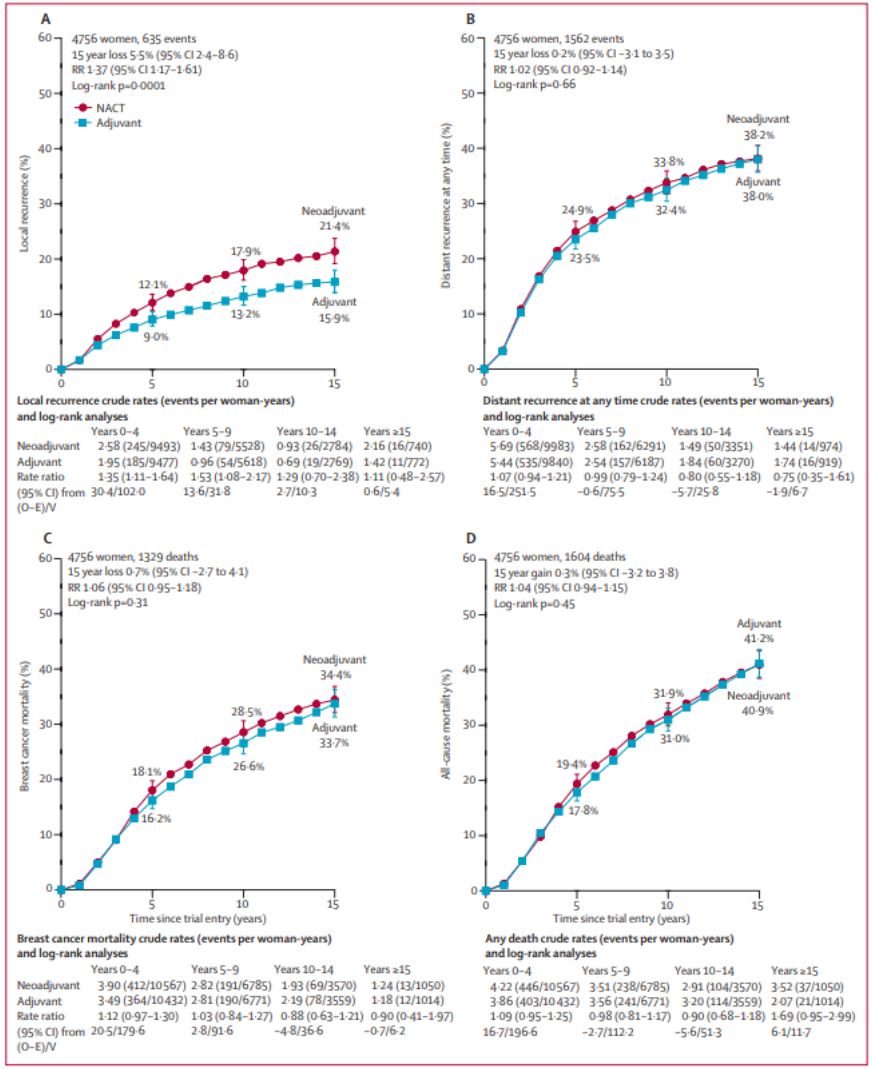


Rastogi J Clin Oncol 26;778, 2008

Patient-level meta-analysis

- Ten randomized trials of neoadj vs adj chemotherapy
- 4756 women randomized between 1983 and 2002
- Median follow-up 9y (IQR 5-14)
- Most patients treated with antrhacycline/non taxane regimens
- Only one trial with anthracycline and taxane
- No trials included trastuzumab
- Some trials allowed omission of surgery in cCR patients

Individual patient data meta-analysis



Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	2·58 (245/9493)	1·43 (79/5528)	0·93 (26/2784)	2·16 (16/740)
Adjuvant	1·95 (185/9477)	0·96 (54/5618)	0·69 (19/2769)	1·42 (11/772)
Rate ratio	1·35 (1·11–1·64)	1·53 (1·08–2·17)	1·29 (0·70–2·38)	1·11 (0·48–2·57)
(95% CI) from (O–E)/V	30·4/102·0	13·6/31·8	2·7/10·3	0·6/5·4

Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
	5·69 (568/9983)	2·58 (162/6291)	1·49 (50/3351)	1·44 (14/974)
	5·44 (535/9840)	2·54 (157/6187)	1·84 (60/3270)	1·74 (16/919)
	1·07 (0·94–1·21)	0·99 (0·79–1·24)	0·80 (0·55–1·18)	0·75 (0·35–1·61)
	16·5/251·5	−0·6/75·5	−5·7/25·8	−1·9/6·7

Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

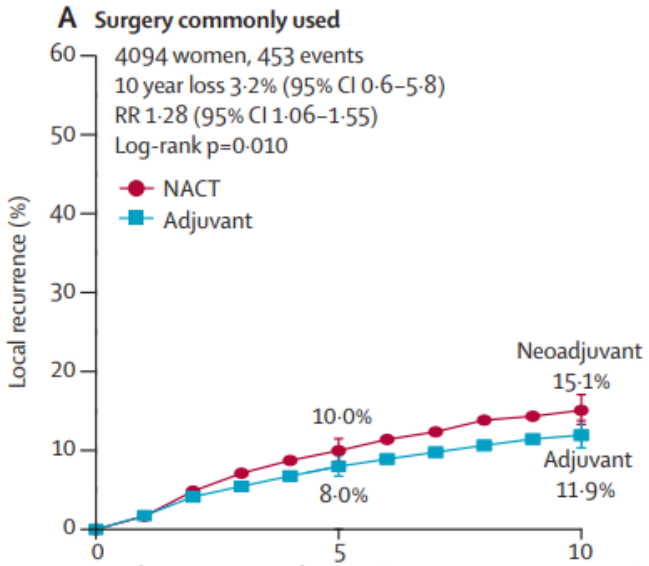
	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	3·90 (412/10567)	2·82 (191/6785)	1·93 (69/3570)	1·24 (13/1050)
Adjuvant	3·49 (364/10432)	2·81 (190/6771)	2·19 (78/3559)	1·18 (12/1014)
Rate ratio	1·12 (0·97–1·30)	1·03 (0·84–1·27)	0·88 (0·63–1·21)	0·90 (0·41–1·97)
(95% CI) from (O–E)/V	20·5/179·6	2·8/91·6	−4·8/36·6	−0·7/6·2

Any death crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
	4·22 (446/10567)	3·51 (238/6785)	2·91 (104/3570)	3·52 (37/1050)
	3·86 (403/10432)	3·56 (241/6771)	3·20 (114/3559)	2·07 (21/1014)
	1·09 (0·95–1·25)	0·98 (0·81–1·17)	0·90 (0·68–1·18)	1·69 (0·95–2·99)
	16·7/196·6	−2·7/112·2	−5·6/51·3	6·1/11·7

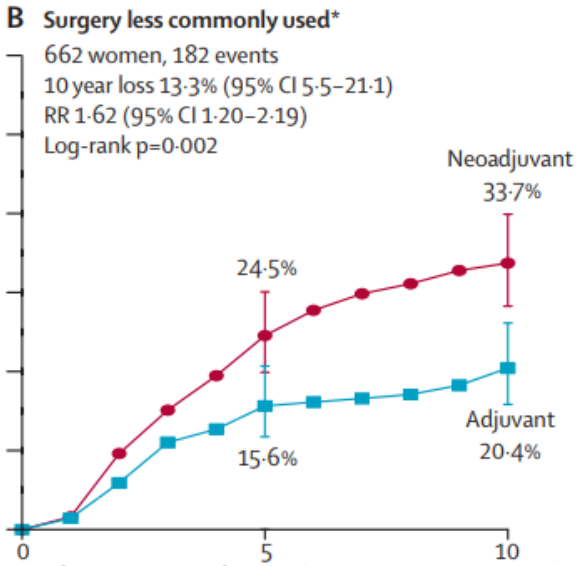
EBCTG Lancet 19;27, 2018

Increase in local recurrence also after excluding studies allowing surgery avoidance



Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	2·12 (173/8164)	1·21 (57/4721)	0·85 (22/2577)
Adjuvant	1·73 (142/8200)	0·94 (45/4778)	0·55 (14/2547)
Rate ratio (95% CI)	1·26 (1·00–1·58)	1·35 (0·91–2·01)	1·32 (0·65–2·69)
from (O–E)/V	17·3/75·2	7·3/24·3	2·1/7·5



Local recurrence crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
5·42 (72/1329)	2·73 (22/806)	2·11 (20/947)
3·37 (43/1277)	1·07 (9/840)	1·61 (16/994)
1·63 (1·12–2·39)	2·30 (1·13–4·70)	1·15 (0·58–2·27)
13·2/26·8	6·3/7·5	1·1/8·2

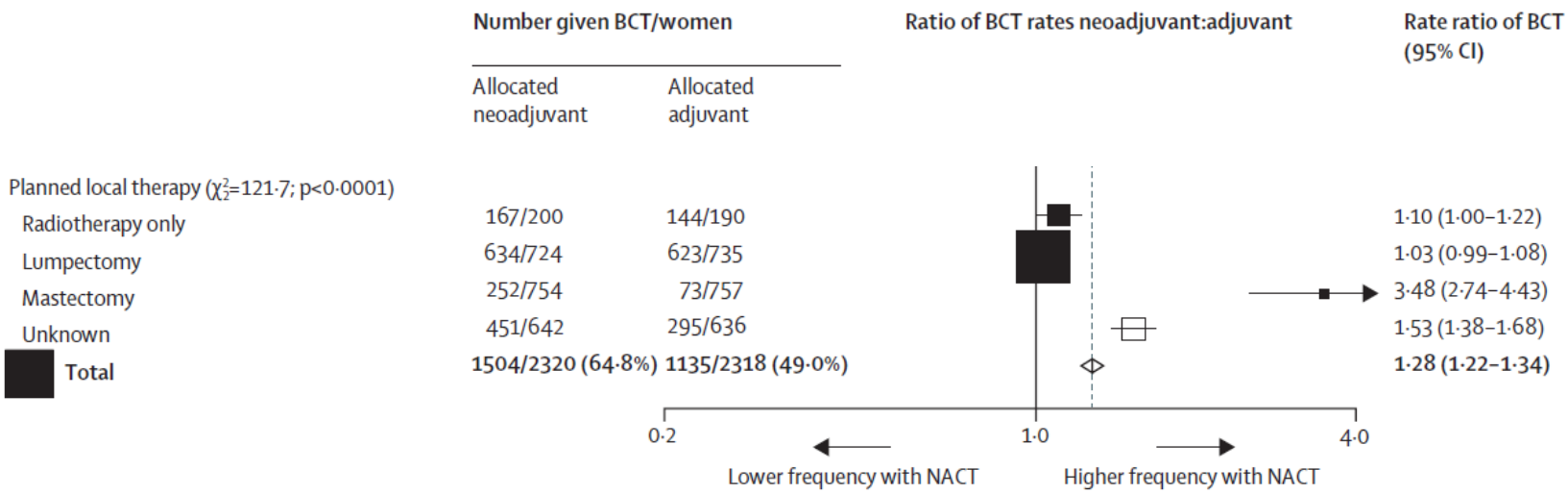
EBCTG Lancet 19;27, 2018

Ipsilateral recurrence rates are not exactly equal in patients randomized to mastectomy vs BCS + RT

Figure 1. Crude Cumulative Incidence of Local Recurrences after Radical Mastectomy and Recurrences in the Same Breast after Breast-Conserving Therapy.

Veronesi NEJM 347;1227, 2002

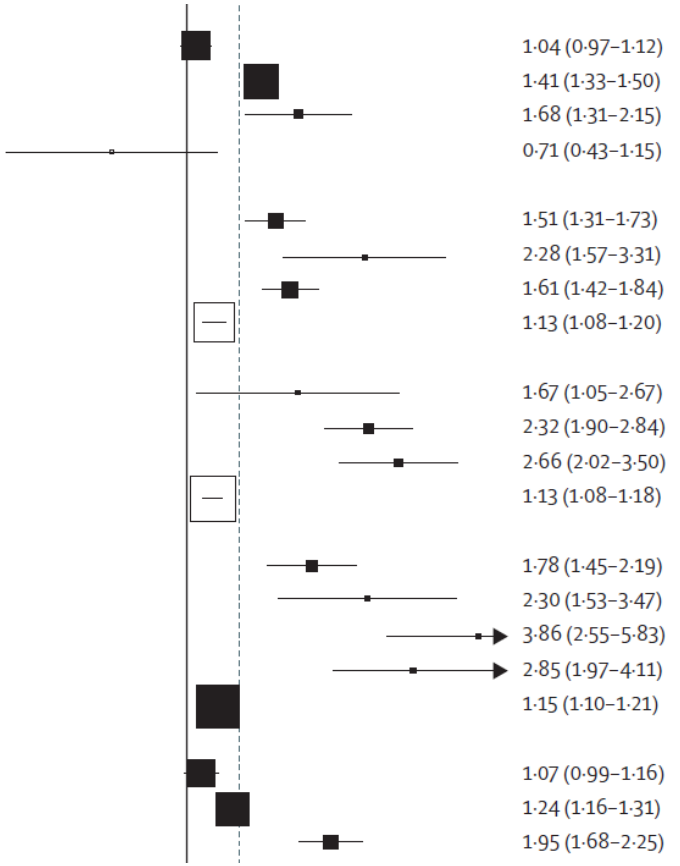
To what extent is BCS increased by the use of neoadjuvant chemotherapy?



EBCTG Lancet 19;27, 2018

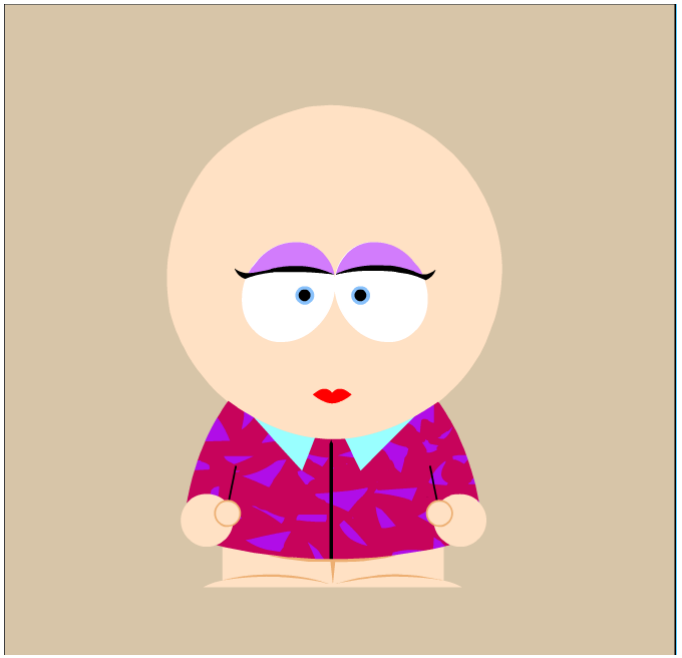
To what extent is BCS increased by the use of neoadjuvant chemotherapy in subgroups?

	Number given BCT/women		Ratio of BCT rates neoadjuvant:adjuvant	Rate ratio of BCT (95% CI)
	Allocated neoadjuvant	Allocated adjuvant		
Clinical tumour size (χ^2_1=43·1; p<0·0001)				
1–19 mm	301/382	299/402		1·04 (0·97–1·12)
20–49 mm	1061/1547	746/1551		1·41 (1·33–1·50)
≥50 mm	124/337	71/323		1·68 (1·31–2·15)
Unknown	18/54	19/42		0·71 (0·43–1·15)
Biopsy ER and PR status (χ^2_2=4·5; p=0·10)				
ER+ and PR+	226/343	150/345		1·51 (1·31–1·73)
ER+ and PR–	54/91	25/98		2·28 (1·57–3·31)
ER– and PR–	278/407	165/406		1·61 (1·42–1·84)
Unknown	946/1479	795/1469		1·13 (1·08–1·20)
Biopsy grade (χ^2_1=2·5; p=0·12)				
Well	32/66	17/60		1·67 (1·05–2·67)
Moderate	186/303	84/317		2·32 (1·90–2·84)
Poor	117/189	46/195		2·66 (2·02–3·50)
Unknown	1169/1762	988/1746		1·13 (1·08–1·18)
Biopsy grade and ER status (χ^2_3=13·7; p=0·003)				
Well or moderate, ER+	141/237	77/234		1·78 (1·45–2·19)
Poor, ER+	45/84	22/92		2·30 (1·53–3·47)
Well or moderate, ER–	76/128	21/138		3·86 (2·55–5·83)
Poor, ER–	71/104	24/103		2·85 (1·97–4·11)
Other or unknown	1171/1767	991/1751		1·15 (1·10–1·21)
Type of neoadjuvant chemotherapy (χ^2_1=44·9; p<0·0001)				
No anthracycline or taxane	329/446	292/439		1·07 (0·99–1·16)
Anthracycline, no taxane	891/1436	696/1438		1·24 (1·16–1·31)
Anthracycline and taxane	284/438	147/441		1·95 (1·68–2·25)



EBCTG Lancet 19;27, 2018

pCR; to what extent should we pursue it?



Does pCR predict better outcome compared with no-pCR?

Responder analysis (11955 patients, 12 clinical trials)

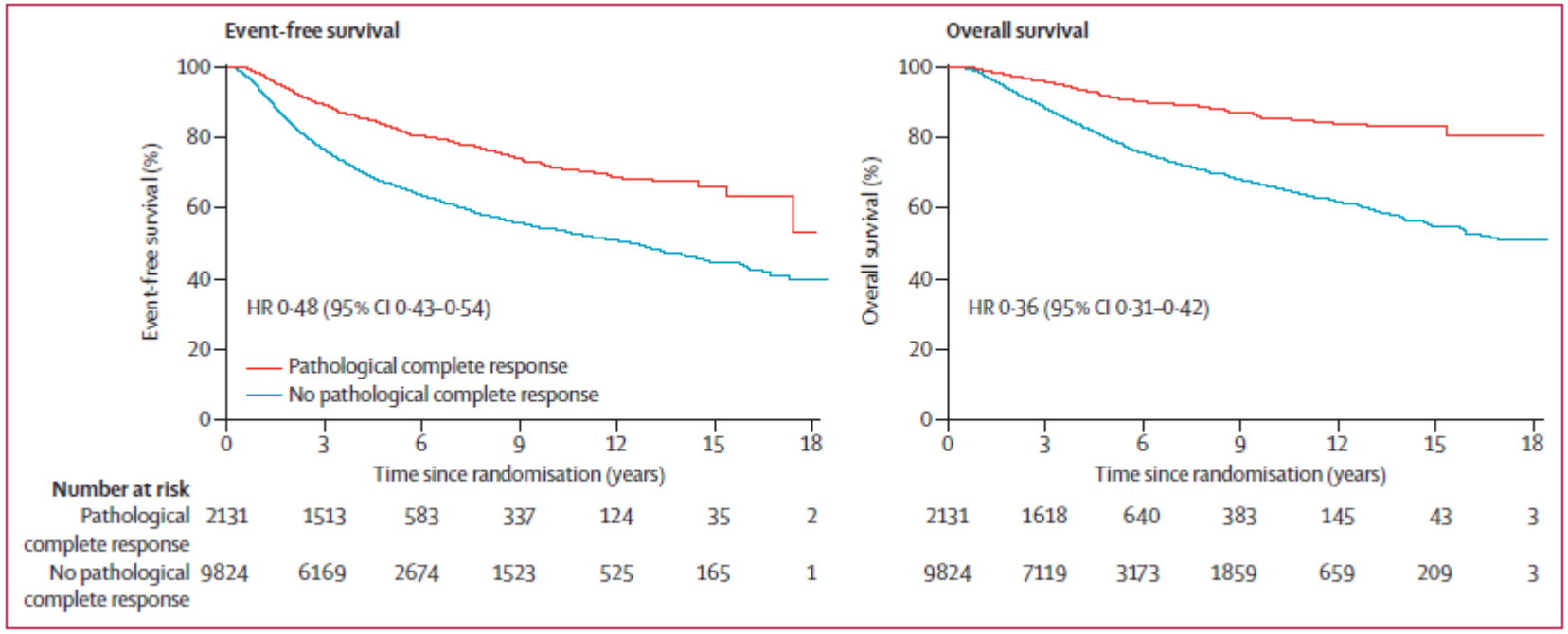


Figure 2: **Associations between pathological complete response and event-free survival and overall survival**

Cortazar e al, Lancet 384; 164, 2014

Which is the definition of pCR that best correlates with outcome?

Responder analysis (11955 patients, 12 clinical trials)

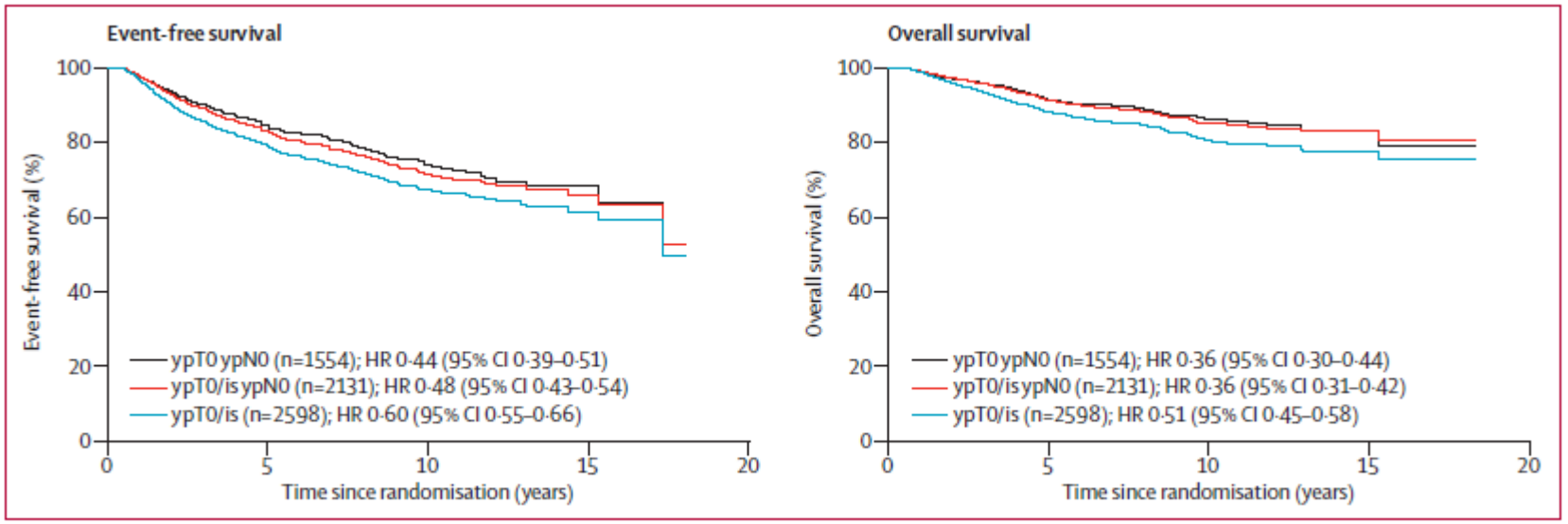


Figure 3: **Associations between three definitions of pathological complete response and event-free survival and overall survival**

Cortazar e al, Lancet 384; 164, 2014

Does pCR predict better outcome in different biologic subsets of breast cancer?

ER+, HER2-

HER2+

Triple Negative

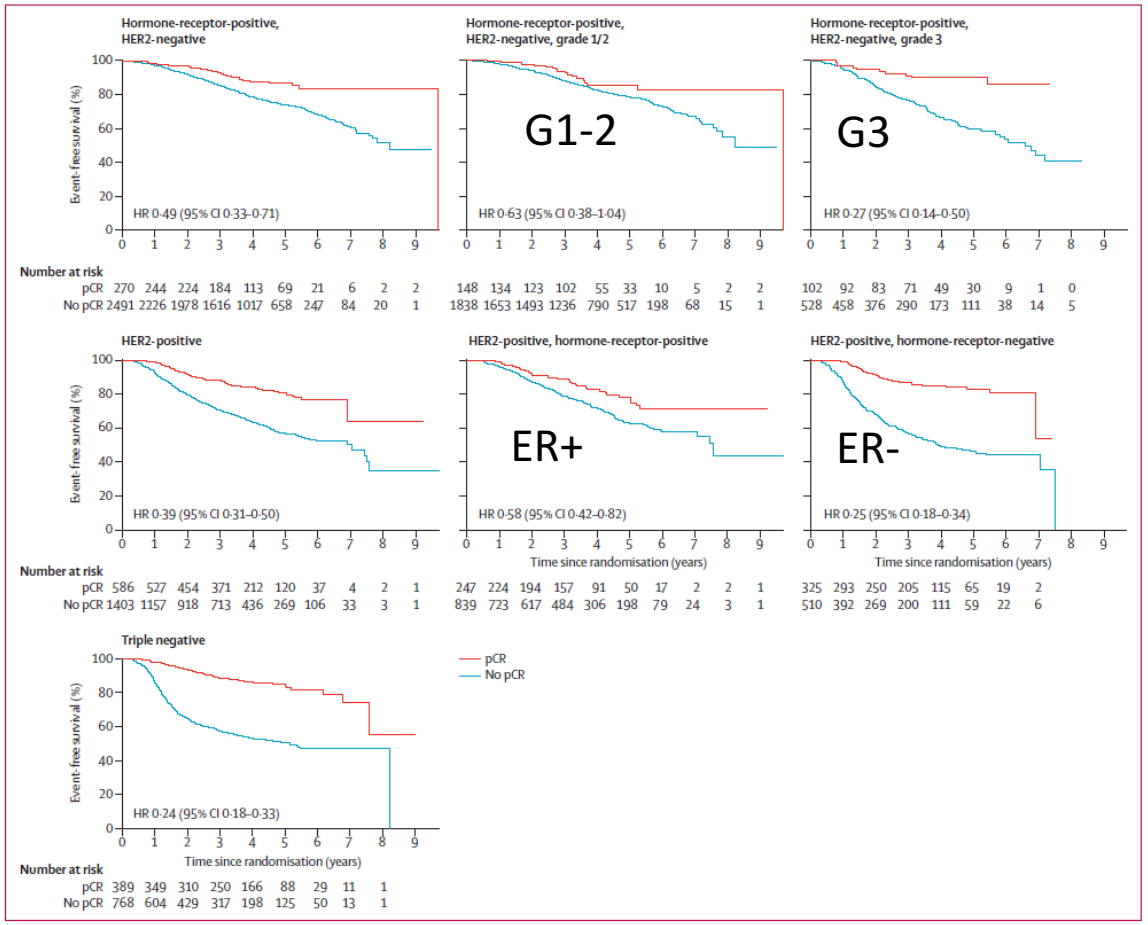


Figure 5: Association between pCR and event-free survival, by breast cancer subtype

Cortazar e al, Lancet 384; 164, 2014

pCR occurs, overall in a minority of breast cancer patients

	N	Non-evaluable patients N	Patients with pCR (evaluable patients) N	Patients with no pCR (evaluable patients) N	pCR rate (evaluable patients) (%)	Odds Ratios (99% CI) [a]
Luminal A-like	515	19	37	459	(7.5)	1.00
Luminal B-like (HER2 negative)	154	7	22	125	(15.0)	2.18 (1.04; 4.58)
Luminal B-like (HER2 positive)	237	7	51	179	(22.2)	3.54 (1.94; 6.45)
HER2 positive (non-luminal)	128	10	43	75	(36.4)	7.11 (3.67; 13.8)
Triple negative	255	34	69	152	(31.2)	5.63 (3.16; 10.0)
Total	**1289**	**77**	**222**	**990**	**(18.3)**	**(*P* < 0.001[b])**

26% with THP

62% with THP

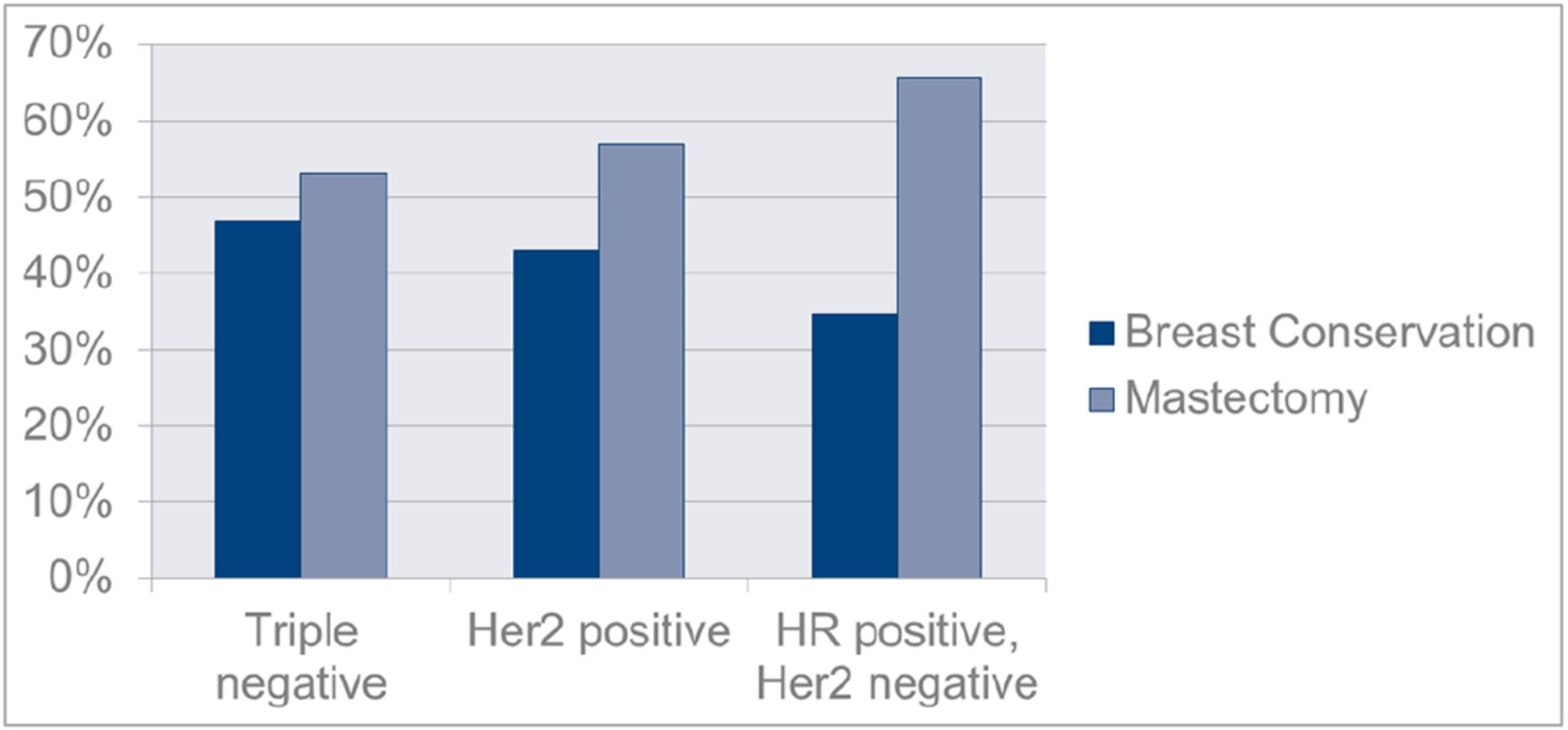
54% with carbo

26% Overall

EORTC 10994/BIG 1-00 phase III trial

Bonnefoi et al, Ann Oncol 25; 1128, 2014

Does pCR predict for increased BCS probability?



ACSOG Z1071

Boughey, Ann Surg 260;608, 2014

Meta-analysis of the relationship between pCR rate and probability of BCS

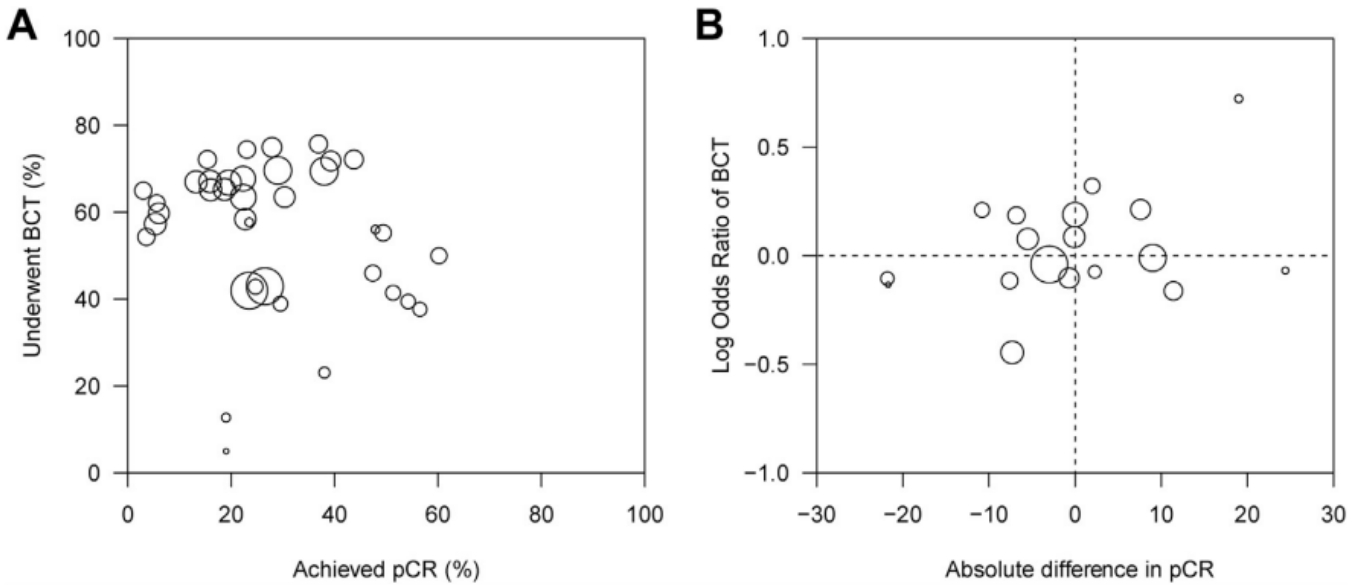
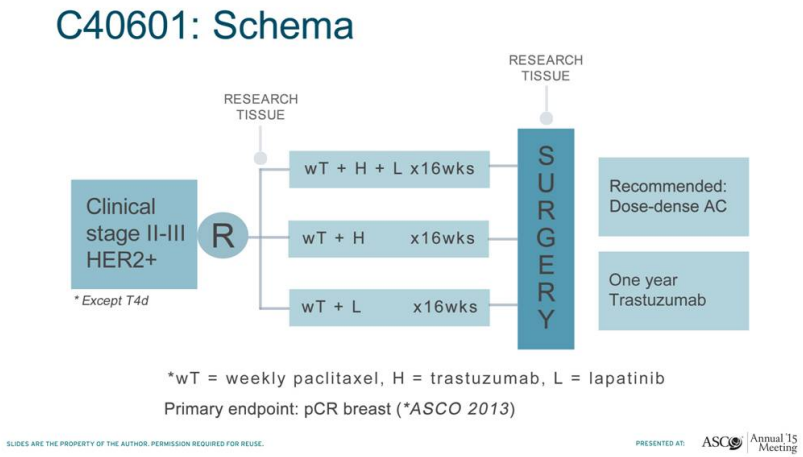
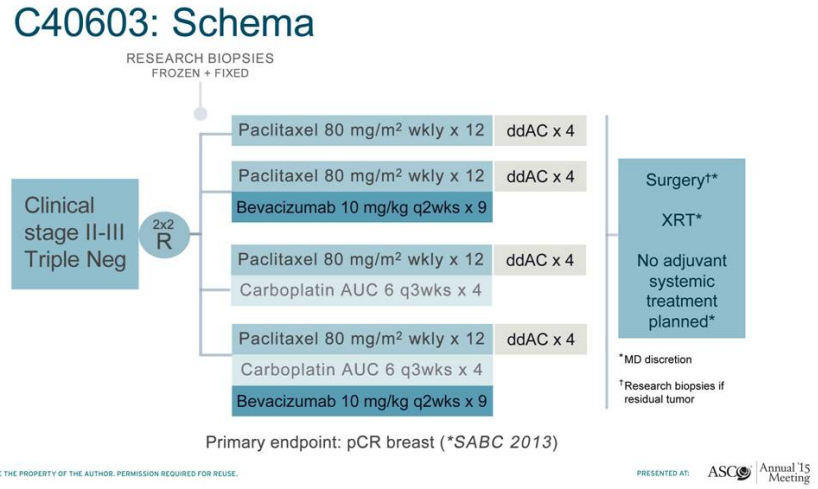


Fig. 3. (A) Scatterplot of the reported rate of patients who achieved pCR versus the rate who underwent breast-conserving therapy per study treatment arm. (B) Scatterplot of the absolute difference in pCR between arms and the log odds of BCT between arms in 18 pairwise contrasts of multi-arm trials. Point sizes are drawn proportional to number of patients in the paired arms. No statistically significant association was observed. pCR, pathological complete response.

Criscitiello Eur J Cancer, Epub 2018

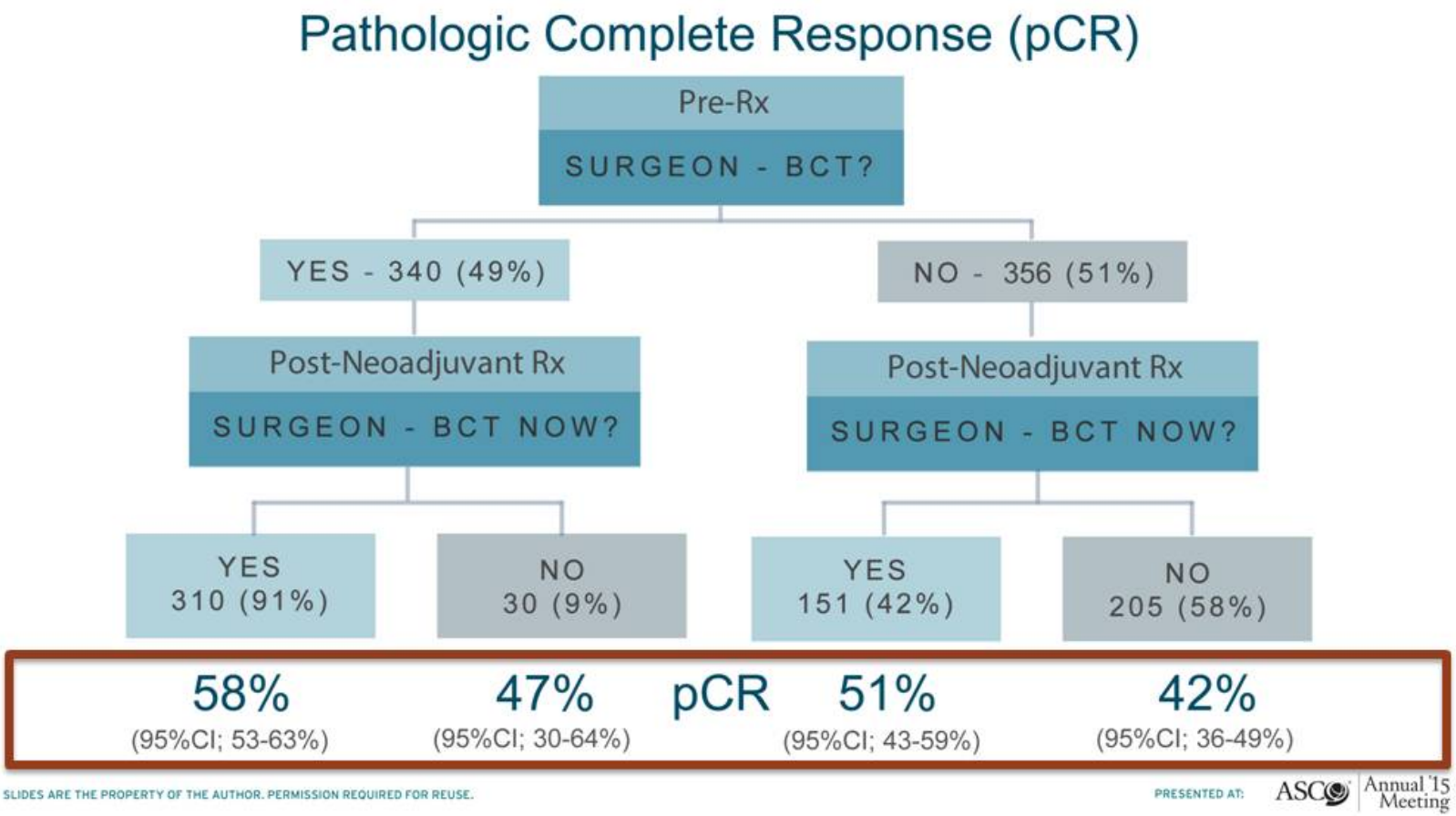
Combined analysis of the CALGB C40601 and C40603





Golshan et al, ASCO 2015

Combined analysis: pCR and BCS-feasibility



Golshan et al, ASCO 2015

What should be «state of the art» adjuvant chemotherapy in the current clinical practice?

- Luminal B tumors
  - EC (either q21d or q14d) x 4 followed by qw paclitaxel
- HER2 positive tumors
  - EC (either q21d or q14d) x 4 followed by qw paclitaxel X 12 + Trastuzumab (and pertuzumab)*
  - Docetaxel-Carboplatinum + trastuzumab x 6 (and pertuzumab)*
- TNBC (regardless of BRCA status)
  - dd EC followed by qw paclitaxel 12 +/- carboplatinum (either AUC 6 q 3 wk or AUC 2 weekly**)

*When available

**No published studies are available with the weekly carboplatinum schedule

Dose dense chemotherapy: the Meta-analysis

Dose-dense (2-weekly) vs standard (3-weekly)

- Same chemotherapy drugs and doses: 7 trials, n=10,004
- Some differences in chemotherapy: 5 trials, n=5,508

Sequential (3-weekly) vs concurrent (3-weekly)

- Same drugs in each group: 5 trials, n=9,644
- Some differences in drugs used: 1 trial, n=1,384

Sequential (2-weekly) vs concurrent (3-weekly)

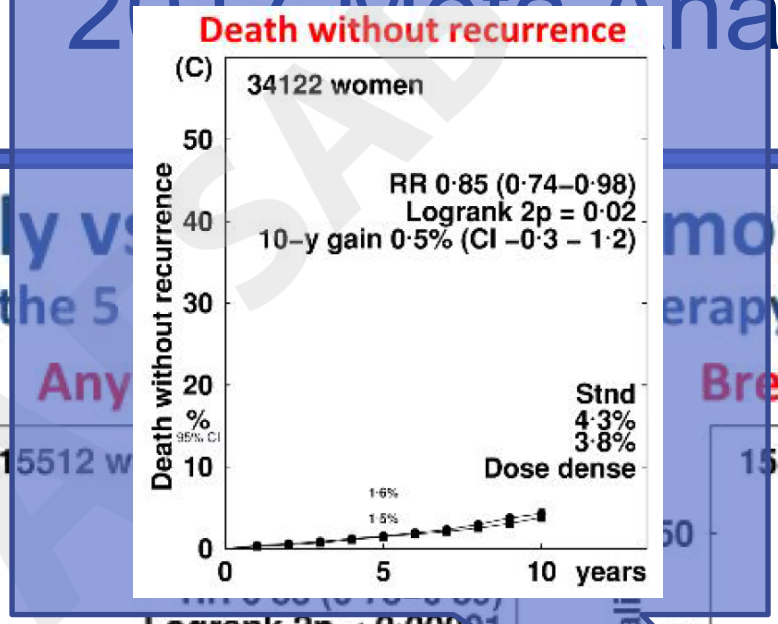
- Some differences in drugs used: 6 trials, n=6,532

Mod. da Gray R, et al. SABCS 2017. Abstract GS1-01

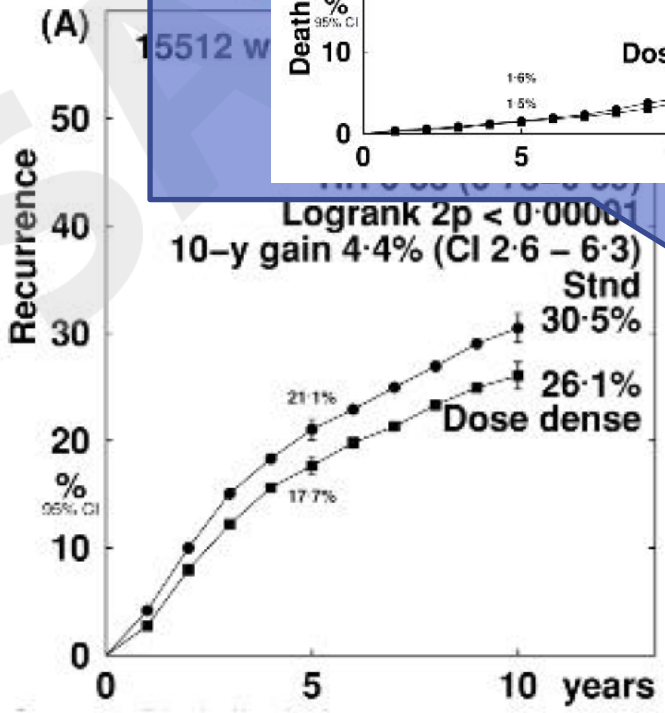
2017 Meta-Analysis

2-weekly vs [illegible] motherapy: all trials

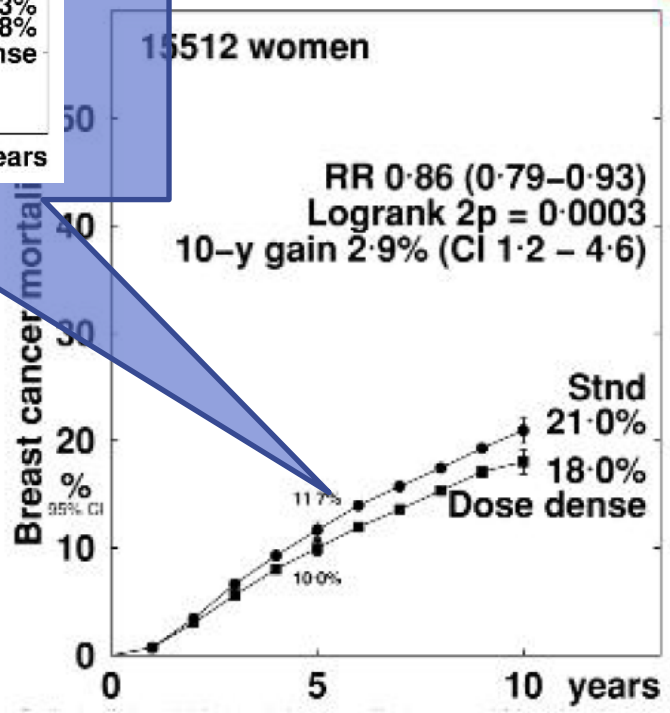
(including the 5 [illegible] erapy differed between arms)



Any [illegible]



Breast Cancer Mortality

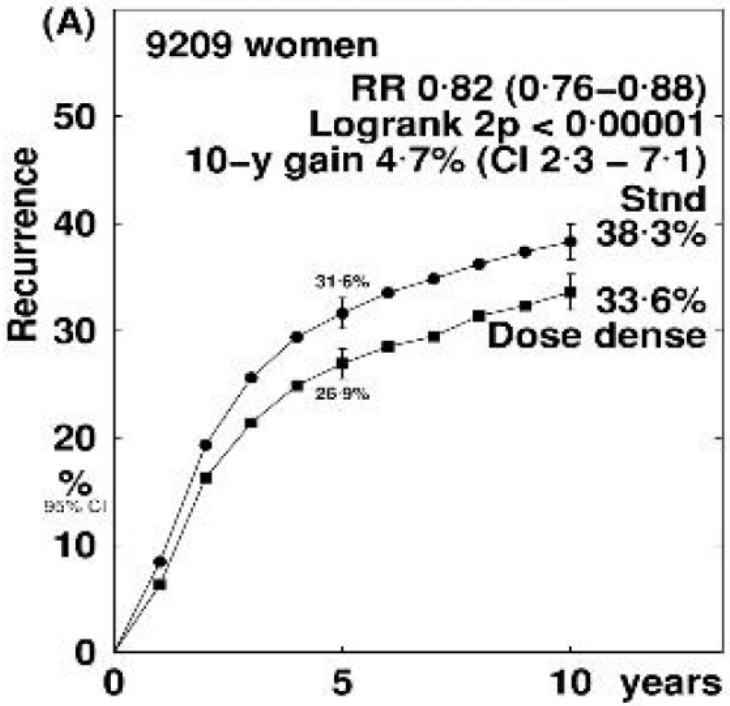


Gray SABCS 2017

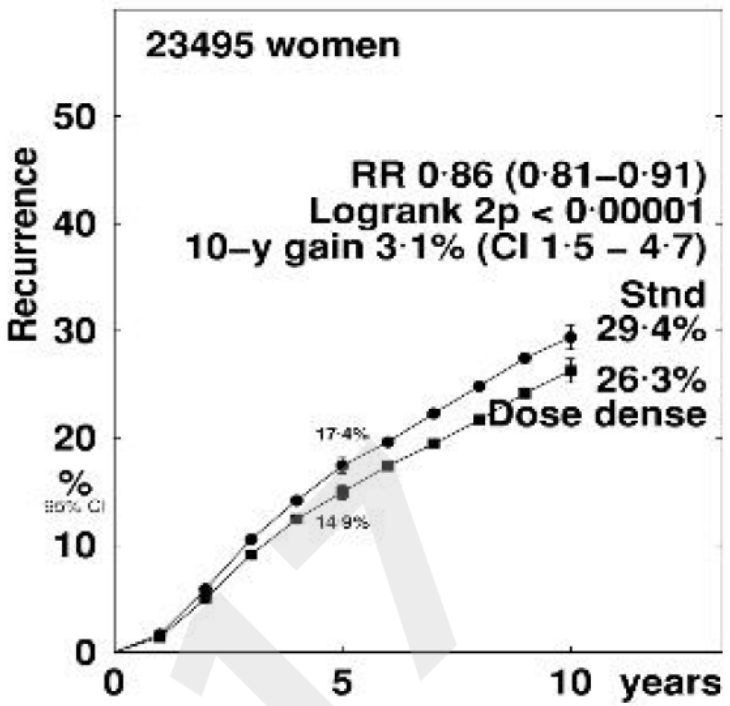
No differences according to ER status

Pooled Analysis: recurrence by ER status

ER- Negative



ER - Positive



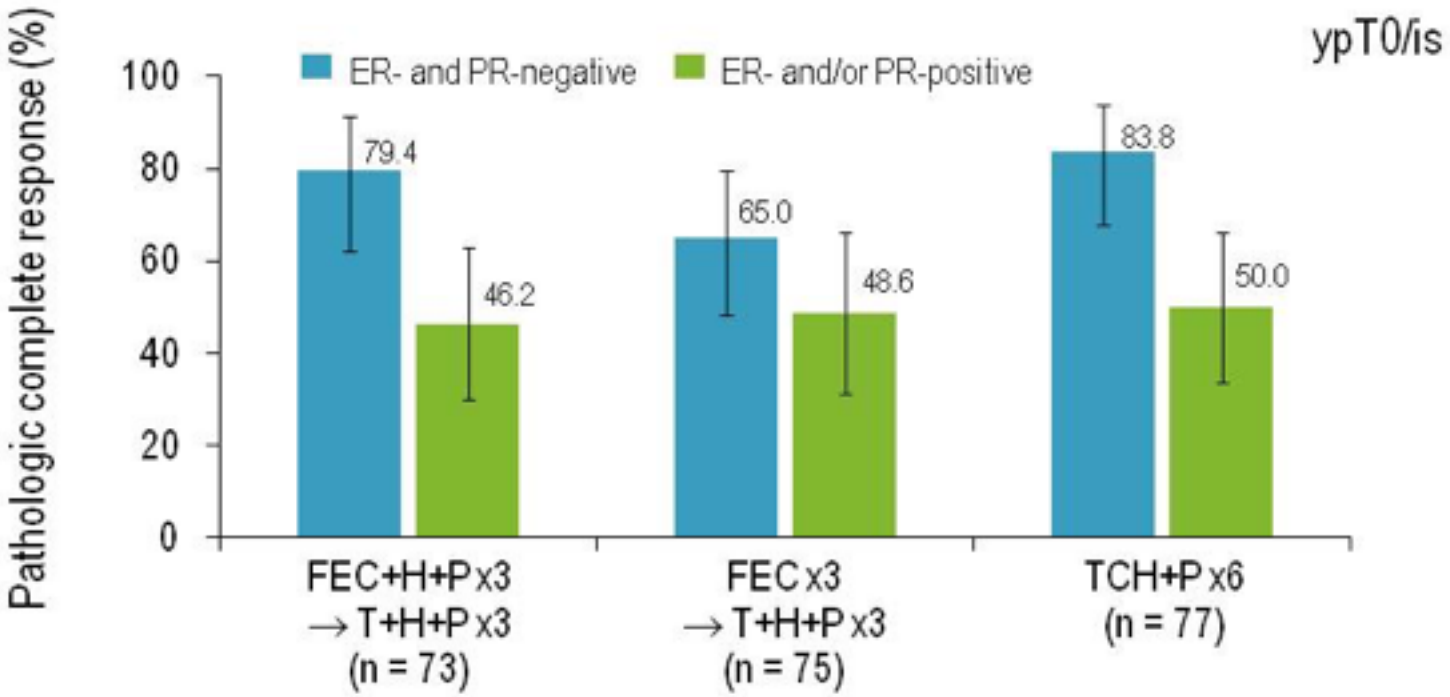
Gray SABCS 2017

Is there an “optimal” or “preferred” dose-dense regimen for high-risk patients?

- q3wAC X 4 → q3wPacli X 4 > q3w AC X 4
  - NSABP B-28 and CALGB 9344
- ddA(E)C X 4 → ddPacli X 4 > q3wA(E)C X 4 → q3wPacli X 4
  - C9741, GIM2
- q3wAC X 4 → wPacli X 12 > q3wAC X 4 → q3wPacli X 4
  - E1119

q2wAC or EC X 4 → wPaclitaxel X 12

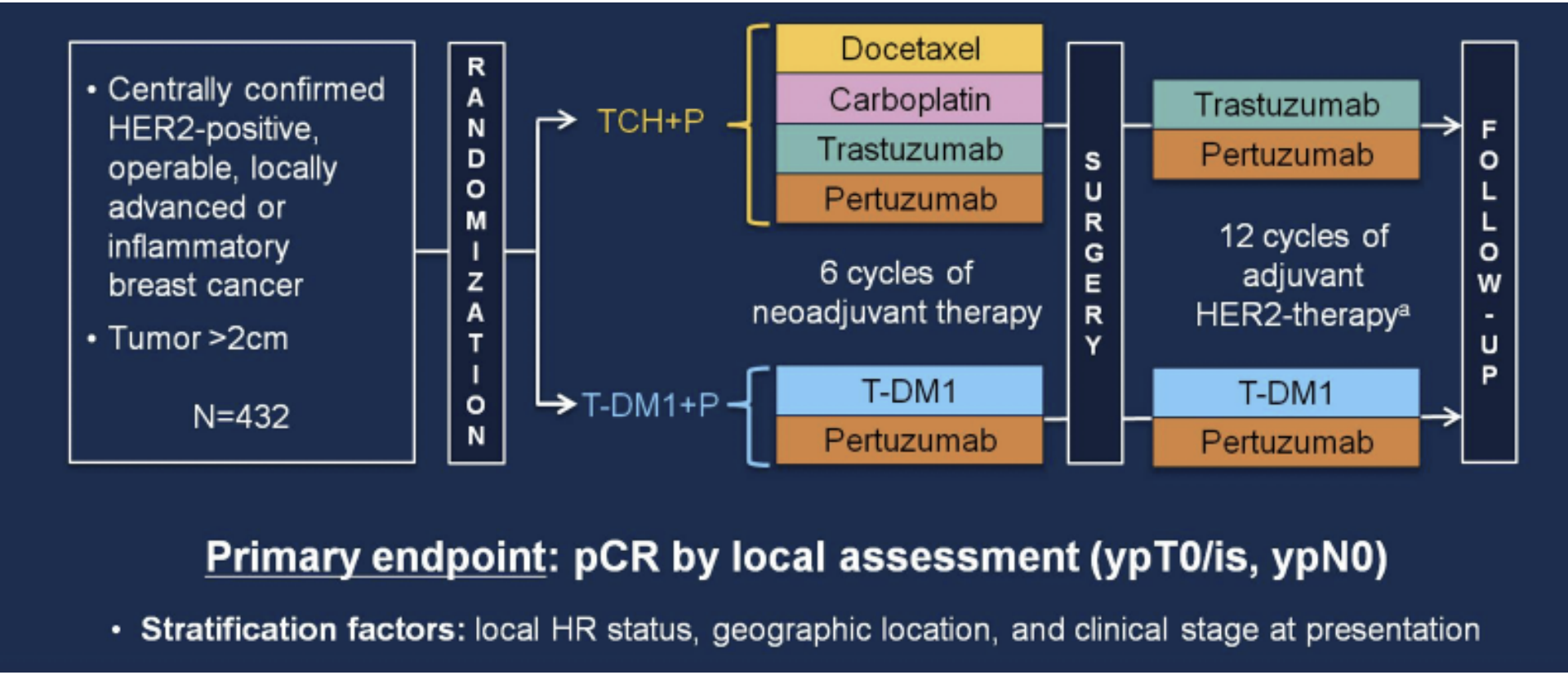
HER2-positive disease; the TRYPHAENA study



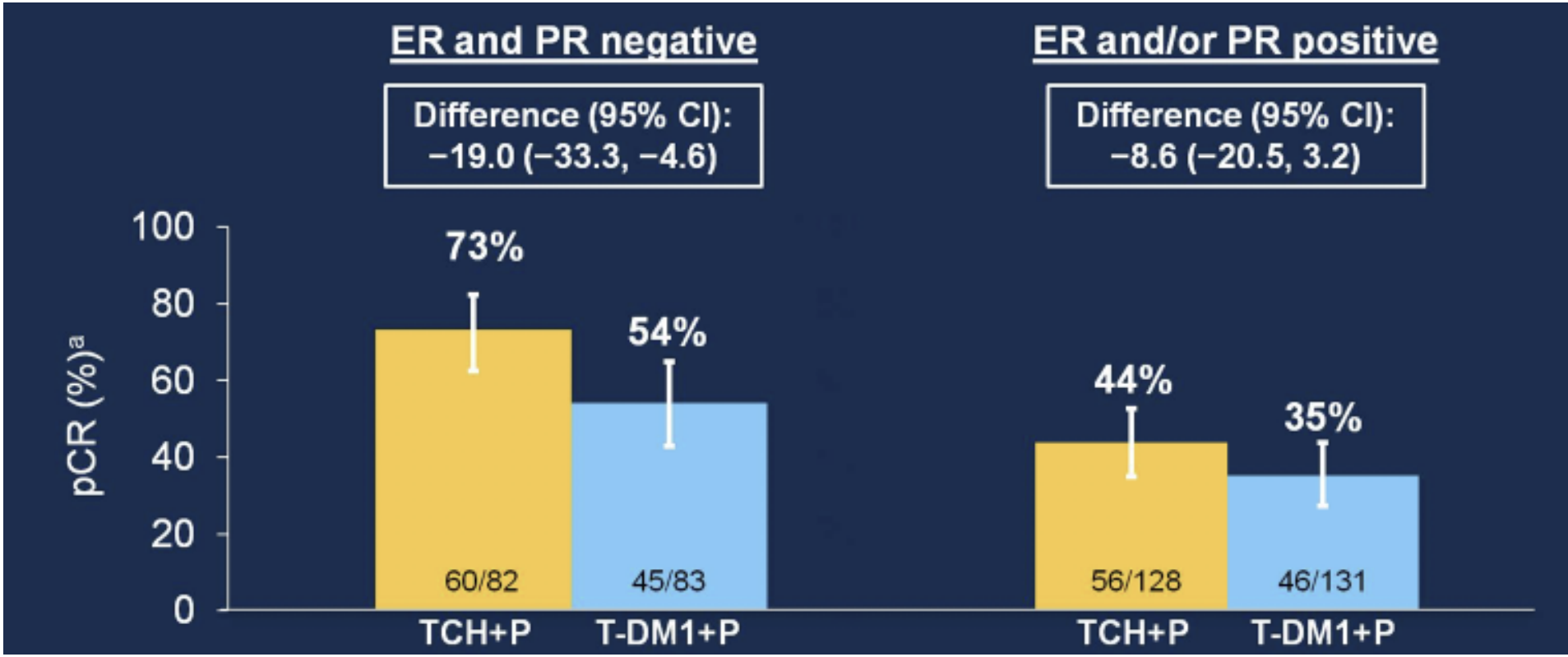
ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; PR, progesterone receptor; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Schneeweiss et al. *Ann Oncol* 2013;24:2278-84

What about T-DM1 with pertuzumab?



pCR rates

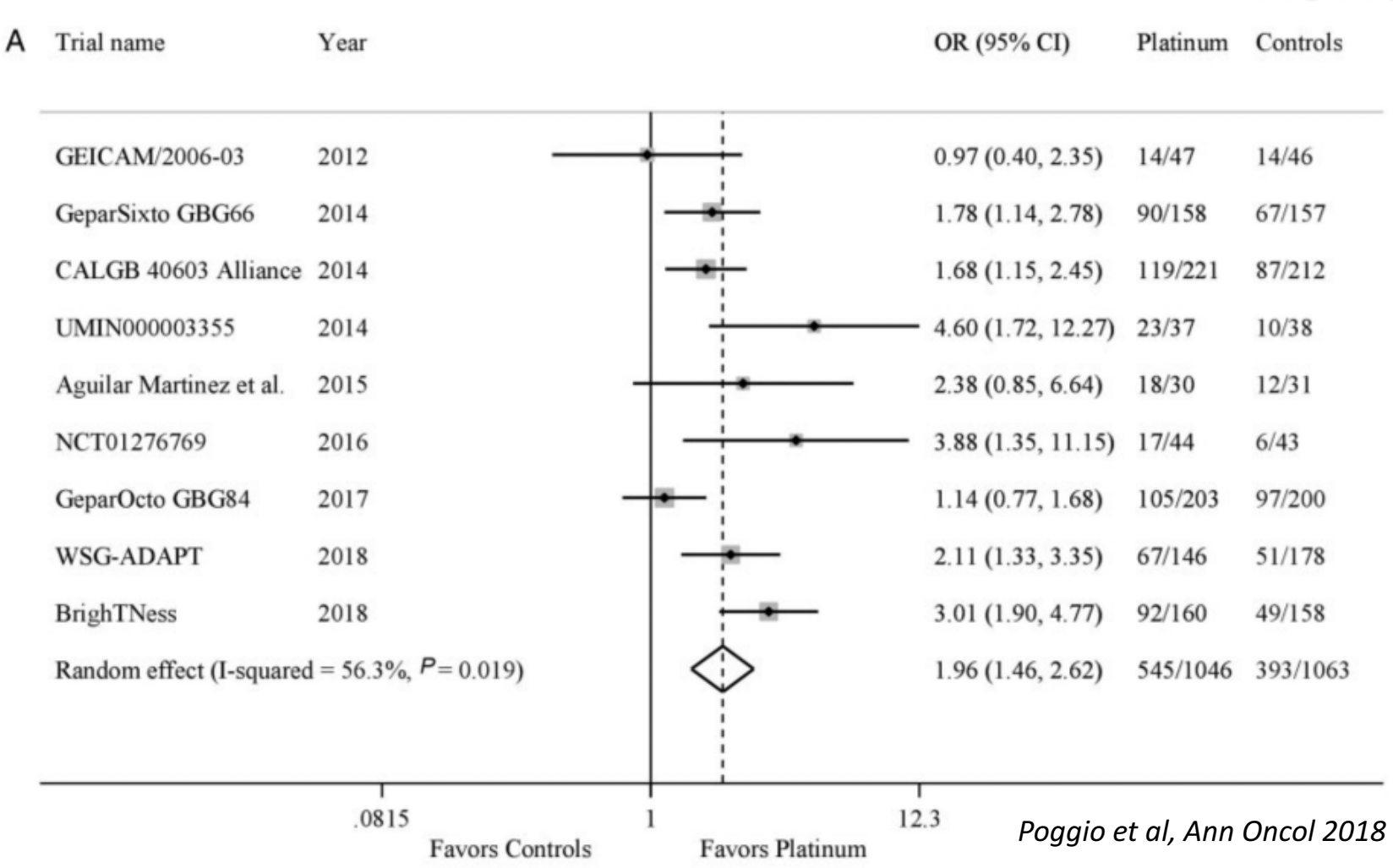

ER and PR negative
Difference (95% CI):
−19.0 (−33.3, −4.6)
ER and/or PR positive
Difference (95% CI):
−8.6 (−20.5, 3.2)
pCR (%)a
100
80
60
40
20
0
73%
54%
44%
35%
60/82
45/83
56/128
46/131
TCH+P
T-DM1+P
TCH+P
T-DM1+P

What about TNBC and carboplatin?

Trial	N randomized	pCR Chemo alone	pCR Chemo+Carboplatin
CALGB 40603	218	39%	49%
GeparSixto	315	37.9%	58.7%
GEICAM 2006-03	94	35%	30%

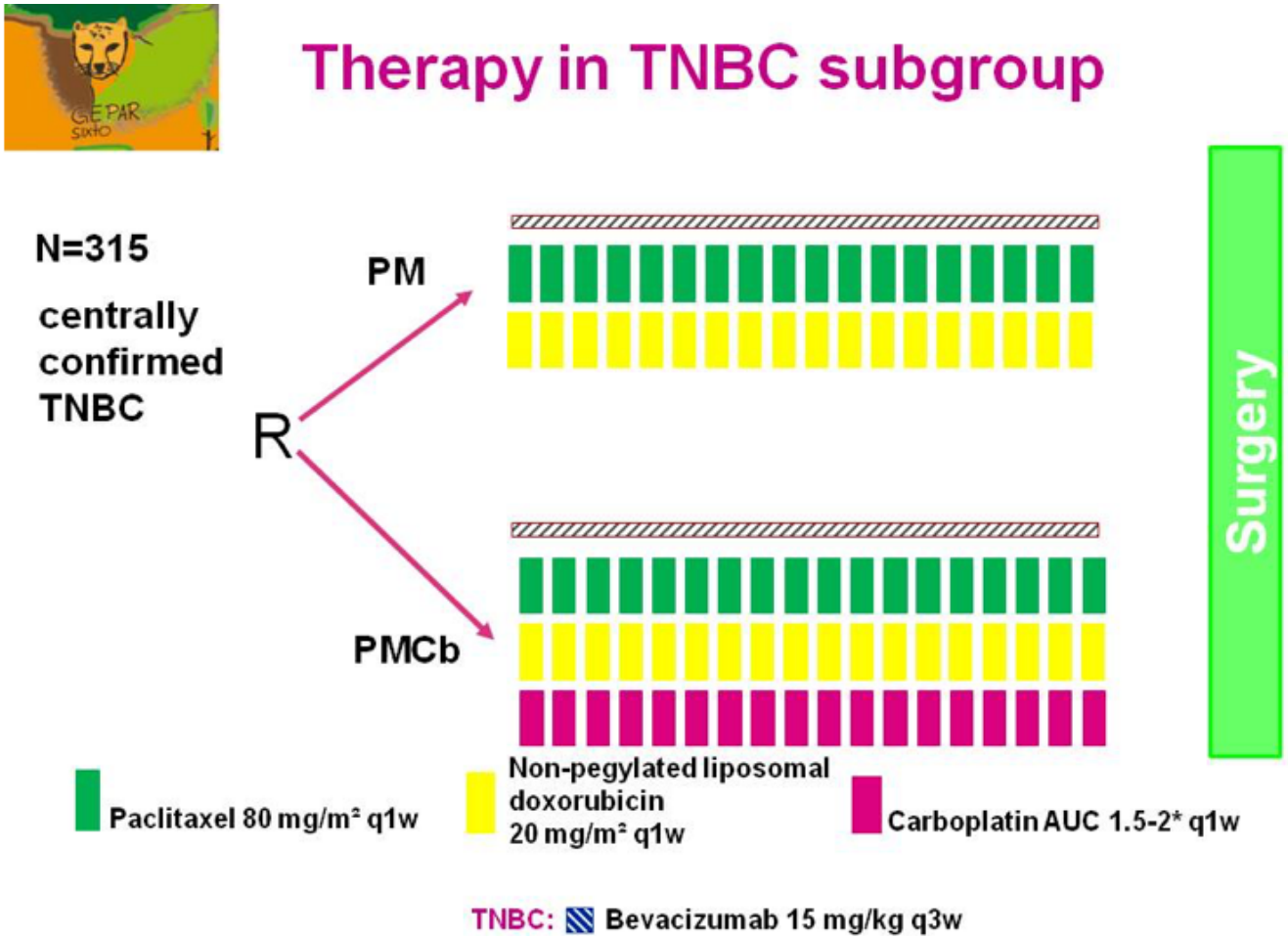
Sikow et al, SABCS 2013, abstr S5-01
Von Minckwitz et al, ASCO 2013, abstr 1004
Alba et al, Breast Cancer Res Treat 136;487, 2012

Meta-analysis



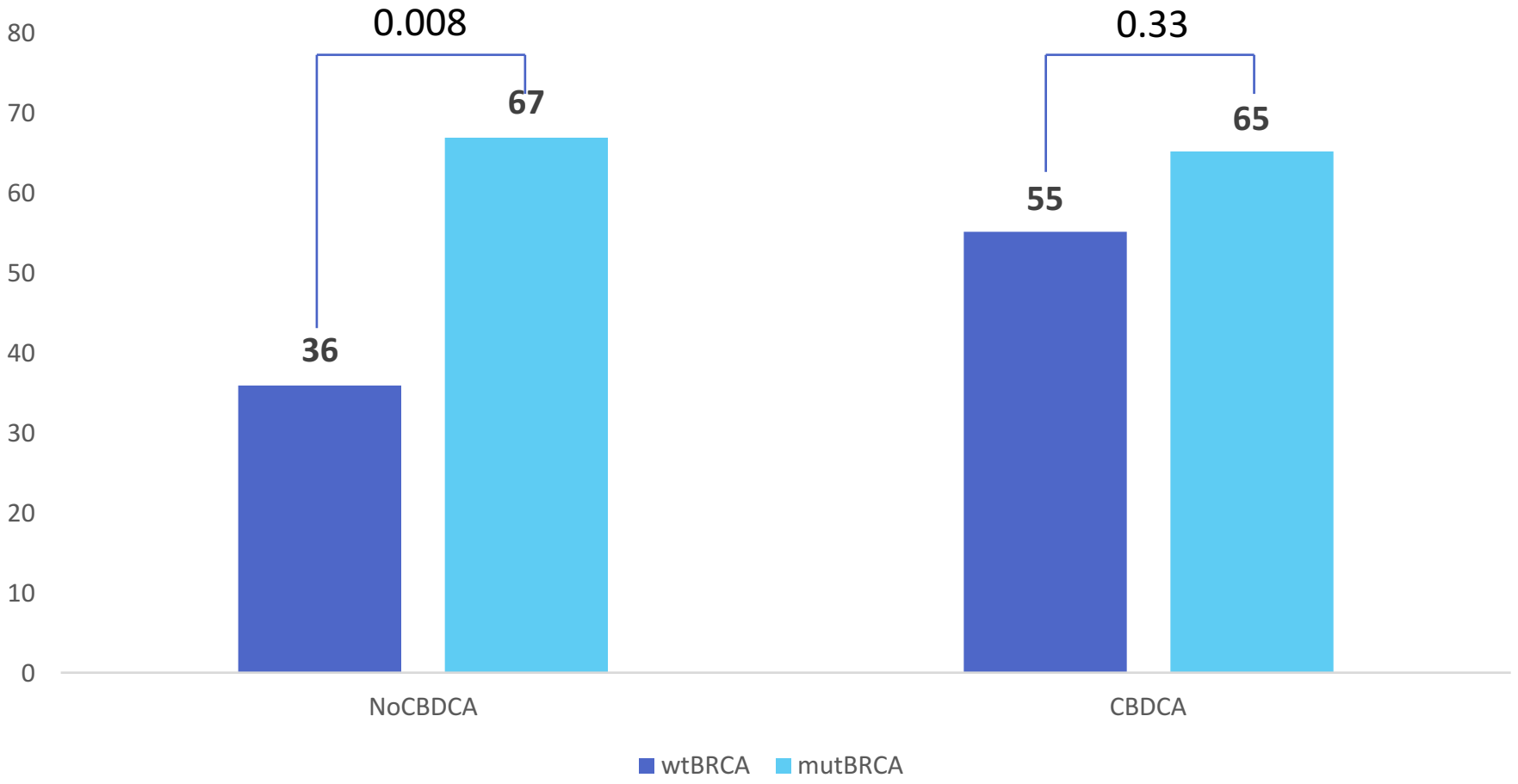
Poggio et al, Ann Oncol 2018

TNBC: addition of carboplatinum



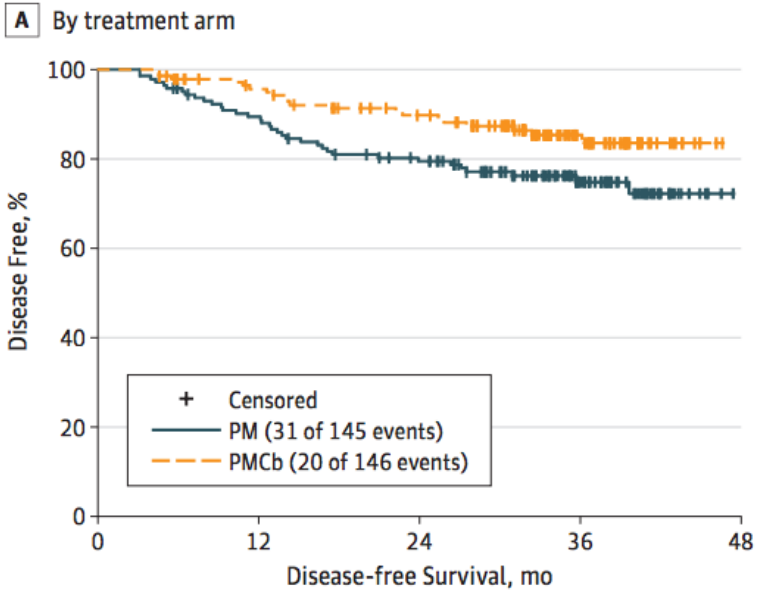
Hahnen Jama Oncol 3;1378, 2017

Benefit of Carboplatinum according to BRCA status; pCR (ypT0/ypN0)

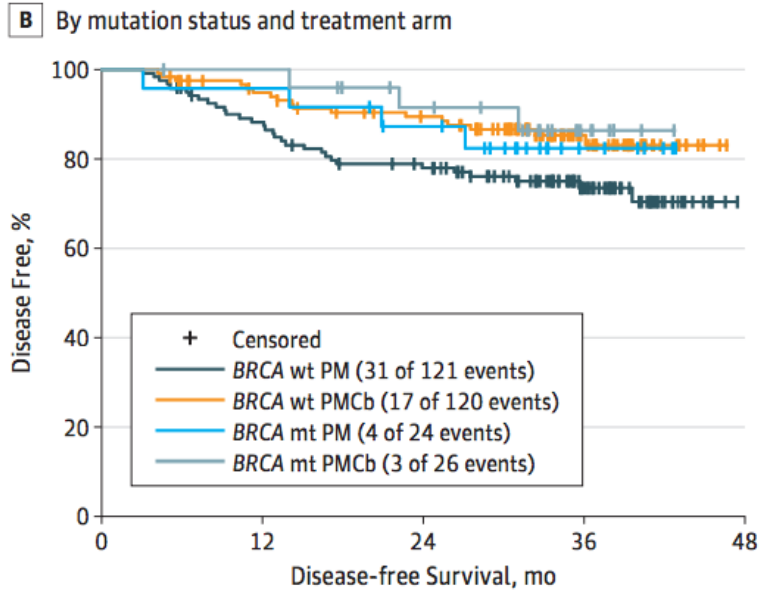


Hahnen Jama Oncol 3;1378, 2017

Benefit of Carboplatinum according to BRCA status



No. at risk					
PM	145	127	107	49	0
PMCb	146	132	115	47	0

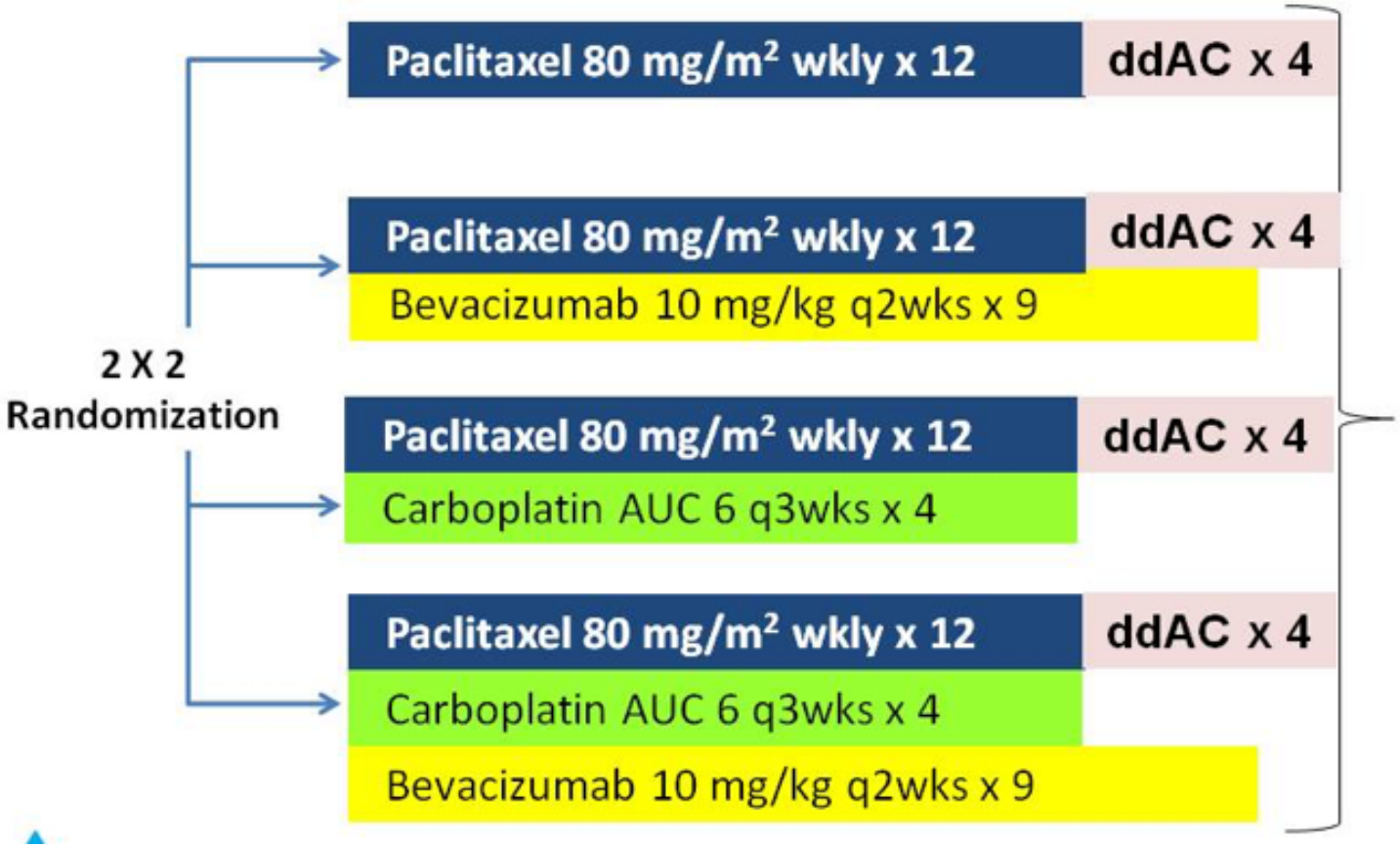


No. at risk					
BRCA wt PM	121	104	88	43	0
BRCA wt PMCb	120	107	95	40	0
BRCA mt PM	24	23	19	6	0
BRCA mt PMCb	26	25	20	7	0

A, Disease-free survival by treatment arm. B, Disease-free survival by *BRCA1* and *BRCA2* mutation status and treatment arm. mt Indicates mutant; PM, paclitaxel and myocet; PMCb, paclitaxel, myocet, and carboplatin; and wt, wild-type.

Hahnen Jama Oncol 3;1378, 2017

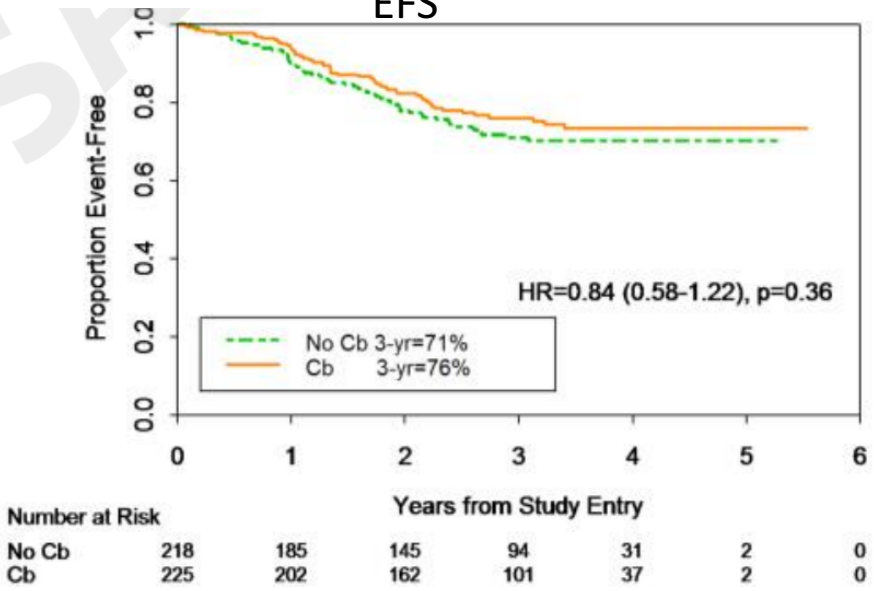
CALGB 40603



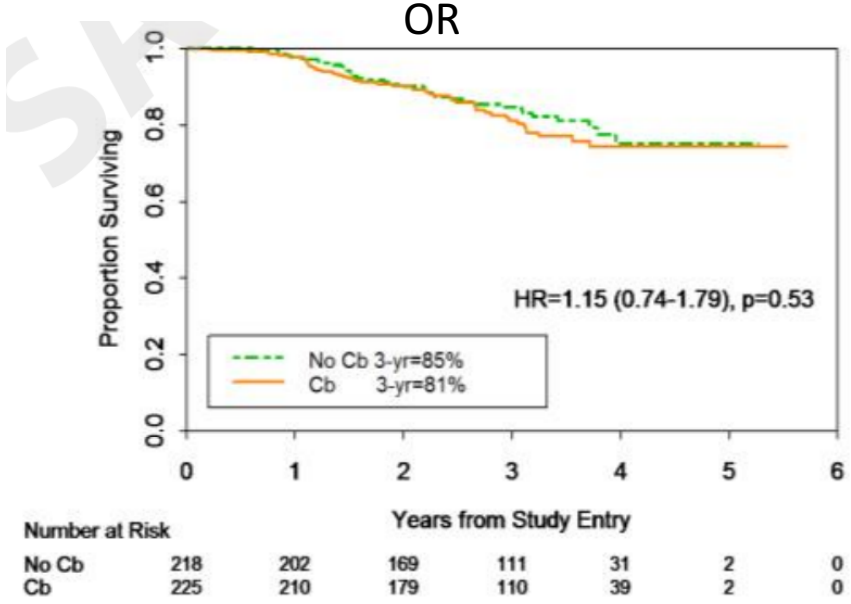
Sikov et al SABCS 2015

EFS and OS analysis

EFS



OR



Sikov et al SABCS 2015

Who are «pathology-wise» the optimal candidates to neoadjuvant chemotherapy?

Tumor size ≥ 2.5 cm

Screening Consent → Assess Eligibility → Patient is Eligible & Randomized → Treatment Consent, Patient On Study

Is Patient Eligible?

(based on stratifying biomarkers)

	MammaPrint Low		MammaPrint High	
	HR+	HR-	HR+	HR–
HER2+	Eligible	Eligible	Eligible	Eligible
HER2–	*Not Eligible**	Eligible	Eligible	Eligible

*May be eligible to participate in Low-Risk Registry Trial (supplement 1)

I-SPY patient selection schema

Could we tailor treatment based on early evaluation of response?

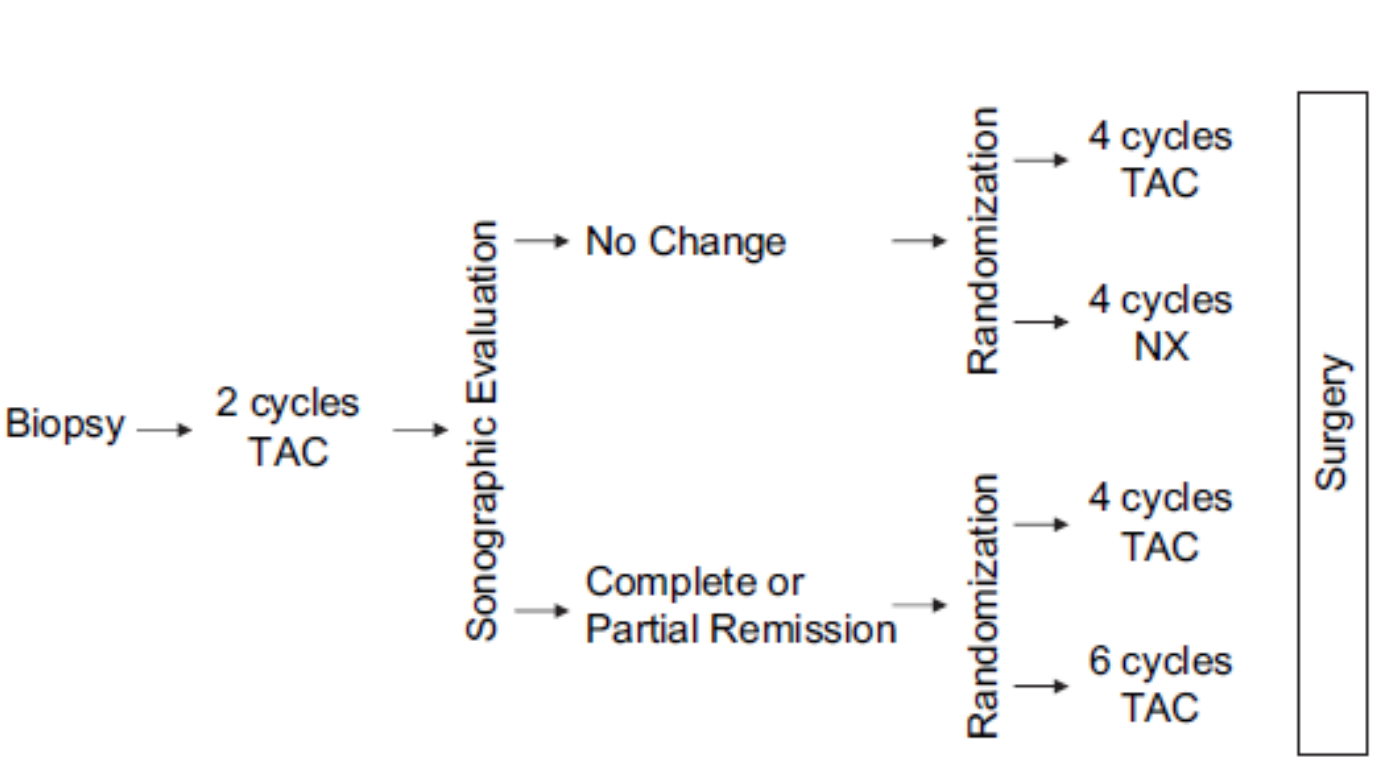
Treatment tailoring based on clinical predictors of pCR

Trial	Initial Regimen	Evaluation of response	Salvage Regimen vs Conventional	pCR in Switch	BCS rates
TAX301	CVAP X 4	UICC (calliper)	Docetaxel x 4	2%	-
			-	-	-
GeparTrio	TAC x 2	Ultrasonography	NX x 4	6.0%	59.8%
			TAC x 4	5.3%	57.3%
GeparQuinto	EC x 4	Imaging (US, MRI, Mammo)	wP x 12 +Everolimus	3.6%	54.4%
			wP x 12	5.6%	61.9%

J Clin Oncol 2002; 20, 1456
J Natl Cancer Inst 2008; 100;542
Eur J Cancer 2013; 49; 2284

CVAP; cyclophosphamide, Vincristine, Doxorubicin, Prednisone
TAC; docetaxel, doxorubicin, cyclophosphamide
NX; vinorelbine, capecitabine
wP; weekly paclitaxel

Adaptive chemotherapy according to response to the initial 2 cycles of neoadjuvant chemotherapy

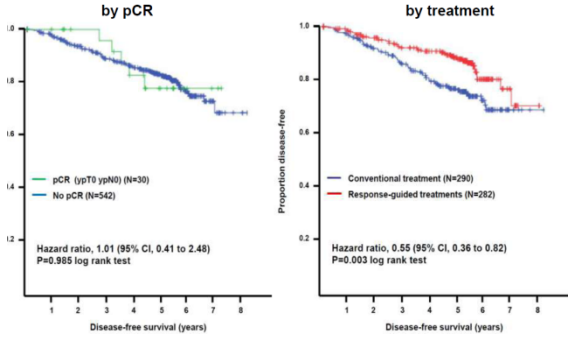


	ORR	pCR
4 cycles TAC	69.5%	5.3%
4 cycles NX	62.5%	6%
4 cycles TAC	74%	21.1%
6 cycles TAC	75%	23.5%

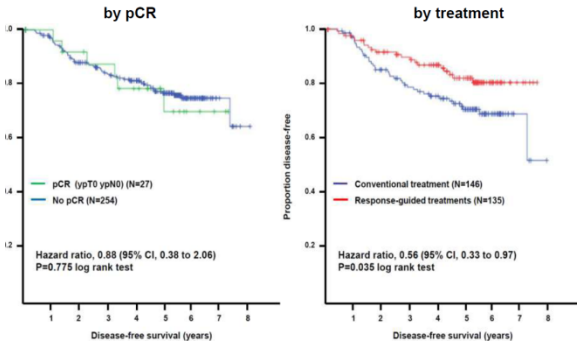
Von Minckwitz et al, JNCI 2008

Response-guided chemotherapy effective in some subgroups of breast cancer patients

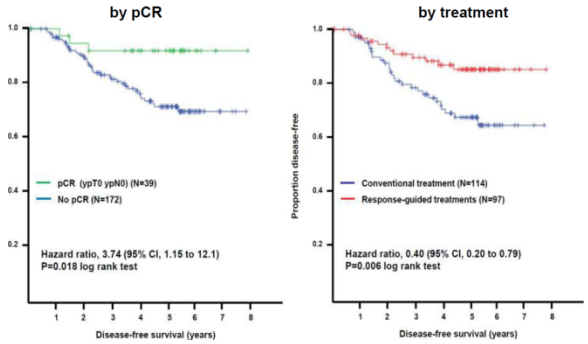
DFS in Luminal A tumors



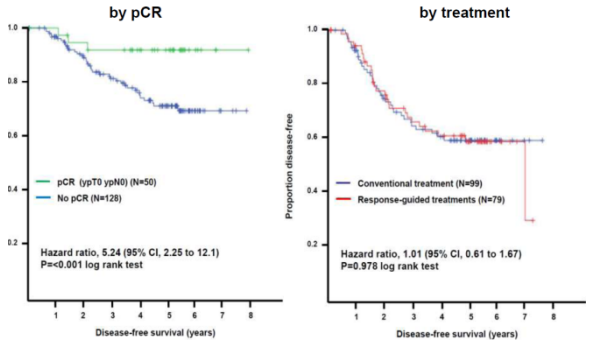
DFS in Luminal B (HER2+) tumors



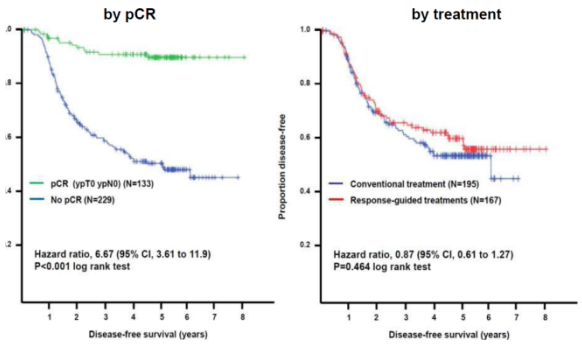
DFS in Luminal B (HER2-)



DFS in HER2+(non-luminal) tumors

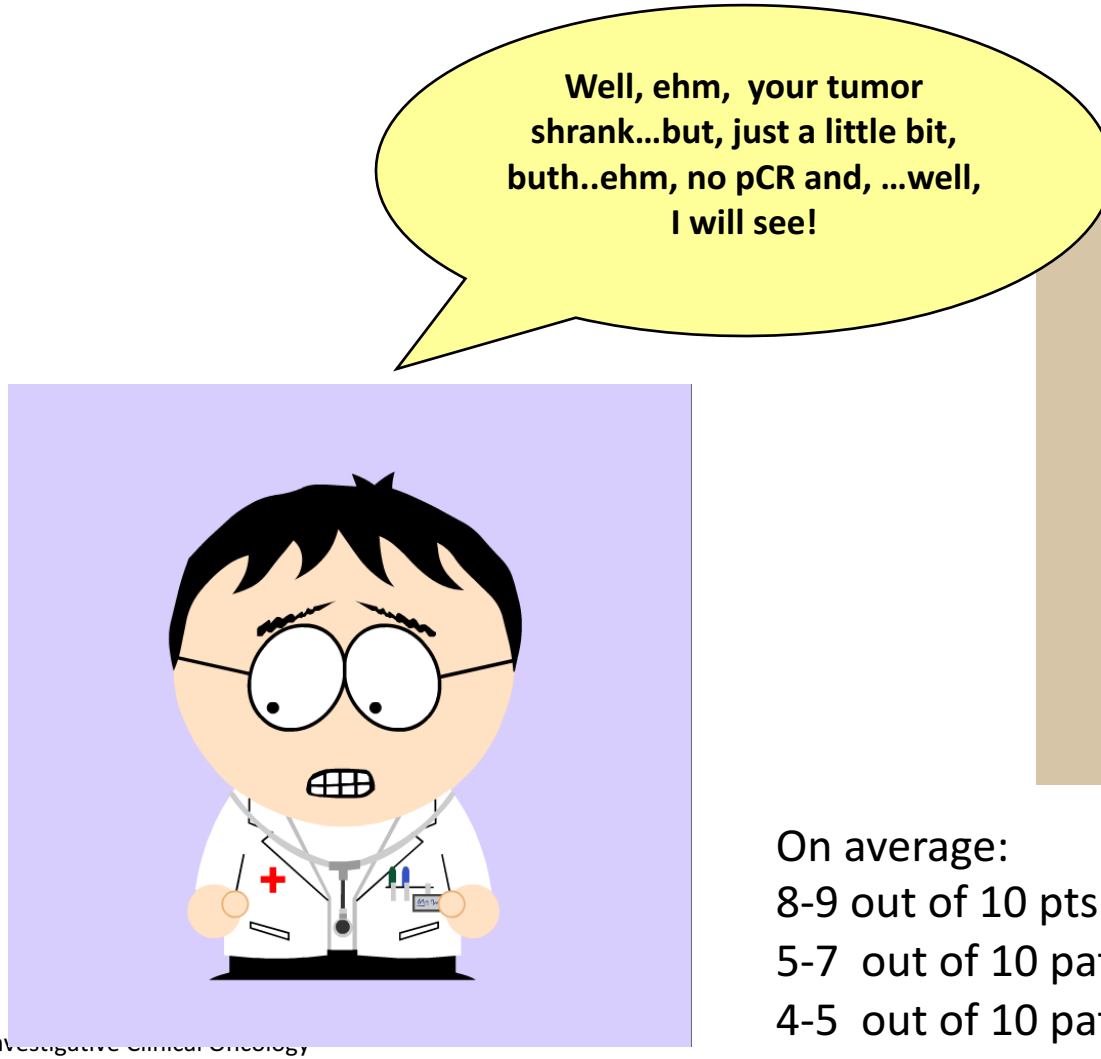


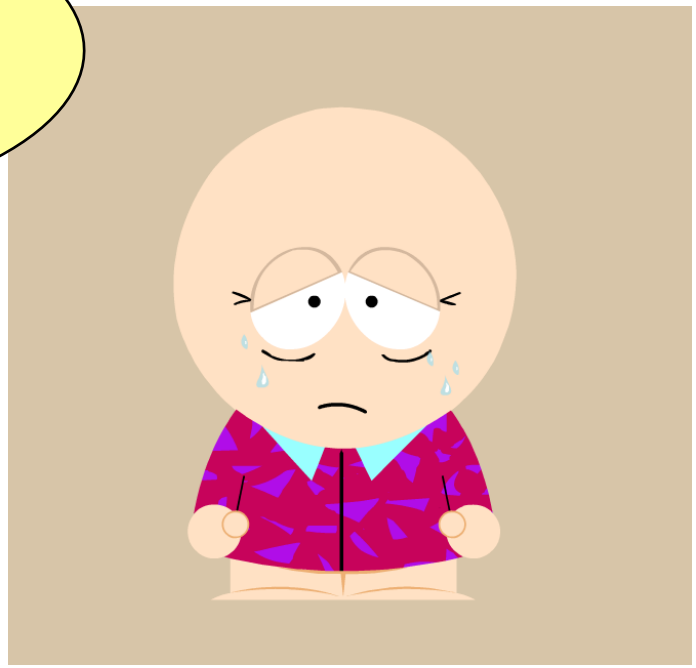
DFS in Triple Negative Tumors



Von Minckwitz J Clin Oncol 31;3623, 2013

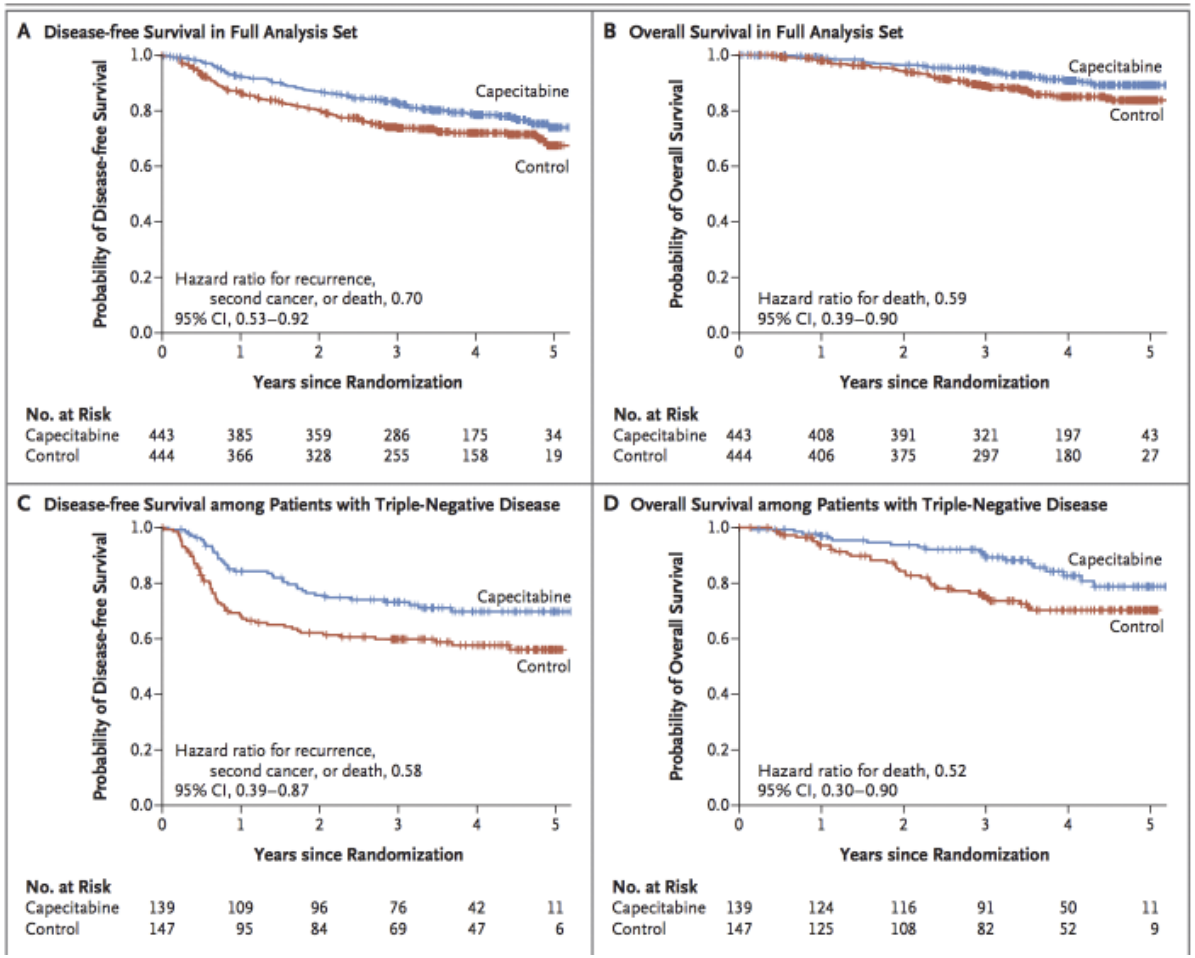
How could we deal with failure to achieve pCR?





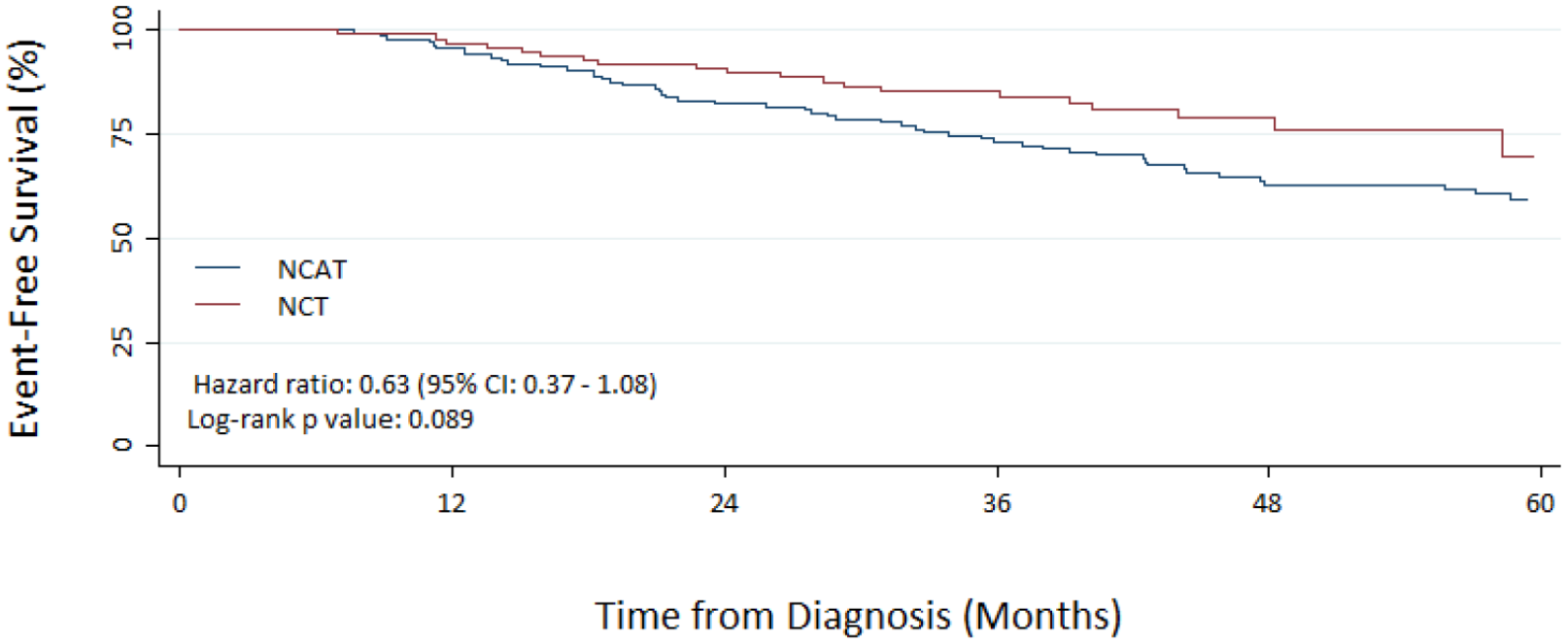
On average:
8-9 out of 10 pts with ER positive disease
5-7 out of 10 patients with triple negative disease
4-5 out of 10 patients with HER2 positive disease

Adjuvant capecitabine in patients with residual disease after NACT



Masuda N Engl J Med 3786;2147, 2017

Prognosis of patients receiving NACT and neoadjuvant vs adjuvant trastuzumab



Effect confined to patients with ER- tumors.

Palmieri et al, Oncotarget epub 2015

Earlier initiation of trastuzumab is associated with better prognosis

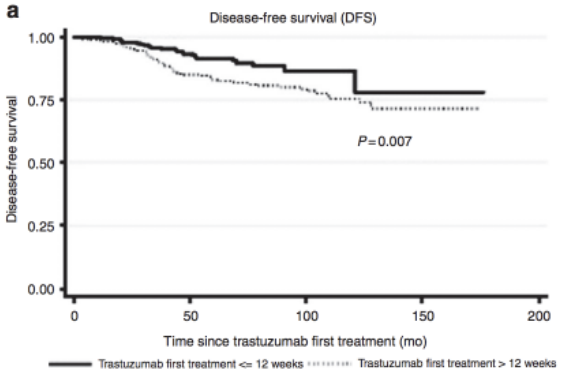


Fig. 3 DFS (**a**) and OS (**b**) of patients with a TFT (time to first trastuzumab) ≤ 12 weeks ($N = 247$) compared with those with TFT > 12 weeks ($N = 244$)

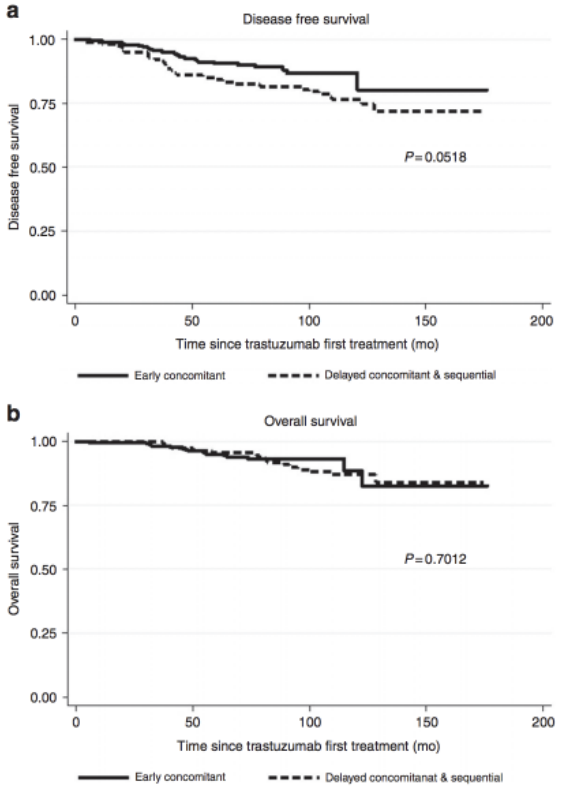
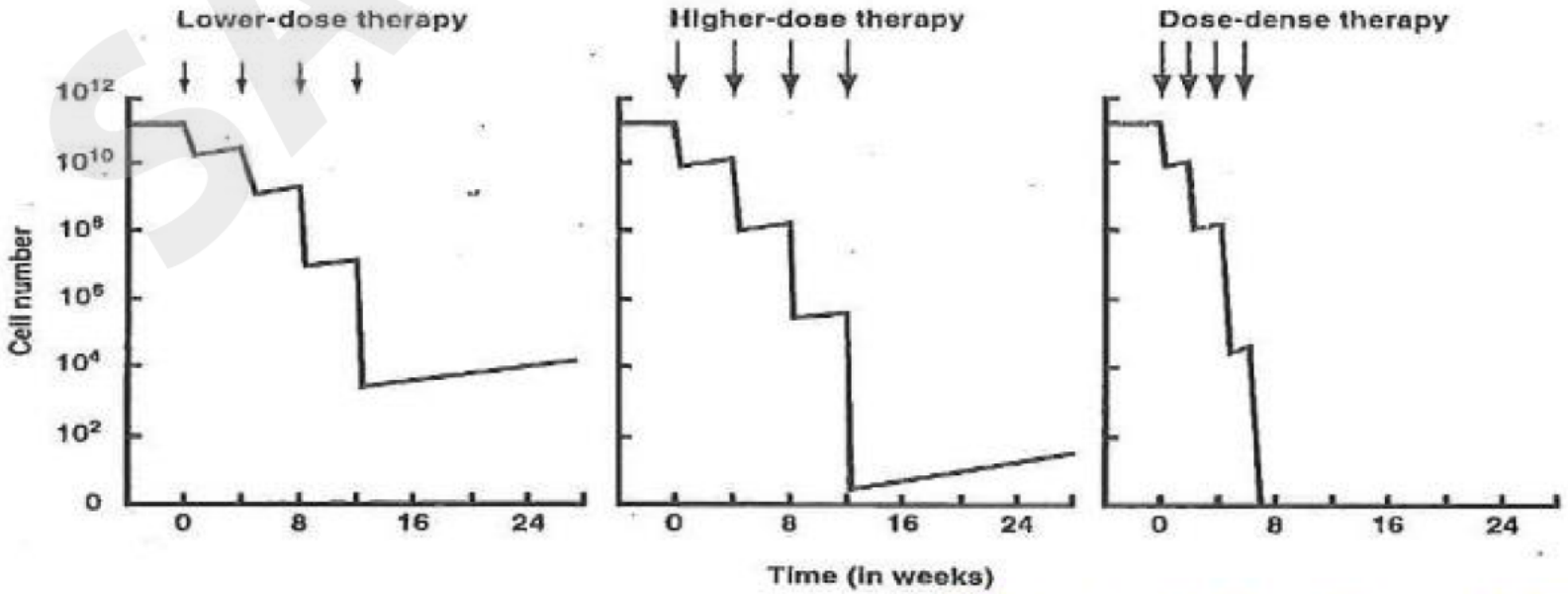


Fig. 4 DFS (**a**) and OS (**b**) of patients treated with *early concomitant* regimens (e.g., TCH and "TCH-like") compared with those treated with *delayed concomitant* (e.g., AC-TH) and *sequential* regimens. TCH (Docetaxel/Carboplatin/Trastuzumab), AC-TH (Doxorubicin/Cyclophosphamide-Docetaxel/Trastuzumab)

Gullo, Br J Cancer 119;374, 2018

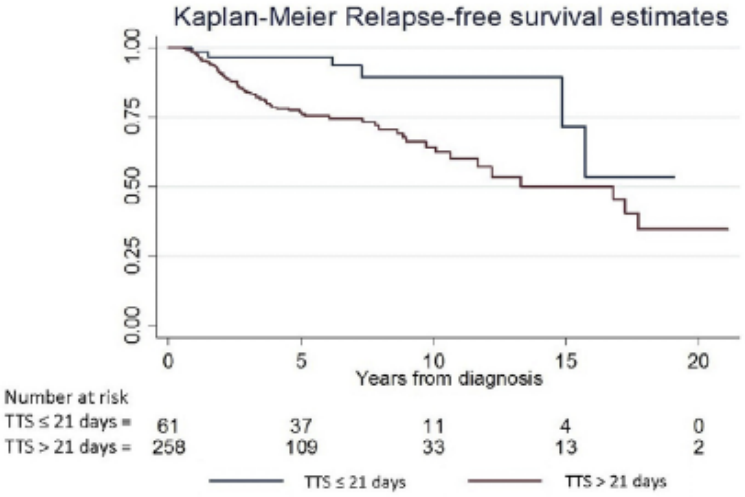
Dose-dense chemotherapy

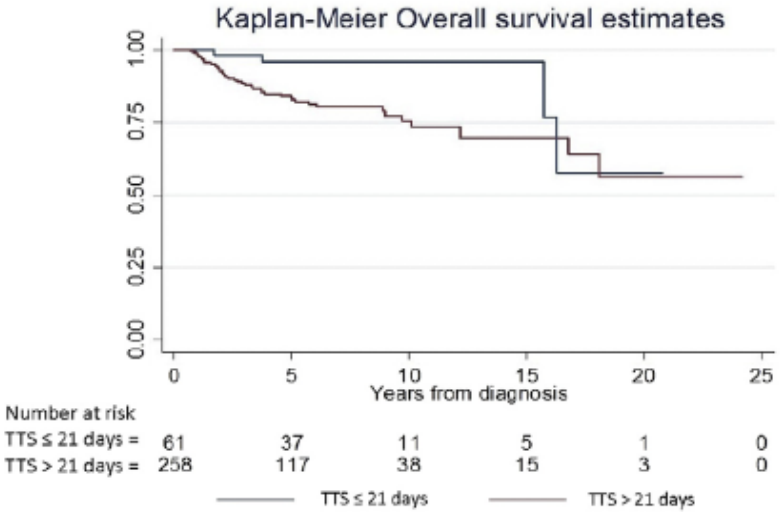
Models of tumour cytoreduction and regrowth following conventional, dose-escalated and dose-dense chemotherapy*



* Norton L. Sem Oncol 1997

Timing of surgery after completion of neoadjuvant chemotherapy and outcomes





Univariate analysis and survival estimates for Relapse Free Survival according to TTS and known prognostic factors.

	Relapse Free Survival					
	5-Years estimate (95% CI)	10-Years estimate (95% CI)	15-Years estimate (95% CI)	HR	95% CI	p
TTS						
TTS ≤ 21 days	0.96 (0.86–0.99)	0.89 (0.72–0.96)	0.71 (0.27–0.91)	1	1.35–7.17	0.008
TTS > 21 days	0.76 (0.70–0.81)	0.64 (0.54–0.72)	0.50 (0.36–0.62)	3.11		
BC subtypes						
Hormone-receptor positive	0.83 (0.75–0.88)	0.66 (0.54–0.76)	0.53 (0.38–0.67)	1		
HER2 positive	0.78 (0.67–0.85)	0.73 (0.61–0.82)	0.73 (0.61–0.82)	1.20	0.70–2.04	0.5
TNBC	0.78 (0.64–0.86)	0.78 (0.64–0.86)	0.46 (0.13–0.74)	1.11	0.60–2.02	0.7
Clinical stage						
I	0.83 (0.27–0.97)	0.83 (0.27–0.97)	0.83 (0.27–0.97)	1		
II	0.83 (0.77–0.88)	0.69 (0.59–0.77)	0.62 (0.48–0.74)	1.59	0.21–11.06	0.6
III	0.69 (0.56–0.79)	0.64 (0.49–0.75)	0.30 (0.09–0.54)	3.19	0.42–23.77	0.2
pCR						
Yes	0.92 (0.81–0.97)	0.92 (0.81–0.97)	0.92 (0.81–0.97)	1	0.09–0.71	0.009
No	0.77 (0.71–0.82)	0.64 (0.55–0.72)	0.49 (0.36–0.61)	0.25		

Omarini et al, Eur J Surg Oncol 43; 613, 2017