Neoadjuvant treatment of breast cancer

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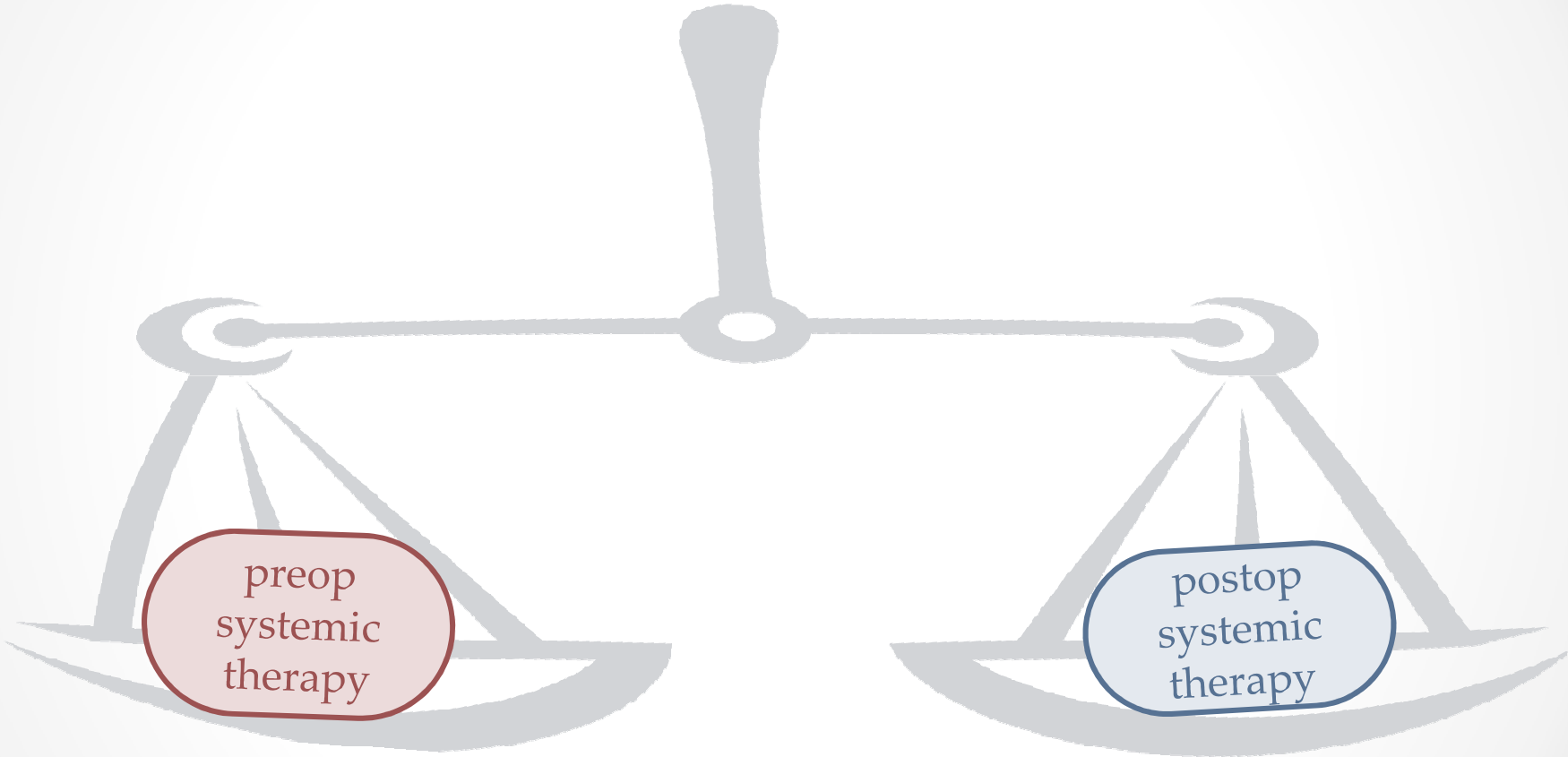
Disclosures

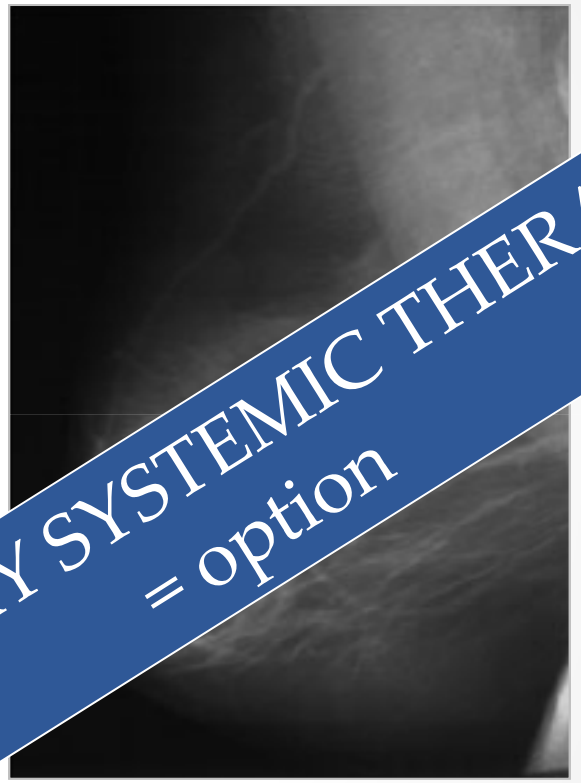
- honoraria: Amgen, AstraZeneca, Clinigen, Egis, Eli Lilly, Novartis, Pfizer, Pierre Fabre, Roche and Sandoz
- travel support: Amgen, AstraZeneca, Egis, Novartis, Pfizer and Roche
- clinical research: Amgen, AstraZeneca, Eli Lilly, Boehringer, Merck, Novartis, Pfizer, Roche and Samsung


preop
systemic
therapy
postop
systemic
therapy

Why preop systemic therapy???

PRIMARY SYSTEMIC THERAPY
= treatment of choice

LOCALLY ADVANCED
OR INFLAMMATORY BC



PRIMARY SYSTEMIC THERAPY
= option

OPERABLE BC

PROS

- earlier treatment of micrometastatic disease
- *in vivo* treatment sensitivity assessment/prognostic information
- translational studies

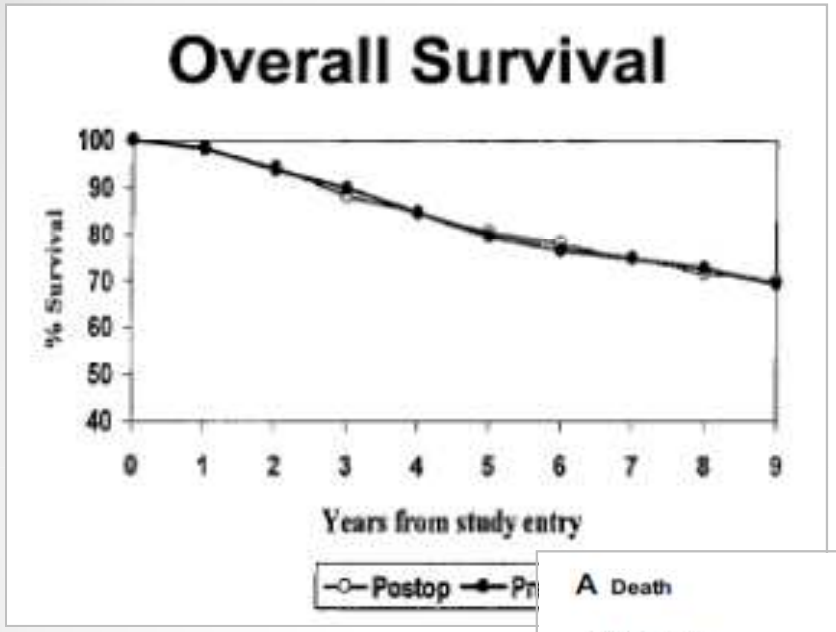
- increased operability of inoperable tumors
- decreased extent of surgery
- time for [illegible]sting

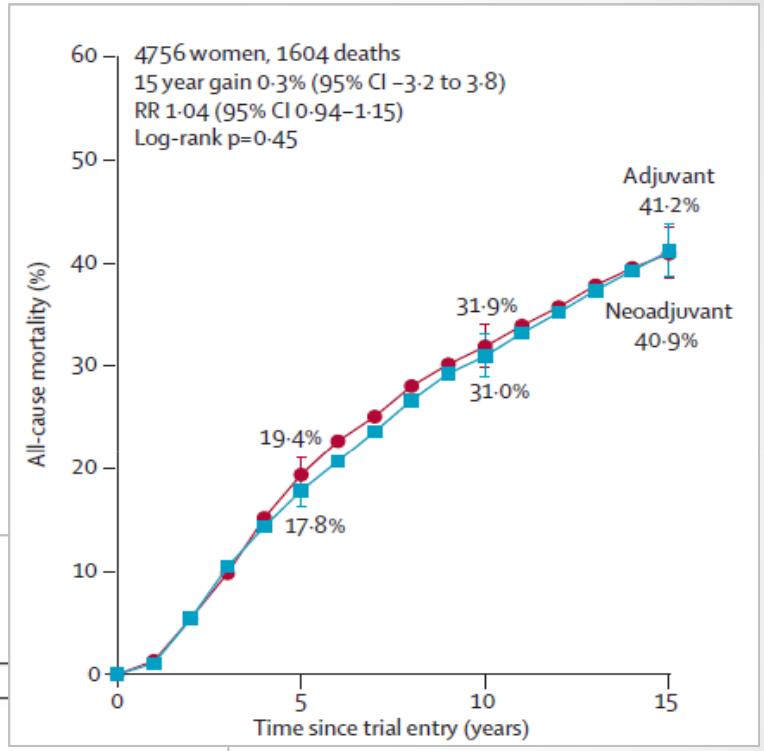
selection for post-neoadjuvant therapies

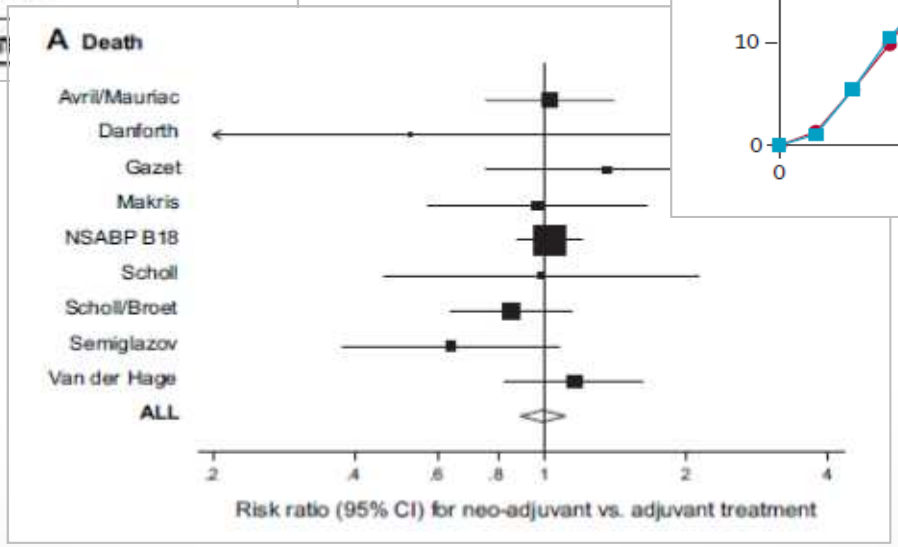
CONS

- delay in local treatment (risk of tumor progression)
- loss of prognostic information from full pathological assessment of untreated tumor
  → risk of under/overtreatment

Efficacy = adjuvant ChT

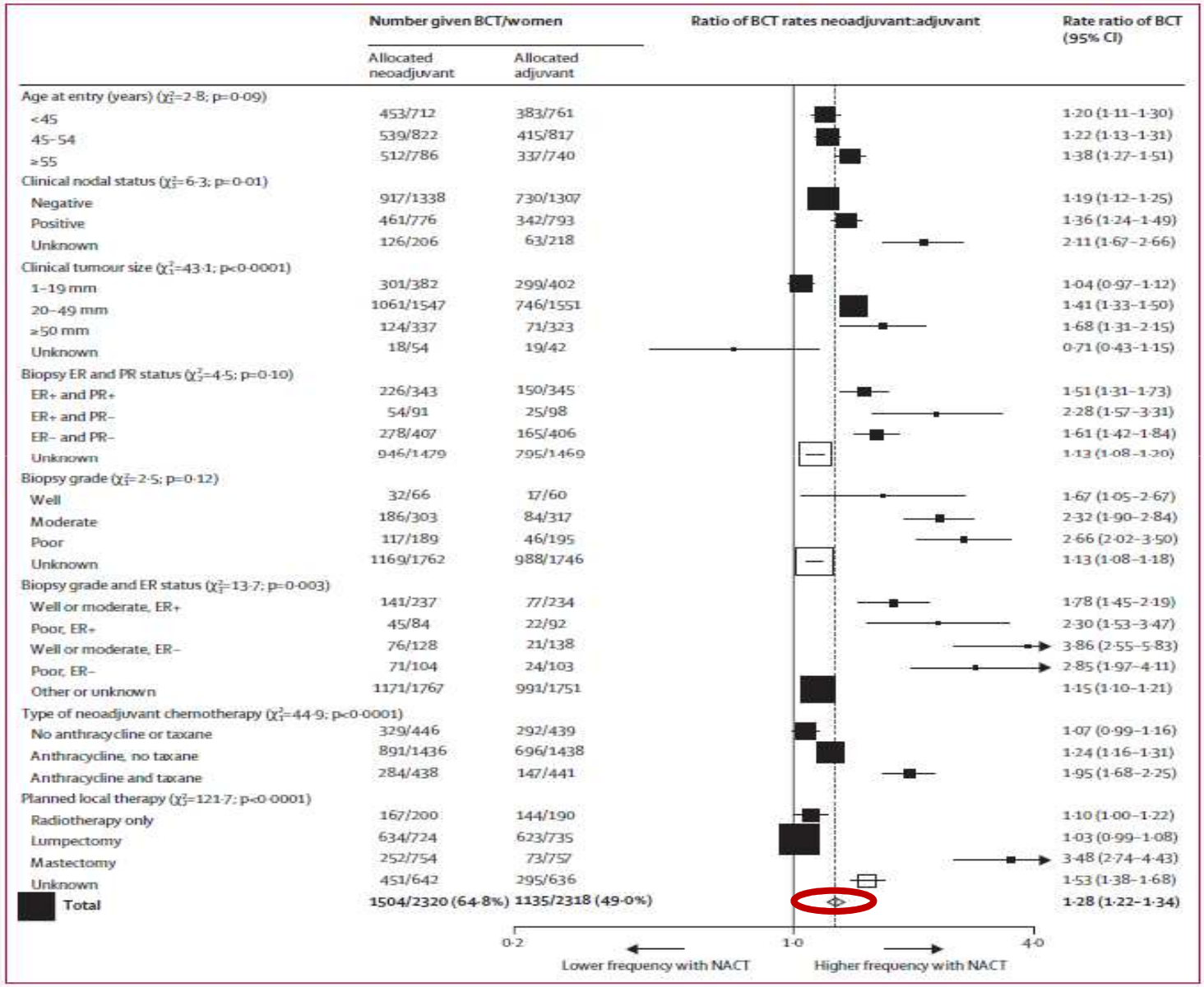






Wolmark, JNCI Monogr 2001, Mauri, JNCI 2005, EBCTCG, Lancet Oncol 2018

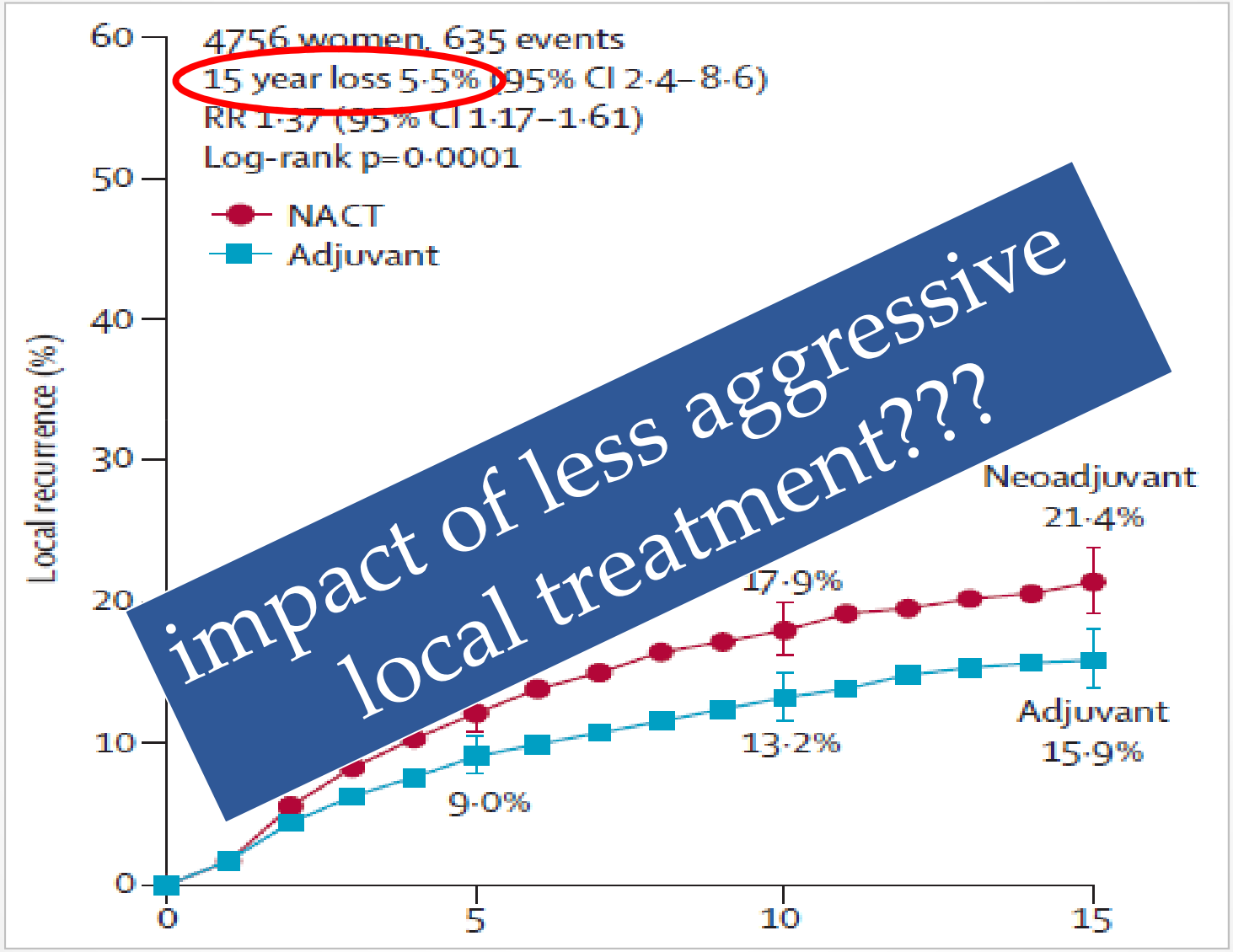
other measures of efficacy…



BCT rate

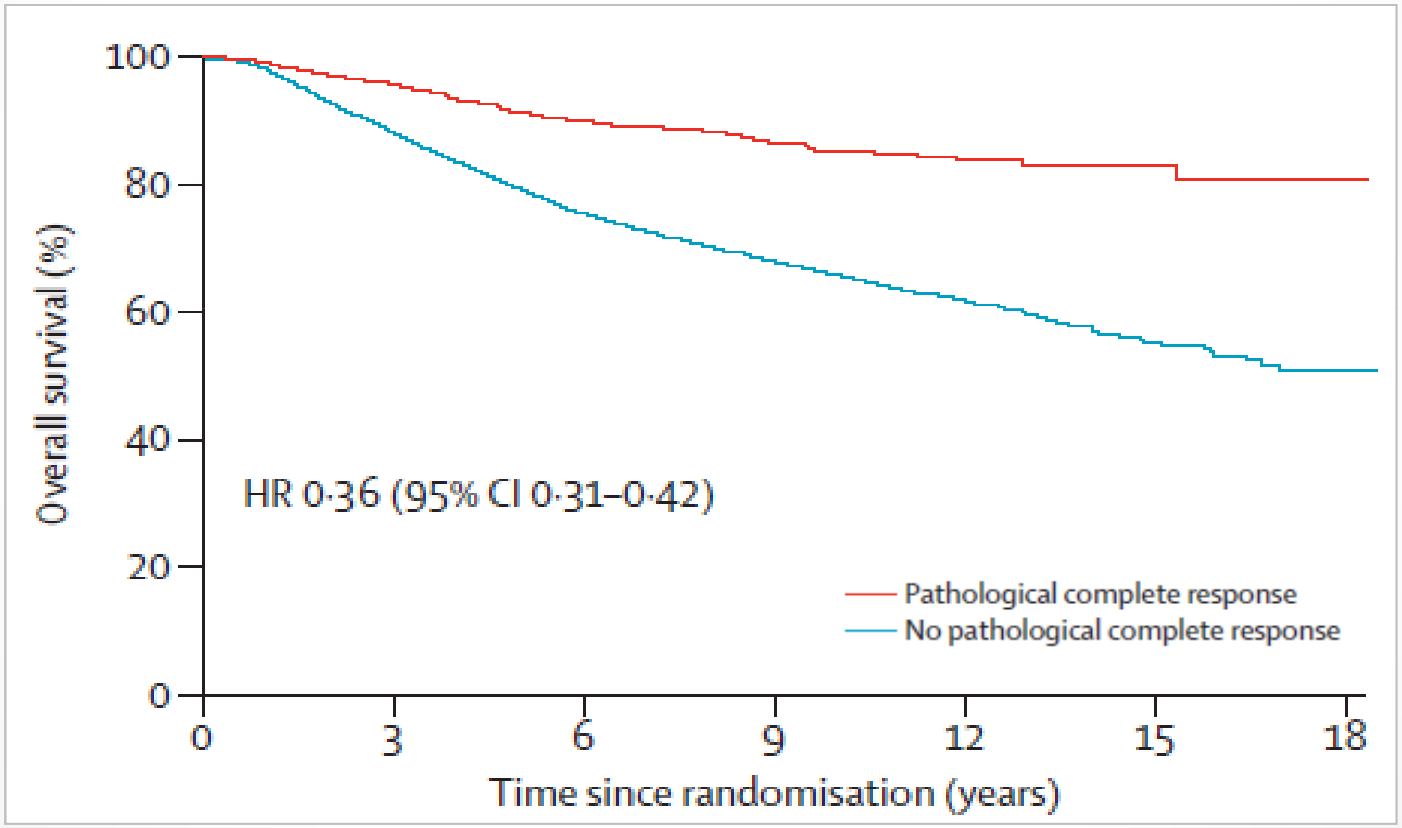
EBCTCG, Lancet Oncol 2018

but…



EBCTCG, Lancet Oncol 2018

Who benefits from preop treatment?

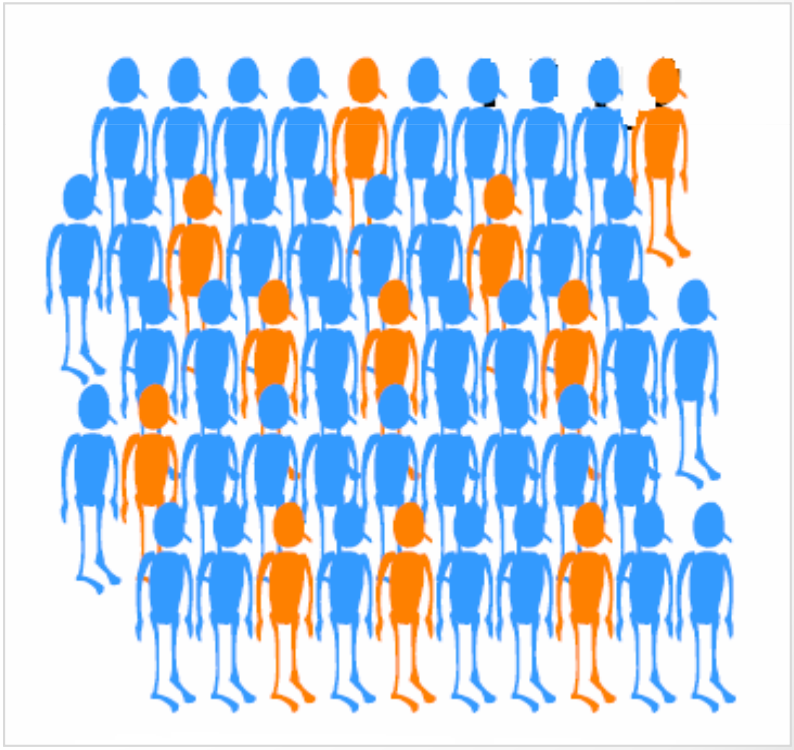


Cortazar, Lancet 2014

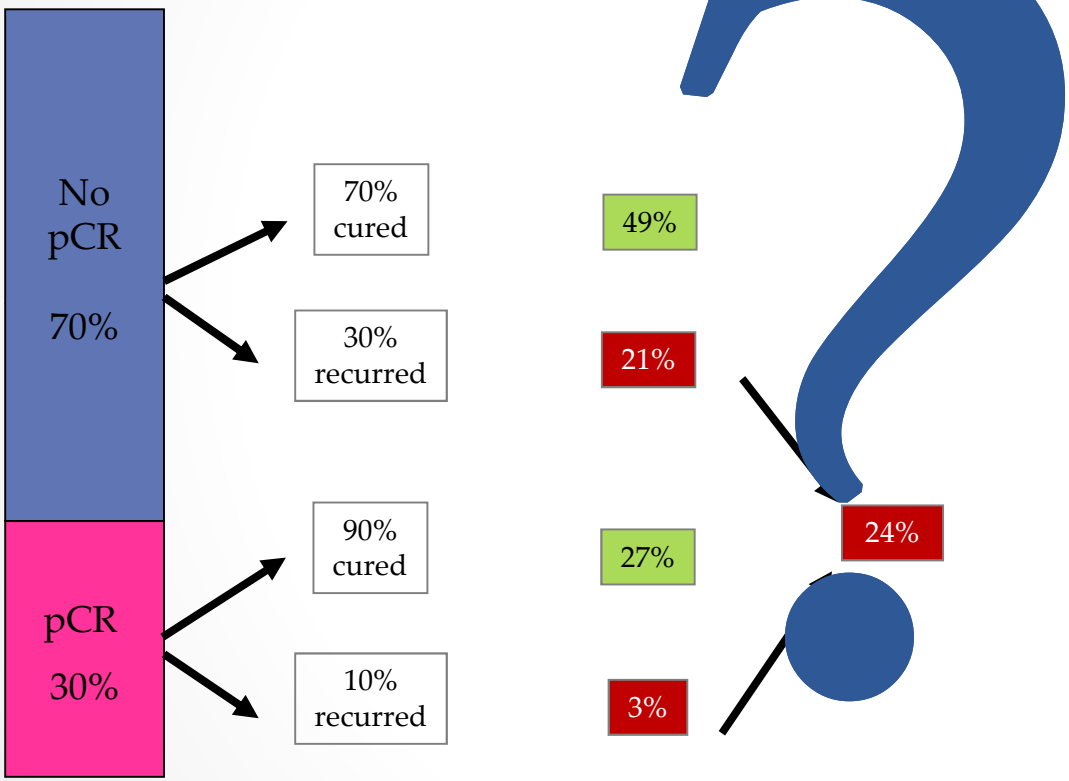
Meaning of pCR

surrogate for cure?

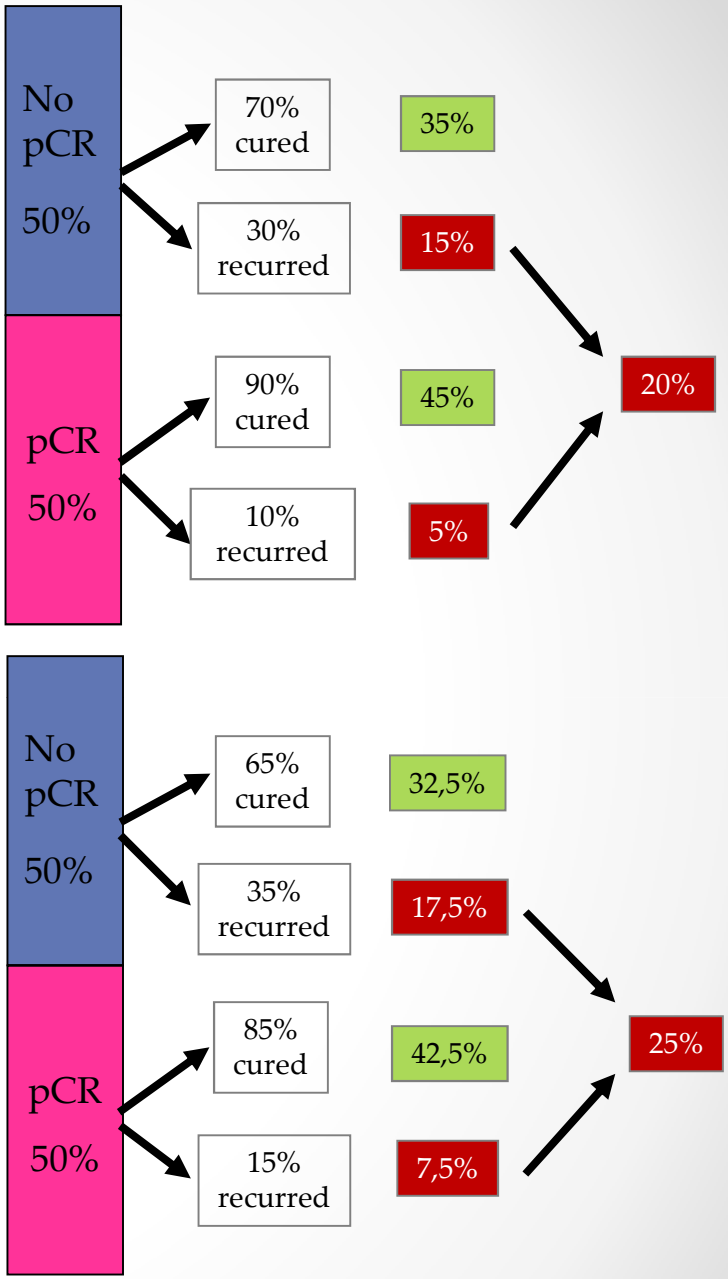
selection of best prognosis patients?



pCR and survival?



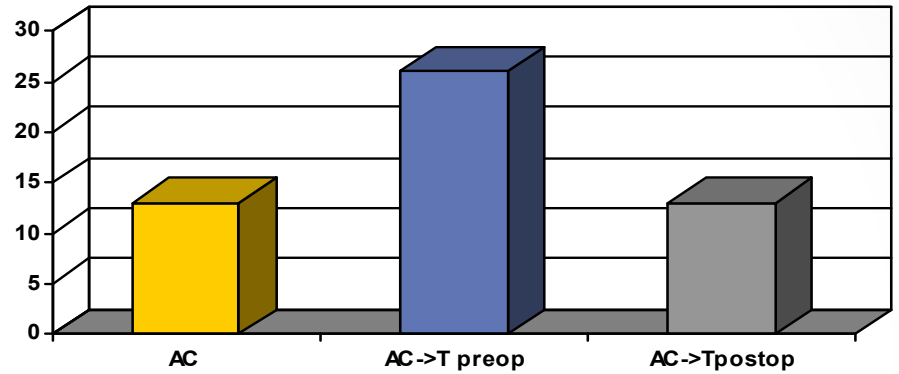
Standard PST



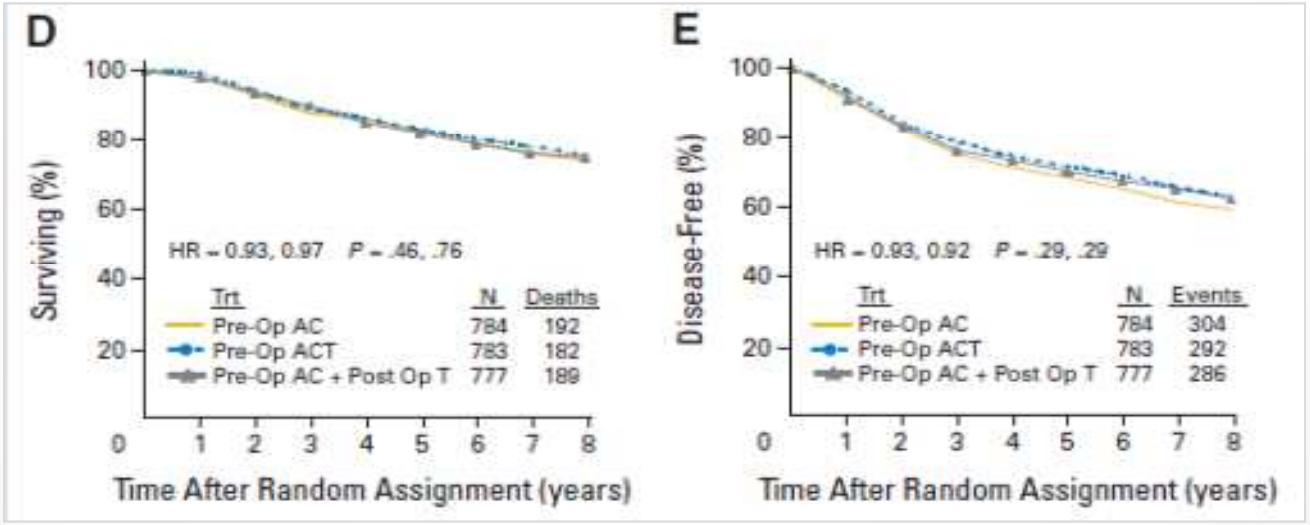
„Better" PST

Does ↑pCR translate into improved long-term outcomes???

NSABP B-27



pCR



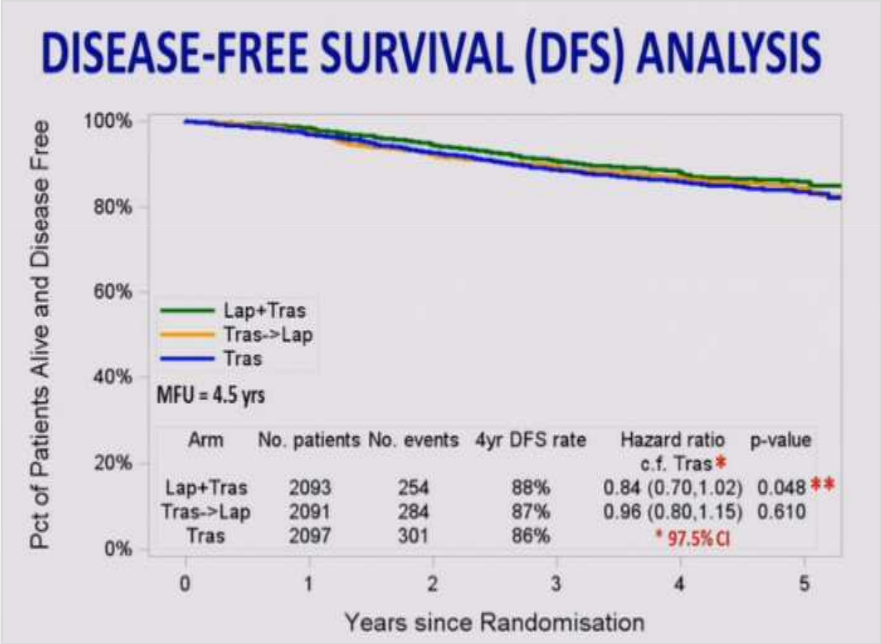
overall survival

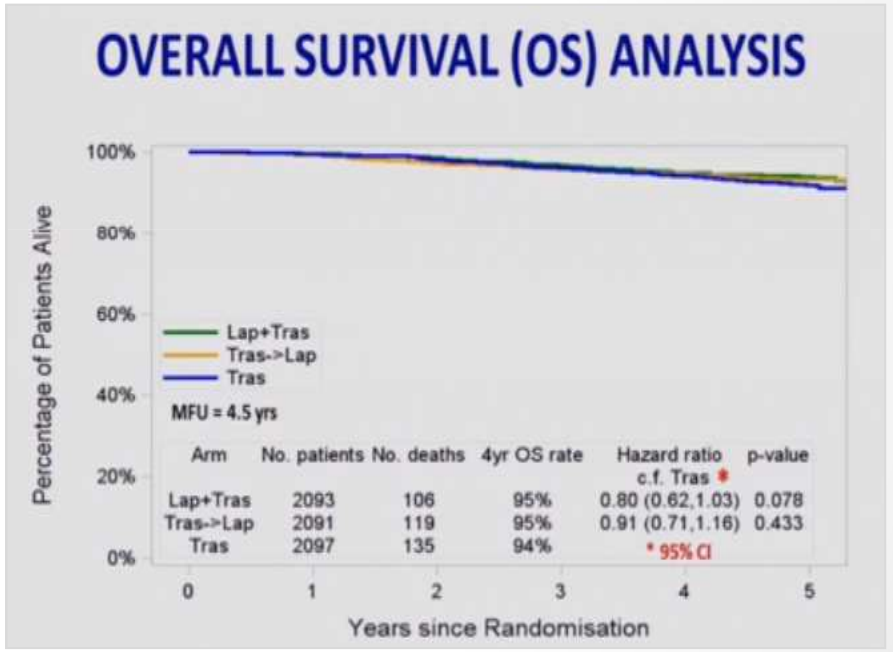
DFS

Rastogi, JCO 2008

Does ↑pCR translate into improved long-term outcomes???

ALTTO



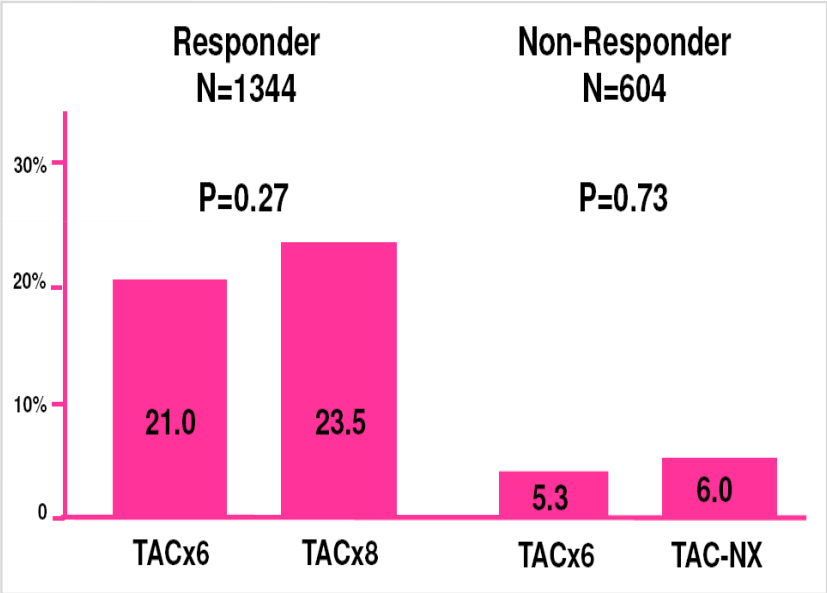


- **The doubling in pCR observed with L + T in NeoALTTO did not translate into improved survival outcomes in ALTTO at 4.5 years median follow-up.**

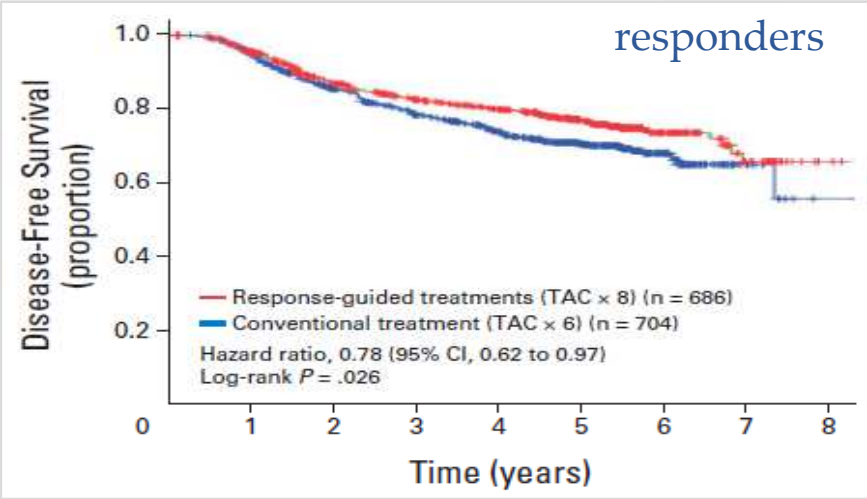
Piccart, JCO 2015

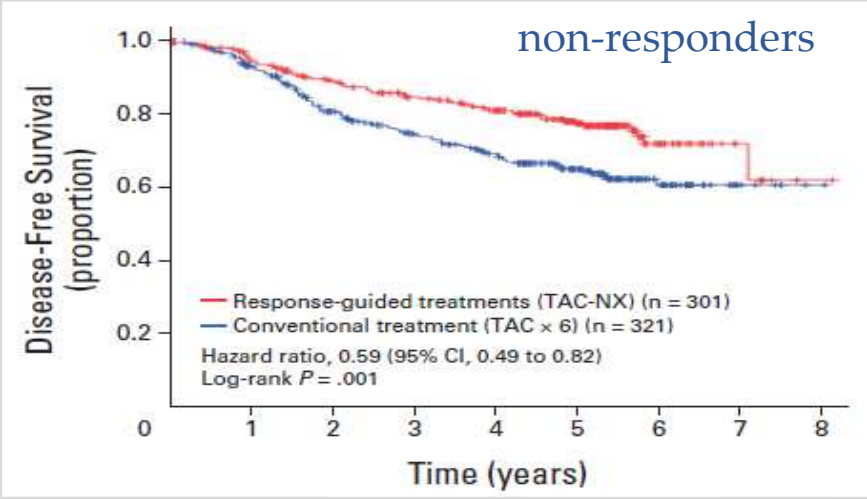
Does pCR translate into improved long-term outcomes???

GeparTrio



pCR

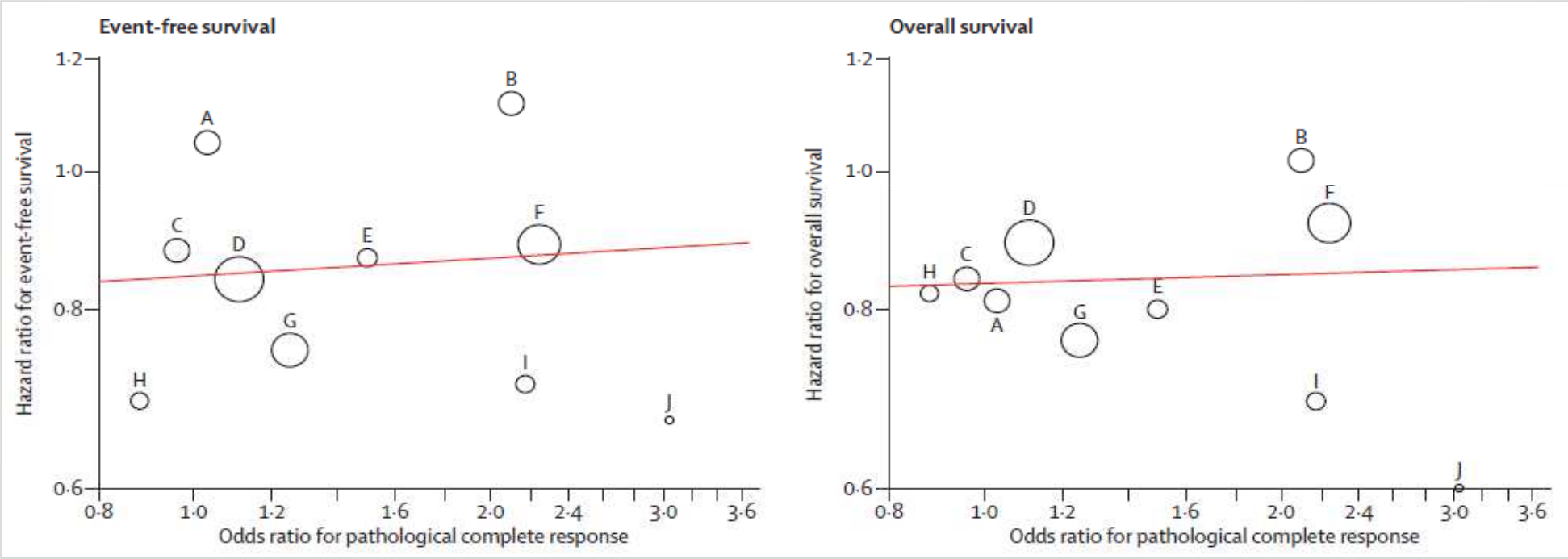




von Minckwitz, JCO 2013

Does↑pCR translate into improved long-term outcomes???

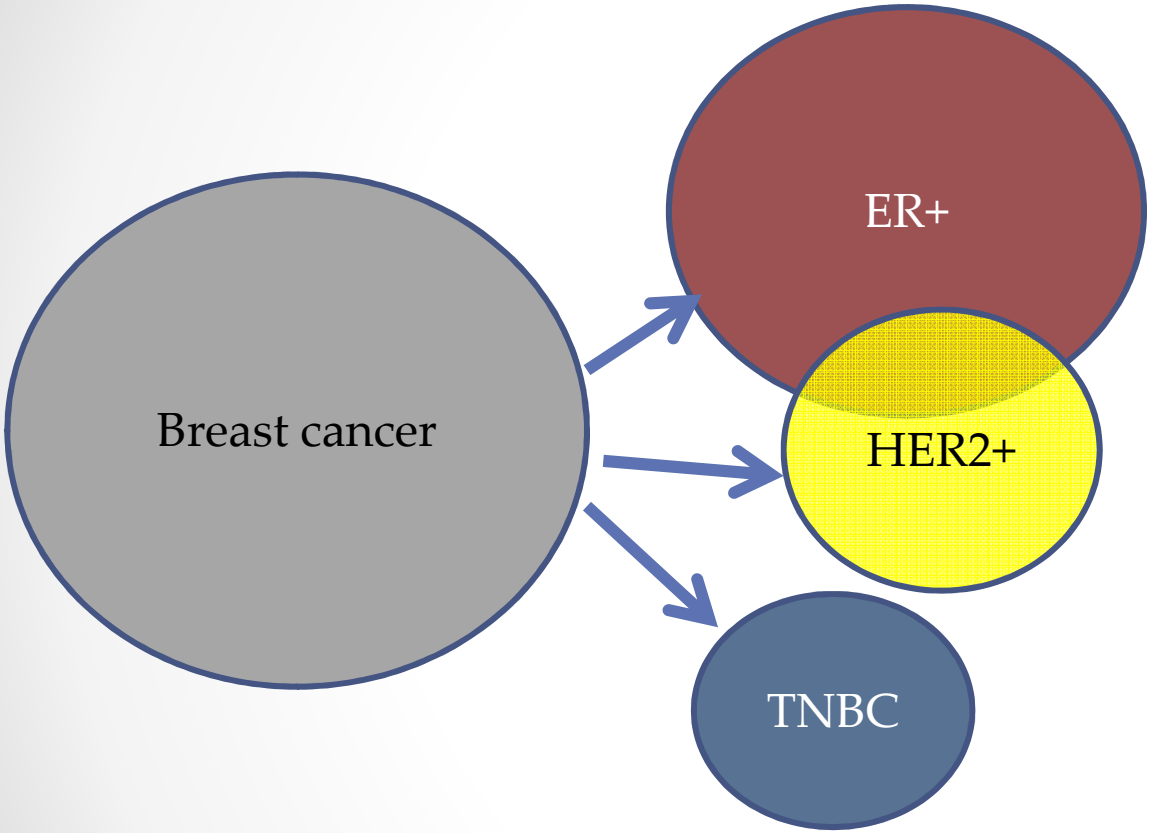
FDA metaanalysis



Cortazar, Lancet 2014

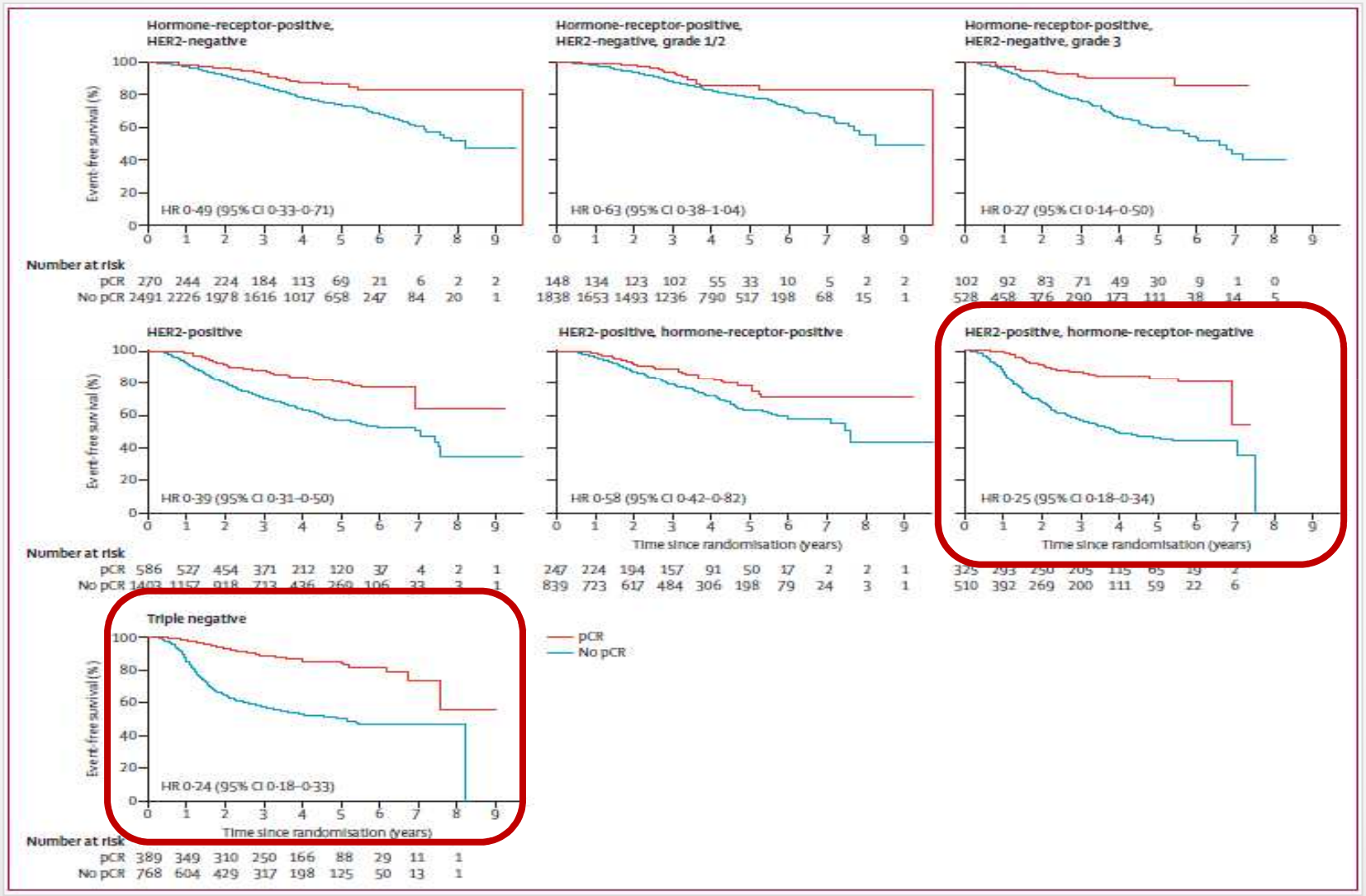
Neoadjuvant systemic therapy

Breast cancer is not a single disease…



- genomic grade/proliferation
- TNBC subtype
- BRCA mutations
- …….

pCR prognostic value by phenotype

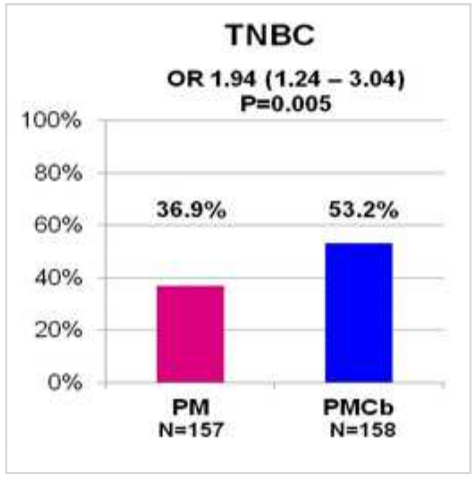


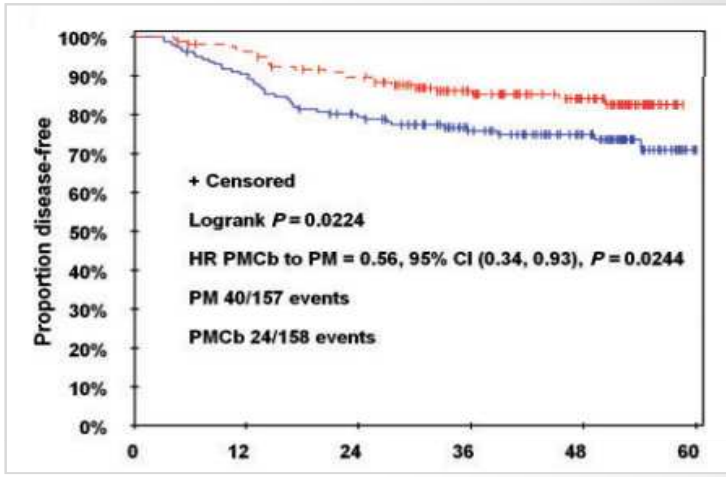
Cortazar, Lancet 2014

TNBC

Role of platinum?

GeparSixto





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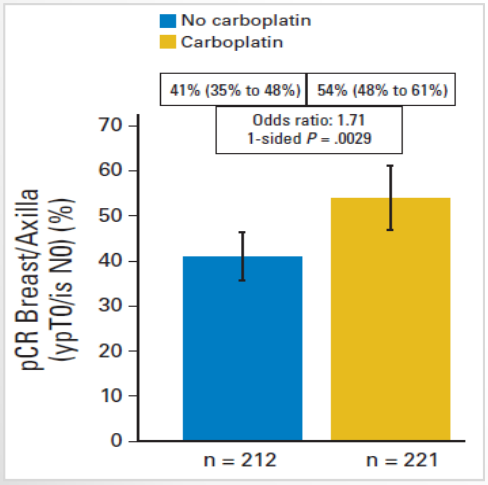
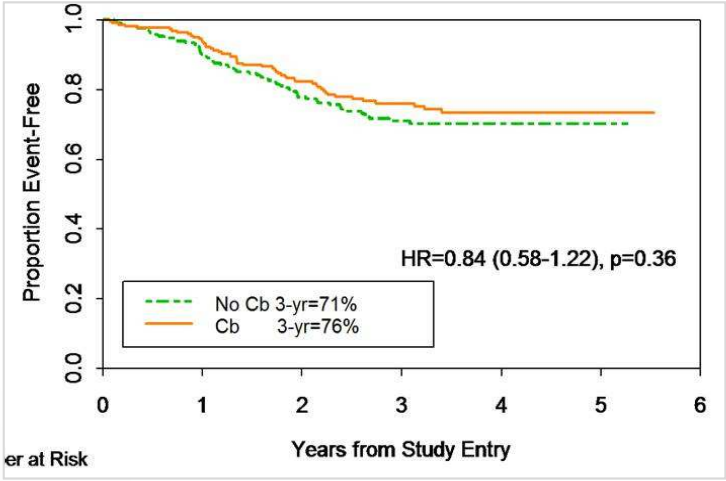
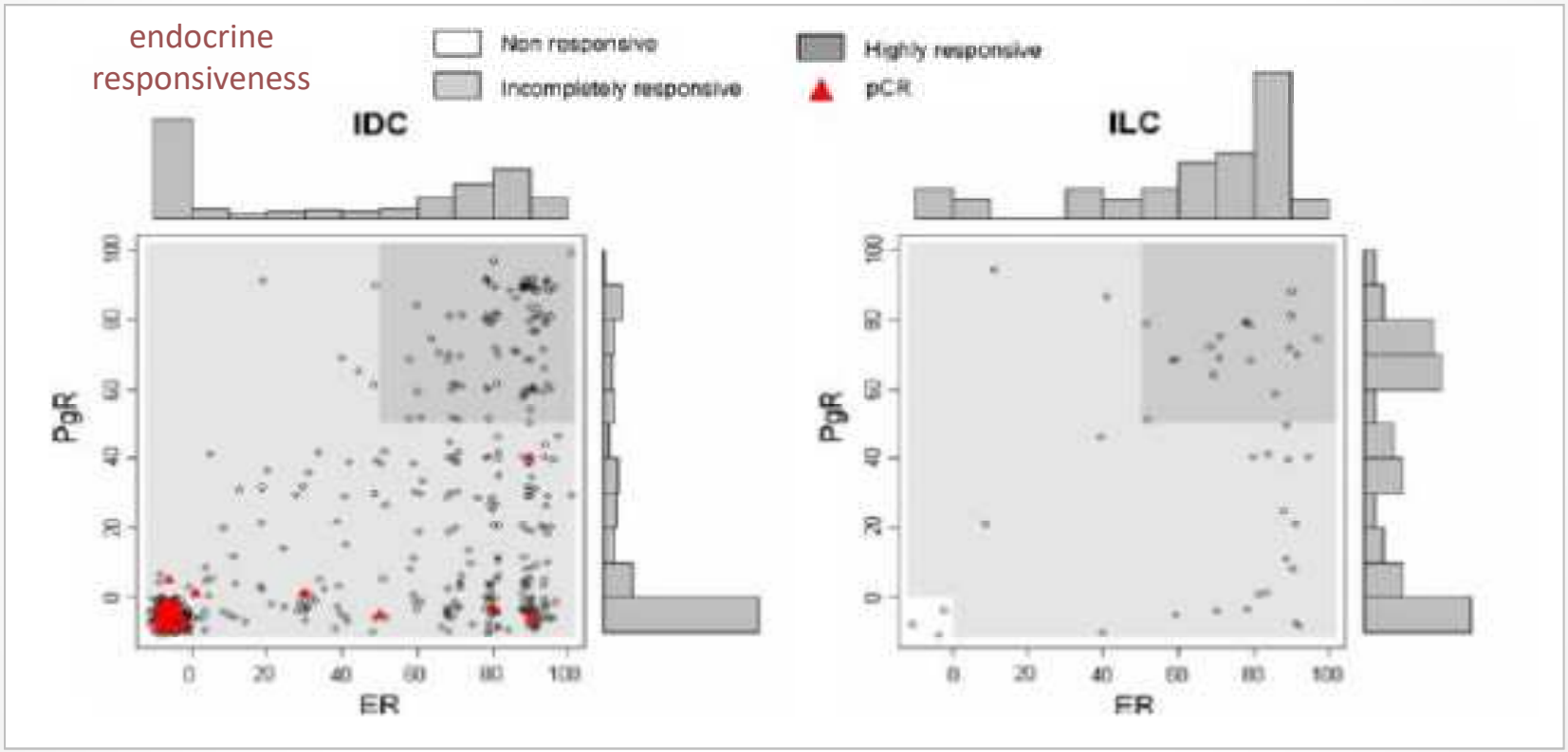




von Minckwitz, Lancet Oncol 2014; Loibl Ann Oncol 2018
Sikov JCO 2015; Sikov, SABCS 2015

Luminal breast cancer

Do luminal BC patients benefit from ChT?

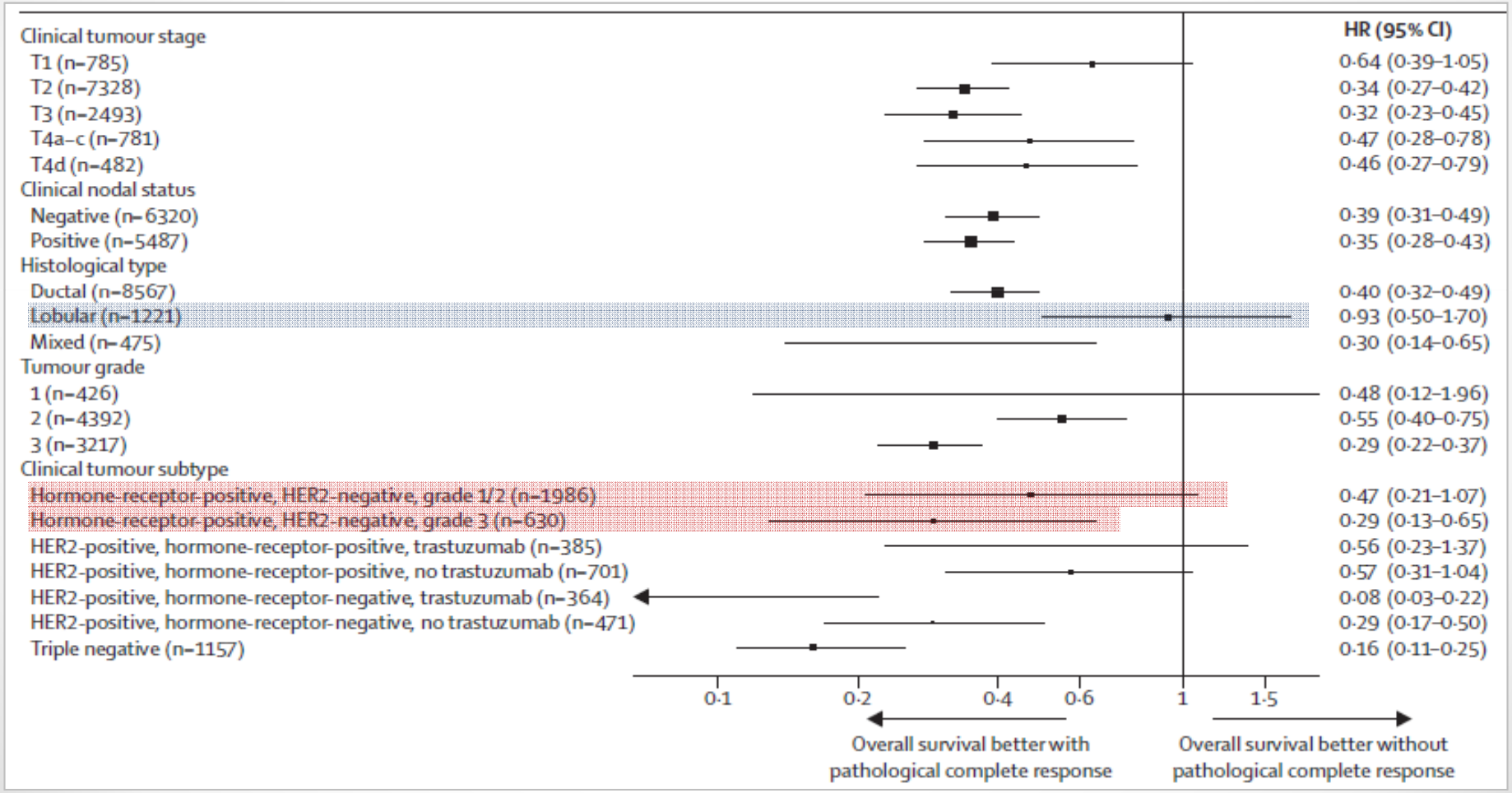


invasive ductal carcinoma

invasive lobular carcinoma

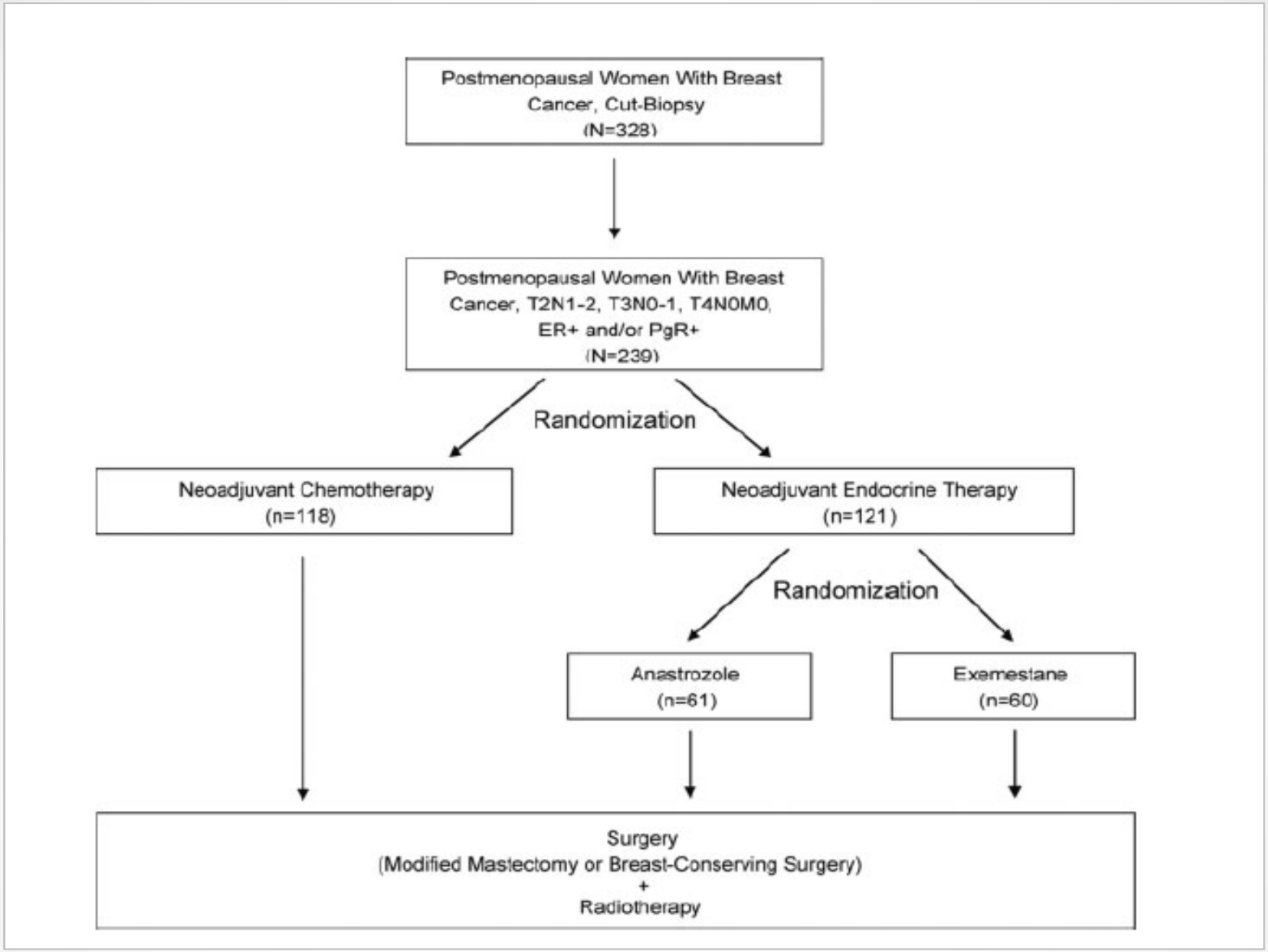
Colleoni, BCRT 2009

Is pCR really important in luminal BC?



Cortazar, Lancet 2014

so maybe endocrine therapy???



328 postmenopausal pts
st. IIB-III

Semiglazov, Cancer 2007

Primary Efficacy Results

Efficacy end point	Endocrine therapy, n=121 No. (%)	Chemotherapy, n=118 No. (%)	P
Clinical response, palpation	78 (64.5)	75 (63.6)	>.5
Complete response	12 (10)	12 (10)	>.5
Partial response	66 (55)	63 (53)	>.5

Overall Objective Response in Patients With High Levels of Estrogen Receptor Expression*

Response	Endocrine therapy, n=70 No. (%)	Chemotherapy, n=63 No. (%)	P
Clinical objective response	49 (70)	38 (60)	.068
Mammography	46 (66)	38 (60)	.088
Breast-conserving surgery	30 (43)	15 (24)	.054

*High levels of estrogen receptor expression are defined as ≥6 Allred score or ≥120 fmol/g.

Adverse Events Related to Treatment

Event	Endocrine therapy, n=121 No. (%)	Chemotherapy, n=118 No. (%)
Neutropenia (grade 2–4)	0	51 (43)
Febrile neutropenia	0	6 (5)
Infection (grade 2–3)	0	2 (2)
Stomatitis (grade 3)	0	8 (7)
Diarrhea	0	8 (7)
Neuropathy		
NCI CTCAE 2	0	35 (30)
NCI CTCAE 3	0	2 (2)
Alopecia	0	93 (79)
Cardiotoxicity (LVEF <50%)	0	8 (7)
Hot flushes (grade 2)	28 (23)	2 (2)
Fatigue (grade 2)	18 (15)	9 (8)
Vaginal bleeding	8 (7)	0
Arthralgia (grade 1–2)	8 (7)	2 (2)
Myalgia	6 (5)	2 (2)

Semiglazov, Cancer 2007

neoPAL

letrozole + palbociclib v. 3x FEC → 3x DXL

		LET PALBO (n=53)	CHEMO (n=53)
Best clinical response	**CR**	**16 (31,4%)**	**15 (30%)**
	PR	**22 (43,1%)**	**23 (46%)**
	SD	13 (25,5%)	12 (24%)
	NA	2	3
Breast surgery	Mastectomy	16 (30,8%)	16 (31,4%)
	Conserving surgery	**36 (69,2%)**	**35 (68,6%)**
	NA	1	2

Cottu, ESMO 2017

Neoadjuvant ET in postmenopausal patients

Trials profile				Study population	Outcomes		
Trial (reference)	Treatment arm (n)	Phase	Duration	Characteristics of populations	Primary endpoint	OR	Downstaging to BCS
P024 [13]	A: Letrozole (162) B: Tamoxifen (175)	IIb–III	4 months	ER+ and/or PgR+ ≥10% Postmenopausal Staging: T2-4a-c, N0-2, M0[α]	OR by clinical palpation	A: 55% B: 36% P < 0.001[#]	A: 45% B: 35% P = 0.022
IMPACT [14]	A: Anastrazole (113) B: Tamoxifen (108) C: Tamoxifen + anastrazole (109)	III	12 weeks	ER staining ≥1% Postmenopausal Operable or potentially operable BC[β]	OR by caliper	A: 37% B: 36% C: 39%	A: 44% B: 31% C: 24% P = 0.23
PROACT [15]	A: Anastrozole (228) B: Tamoxifen (223)	III	3 months	ER+ and/or PgR+ Postmenopausal Operable or potentially BC[γ]	OR by ultrasound	A: 39.5% B: 35.4%	A: 43.0%* B: 30.8%* P = 0.04
Russian trial [20]	A: Exemestane (76) B: Tamoxifen (75)	NA	3 months	ER+ and/or PgR+ Postmenopausal T2-4, N0-2, M0	OR by clinical palpation	A: 76.3% B: 40.0% P = 0.05	A: 36.8% B: 20.0% P = 0.05

Barroso-Sousa, Ecancermedicalscience 2016

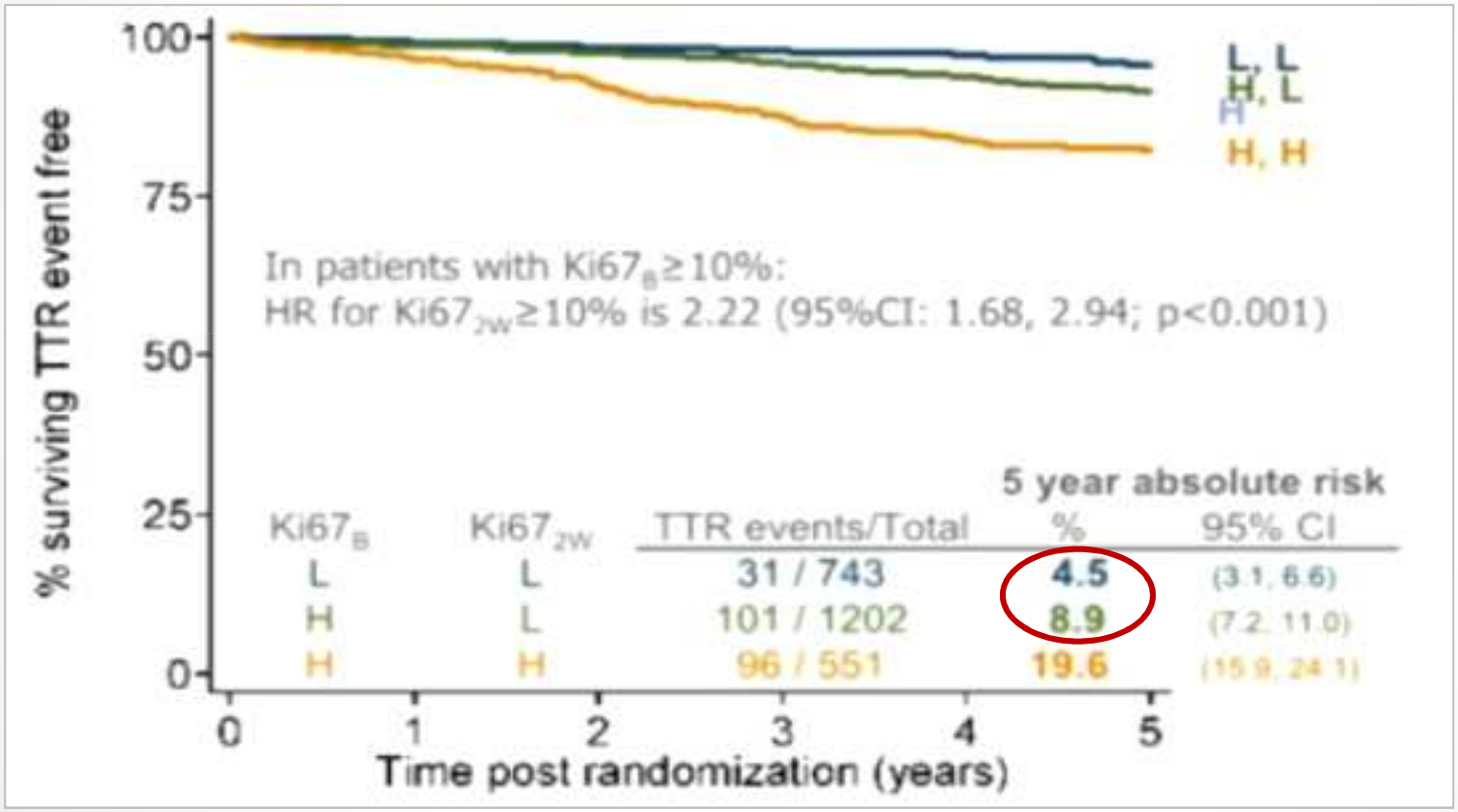
Neoadjuvant ET in premenopausal patients

	Anastrozole plus goserelin (n=98)	Tamoxifen plus goserelin (n=99)
Best overall tumour response		
Calliper*		
CR	12 (12·2%)	7 (7·1%)
PR	57 (58·2%)	43 (43·4%)
CR+PR	69 (70·4%)	50 (50·5%)
Ultrasound†		
CR	1 (1·0%)	0
PR	56 (57·1%)	42 (42·4%)
CR+PR	57 (58·2%)	42 (42·4%)
MRI or CT‡		
CR	2 (2·0%)	0
PR	61 (62·2%)	37 (37·4%)
CR+PR	63 (64·3%)	37 (37·4%)
Histopathological response§		
Grade 0 (no response)	12 (12·2%)	19 (19·2%)
Grade 1a (mild response)	42 (42·9%)	44 (44·4%)
Grade 1b (moderate response)	28 (28·6%)	18 (18·2%)
Grade 2 (marked response)	12 (12·2%)	9 (9·1%)
Grade 3 (complete response)	1 (1·0%)	0
Missing	3 (3·1%)	9 (9·1%)
Grade ≥1b	41 (41·8%)	27 (27·3%)

Masuda, Lancet Oncol 2012

How to predict the efficacy of NET???

POETIC



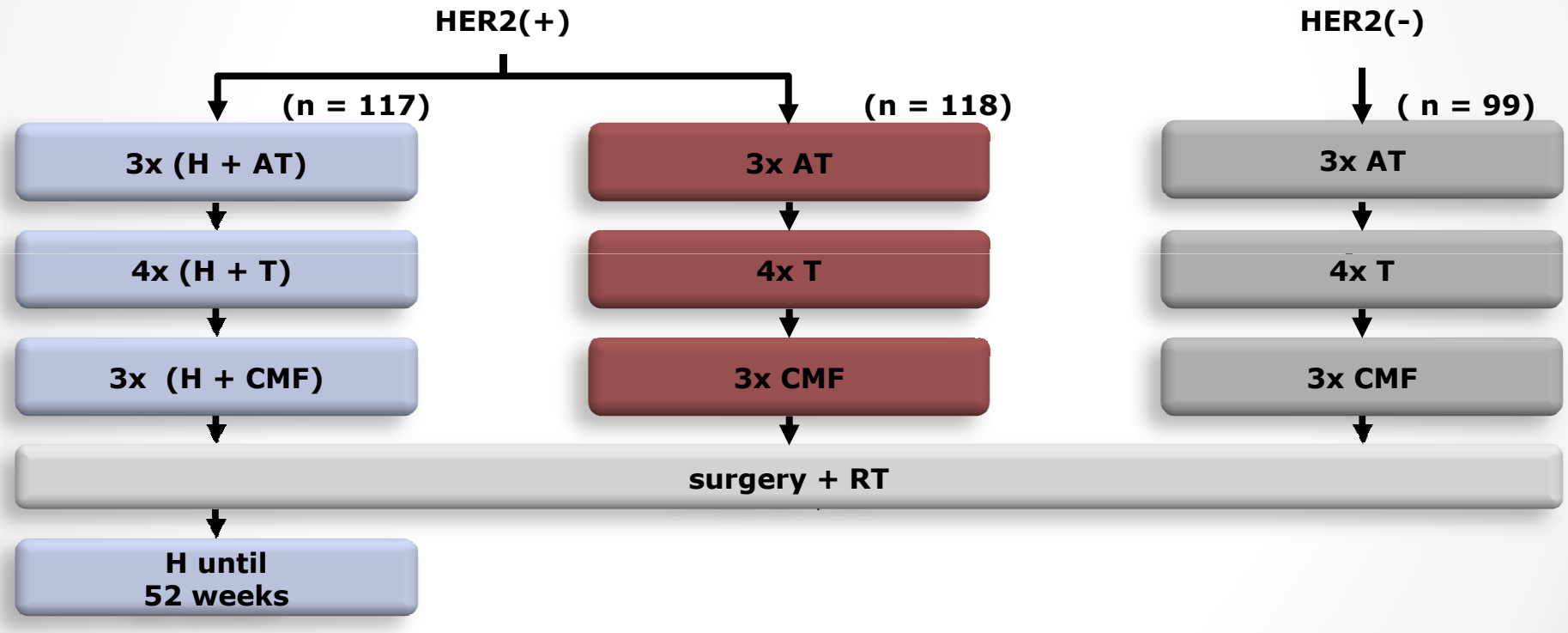
tumor Ki67 expression

4486 postmenopausal ER/PgR (+) BC

HER2+ breast cancer

Preoperative trastuzumab

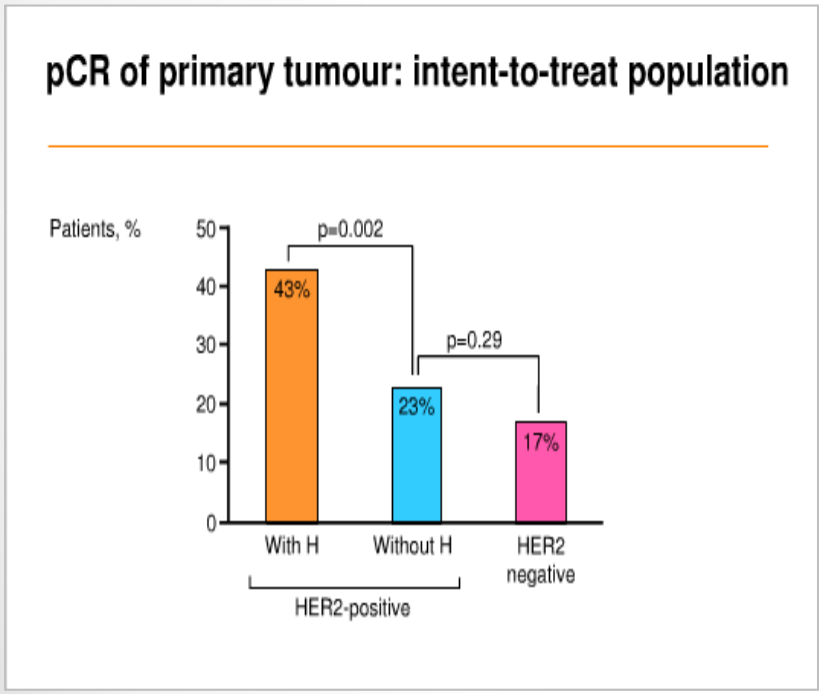
NOAH

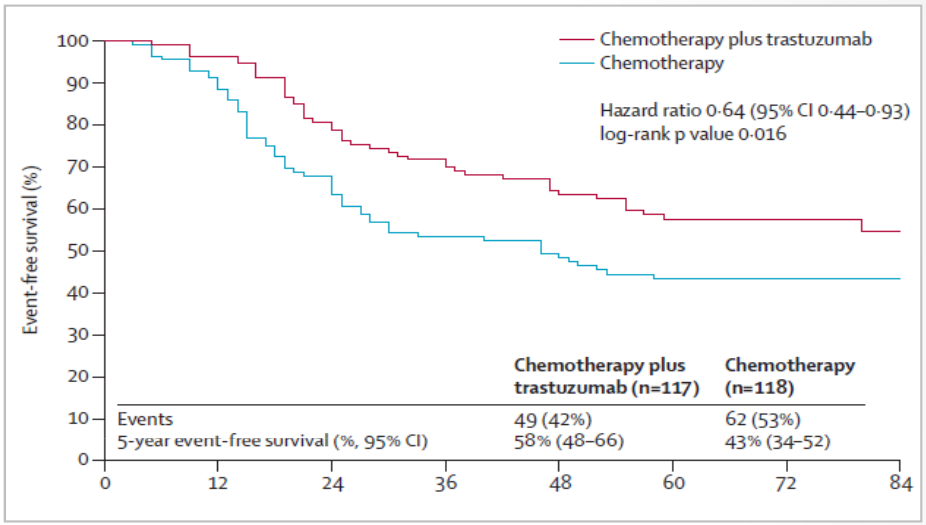


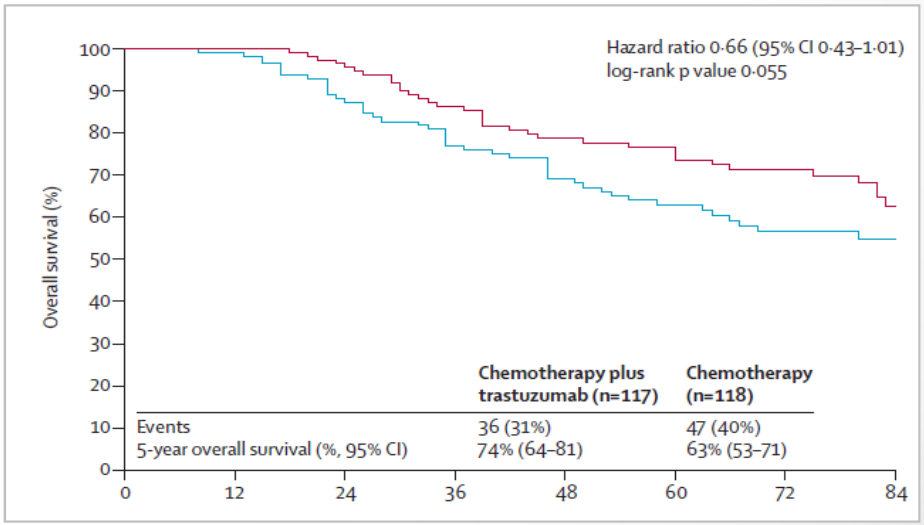
Gianni, Lancet Oncol 2014

Preoperative trastuzumab

NOAH



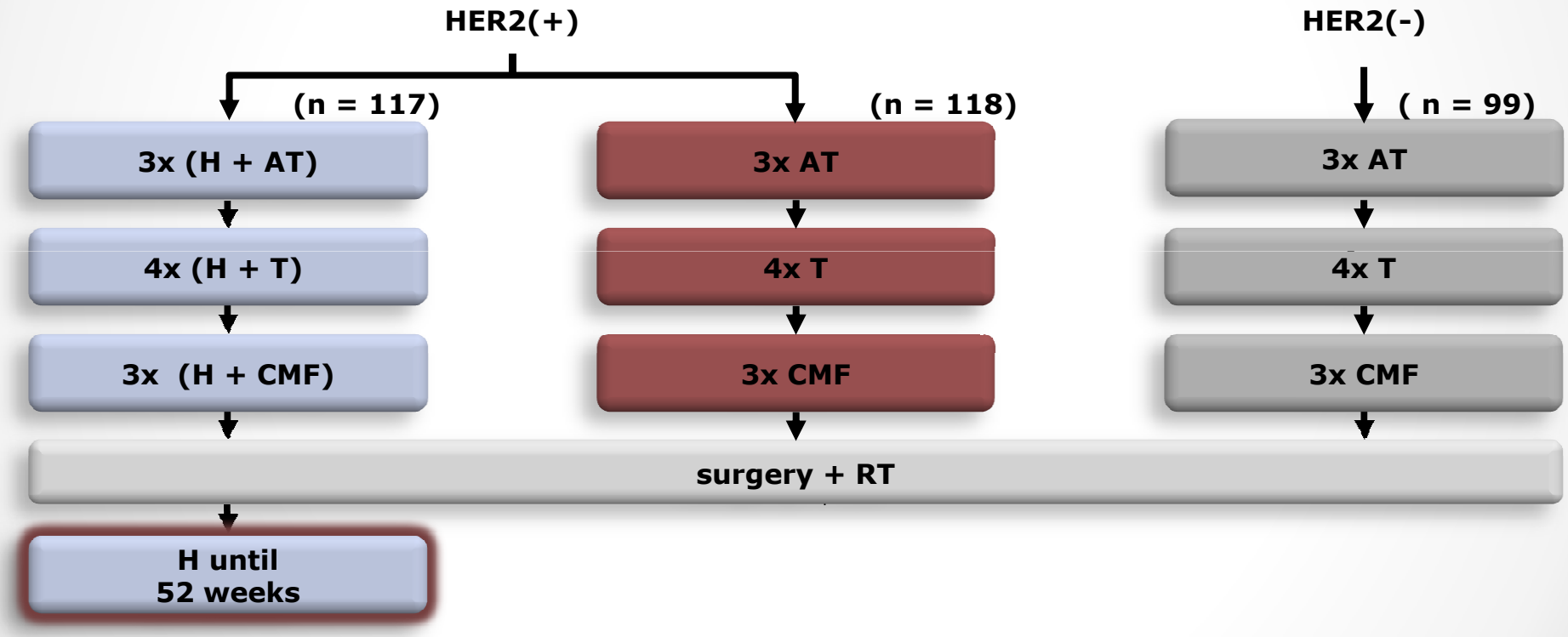




Gianni, Lancet Oncol 2014

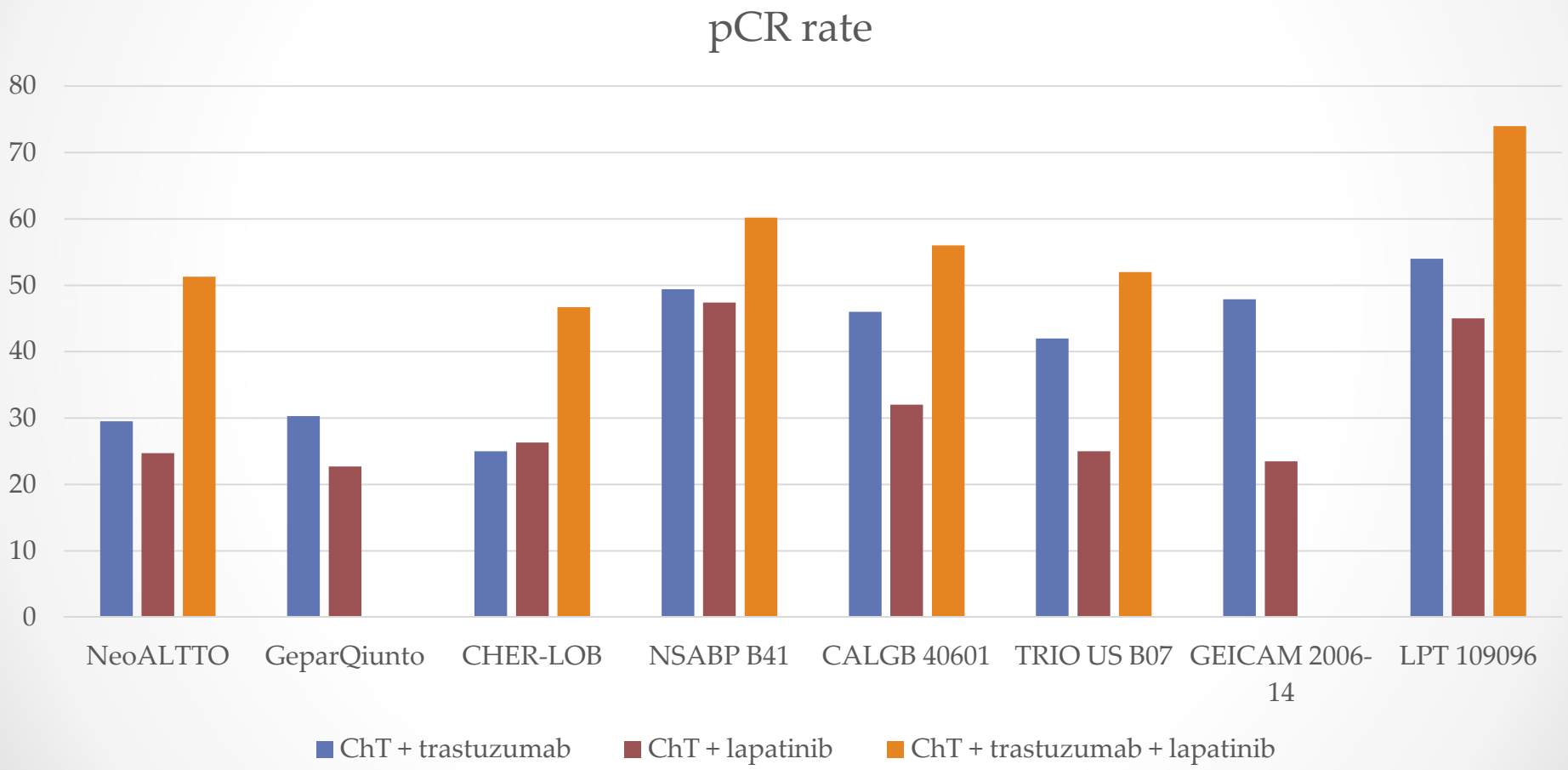
Preoperative trastuzumab

NOAH



Gianni, Lancet Oncol 2014

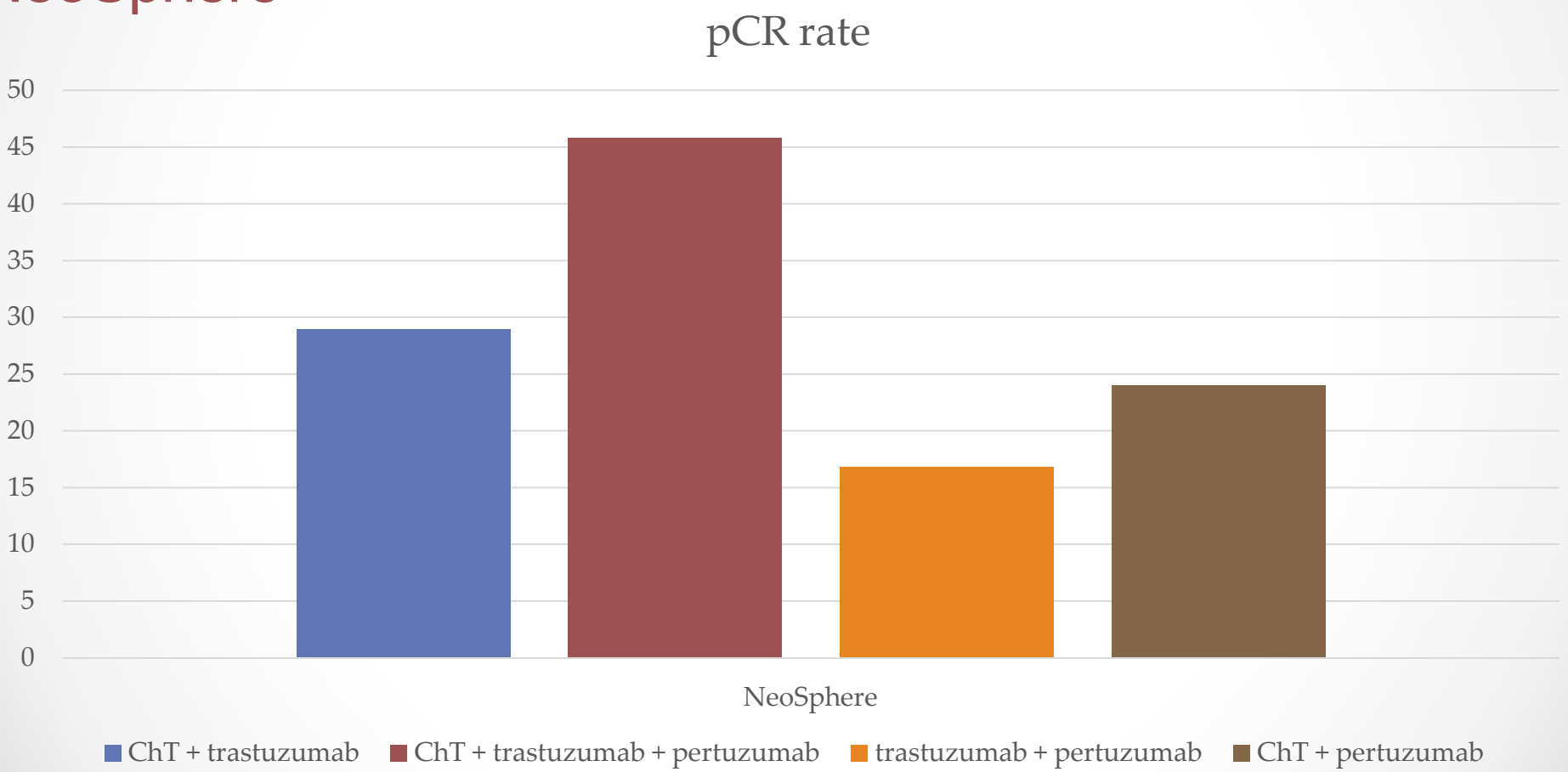
Dual blockade – trastuzumab + lapatinib



Loibl, Lancet 2017

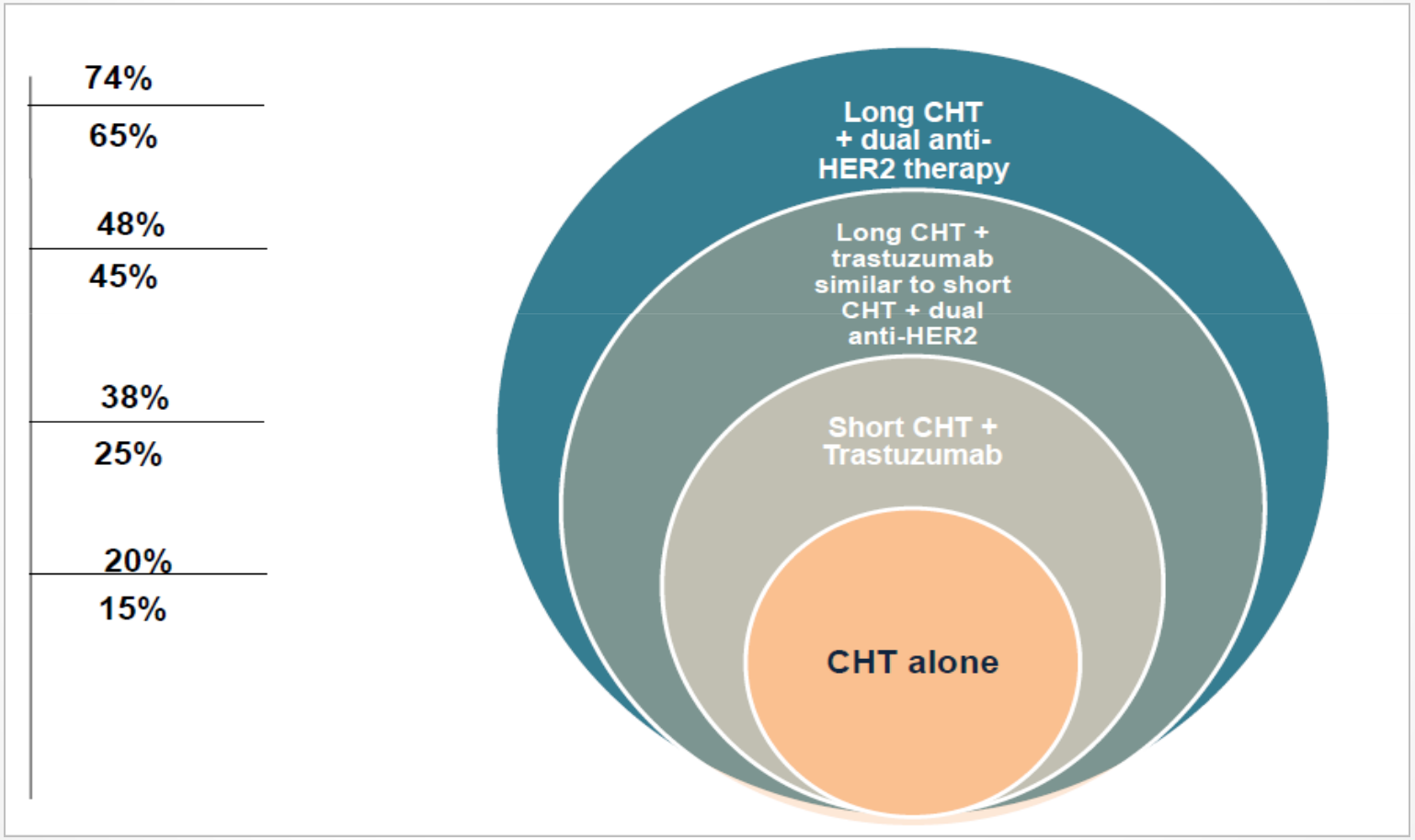
Dual blockade – trastuzumab + pertuzumab

NeoSphere



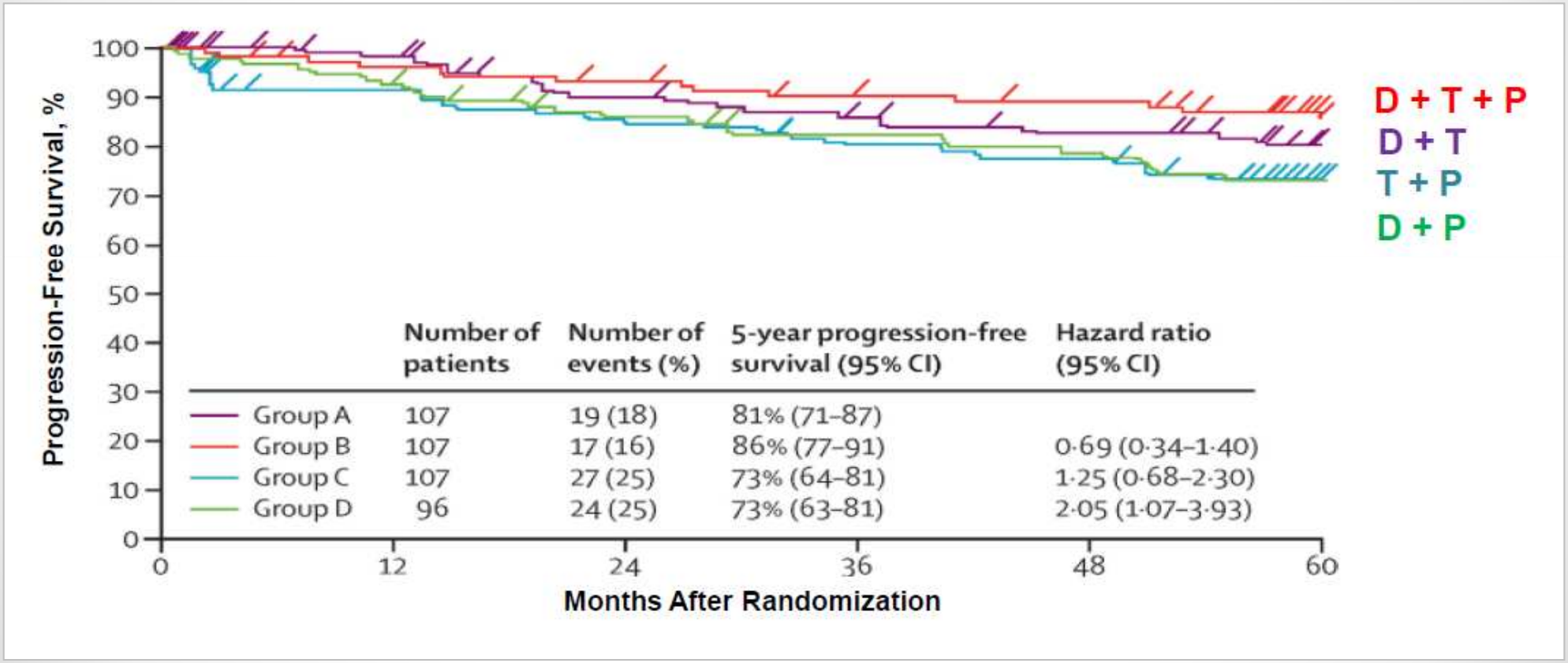
Gianni, Lancet Oncol 2012

pCR in HER2+ breast cancer



Loibl, Curr Opin Obstet Gynecol 2015

Dual blockade – trastuzumab + pertuzumab

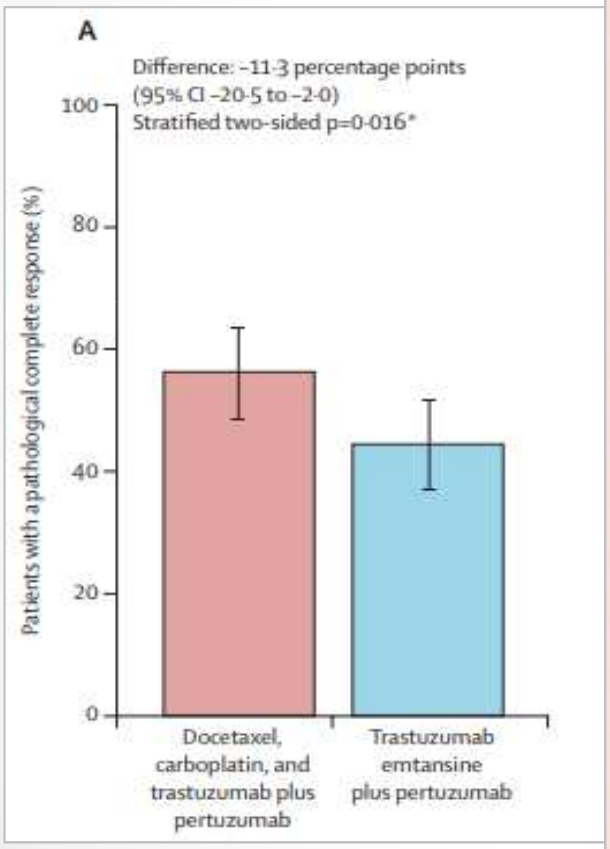


	Number of patients	Number of events (%)	5-year progression-free survival (95% CI)	Hazard ratio (95% CI)
Group A	107	19 (18)	81% (71–87)	
Group B	107	17 (16)	86% (77–91)	0·69 (0·34–1·40)
Group C	107	27 (25)	73% (64–81)	1·25 (0·68–2·30)
Group D	96	24 (25)	73% (63–81)	2·05 (1·07–3·93)

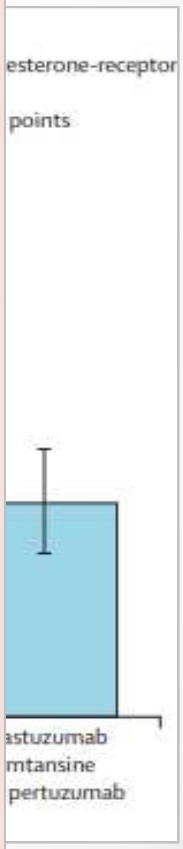
Gianni, Lancet Oncol 2016

Can we de-escalate???

KRISTINE



	Trastuzumab emtansine plus pertuzumab (n=223)			Docetaxel, carboplatin, and trastuzumab plus pertuzumab (n=219)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Nausea	76 (34%)	0	0	125 (57%)	3 (1%)	0
Diarrhoea	72 (32%)	2 (<1%)	0	128 (58%)	32 (15%)	1 (<1%)
Fatigue	62 (28%)	3 (1%)	0	81 (37%)	7 (3%)	0
Headache	51 (23%)	1 (<1%)	0	27 (12%)	1 (<1%)	0
Alanine aminotransferase increased	45 (20%)	3 (1%)	0	18 (8%)	4 (2%)	0
Aspartate aminotransferase increased	32 (14%)	1 (<1%)	0	16 (7%)	1 (<1%)	0
Asthenia	31 (14%)	0	0	49 (22%)	6 (3%)	0
Rash	30 (14%)	0	0	48 (22%)	1 (<1%)	0
Epistaxis	29 (13%)	1 (<1%)	0	23 (11%)	0	0
Dysgeusia	22 (10%)	0	0	43 (20%)	0	0
Pyrexia	22 (10%)	0	0	26 (12%)	2 (<1%)	0
Vomiting	17 (8%)	1 (<1%)	0	61 (28%)	7 (3%)	0
Constipation	15 (7%)	0	0	37 (17%)	0	0
Dizziness	15 (7%)	0	0	18 (8%)	1 (<1%)	0
Decreased appetite	14 (6%)	0	0	32 (15%)	3 (1%)	0
Stomatitis	14 (6%)	0	0	47 (22%)	1 (<1%)	0
Abdominal pain	13 (6%)	1 (<1%)	0	26 (12%)	2 (<1%)	0
Anaemia	13 (6%)	2 (<1%)	0	54 (25%)	21 (10%)	0
Mucosal inflammation	10 (5%)	0	0	28 (13%)	1 (<1%)	0
Hypertension	8 (4%)	1 (<1%)	0	7 (3%)	7 (3%)	0
Peripheral sensory neuropathy	8 (4%)	1 (<1%)	0	18 (8%)	0	0
Upper respiratory tract infection	8 (4%)	0	0	7 (3%)	1 (<1%)	0
Anxiety	7 (3%)	0	0	9 (4%)	1 (<1%)	0
Neuropathy peripheral	7 (3%)	0	1 (<1%)	20 (9%)	1 (<1%)	0
Thrombocytopenia	7 (3%)	0	1 (<1%)	18 (8%)	3 (1%)	1 (<1%)
Weight decreased	7 (3%)	0	0	18 (8%)	1 (<1%)	0
Back pain	6 (3%)	1 (<1%)	0	12 (6%)	0	0
Platelet count decreased	6 (3%)	2 (<1%)	1 (<1%)	16 (7%)	9 (4%)	2 (<1%)
Alopecia	4 (2%)	0	0	138 (63%)	2 (<1%)	0

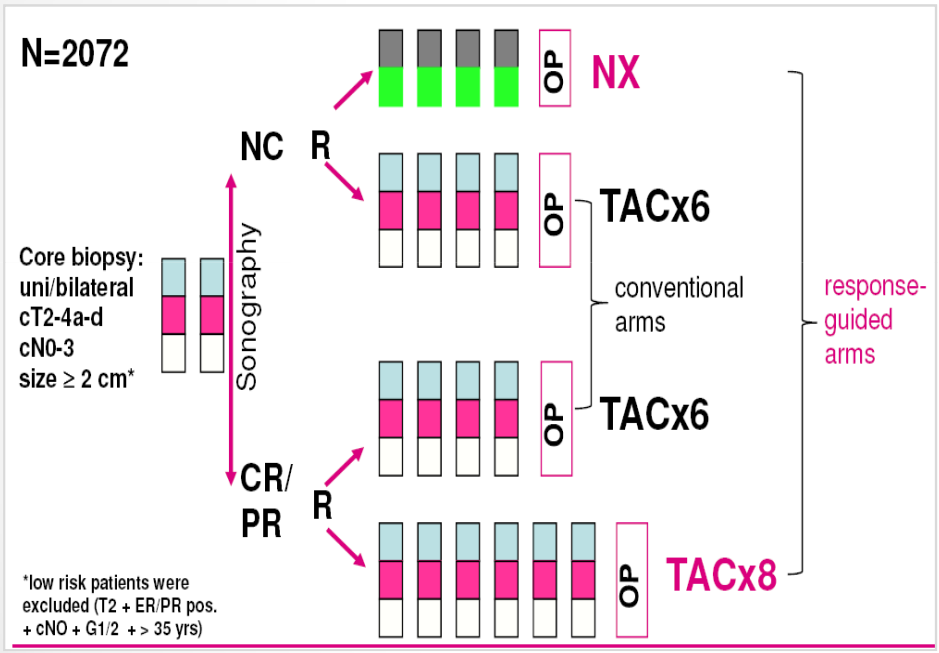


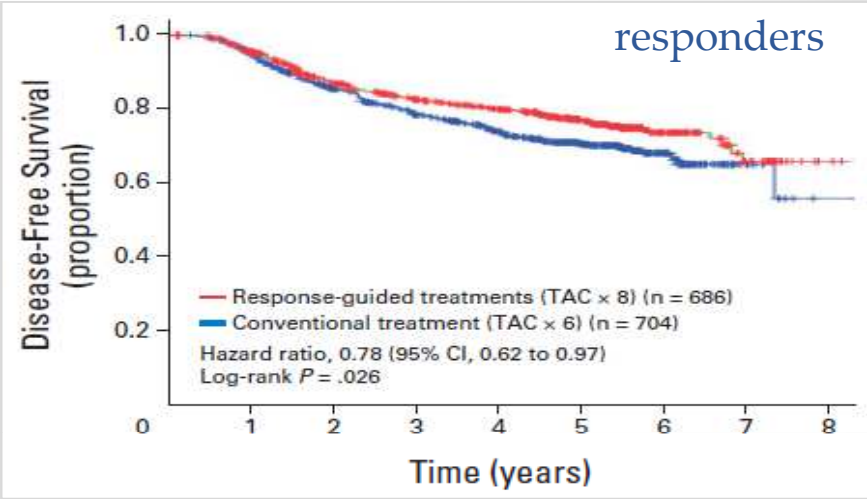
Hurvitz, Lancet Oncol 2018

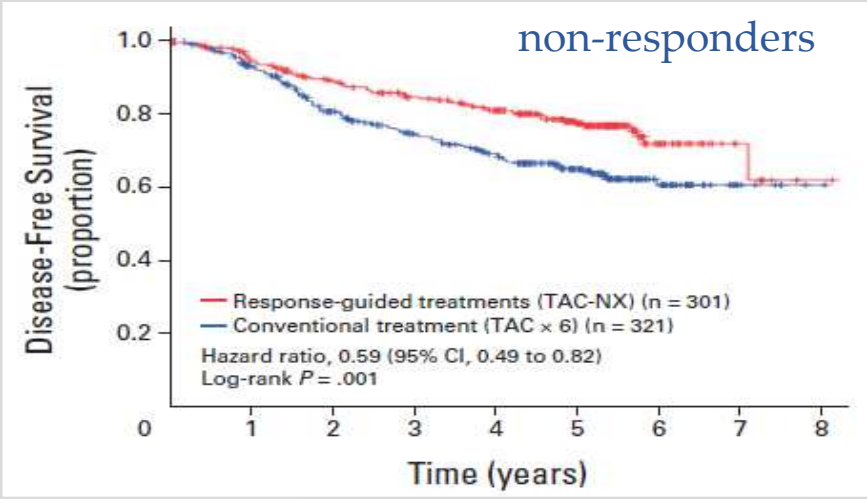
Can we improve the outcome in poor responders???

Response guided treatment????

GeparTrio

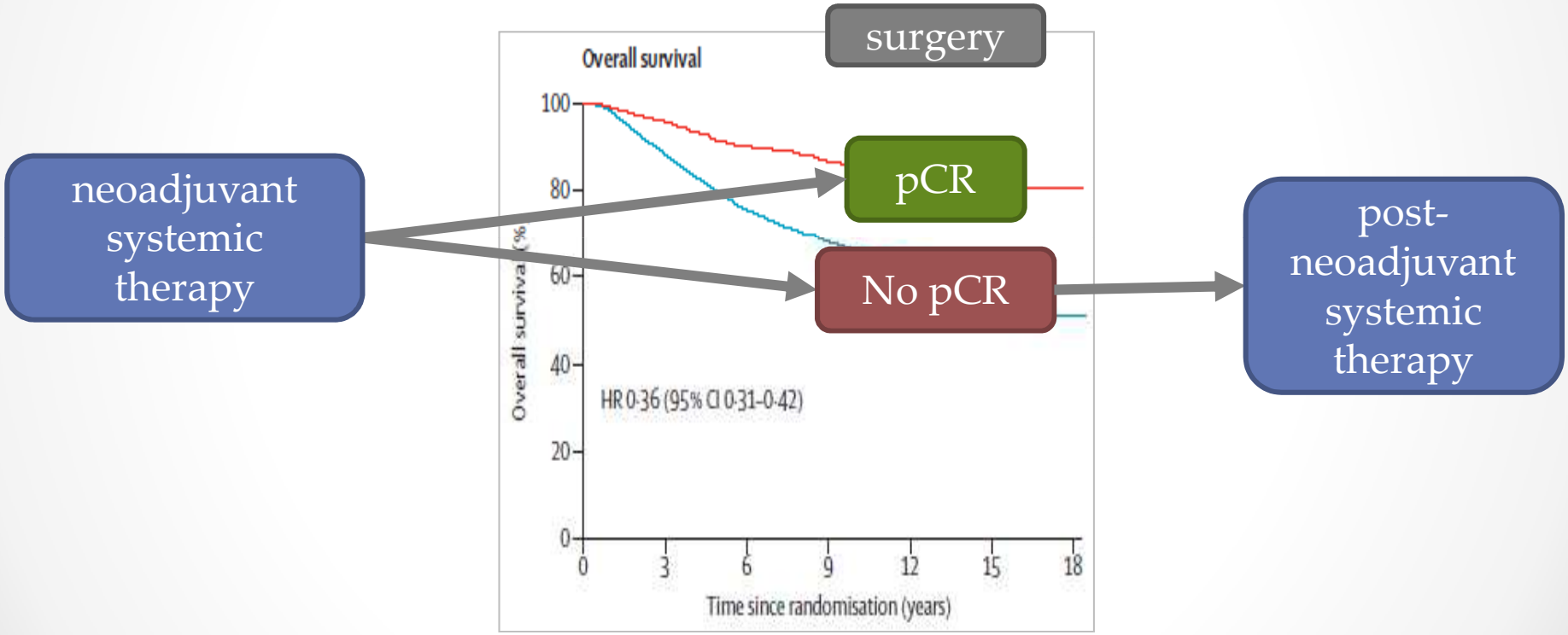




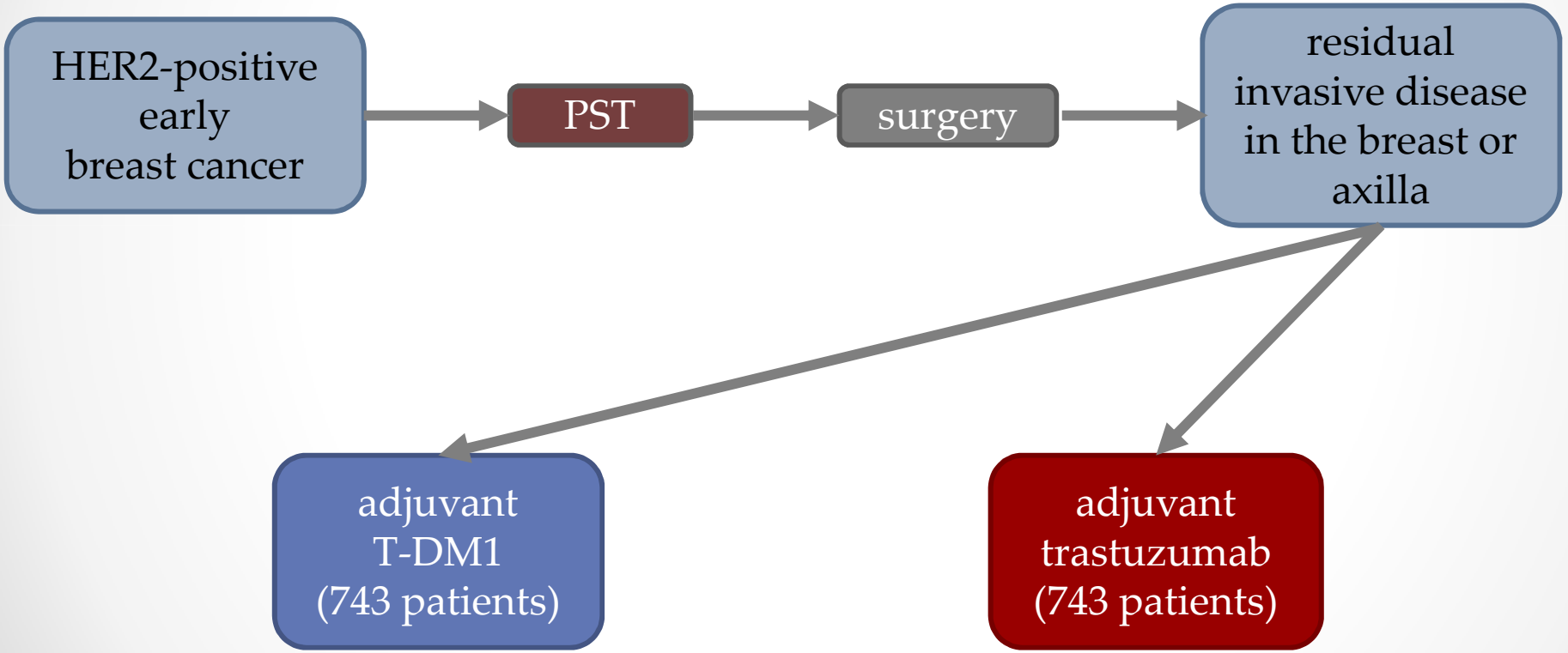


von Minckwitz, JCO 2013

Concept of post-neoadjuvant therapy

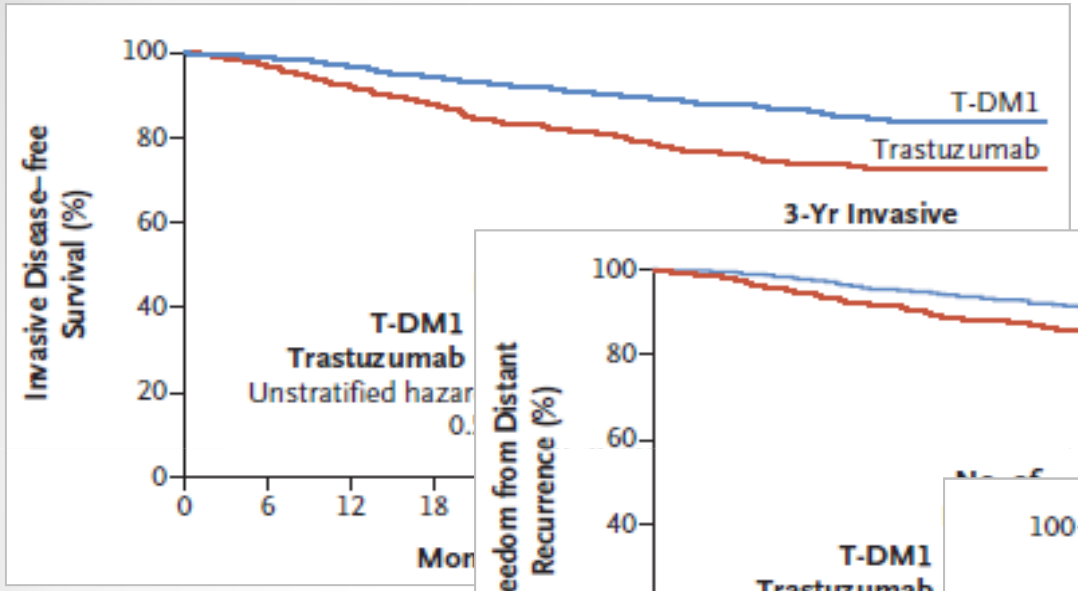


KATHERINE

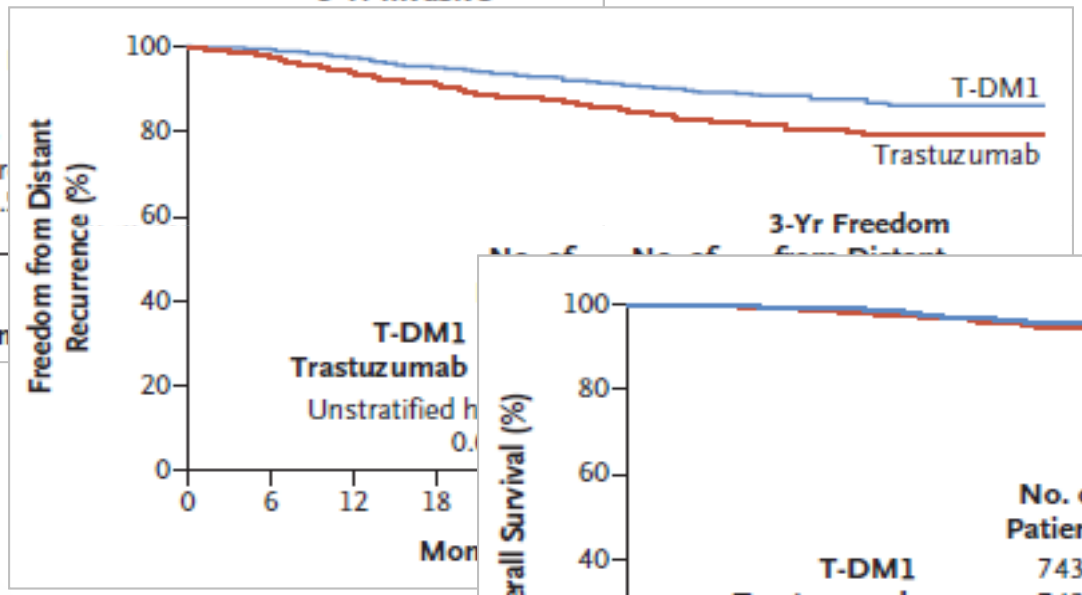


von Minckwitz, NEJM 2018

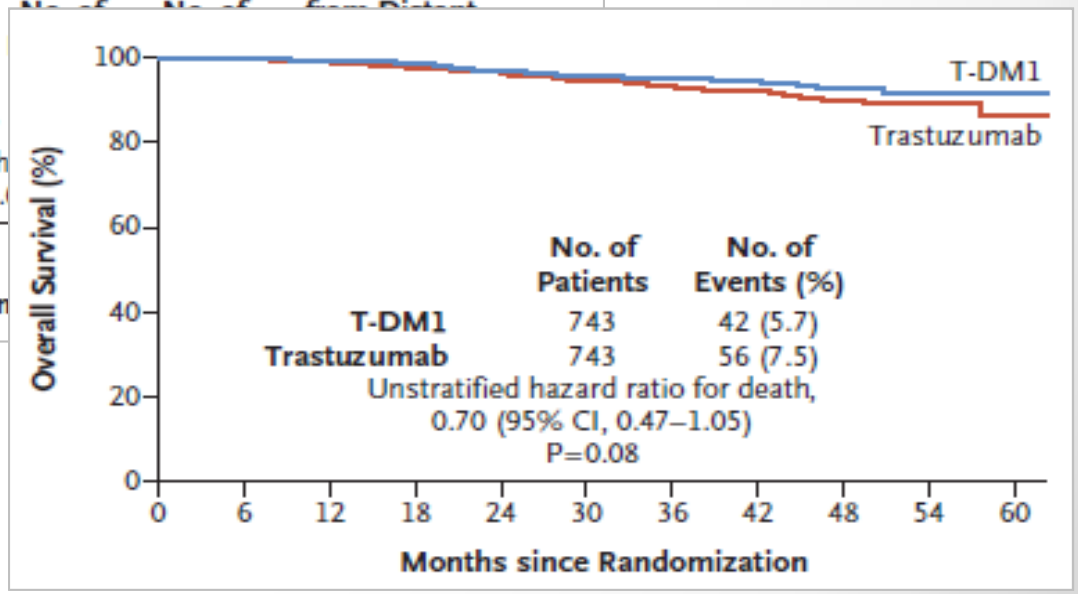
KATHERINE



iDFS



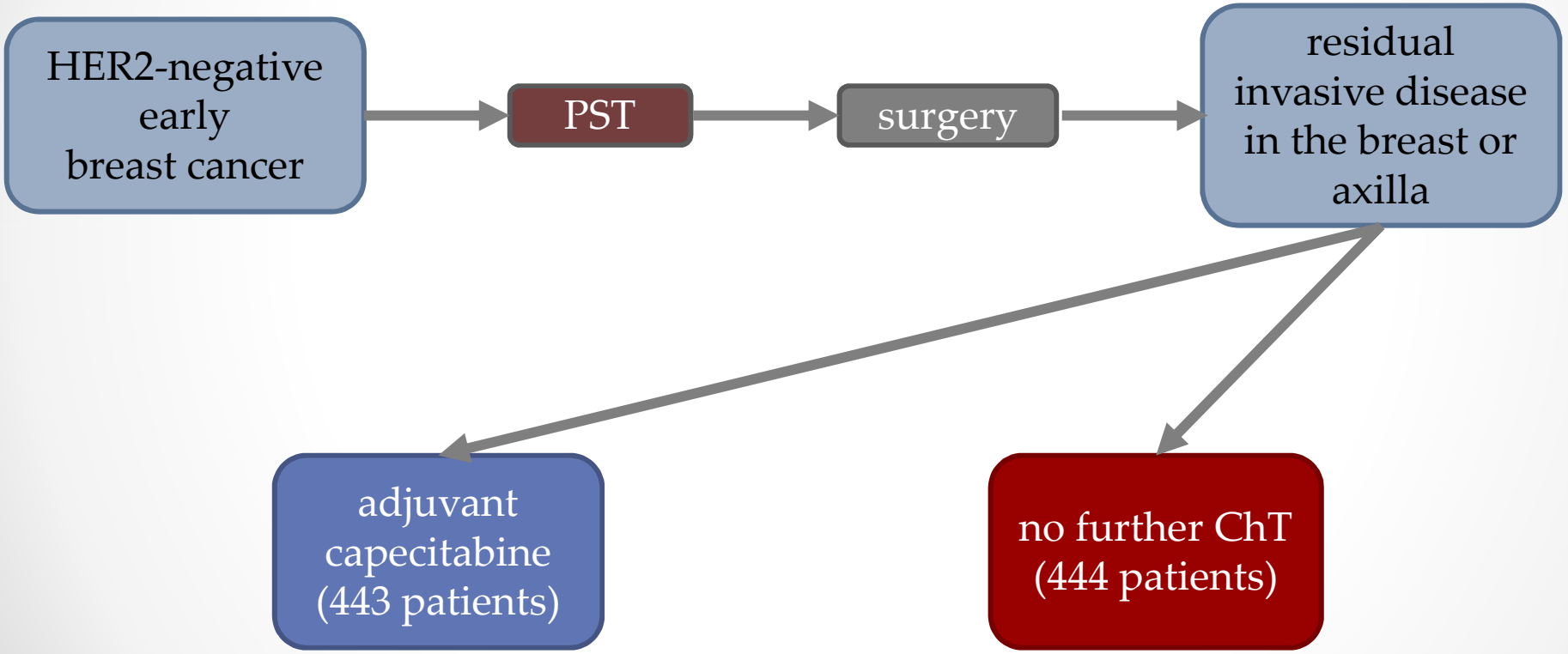
freedom from distant recurrence



OS

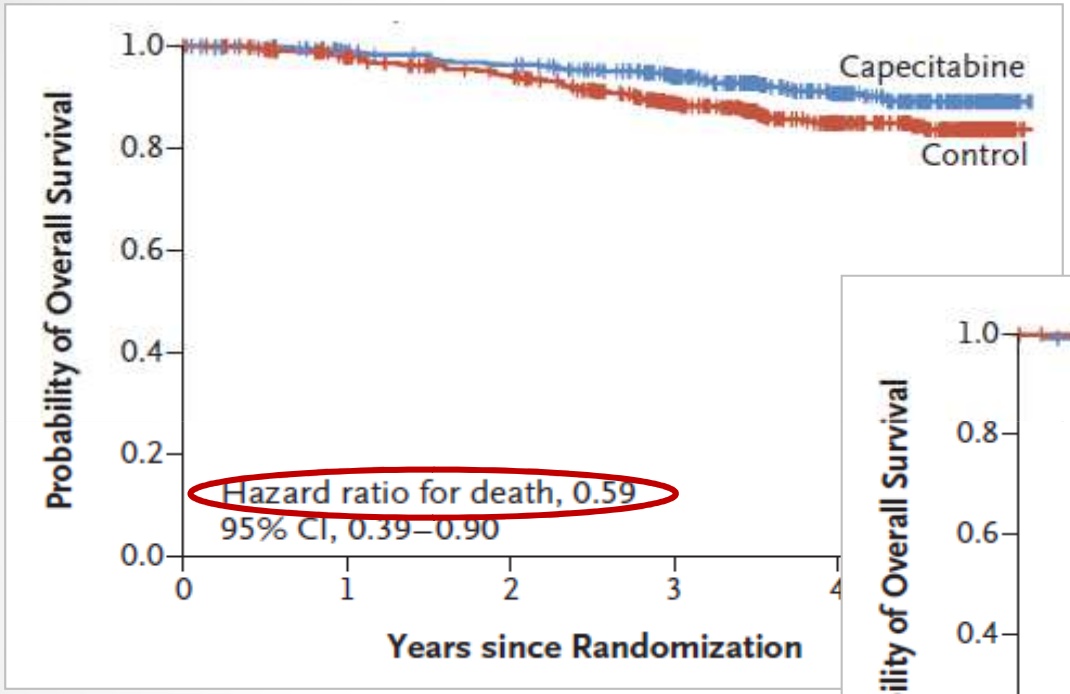
von Minckwitz, NEJM 2018

CREATE-X

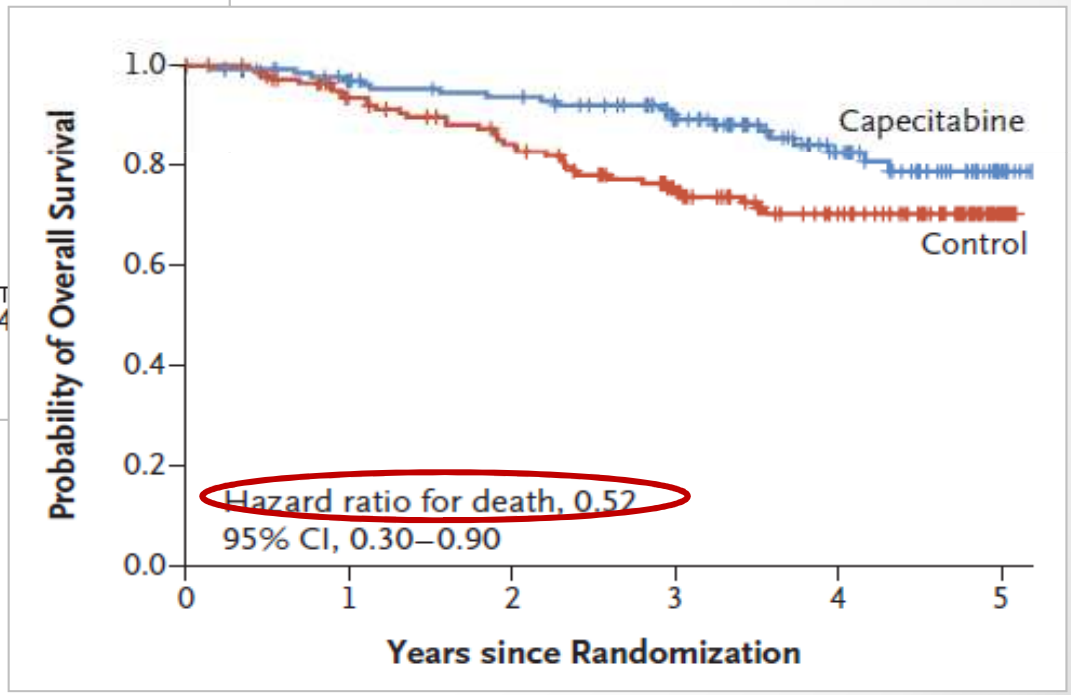


Masuda, NEJM 2017

CREATE-X



all patients



TNBC

Masuda, NEJM 2017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TOGETHER
433
TOGETHER
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