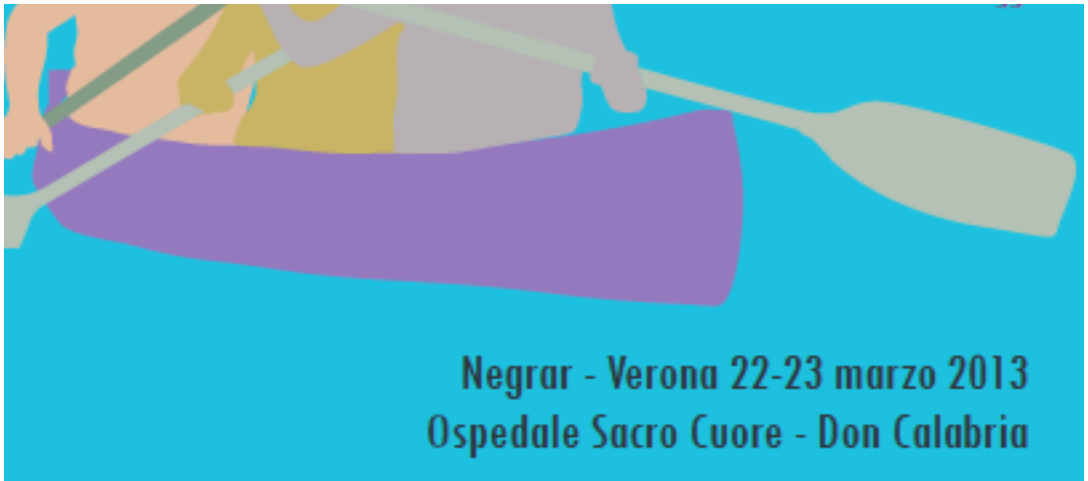
La malattia residua dopo terapia neoadiuvante

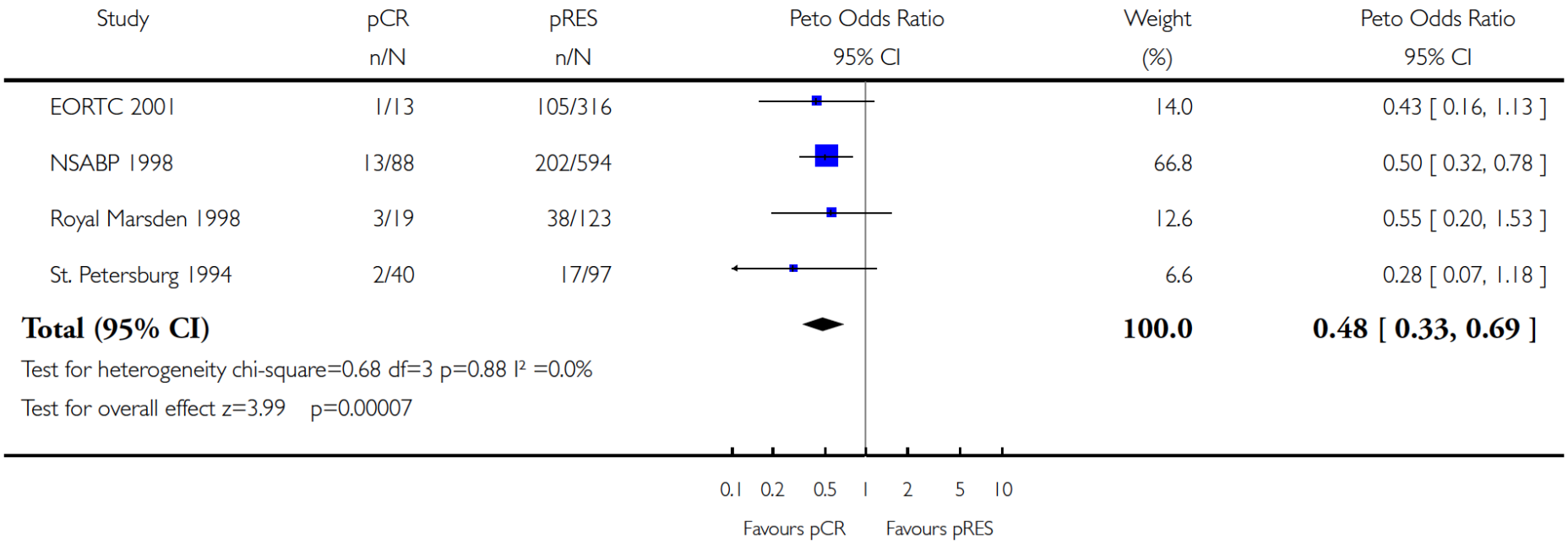
Valentina Guarneri



Preoperative chemotherapy for women with operable breast cancer (Review)

THE COCHRANE COLLABORATION®

pCR vs residual disease, Overall Survival



Primary systemic therapy in breast cancer

- The upfront utilization of systemic therapy provides an vivo assessment of treatment effect, and allows to identify subgroups of patients with very different prognosis
- However, the classification of responses in pCR versus non-pCR is a useful prognostic indicator for those patients with pCR, but it oversimplifies the different prognostic categories for the patients with less than pCR.
- Non-pCR category group includes patients where preoperative chemotherapy has induced an important down-staging as well as patients with highly resistant disease.
- The majority of patients does not achieve a pCR:
  - pCR rate with conventional anthra-taxanes is 20-40% in TNBC, less than 10% in HR +; 40-60% of HER2+ (+trastuzumab)

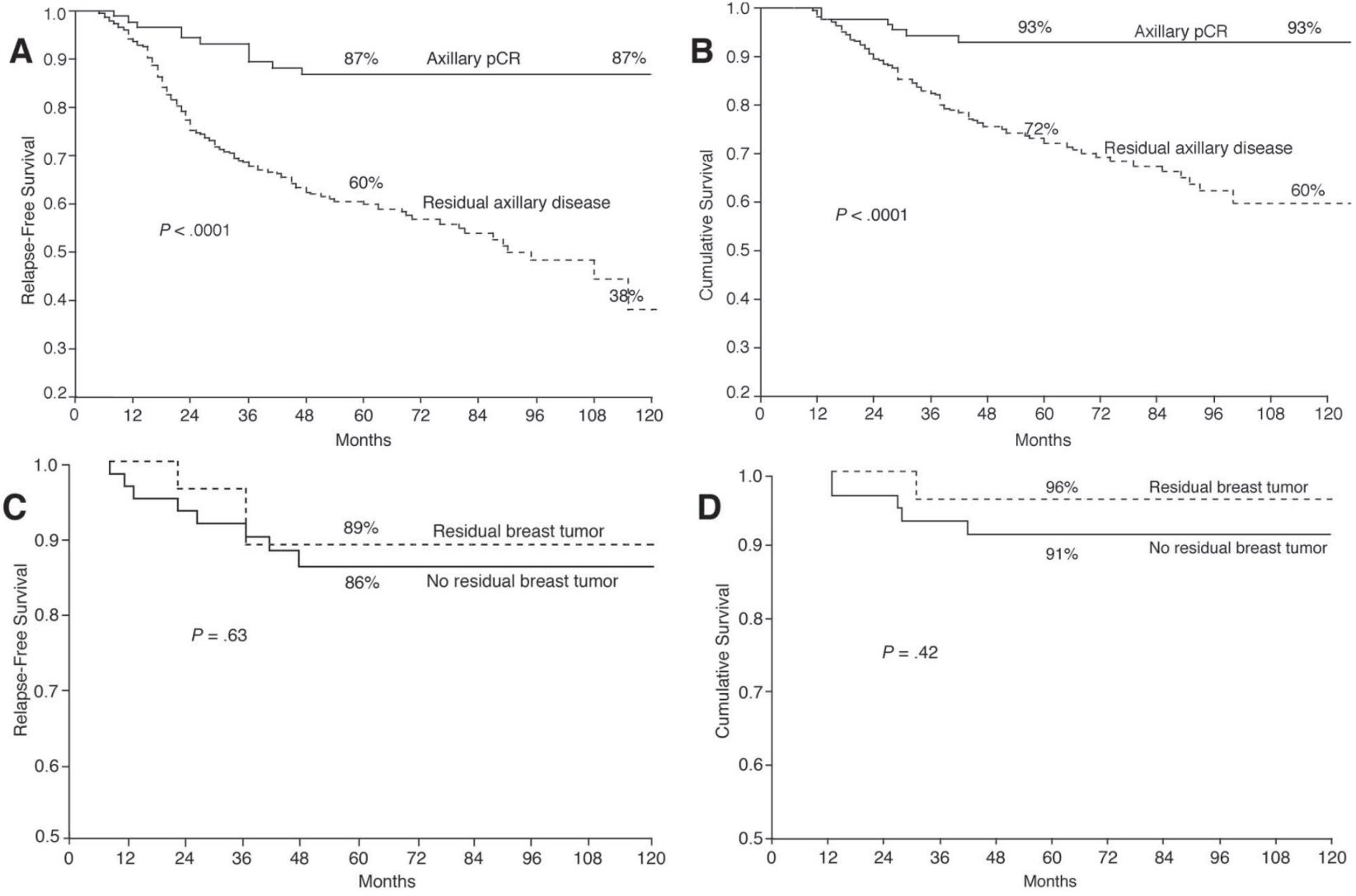
Prognostic value of nodal involvement after PCT

152 patients with T1-T3 tumors and cytologically proven axillary metastatic LN

Axillary status at surgery	5 yr DFS rate
No involved nodes (23%)	73.5% ± 14.9
Residual nodal disease (77%)	48.7% ± 9.2

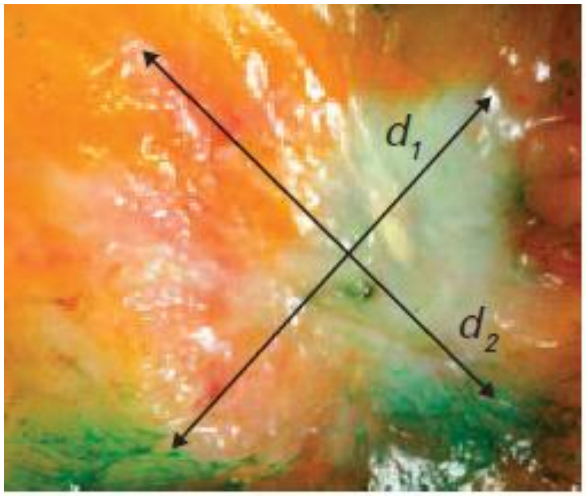
Rouzier, J Clin Oncol 2002

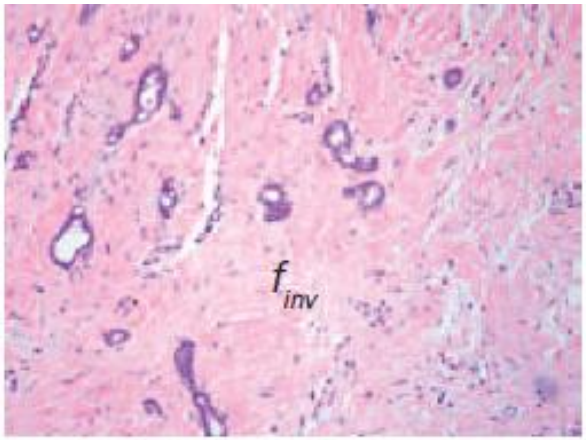
Outcome of cytologically proven N+ BC with yN0 disease after neoadjuvant therapy

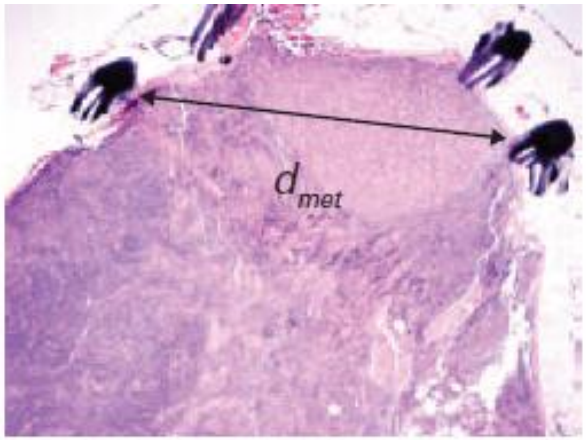


Hennessy B et al, J Clin Oncol 2005

Residual breast Cancer Burden (RCB) to predict survival after neoadjuvant chemotherapy





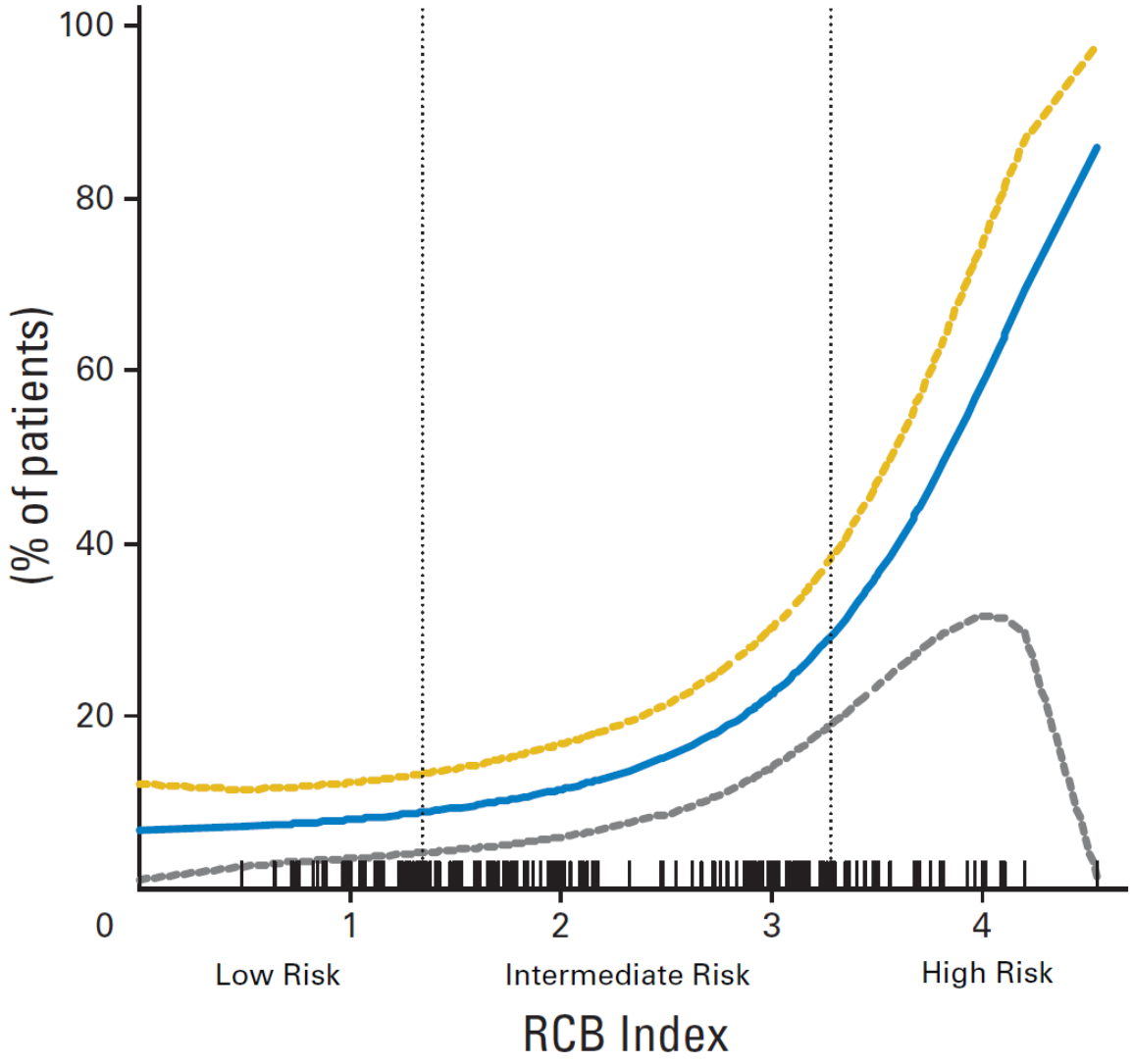


Variable	Hazard Ratio (95% CI)	P
Primary tumor bed dimensions ($\sqrt{d_1 d_2}$)	1.24 (1.04 to 1.48)	.02
Cellularity fraction of invasive cancer (f_{inv})	7.37 (2.16 to 25.1)	.001
Size of largest metastasis (d_{met})	1.17 (0.99 to 1.38)	.06
No. of positive lymph nodes	1.11 (1.04 to 1.19)	.002

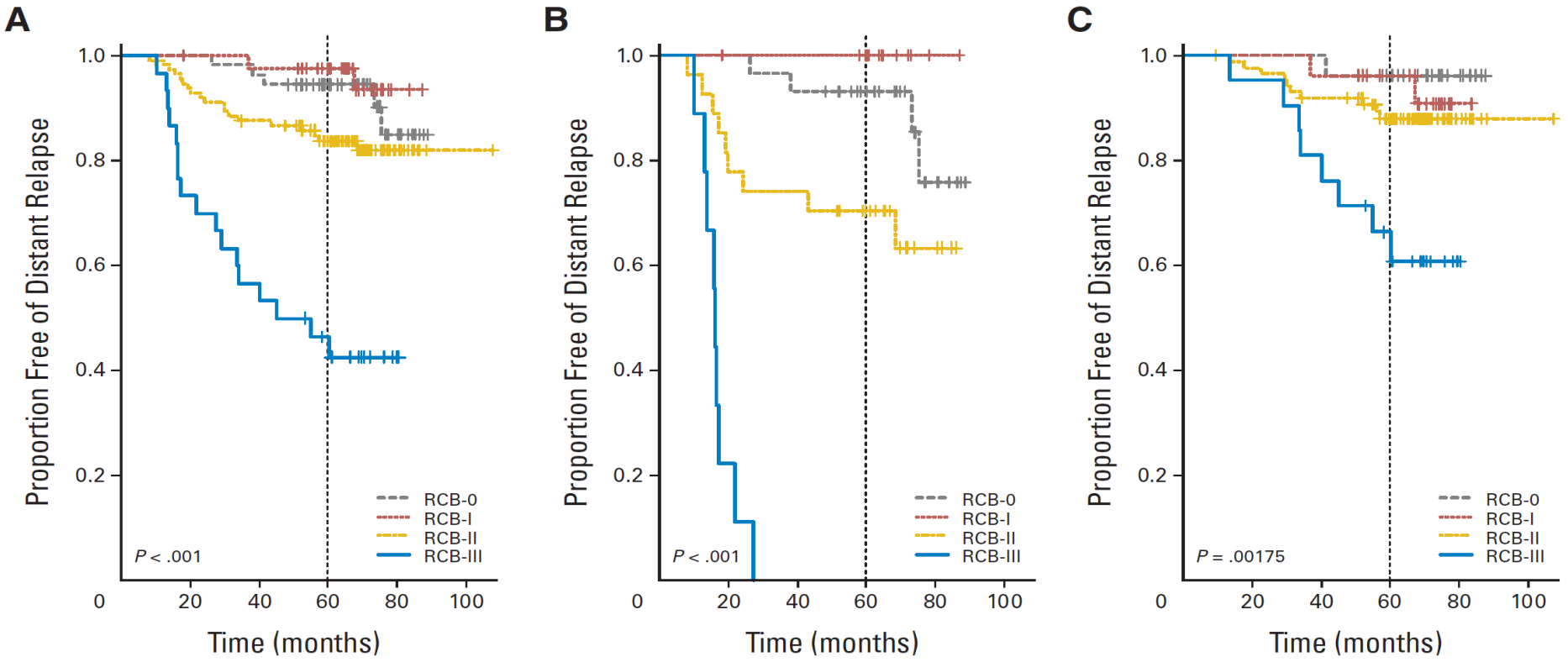
$$RCB = 1.4(f_{inv} d_{prim})^{0.17} + [4(1 - 0.75^{LN}) d_{met}]^{0.17}$$

WF Symmans et al, J Clin Oncol 2007

Likelyhood of 5-year Distant recurrence as a continuous function of RCB



Likelyhood of Distant Recurrence according to RCB class

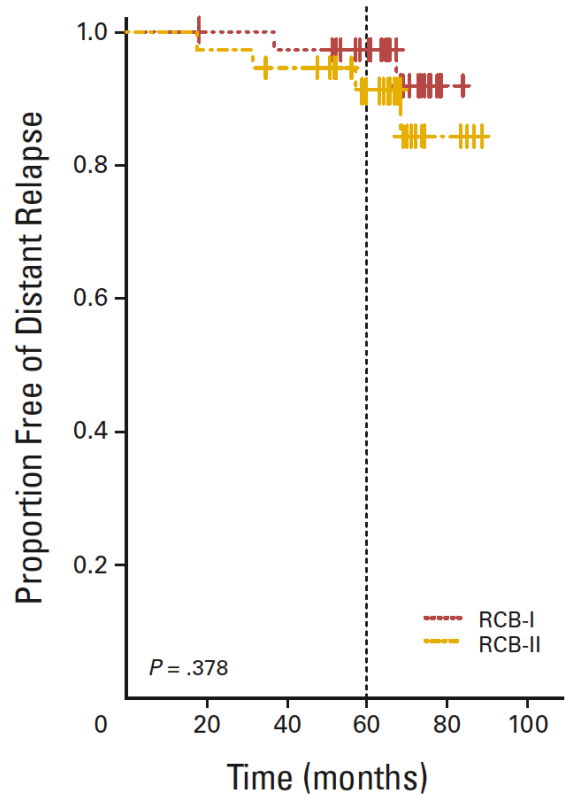


All patients

HR-

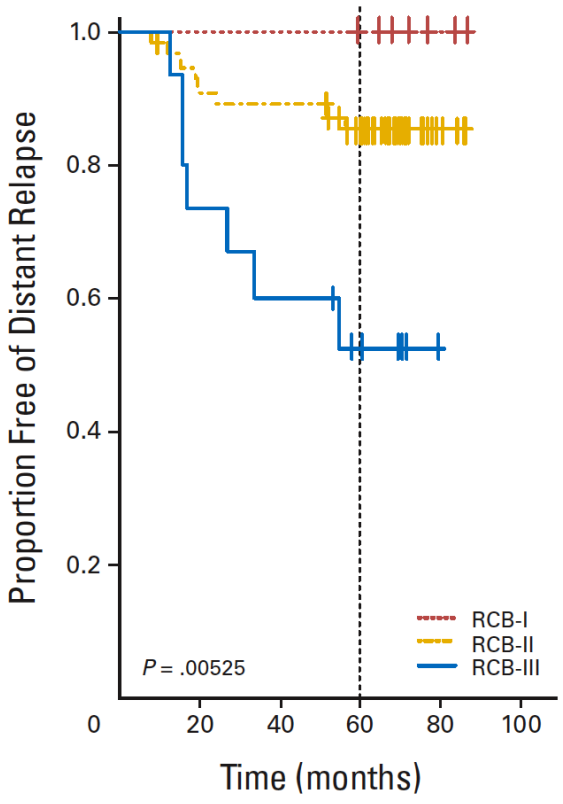
HR+

RCB and post-therapy yAJCC stage group



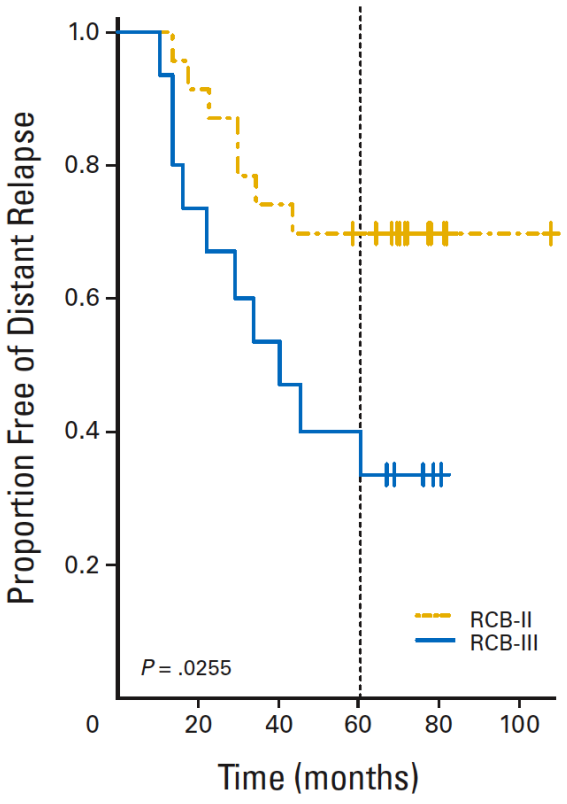
o. at risk
CB-I 34 34 33 28 2
CB-II 36 36 34 24 5

yAJCC stage I



No. at risk
RCB-I 8 8 8 8 3
RCB-II 55 50 49 40 5
RCB-III 15 12 10 7 1

yAJCC stage II

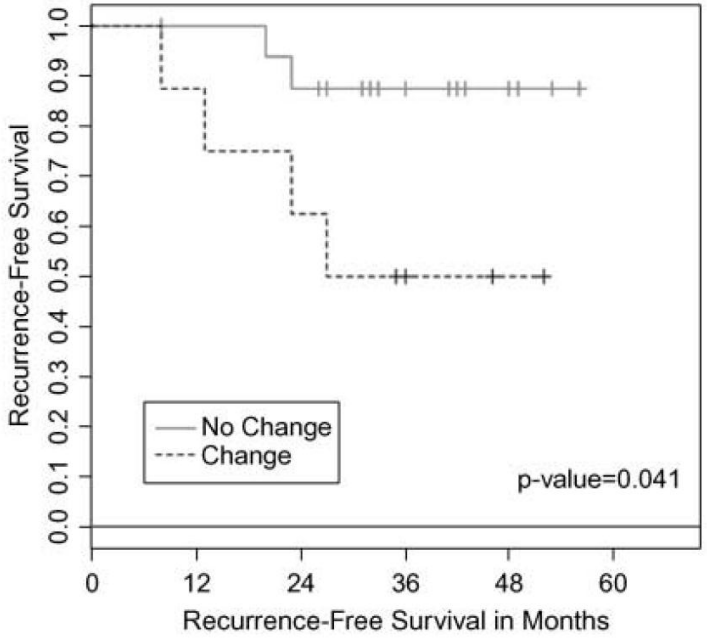


No. at risk
RCB-II 23 22 18 16 5 2
RCB-III 15 12 9 7 2 1

yAJCC stage III

Loss of HER2 Amplification after trastuzumab based PCT

Status	No. patients	No. events	Median follow-up time (mo)	3-y estimates		5-y estimates		*P*
				%	95% CI	%	95% CI	
Overall	142	17	33.5	87.8	82.4-93.6	86.20	80.1-92.8	
pCR			33.5					
Yes	72	4		95.7	91.0-100	92.90	86.0-100	
No	70	13		80.1	70.8-90.5	—		0.0175
HER2 Status in Residual Tissue	25	6	37.0	74.9	59.4-94.5	—	—	
Amplified	17	2		87.5	72.7-100	—	—	
Not Amplified	8	4		50.0	25.0-100	—	—	0.041



E Mittendorf, Clin Cancer Res 2009

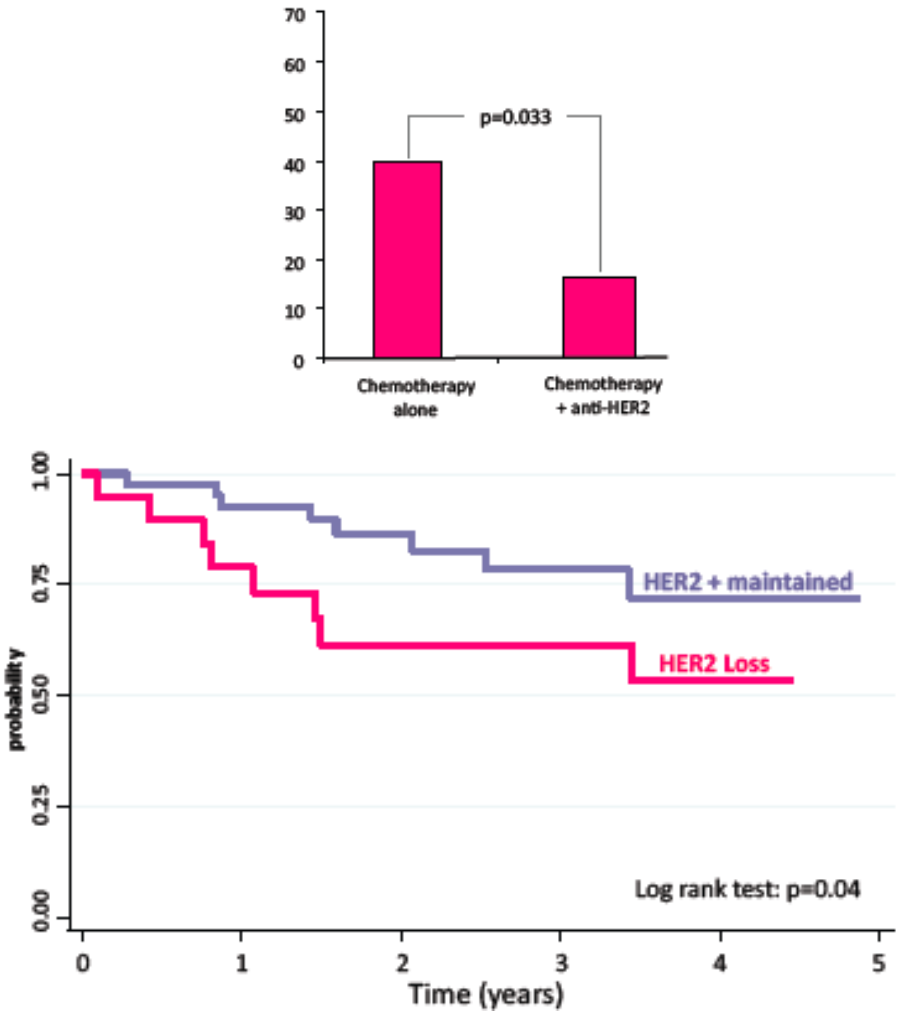
Prognostic role of HER2 loss after PCT

Patient characteristics per treatment cohort

	Cohort A (N=42) CT	Cohort B (N=61) CT+ anti-HER2
Median age, (min; max)	49 yrs (29;76)	49 yrs (26;80)
Stage: IIA	15 (35.7%)	23 (37.7%)
IIB	15 (35.7%)	24 (39.3%)
III	12 (28.6%)	14 (23%)
Histology: Ductal	27 (64.3%)	51 (83.6%)
Lobular	1 (2.4%)	2 (3.3%)
Other/NA	14 (33.3%)	8 (13.1%)
Histologic Grade 1-2	11 (26.2%)	2 (3.3%)
3	28 (66.7%)	48 (78.7%)
NA	3 (7.1%)	11 (18%)
Hormone receptor		
ER & PgR <10%	13 (31%)	23 (37.7%)
ER &/or PgR>10%	28 (66.7%)	37 (60.7%)
NA	1 (2.4%)	1 (1.6%)
Median Ki67 (min;max)	25% (8%;75%)	30% (10%;90%)

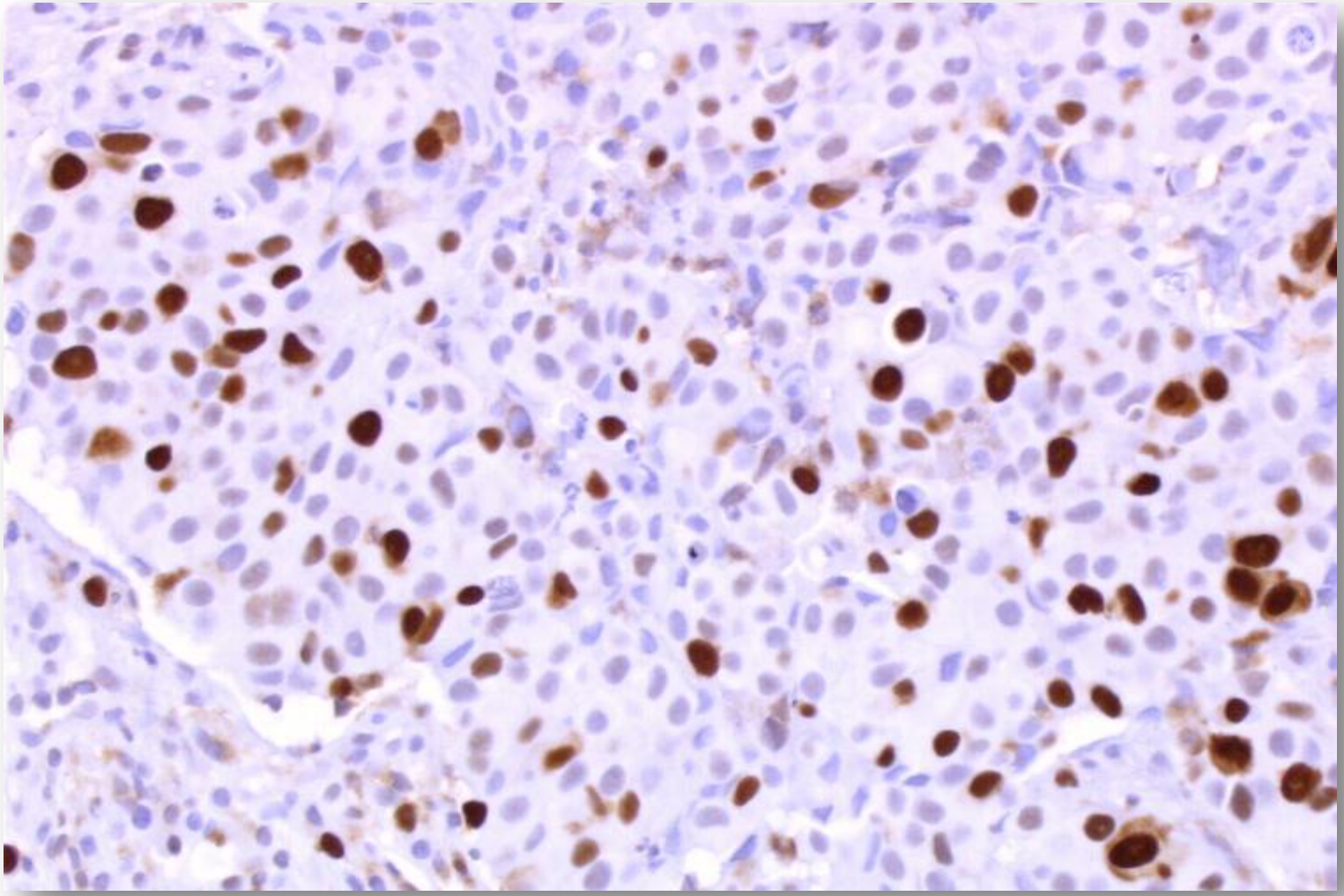
NA: not available

Fig. 2: HER2 loss per treatment cohort



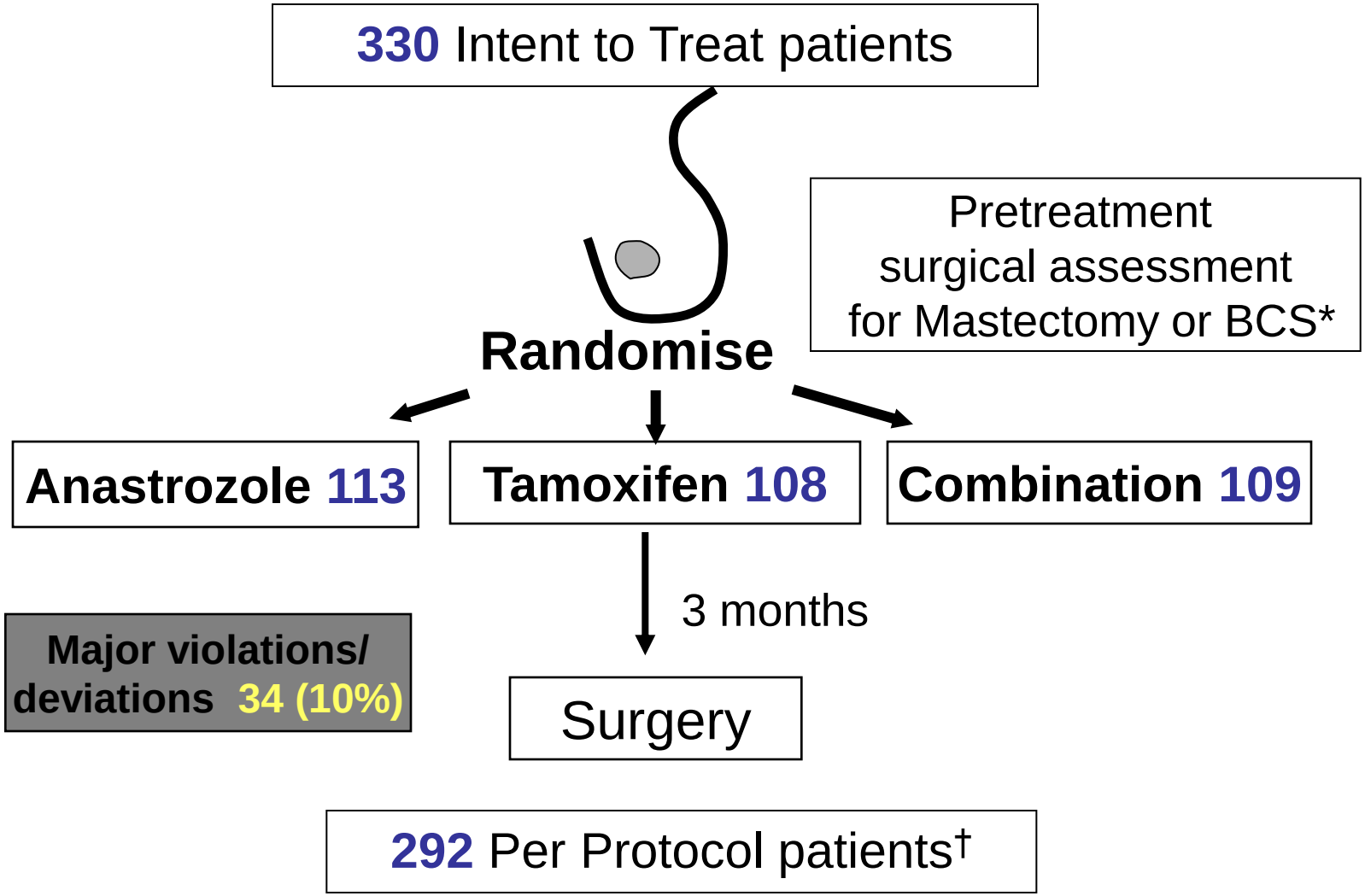
Guarneri V et al, ASCO 2012 poster presentation

Ki-67: son of a lesser God

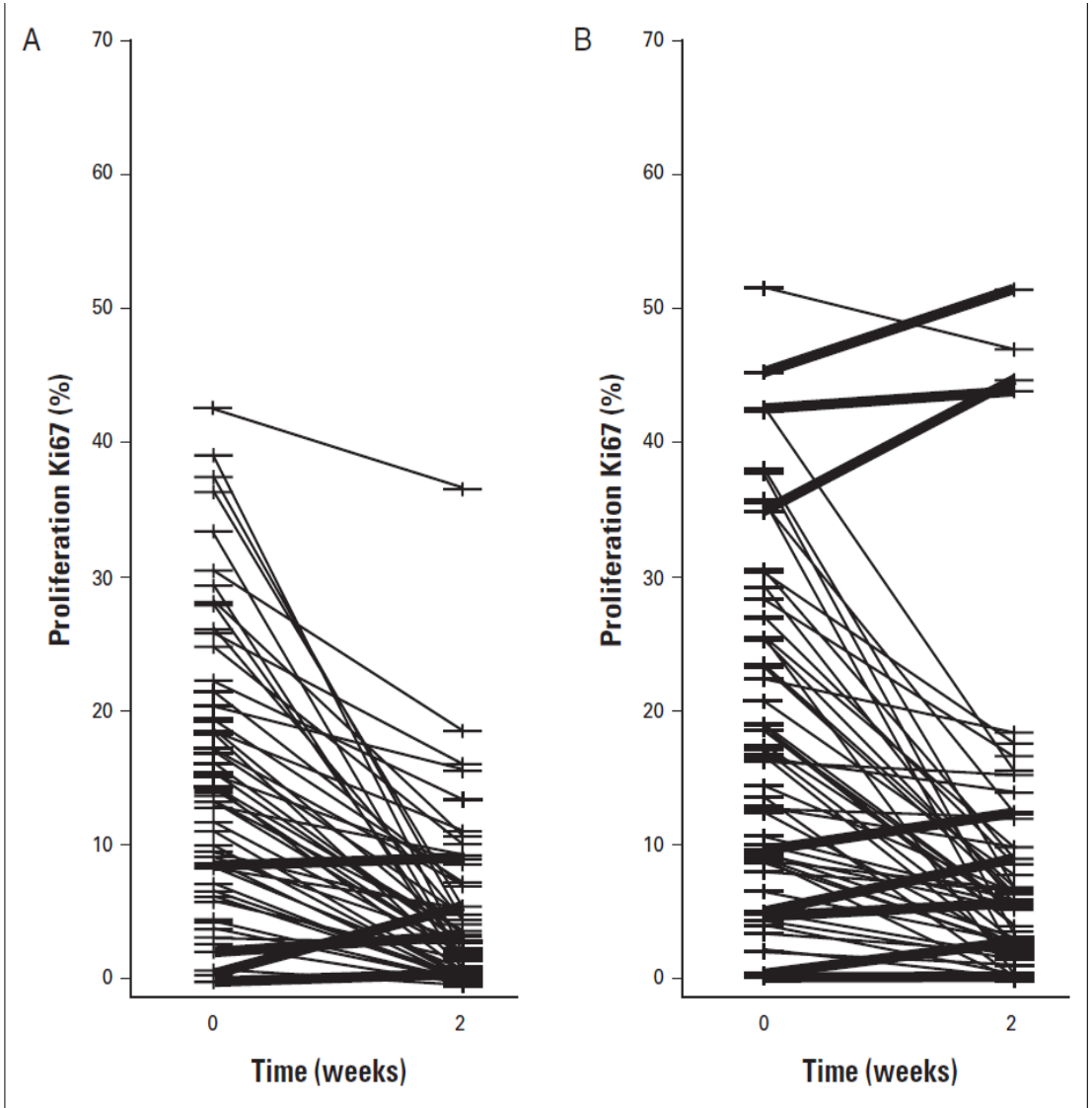


Courtesy of Beppe Viale

IMPACT Trial

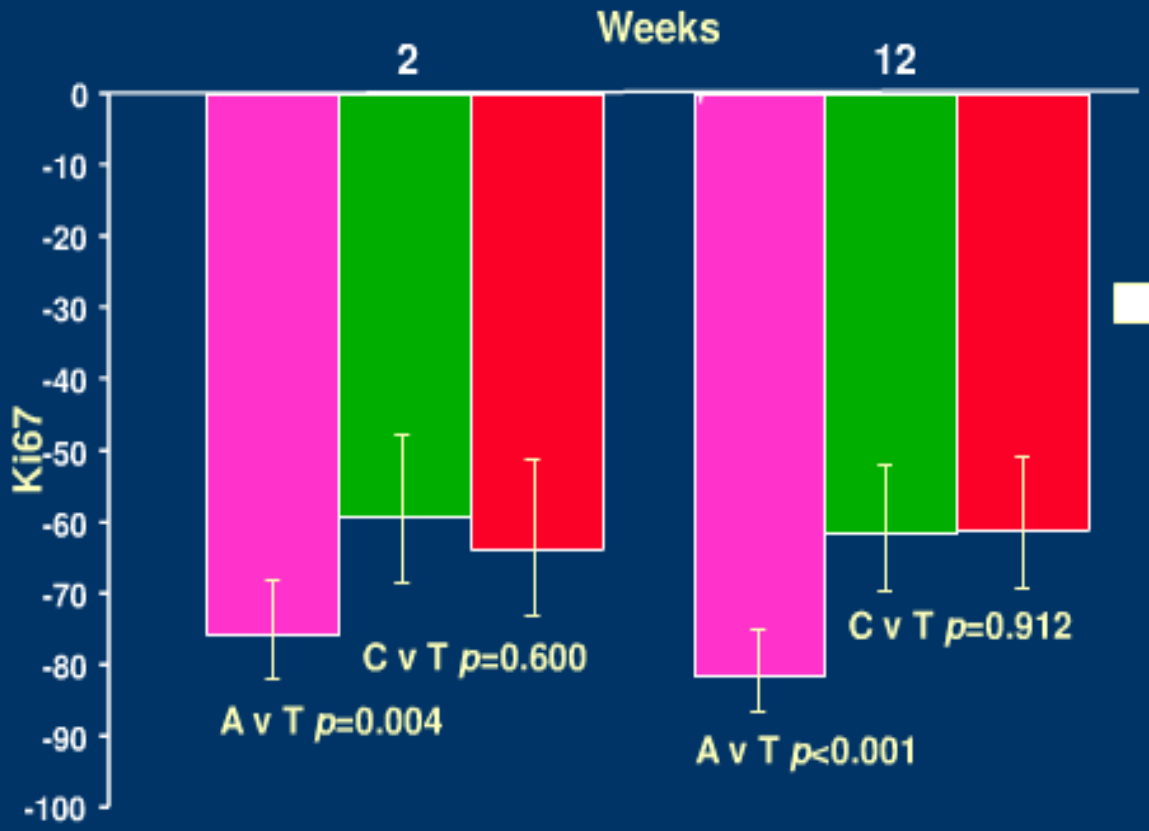


Individual changes in Ki67 after 2 weeks



Dowsett et al. J Clin Oncol 2005

IMPACT (A v Tam v Combination)
% Ki67 Change from Baseline* During Treatment



Both 2 week and 12 week predict ATAC

* Via transformation of geometric mean proportion of baseline

Prognostic Value of Ki67 Expression After Short-Term Presurgical Endocrine Therapy for Primary Breast Cancer

Mitch Dowsett, Ian E. Smith, Stephen R. Ebbs, J. Michael Dixon, Anthony Skene, Roger A'Hern, Janine Salter, Simone Detre, Margaret Hills, Geraldine Walsh

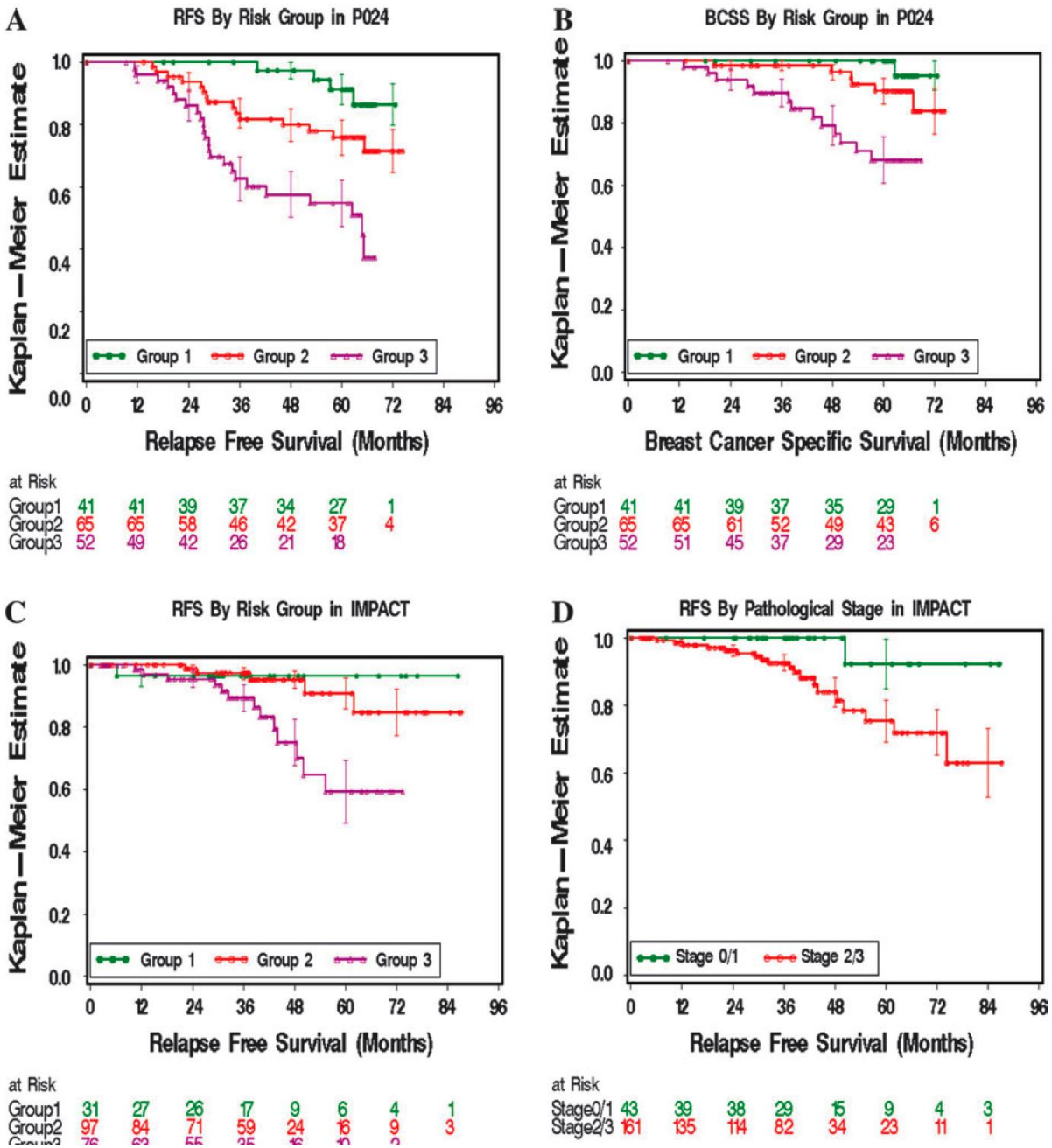
	Univariate analysis			Multivariable analysis†	
Factor	No. of events/No. of patients	HR (95% CI)	*P*	HR (95% CI)	*P*
Tumor size at baseline, per 1-cm increase	25/156	1.66 (1.35 to 2.04)	<.001	1.69 (1.36 to 2.1)	<.001
Nodal status at baseline, positive vs. negative	25/157	1.43 (0.6 to 3.44)	.42	–	–
Ki67 expression at baseline, per 2.7-fold increase	25/157	1.85 (1.06 to 3.22)	.03	–	–
Ki67 expression after 2 wk of treatment, per 2.7-fold increase	25/158	2.09 (1.41 to 3.08)	<.001	1.95 (1.23 to 3.07)	.004
ER level at baseline, per 2.7-fold increase	25/158	0.35 (0.2 to 0.62)	<.001	–	–
ER level after 2 wk of treatment, per 2.7-fold increase	25/154	0.62 (0.5 to 0.77)	<.001	0.78 (0.62 to 0.99)	.04
TUNEL level at baseline, per 2.7-fold increase	25/148	1.52 (0.76 to 3.03)	.24	–	–
TUNEL level after 2 wk of treatment, per 2.7-fold increase	23/141	1.65 (0.86 to 3.16)	.13	–	–
Adjuvant chemotherapy after surgery, yes vs. no	25/158	0.88 (0.35 to 2.21)	.78	–	–

J Natl Cancer Inst 2007

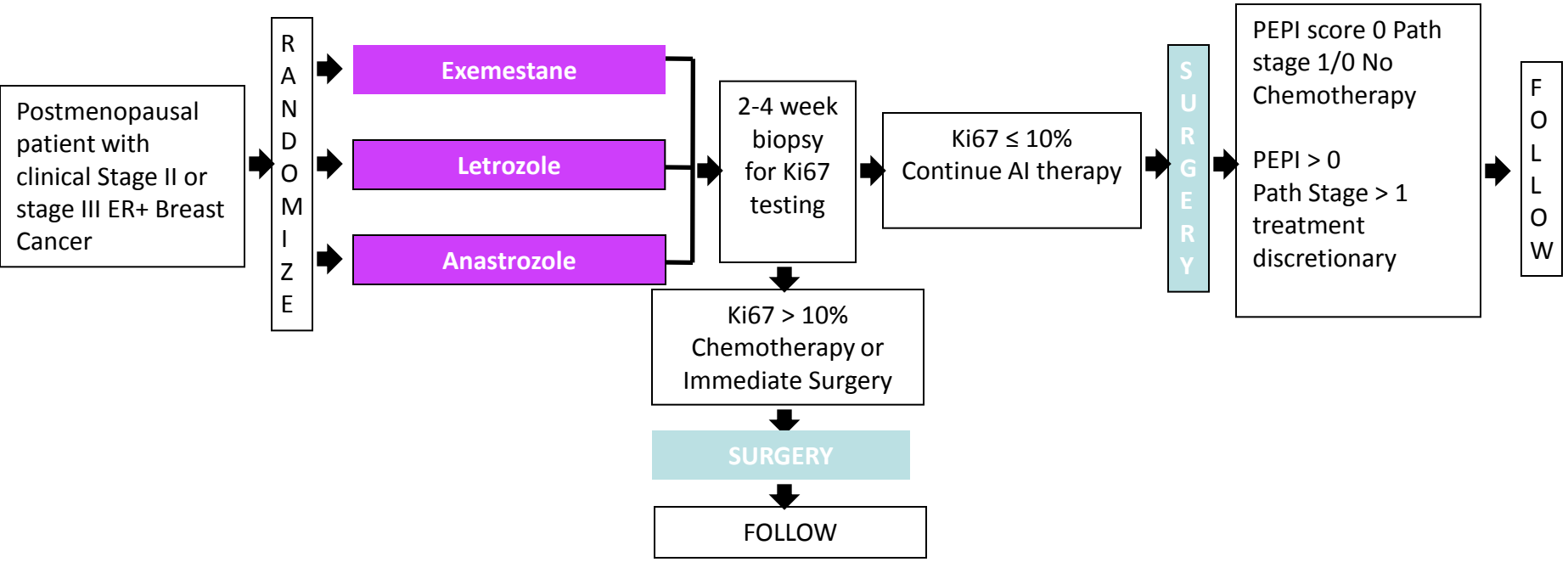
The preoperative endocrine prognostic index (PEPI)

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

Ellis M et al, JNCI 2008


A
RFS By Risk Group in P024
Kaplan—Meier Estimate
1.0
0.8
0.6
0.4
0.2
0.0
Group 1
Group 2
Group 3
0 12 24 36 48 60 72 84 96
Relapse Free Survival (Months)
at Risk
Group1 41 41 39 37 34 27 1
Group2 65 65 58 46 42 37 4
Group3 52 49 42 26 21 18
B
BCSS By Risk Group in P024
Kaplan—Meier Estimate
1.0
0.8
0.6
0.4
0.2
0.0
Group 1
Group 2
Group 3
0 12 24 36 48 60 72 84 96
Breast Cancer Specific Survival (Months)
at Risk
Group1 41 41 39 37 35 29 1
Group2 65 65 61 52 49 43 6
Group3 52 51 45 37 29 23
C
RFS By Risk Group in IMPACT
Kaplan—Meier Estimate
1.0
0.8
0.6
0.4
0.2
0.0
Group 1
Group 2
Group 3
0 12 24 36 48 60 72 84 96
Relapse Free Survival (Months)
at Risk
Group1 31 27 26 17 9 6 4 1
Group2 97 84 71 59 24 16 9 3
D
RFS By Pathological Stage in IMPACT
Kaplan—Meier Estimate
1.0
0.8
0.6
0.4
0.2
0.0
Stage 0/1
Stage 2/3
0 12 24 36 48 60 72 84 96
Relapse Free Survival (Months)
at Risk
Stage0/1 43 39 38 29 15 9 4 3
Stage2/3 161 135 114 82 34 23 11 1

ACOSOG Z1031 COHORT B



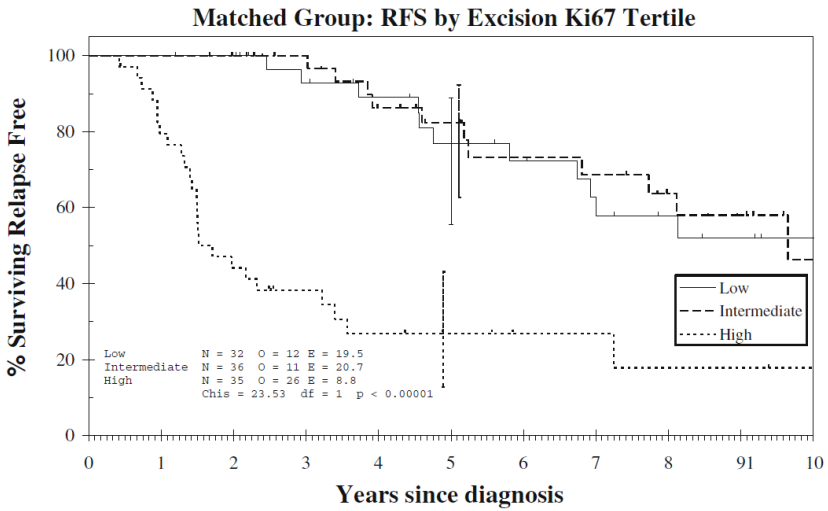
Amendment 6

Activated October 1st 2009

http://www.ctsu.org/

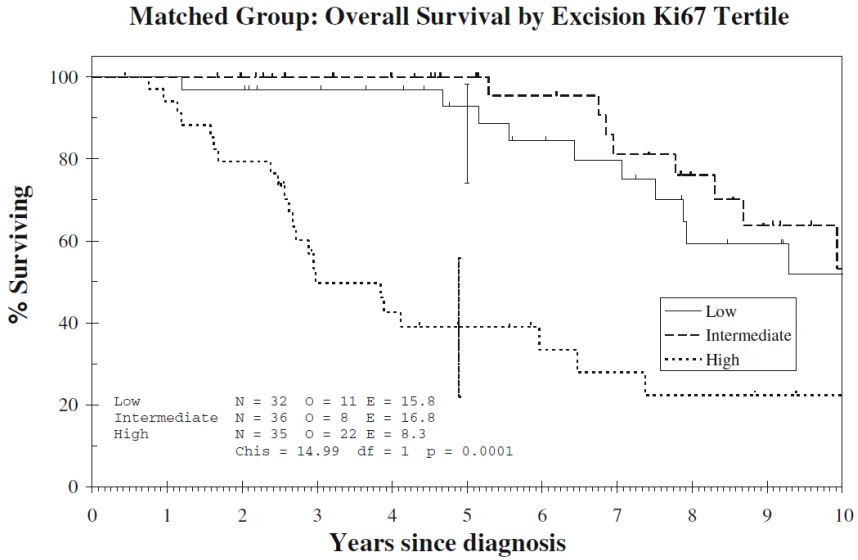
PEPI: Preoperative Endocrine Prognostic Index

Prognostic significance of Ki 67 before and after PCT



Number at risk

Low	32	31	31	26	23	18	16	12	10	8	6
Intermediate	36	35	34	30	24	20	16	15	11	8	4
High	35	27	15	10	7	5	3	3	2	2	1



Number at risk

Low	32	31	31	28	26	22	19	17	11	10	7
Intermediate	36	35	34	30	28	24	21	17	13	9	5
High	35	32	27	14	12	9	6	5	4	3	2

Jones R et al, Breast Cancer Res Treat 2009

Prognostic model based on nodal status and post-therapy Ki 67 in patients with residual disease after PCT

- 221 patients with clinical stage II-III BC treated with PCT were included
- A pCR was obtained in 8.8% of the cases
- HR negativity, HER2 positivity and poor differentiation were significant predictors of pCR

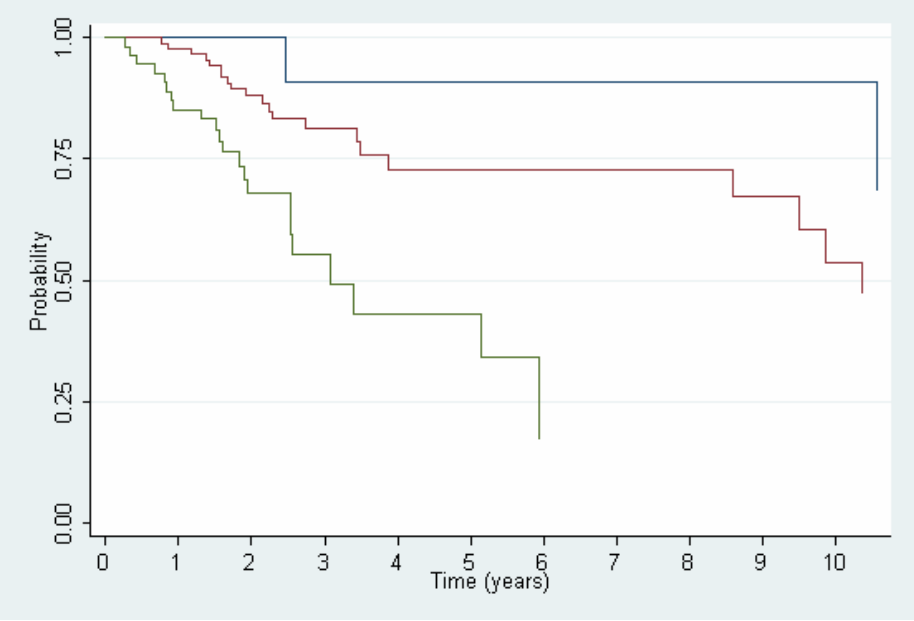
	5-year DFS (95% CI)	*P* value[a]	5-year OS (95% CI)	*P* value[a]
All patients	69.3% (60.1% to 76.9%)		82.8 (72.3% to 89.6%)	
Ki-67 <15%	77.2% (61.0% to 87.2%)		87.8% (69.0% to 95.5%)	
Ki-67 ≥15%	50.2% (32.2% to 65.8%)	0.0001	73.1% (51.1% to 86.4%)	0.0078
p53 <10%	68.8% (51.4% to 81.1%)		81.4% (62.5% to 91.4%)	
p53 ≥10%	48.6% (25.8% to 68.1%)	0.092	73.1% (45.1% to 88.4%)	0.457
EGFR <1%	67.1% (54.5% to 77.0%)		80.9% (65.4% to 90.1%)	
EGFR ≥1%	62.8% (28.9% to 84.3%)	0.469	63.7% (17.3% to 89.1%)	0.068
VEGFR2 ≤15%	70.4% (56.8% to 80.4%)		84.1% (65.7% to 93.1%)	
VEGFR2 >15%	57.5% (32.9% to 75.8%)	0.615	72.4% (45.3% to 87.7%)	0.346

V Guarneri et al, Ann Oncol 2009

Survival according to risk groups

- In the multivariate analysis, post-therapy Ki 67 and nodal status were the only factors significantly related with patients outcome
- 187 patients with residual disease after PCR were classified as follows:

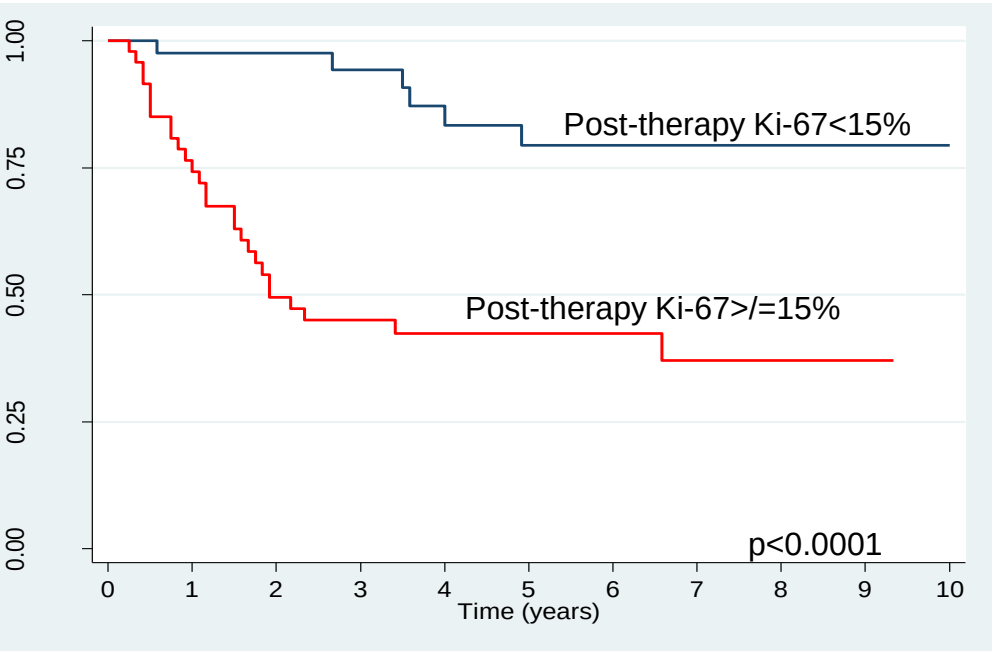
	HR (relapse)	p	HR (death)	p
Low risk (low ki67, N-), 14%	ref		ref	
Intermediate risk (high Ki67 or N+), 54%	3.1		2.4	
High risk (high ki67 and N+), 31%	9.3	<0.0001	6.5	0.042

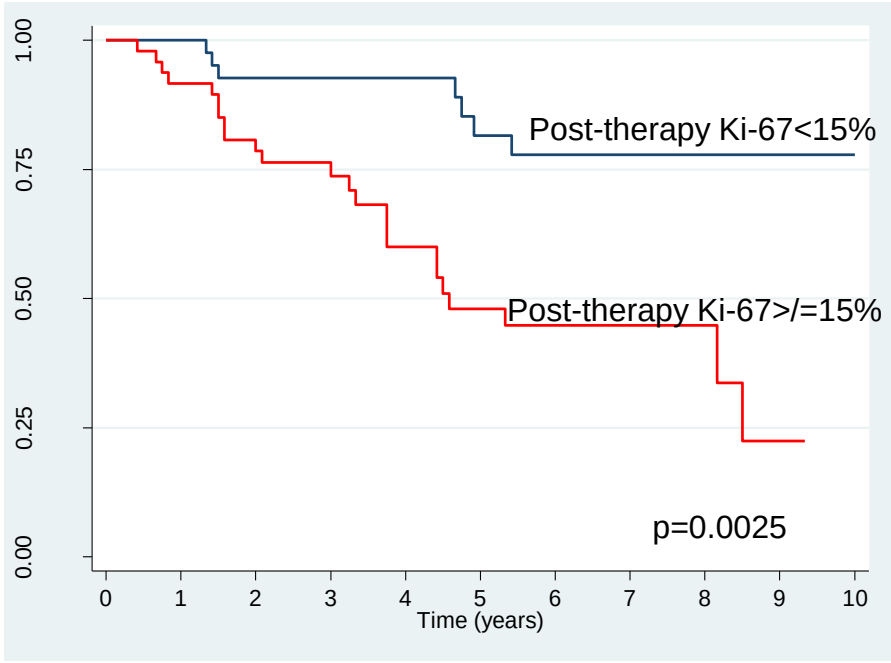


V Guarneri et al, Ann Oncol 2009

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History®

High Ki-67 in residual disease following preoperative chemotherapy is an independent predictor of recurrence and death in breast cancer patients





V. Guarneri, ASCO 2010

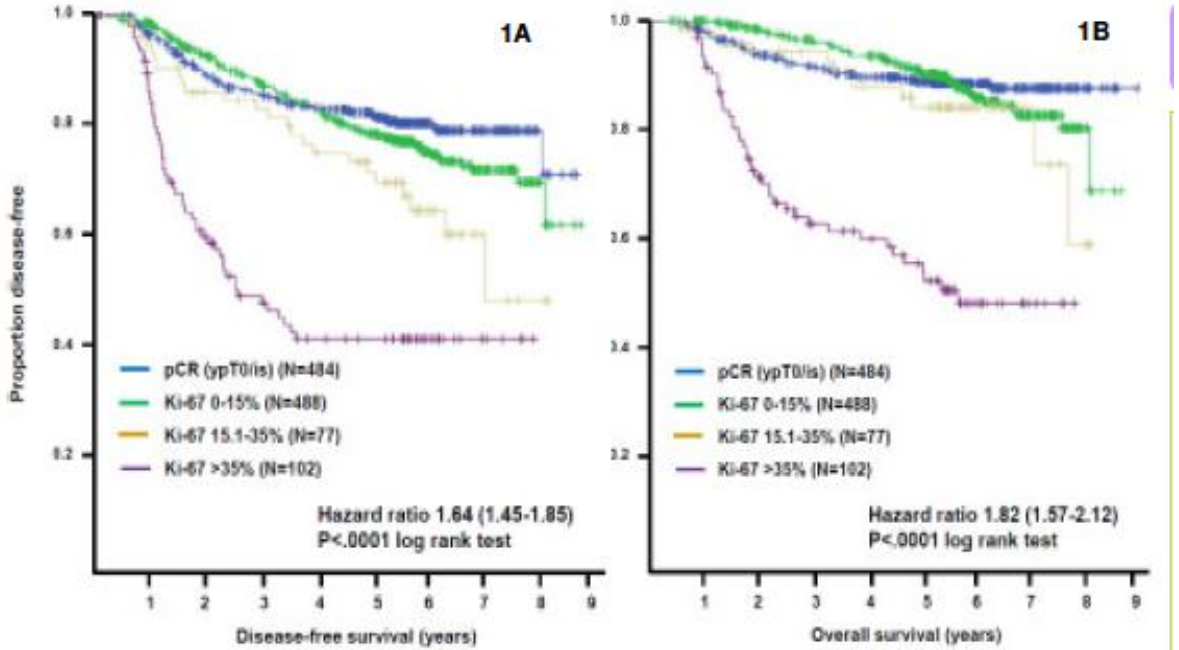
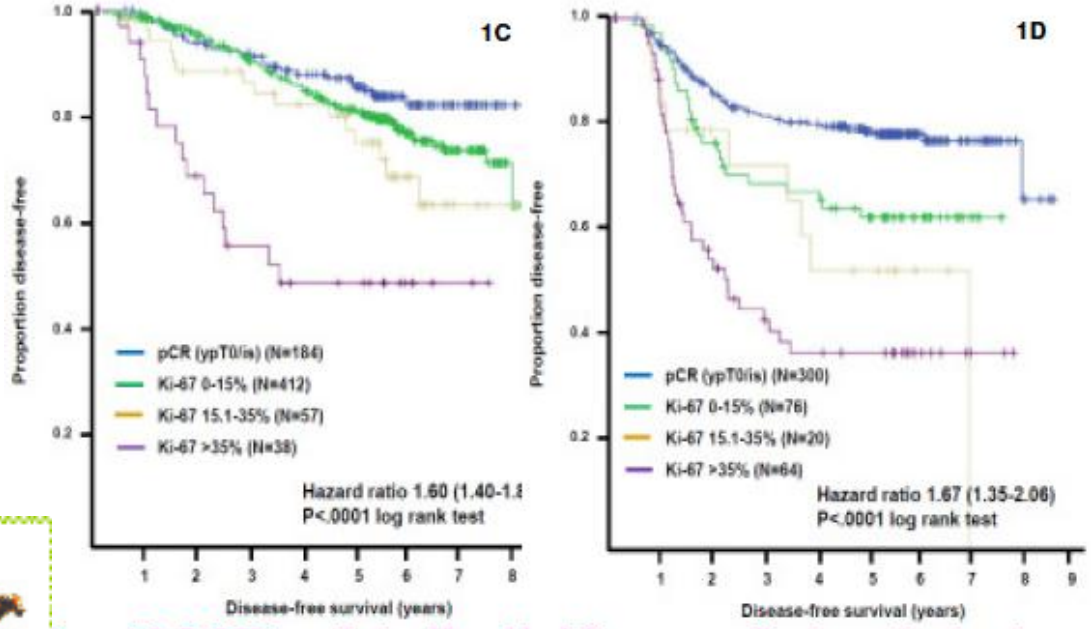


Figure 1 A+B: DFS (A) and OS (B) in patients with different post-treatment KI-67 status

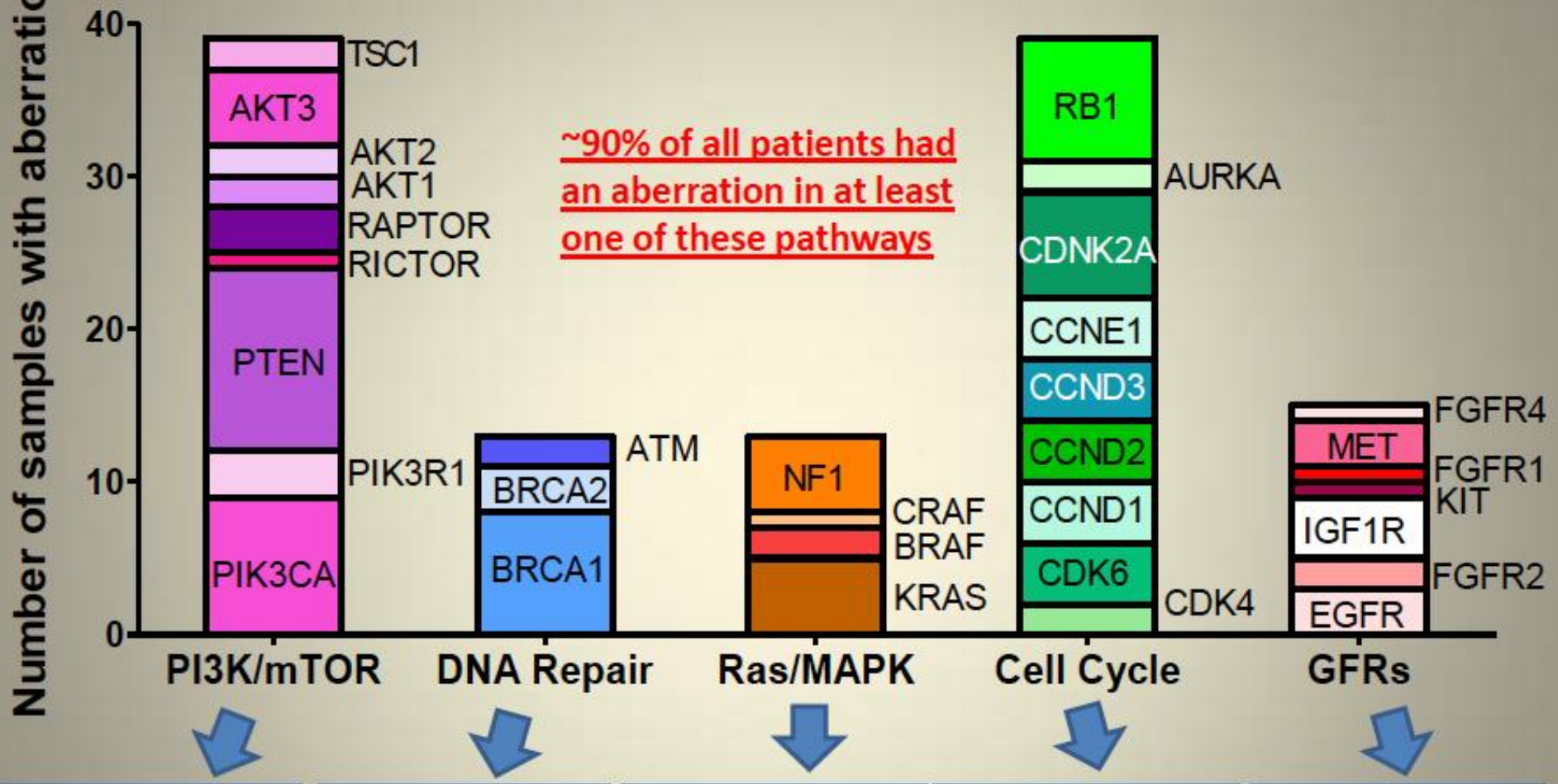


igure 1 C+D: DFS in patients with residual disease according to post-treatment
i-67 in HR-positive (C) and HR-negative (D) disease

GEPAR-TRIO

GBG
GERMAN
BREAST
GROUP

Clinically targetable pathways in TNBC



~90% of all patients had an aberration in at least one of these pathways

PI3K/mTOR inhibitors	DNA-repair targeting agents	RAF/MEK inhibitors	Cell cycle/mitotic spindle inhibitors	Targeted RTK inhibitors

PST: a step forward precision cancer medicine

- In vivo test of treatment efficacy
- Patient & tumor characteristics are crucial to choose the most appropriate therapy
- Patients still at high risk of relapse after receiving the best neoadjuvant therapy are the optimal candidates for testing new agents/strategies
- Molecular characterization of residual disease might give insights into biology of micrometastatic disease