Neoadjuvant therapy for ER-positive breast cancers

M. Colleoni

International Breast Cancer Study Group (IBCSG),

Research Unit in Medical Senology,

European Institute of Oncology

Marco Colleoni has no relevant financial relationships to disclose

Neoadjuvant therapy for ER-positive breast cancers

Primary goals –treatment choice for women with early breast cancer:

- Integrate tumor biology and tumor extent into an estimate of responsiveness to treatment and outcome
- Utilize tumor biology, host biology and disease extension to obtain an optimal management strategy

Neoadjuvant therapy for ER-positive breast cancers

Trials are conducted to compare treatments

Often the results indicate that one treatment is better than the other, on average…

Degree of consensus on the specific treatment to use for "niches" of patients or the individual patient is low…

Limits of studies focusing on Neoadjuvant therapy for ER-positive breast cancers

Studies designed in an era when preoperative therapies were prescribed according to stage

Different cut-off and methodology in the definition of predictive features

Reliable histopathological assessment (P024 study: on central laboratory ER testing 12% of patients had ER- tumors)

Different adjuvant treatments

Studies not enough powered for the outcome questions

Follow-up too short (Patients with endocrine responsive disease continue to relapse after several years of diagnosis)

Questions to be debated

- End points (pCR, Ki67, PEPI score)
- Patterns requiring chemotherapy
- Genomic signatures
- Selection of treatment according to subtypes
- Duration
- Endocrine therapy for premenopausal pts with ER+ disease
- Endocrine therapy for postmenopausal pts with ER+ disease
- Combination with Targeted agents
- Concurrent chemo-endocrine therapy
- Luminal “special type”

Pathological Complete Response (pCR)

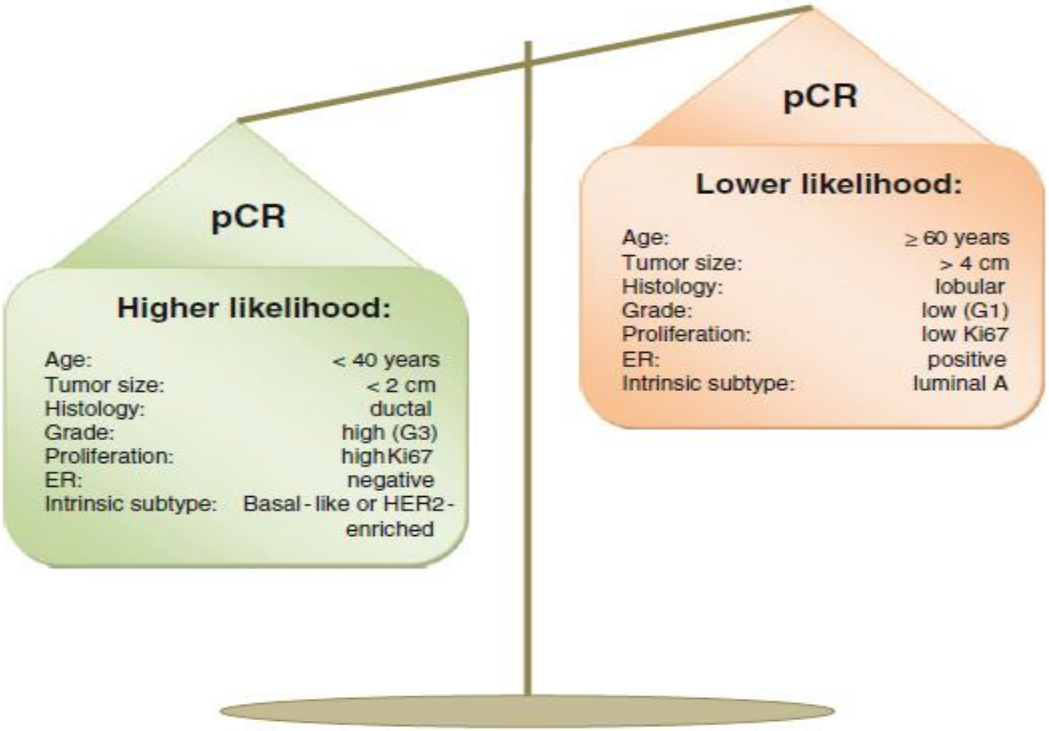
The definition of pCR should be based on histopathologic assessment, including absence of invasive cancer in both breast and lymph nodes

Patients with complete response in the breast but positive lymph nodes in the axilla have a far worse prognosis than patients with true pCR

The presence, extent, and classification of ductal carcinoma-in situ (DCIS) should be reported separately

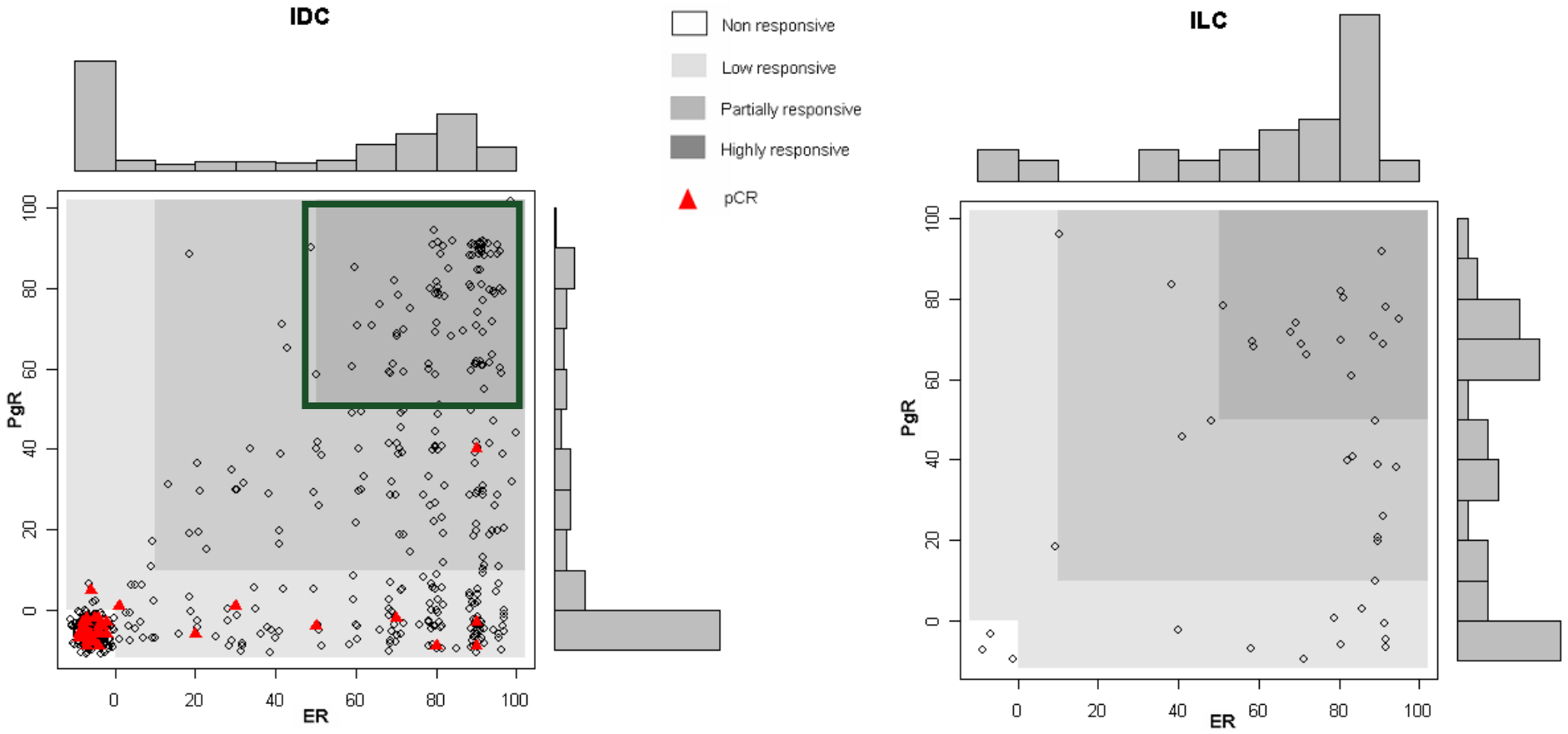
Ann Surg Oncol 2012; 19:1508-16

Likelihood of pCR in Neoadjuvant chemotherapy



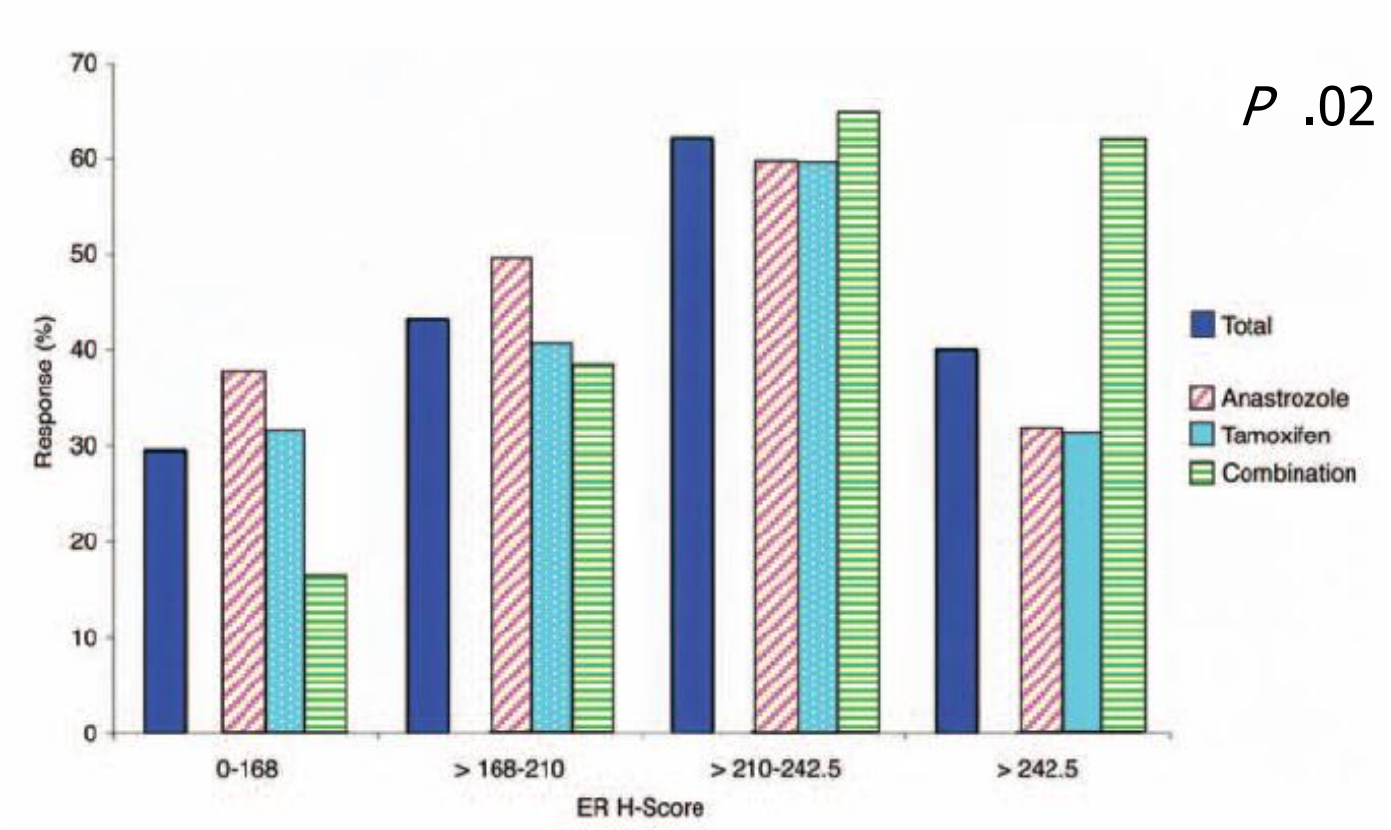
Ann Surg Oncol 2012;19:1508-16

Neoadjuvant Chemotherapy: degree of endocrine responsiveness and pCR



Breast Cancer Res Treat 2009; 116:359–369

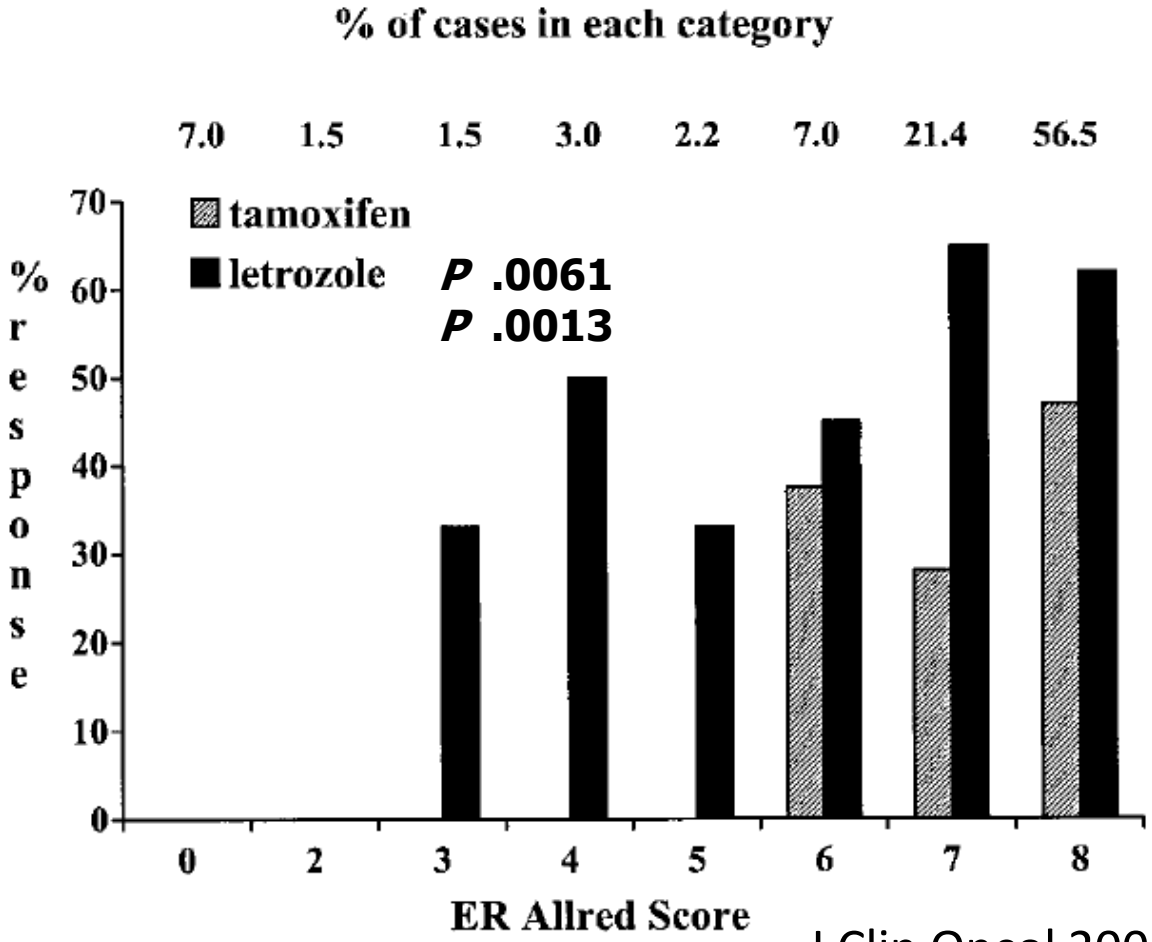
IMPACT study: Objective response rate versus ER H score, by quartiles



P .02

J Clin Oncol 2005; 23:5108-5116

P024 study Clinical response rate versus ER Allred score



J Clin Oncol 2001; 19:3808-3816

pCR: a reliable marker of outcome?

pCR after preoperative chemotherapy has been shown to correlate with survival

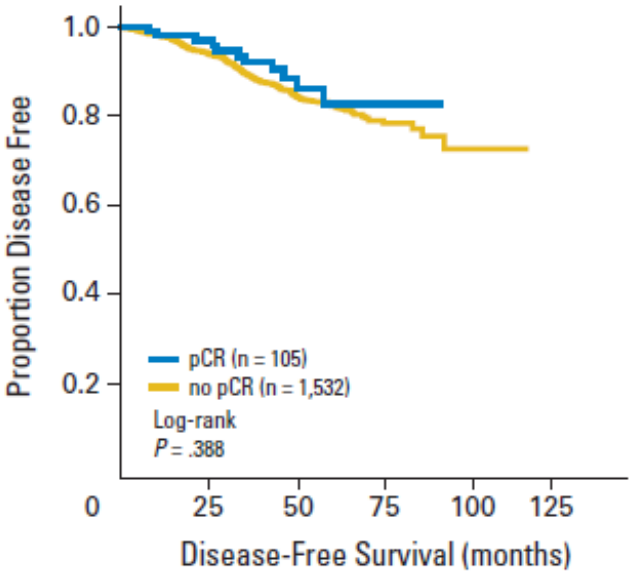
An optimal definition of pCR (including axillary nodal status) is critical

Pathologist Challenge

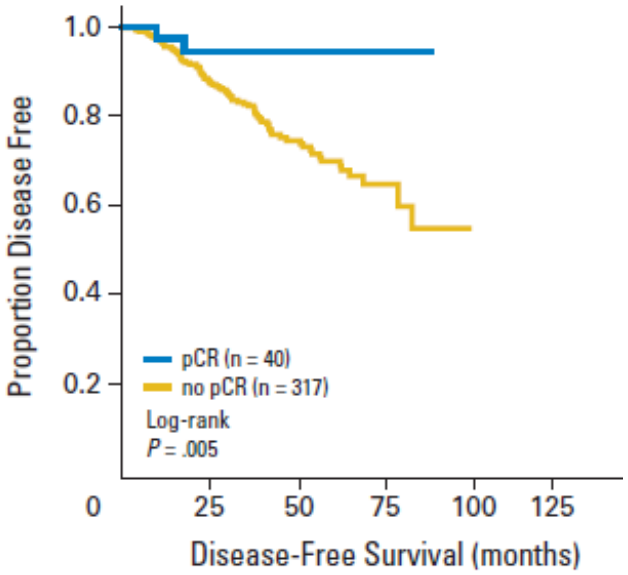
Relationship not perfect with the outcome of interest (DFS, OS); it can depend on both tumor subtype and specific therapy

Prognostic impact of pCR on DFS according to breast cancer intrinsic subtype

Luminal A–like tumors.
ER positive and/or PgR positive, HER2 negative, grade 1 or 2



Luminal B/HER2-negative–like tumors.
ER positive and/or PgR positive, HER2 negative, grade 3



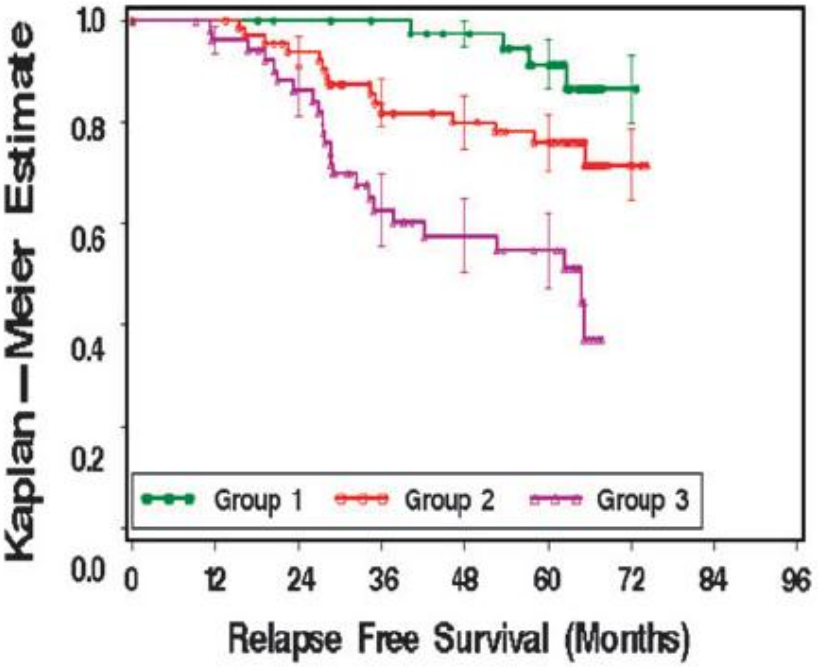
J Clin Oncol 2012; 30:1796-1804

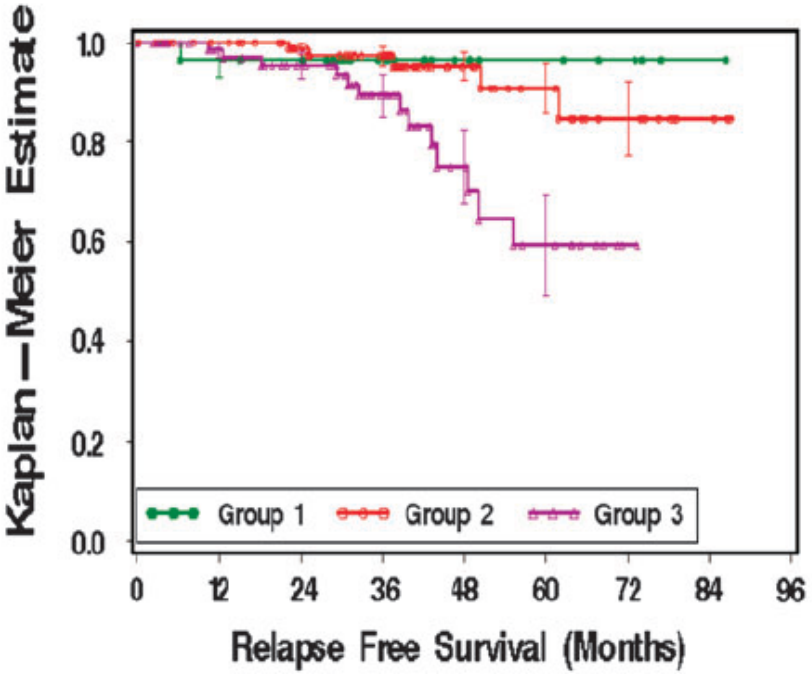
The preoperative endocrine prognostic index (PEPI)

Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Pathological tumor size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0%–2.7% (0–1†)	—	0	—	0
>2.7%–7.3% (1–2†)	1.3	1	1.4	1
>7.3%–19.7% (2–3†)	1.7	1	2.0	2
>19.7%–53.1% (3–4†)	2.2	2	2.7	3
>53.1% (>4†)	2.9	3	3.8	3
ER status, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0

J Natl Cancer Inst 2008; 100: 1380 – 1388

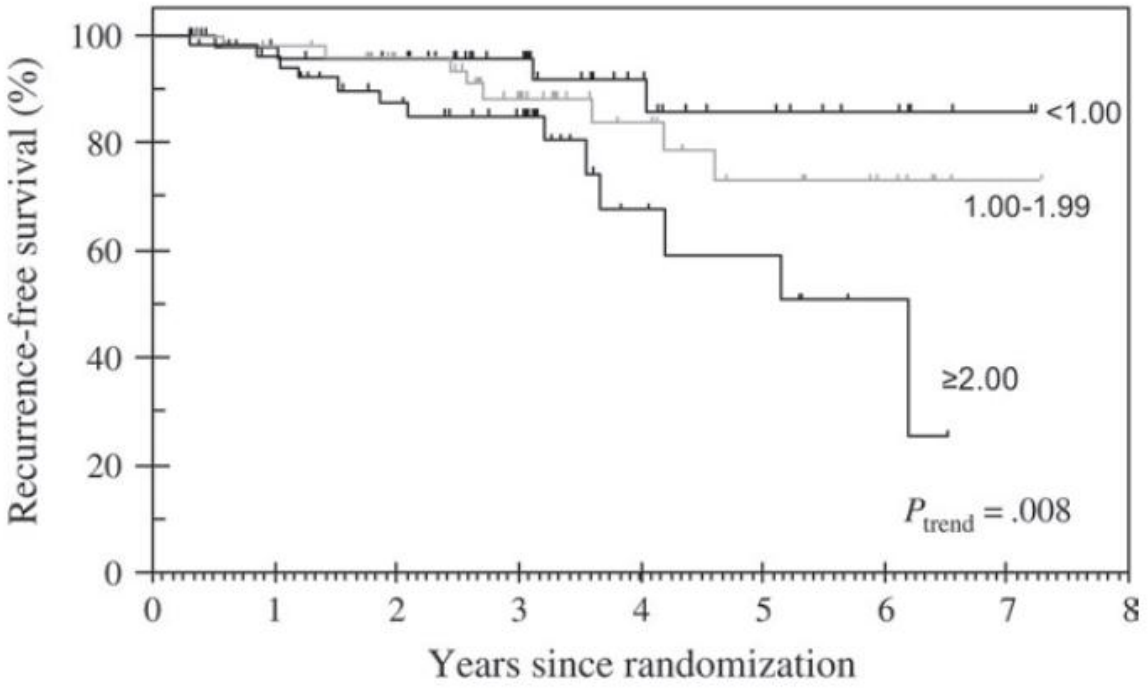
Relapse-free survival by risk-group in P024 and IMPACT study





J Natl Cancer Inst 2008;100: 1380 – 1388

Recurrence-free survival according to tertiles of tumor Ki67 expression after 2 weeks of treatment



J Natl Cancer Inst 2007; 99:167–70

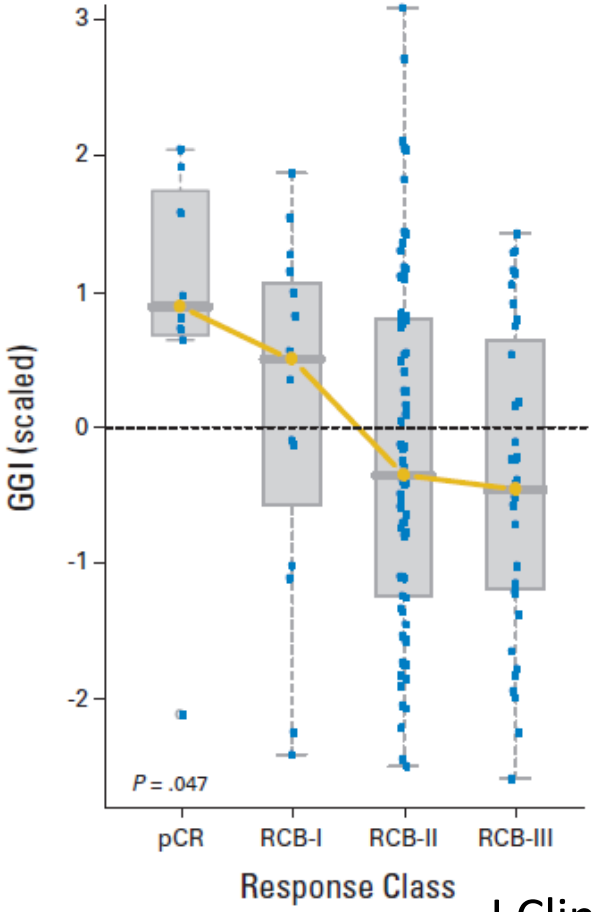
BIG and NABCG proposals for standard definitions and endpoints in neoadjuvant breast cancer clinical trials

Ki67: for patients receiving neoadjuvant endocrine treatment in the context of clinical trials, we recommend assessment of Ki67 on baseline biopsy samples, on biopsy specimens collected during treatment, and on surgical specimens for research purposes

PEPI: we recommend assessment of the PEPI score 12–16 weeks after treatment in neoadjuvant trials using endocrine therapy, for research purposes

Lancet Oncol 2012; 13: e240–48

Distribution of the continuous genomic grade index (GGI) within response groups defined by the residual cancer burden (RCB) for ER-positive disease



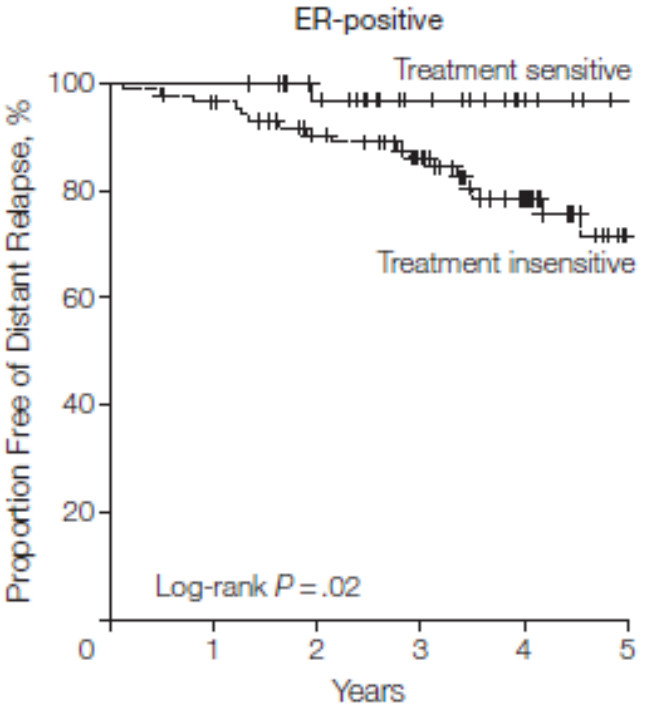
J Clin Oncol 2009; 27:3185-3191

Performance of Genomic Signatures for Predicting Pathologic Response

	Prediction of Pathologic Response					
	Discovery Cohort (n = 310)			Validation Cohort (n = 198)		
Predictor	No. (%)[a]	PPV[b]	NPV[b]	No. (%)[a]	PPV[b]	NPV[b]
Genomic Grade Index, high	301 (29)	36 (30 to 43)	88 (79 to 93)	101 (30)	40 (28 to 54)	84 (70 to 93)
Genomic subtype classifier, luminal B or basal-like	301 (29)	40 (32 to 48)	85 (78 to 90)	101 (30)	40 (25 to 56)	78 (65 to 87)
Genomic predictor of pathologic complete response	301 (29)	46 (37 to 55)	83 (77 to 88)	101 (30)	40 (24 to 58)	75 (63 to 85)
ER-stratified genomic predictor of pathologic complete response/ RCB-I[e]	301 (29)	69 (60 to 77)	100 (98 to 100)	101 (30)	42 (28 to 57)	81 (68 to 91)
Predictive test, treatment sensitive[e,f,g]	256 (31)	78 (66 to 88)	84 (78 to 89)	91 (33)	56 (31 to 78)	73 (61 to 82)

JAMA 2011; 305: 1873-1881

ER-positive Analysis of Genomic Predictions in the Validation Cohort



JAMA 2011; 305: 1873-1881

Predictive value of the baseline PAM50-Based Intrinsic Subtype. ACOSOG Z1031

PAM50 analysis identified AI-unresponsive nonluminal subtypes (HER-2 enriched or basal-like) in 3.3% of patients

Clinical response and surgical outcomes were similar in luminal A (LumA) versus luminal B tumors

PEPI of 0 (best prognostic group) was highest in the LumA subset (27.1% v 10.7%; P .004)

J Clin Oncol 2011; 29: 2342-2349

Genomic signatures

Gene expression profiling would not be possible in the direct future for the majority of patients

Lack of a standardized molecular class prediction method

Large number of variables (genes) in small data sets

Still imperfect in the identification of the population which can avoid chemotherapy or candidate to pCR

Selection of treatment according to subtypes

Surrogate definitions of intrinsic subtypes of breast cancer

Intrinsic Subtype	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** ER and/or PgR positive HER2 negative Ki-67 low (<14%)	Optimal cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping. Local quality control of Ki-67 staining is important
Luminal B	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high **'Luminal B (HER2 positive)'** ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Genes indicative of higher proliferation are poor prognostic markers in multiple genetic assays. Operationally useful to distinguish 'luminal B HER2 positive' as both endocrine and anti-HER2 therapy may be indicated
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent	The majority of HER2 positive tumours are endocrine-receptor negative
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	Approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype but 'triple negative' also includes some special histological types such as medullary and adenoid cystic carcinoma

Ann Oncol. 2011; 22: 1736-47
Lancet Oncol 2012; 13: e240–48

Neoadjuvant Chemotherapy and Endocrine Therapy. For Which Patients?

The choice of neoadjuvant chemotherapy should be made on the same basis as applied in the selection of postoperative adjuvant treatments (e.g. high histological grade, high proliferation as measured by Ki-67, low hormone receptor status, …)

Cytotoxic neoadjuvant therapy not supported for tumors with low proliferation or high endocrine responsiveness

Neoadjuvant endocrine therapy is an option for postmenopausal patients with highly endocrine-responsive disease

Ann Oncol. 2011 ;22: 1736-47

For how long the neoadjuvant treatment should be used?

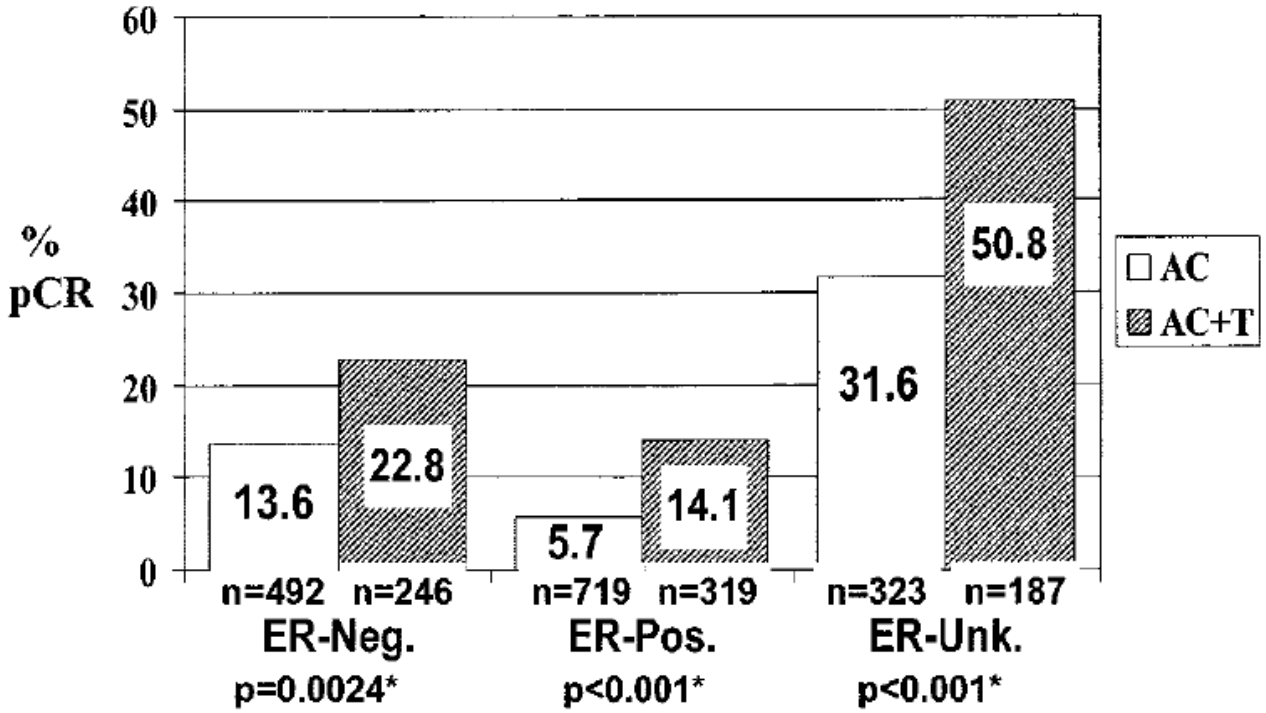
In routine practice, the same regimens should be used for neoadjuvant chemotherapy as in the adjuvant setting (anthracyclines and taxanes concurrently or sequentially for at least 6 cycles or 6 months, respectively) with no chemotherapy regimen preferred

All chemotherapy should be provided before surgery rather than split into preoperative and postoperative phases

Neoadjuvant endocrine therapy should be continued for a minimum of 4 months

Ann Surg Oncol 2012;19:1508-16

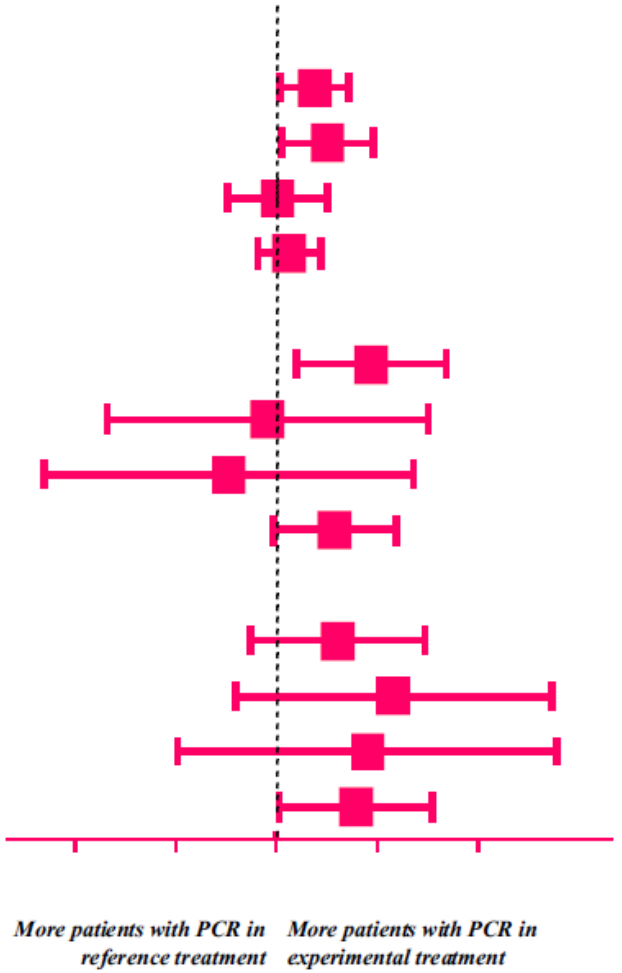
Pathologic tumor responses according to estrogen receptor status in NSABP B-27 study



J Clin Oncol 2003; 21:4165-4174

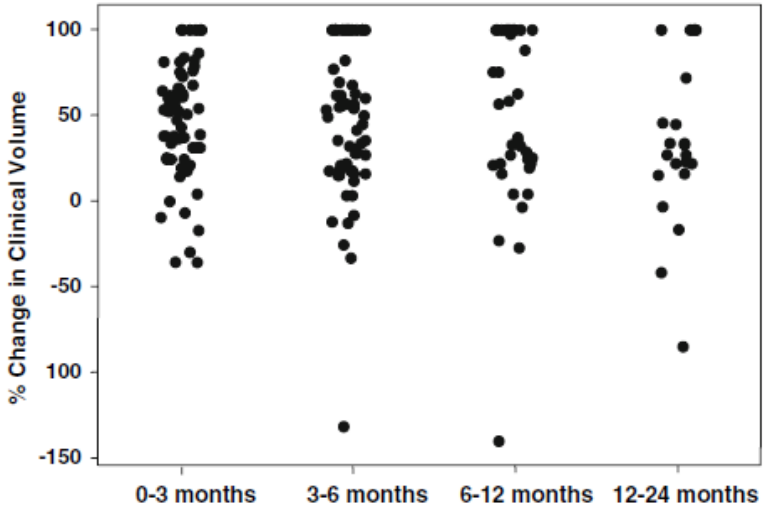
Association of pCR with treatment characteristics in 7 neoadjuvant German studies

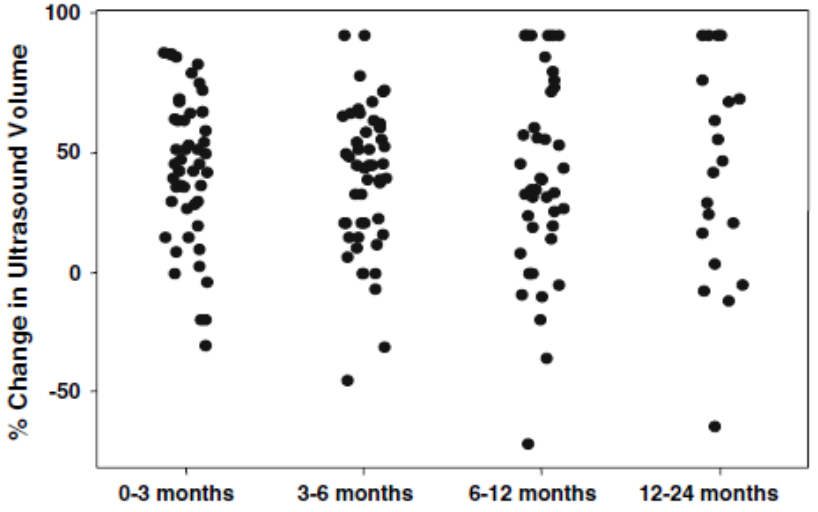
Number of cycles (per 2 additional cycles)	
HER2 - / HR +	*1.30 (1.02 to 1.65)*
HER2 + / HR +	*1.42 (1.04 to 1.94)*
HER2 + / HR -	*1.00 (0.71 to 1.41)*
HER2 - / HR -	*1.09 (0.88 to 1.35)*
Antracycline (high vs low dose)	
HER2 - / HR +	*1.92 (1.14 to 3.21)*
HER2 + / HR +	*0.94 (0.31 to 2.85)*
HER2 + / HR -	*0.72 (0.20 to 2.58)*
HER2 - / HR -	*1.49 (0.98 to 2.27)*
Taxane (high vs low dose)	
HER2 - / HR +	*1.52 (0.84 to 2.76)*
HER2 + / HR +	*2.23 (0.75 to 6.61)*
HER2 + / HR -	*1.87 (0.51 to 6.92)*
HER2 - / HR -	*1.73 (1.02 to 2.94)*



The Breast 2011; S3, S142–S145

Individual values for % reduction in clinical and ultrasound volume during letrozole between time intervals 0–3 mos, 3–6 mos, 6–12 mos and 12–24 mos

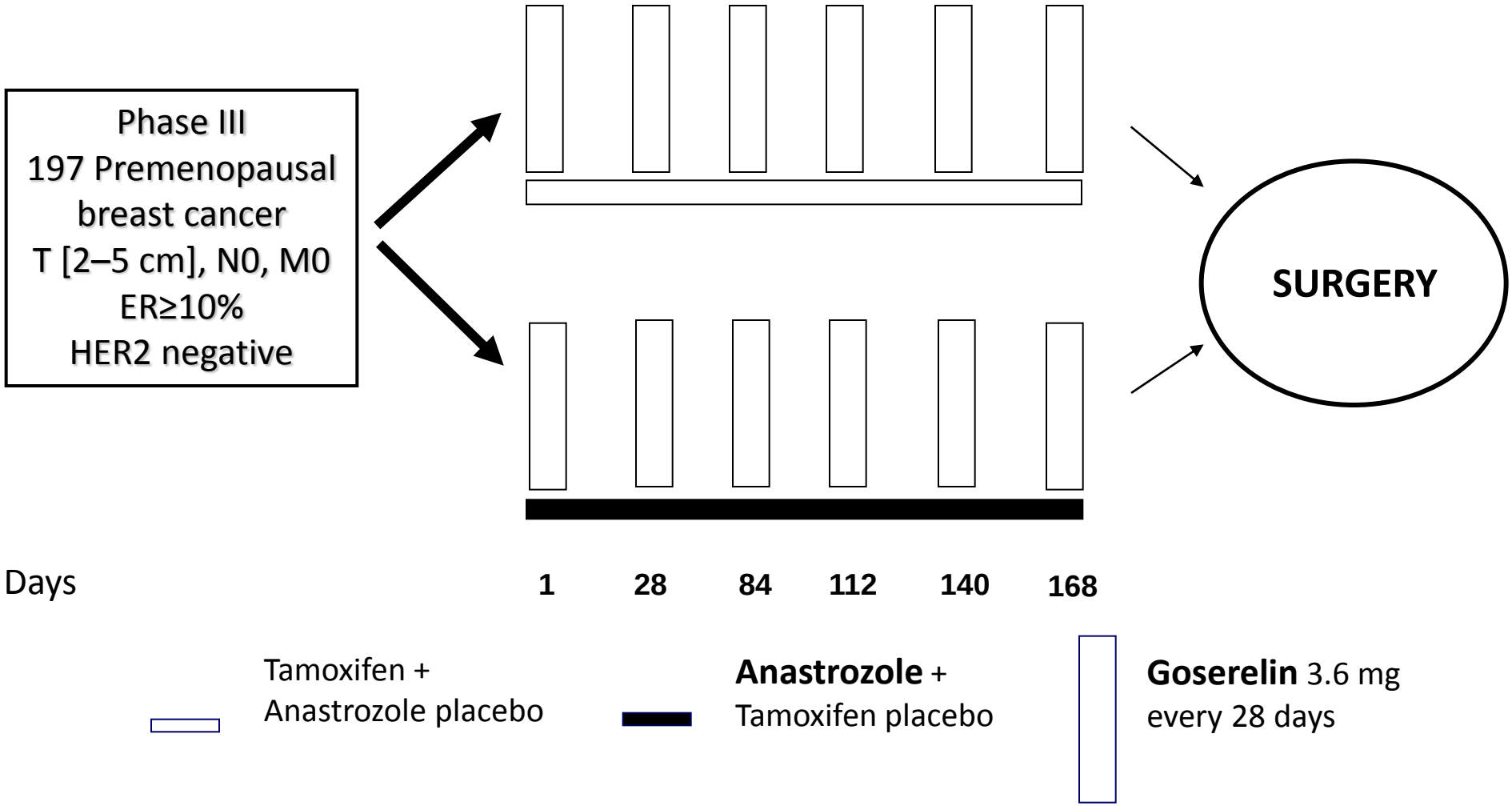




Breast Cancer Res Treat 2009; 113:145–151

Neoadjuvant endocrine therapy for premenopausal pts with ER+ disease

STAGE STUDY



Lancet Oncol 2012; 13: 345-52

STAGE study: RESULTS

	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%)

Lancet Oncol 2012;13: 345-52

Summary of the P024, IMPACT and PROACT trials

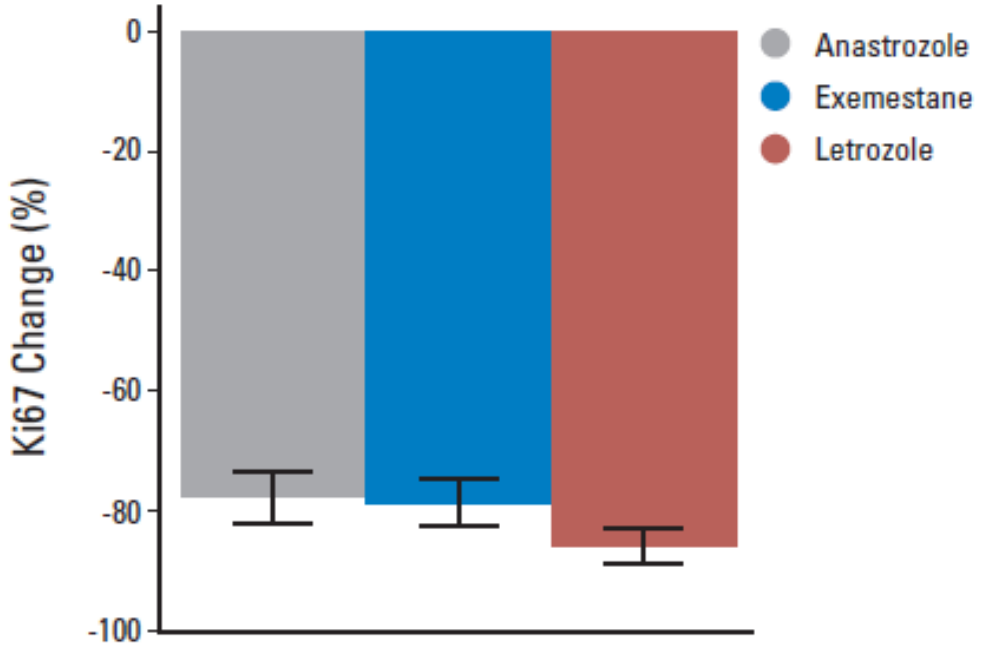
	Letrozole P024	IMPACT	PROACT
	Postmenopausal women, HT+ breast cancer		
N	337	330	451
HR positivity	ER/PR > 10%	ER > 1%	ER + / PR +
Neoad ET	L x 4 months T for 4 months	A x 12 weeks A+T x 12 weeks T x 12 weeks	A x 3 months T x 3 months
Concomitant CT	NO	-	YES
Response	55% (L) vs 36% (T); p<0.001	37% (A) vs 39% (A+T) vs 36% (T)	39.5% (A) vs 35.4% (T)

ACOSOG Z1031 Clinical Response Based on ITT Population

Response	Exemestane (n = 124)		Letrozole (n = 127)		Anastrozole (n = 123)	
	No.	%	No.	%	No.	%
Clinical response at week 16 (WHO criteria with caliper measurements)						
Complete response	27	21.8	27	21.3	22	17.9
Partial response	51	41.1	68	53.5	63	51.2
No change	28	22.6	20	15.7	20	16.3
Disease progression	8	6.5	6	4.7	9	7.3

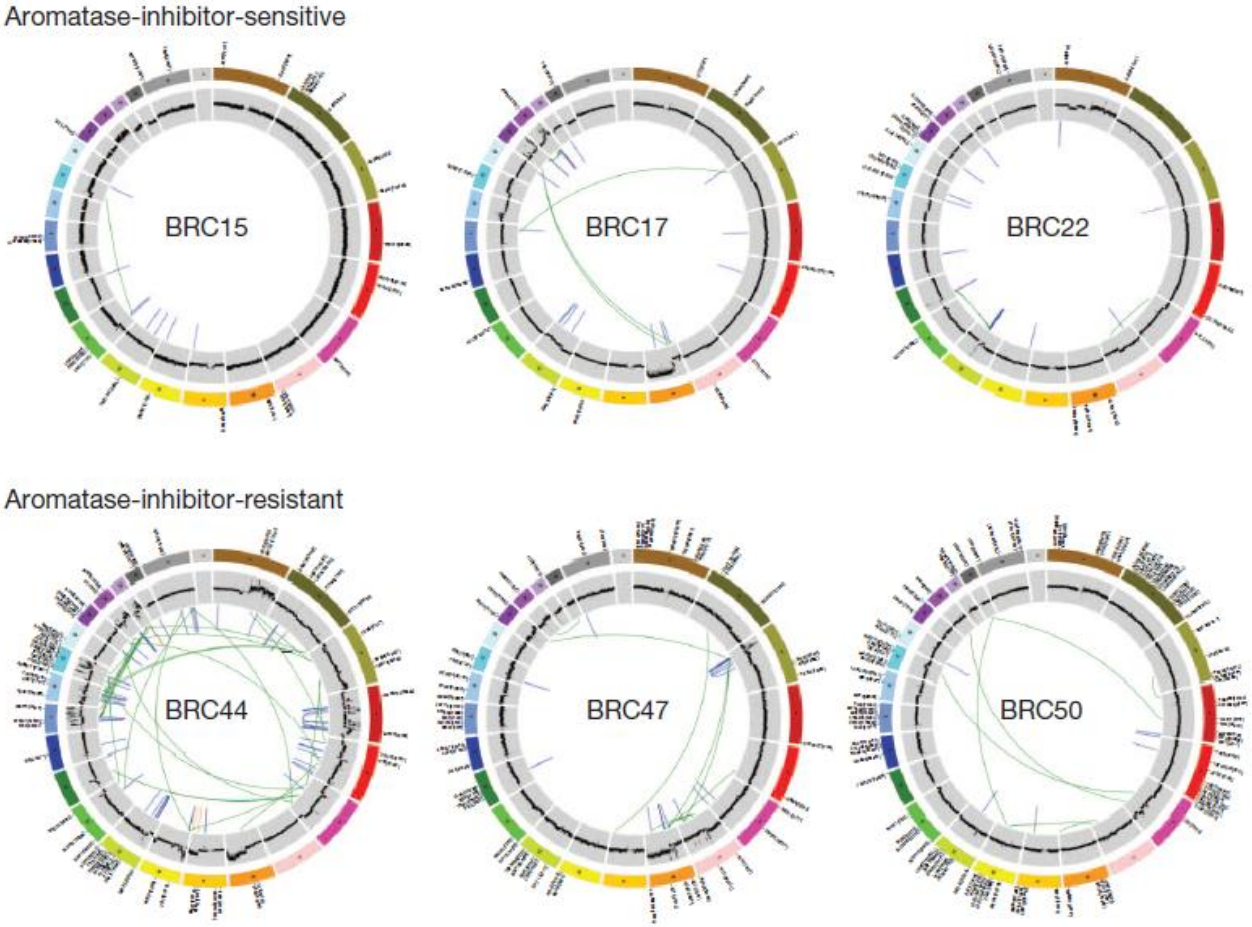
J Clin Oncol 2011; 29: 2342-2349

ACOSOG Z1031. Mean percentage suppression of Ki67 from baseline by treatment arm



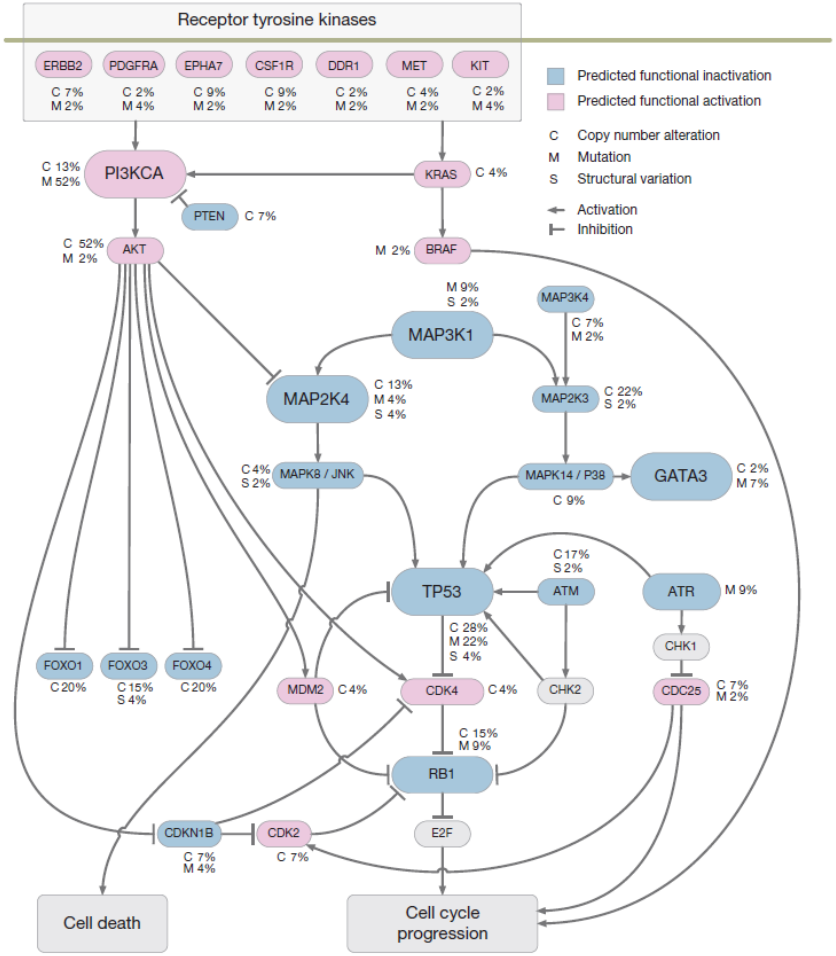
J Clin Oncol 2011; 29:2342-2349

Neoadjuvant aromatase inhibitor and genome-wide somatic mutations. Three on-treatment Ki67 ≤ 10% (top panel) and three on-treatment Ki67 > 10% (bottom panel)



Nature 2012; 486: 353-60

Key cancer pathway components altered in luminal breast tumours



Nature 2012; 486: 353-60

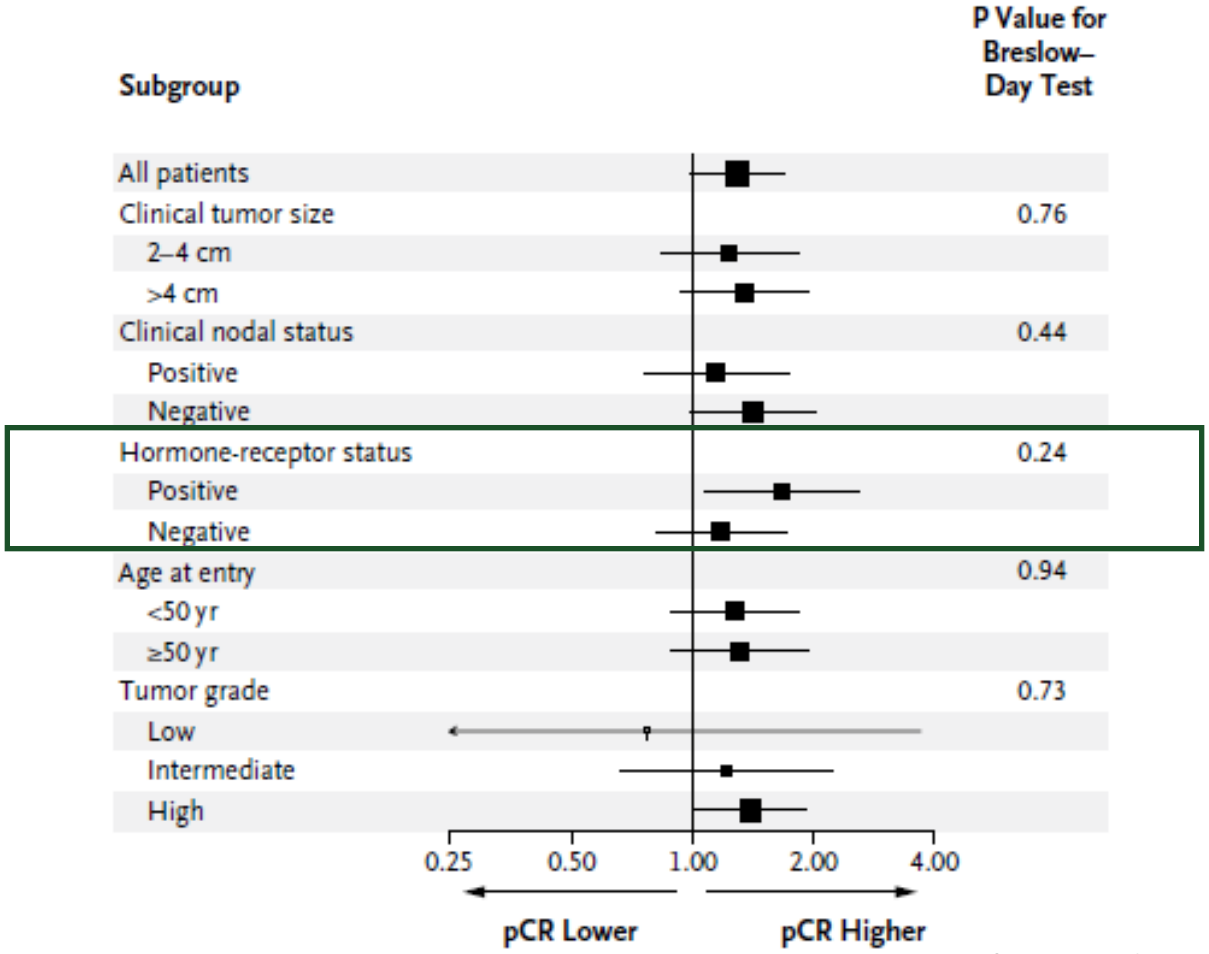
Everolimus Plus Letrozole Compared With Placebo Plus Letrozole in Patients With ER+ Breast Cancer

Response by Evaluation Type	Treatment Arm: Everolimus + Letrozole (n = 138) No.	Everolimus + Letrozole (n = 138) %	Placebo + Letrozole (n = 132) No.	Placebo + Letrozole (n = 132) %
Clinical palpation				
Complete response	18	13.0	12	9.1
Partial response	76	55.1	66	50.0
No change	34	24.6	39	29.5
Progressive disease	6	4.3	13	9.8
Not available/not assessable	4	2.9	2	1.5
Overall response*	94	68.1	78	59.1
95% CI		60.3 to 75.9		50.7 to 67.5
χ^2 test P		.0616		
Ultrasound				
Complete response	7	5.1	1	0.8
Partial response	73	52.9	61	46.2
No change	43	31.2	54	40.9
Progressive disease	4	2.9	9	6.8
Not available/not assessable	11	8.0	7	5.3
Overall response*	80	58.0	62	47.0
95% CI		49.7 to 66.2		38.5 to 55.5
χ^2 test P		.0352		

J Clin Oncol 2009; 27:2630-2637

Bevacizumab for HER2 negative breast cancer

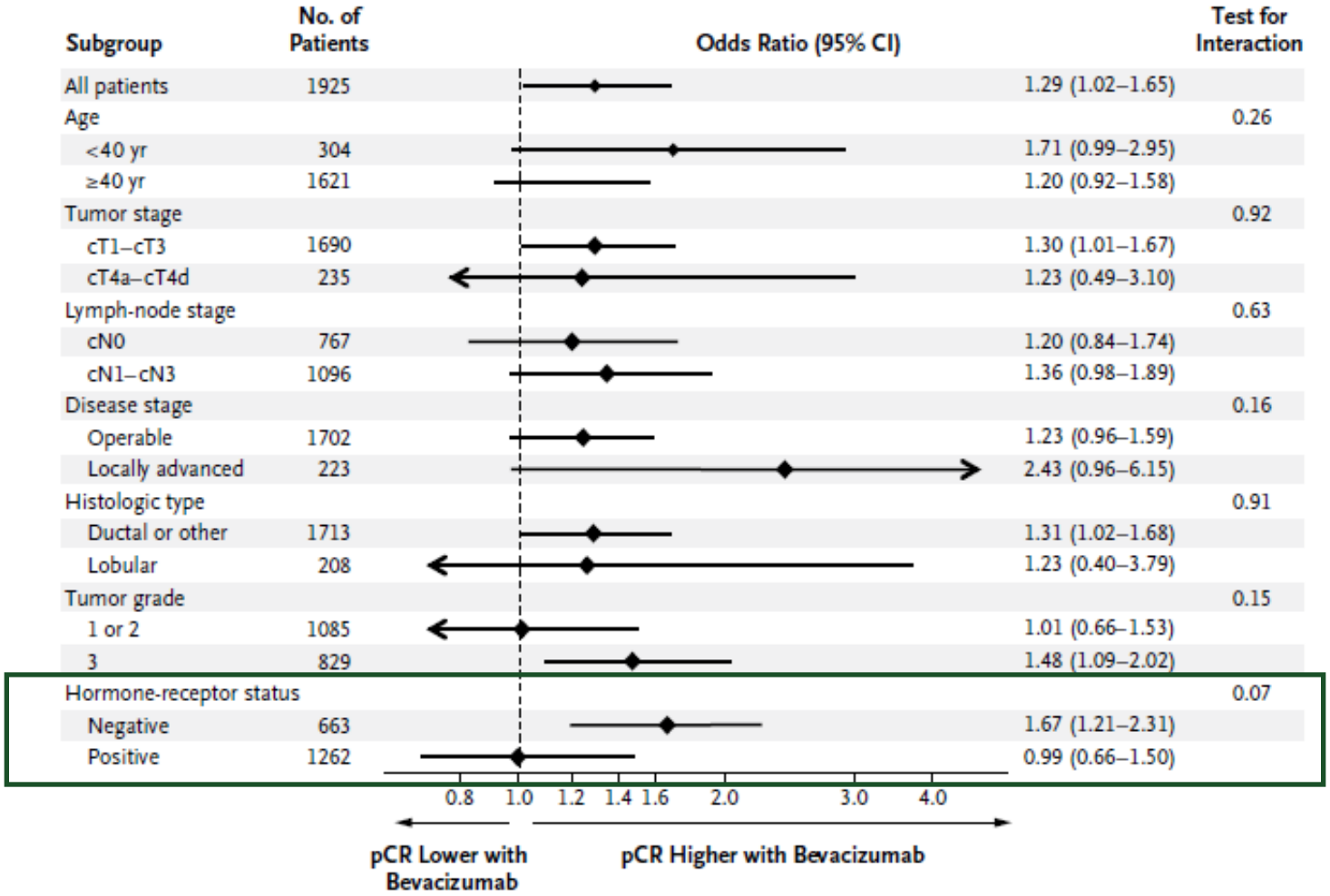
NSABP B-40 trial



N Engl J Med 2012; 366:310-20

Bevacizumab for HER2 negative breast cancer.

GeparQuinto trial



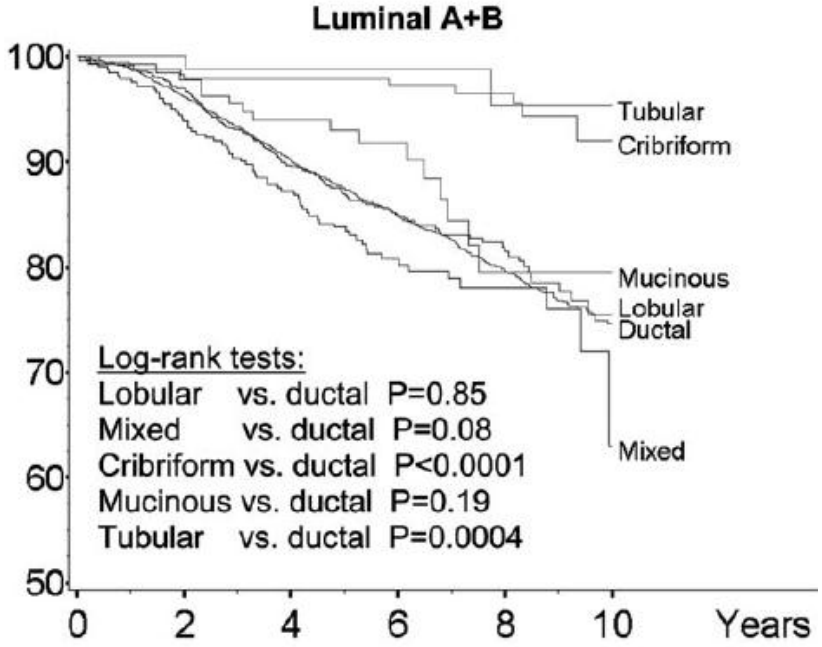
N Engl J Med 2012; 366: 299-309

LET vs LET-CYC: Distribution of Disease Response According to Treatment Arm

	LET		LET-CYC	
	No.	%	No.	%
Not assessable	1	1.7	—	
Progressive disease	3	5.3	3	5.3
Stable disease	12	21.0	4	7.1
Partial response	18	31.6	25	43.8
Complete response	23	40.3	25	43.8
Overall response	41	71.9	50	87.7
95% CI	60.8% to 83.8%		78.6% to 96.2%	
Pathologic response	2	3.5	2	3.5
Residual in situ carcinoma	1	1.8	1	1.8

J Clin Oncol 2006; 24:3623-3628

Disease-free survival according to histological subtypes for luminal A and luminal B subtypes



Patients at risk

Ductal	5706	5177	4562	2577	1091	201
Lobular	851	801	703	408	187	38
Mixed	338	303	266	149	58	7
Cribriform	250	231	219	166	99	19
Mucinous	143	130	114	60	24	2
Tubular	83	79	73	56	25	9

Ann Oncol 2012; 23: 1428–1436

Lobular carcinoma (ILC): a distinct responsiveness

Author	Pts	%pCR IDC	%pCR ILC
Cristofanilli	1034	15	**3**
von Minckwitz	6377	21	**9**
Tubiana	860	9	**1**
Colleoni	533	8.2	**0**

Summary

ER-positive, HER-2-negative operable breast cancer represents a mixed group of tumors where the identification of distinct clinical entities is the key achievement for proper management

Limited information on tailoring Neoadjuvant treatment for an individual patient

Summary

On the one extreme, patients with ER-positive, HER2-negative disease may have tumors with very low risks of recurrence, where there is little evidence supporting the use of neoadjuvant therapy

On the other extreme, patients may present with high-risk, highly proliferative disease, where prolonged neoadjuvant chemotherapy appears clearly justified

Summary

Patients and their physicians must weigh the costs and benefits of all therapeutic options

Tailored neoadjuvant treatment investigation on specific niches of patients is key to make progress on how to treat individual patients with ER-positive, HER2-negative breast cancer