Selection of Optimal Candidates for Preoperative Systemic Therapy (PST) for Primary Breast Cancer

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Preoperative Systemic Therapy: Potential Advantages

- Improved Tumor Downstaging
  - Inoperable → Operable
  - Mastectomy → BCT
    - Improves the rate of breast conservation surgery
- Provides in vivo assessment of anti-tumor effects
- Provides opportunity to assess surrogate biological endpoints
- May expedite new drug development
- Early initiation of systemic therapy
- Inhibition of post-surgical growth spurt

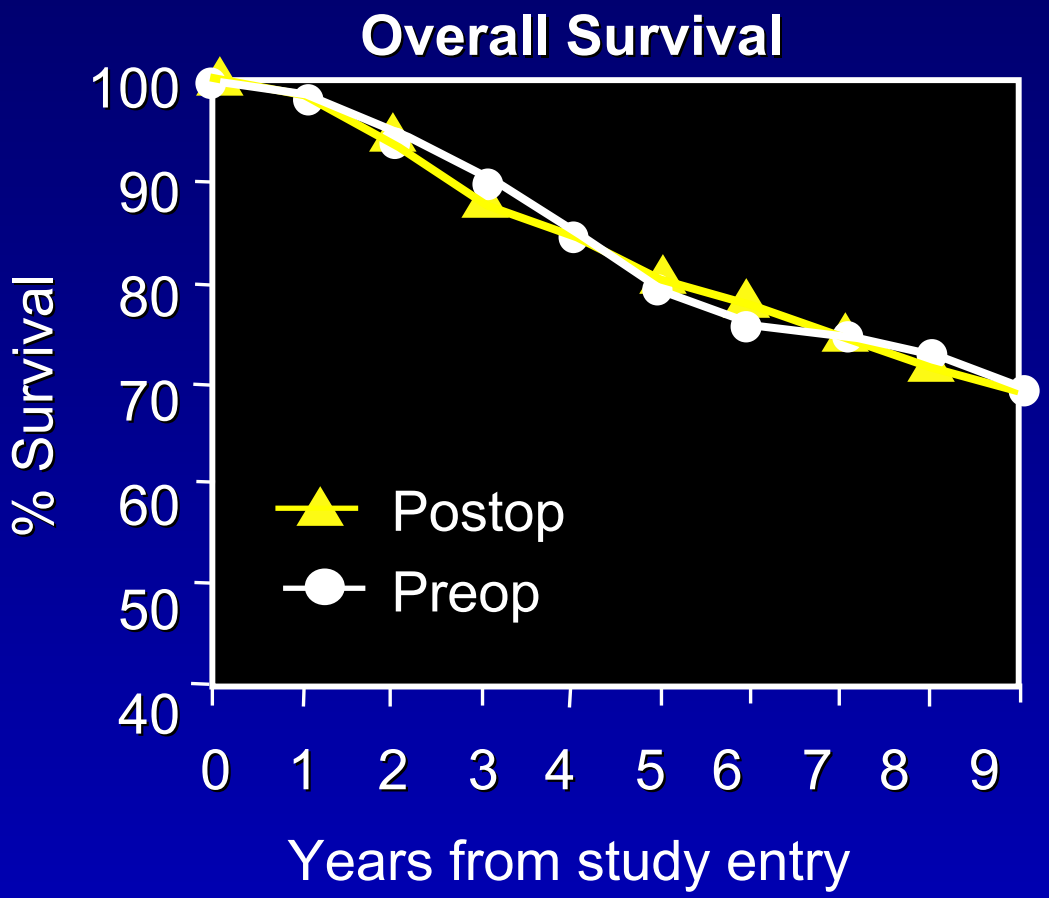
Prospective Randomized Trials:
Preoperative vs. Adjuvant Chemotherapy In LABC

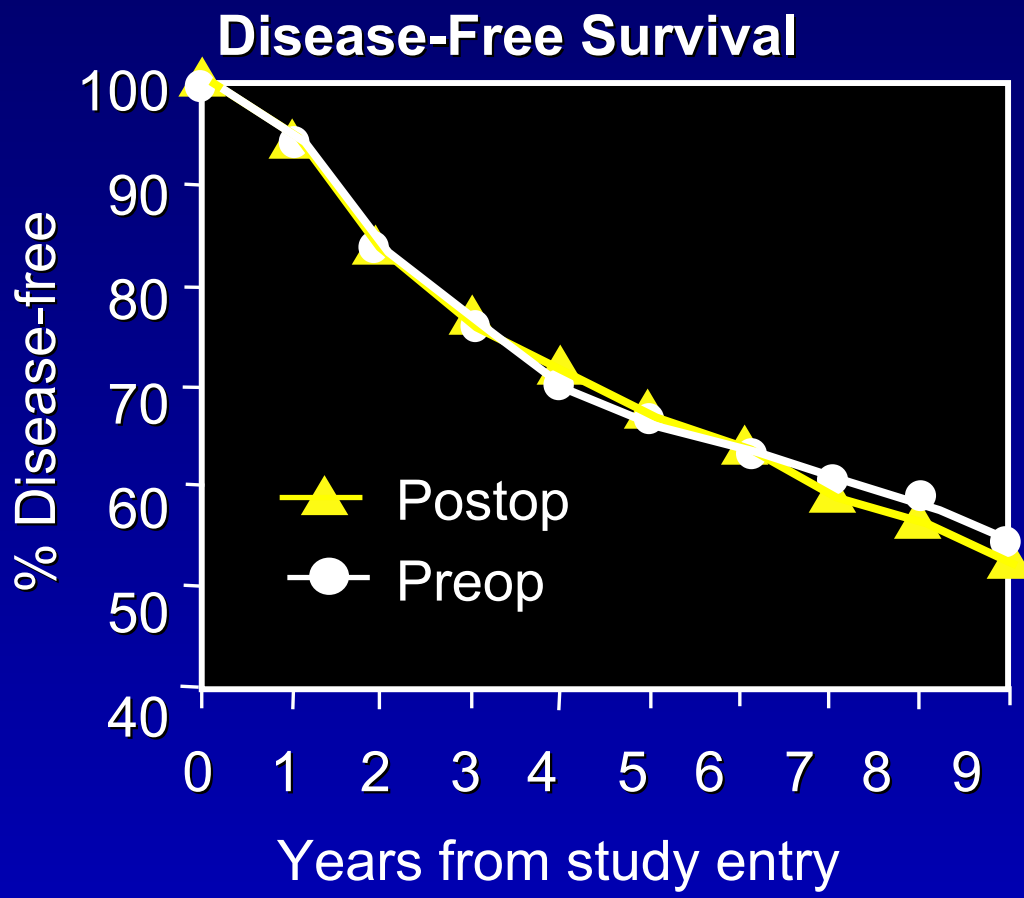
Author	Year	# Pts	F/U Mos	OS (%)	DFS (%)
Schaake-Koning	1985	39	66	37	24
		34		37	24
Mauriac	1991	133	34	**95** *	80
		134		**88** *	79
Pierga	1992	200	36	93	68
		190		86	66
Scholl	1994	196	54	**86** *	59
		194		**78** *	55
Semiglazov	1994	137	53	86	**81** *
		134		78	**71** *
Gervasio	1994	81	120	57	42
		90		53	40

*$P < 0.05$

Schaake-Koning C, *IJROBP* 9:1023-8, 1983; Mauriac L, *Ann Oncol* 10:47-52, 1999; Scholl SM, *Eur J Cancer* 30A:645-52, 1994
Semiglazov VF, Ann Oncol 5:591-5, 1994; Gervasio H, *Eur J Cancer* 29A(S6):S71, (abst 362), 1993

B-18
Overall and Disease-Free Survival





Wolmark et al. J Natl Cancer Inst Monogr 2001;30:96-102.

Breast-Conserving Surgery after PST

Randomized Phase III Trials of PST vs. ACT for Primary Operable Breast Cancer

Trial (n)	TNM	CT regimen	F/U in months	% pCR	BCS rate: NACT/ACT
NSABP B-18 (n=1523)	T_{1-3} N_{0-1}	AC x 4	114	9	**67/60** *P*=0.002
ECTO (n=892)	T_{1-3} N_{0-1}	AP x 4 → CMF x 4	43	23	**71/35** *P*<0.0001
EORTC 10902 (n=698)	T_{1c-4b} N_{0-1}	FEC x 4	56	4	**35/22** *P* N/A
ABCSG (n=423)	T_{1-3} N_{0-2}	CMF X 3	N/A	6	**67/60** NS
S6 (N=390)	T_{1-3} N_{0-2}	CAF 4	105	N/A	**82/77** NS

What Patients are Optimal Candidates for Preoperative Chemotherapy for Primary Breast Cancer?

Simple answer:

All Patients known to be candidates for adjuvant chemotherapy are candidates for preoperative chemotherapy

Do All Patients Benefit Equally from Preoperative Chemotherapy?

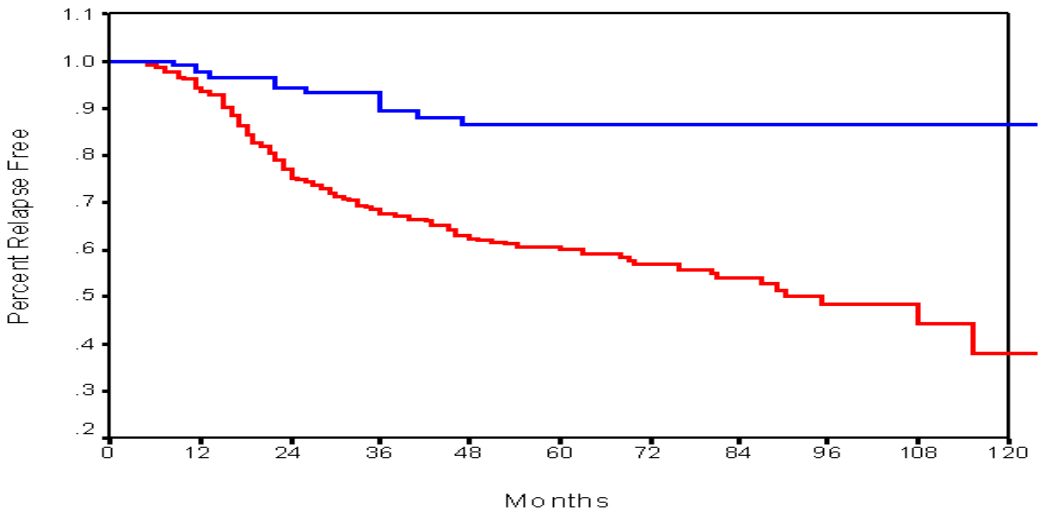
How Should we Define pCR?

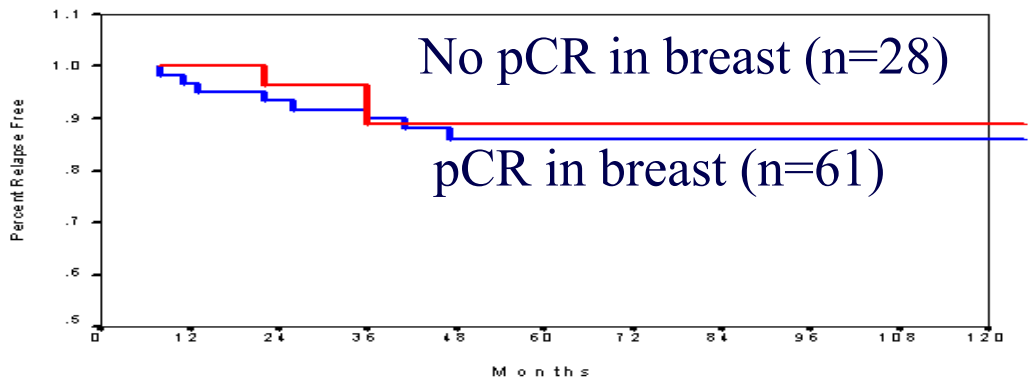
Definitions of Pathological Complete Remission (pCR)

- Malignant cells undetectable in breast and lymph nodes
- Invasive tumor undetectable in breast and lymph nodes (DCIS allowed)
- Invasive disease absent in breast
- Total or near total therapeutic effect in the primary tumor and evidence of therapeutic effect in lymph nodes, no metastasis

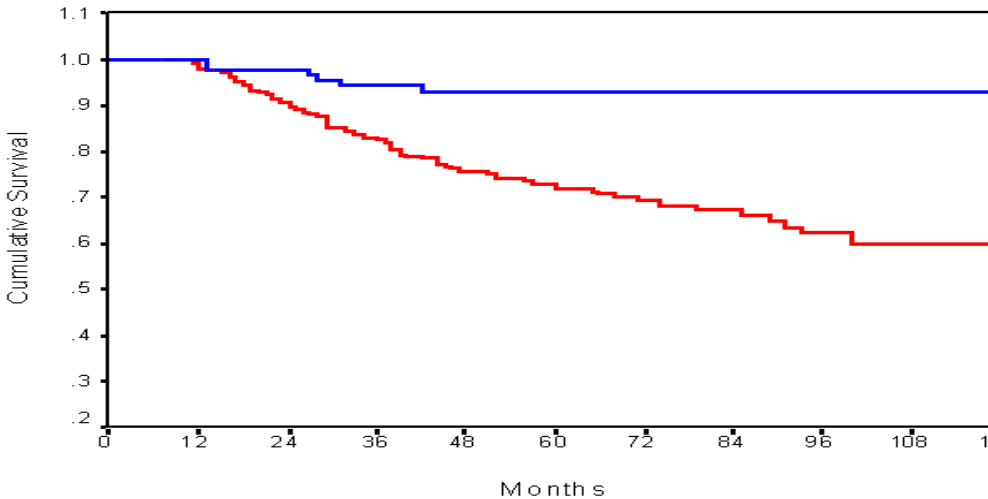
Outcome by Pathological Nodal Status After Preoperative Chemotherapy

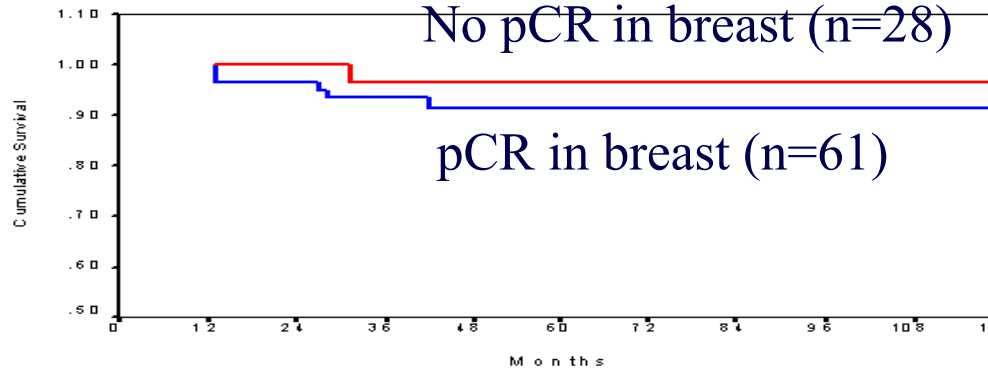
Relapse-free Survival





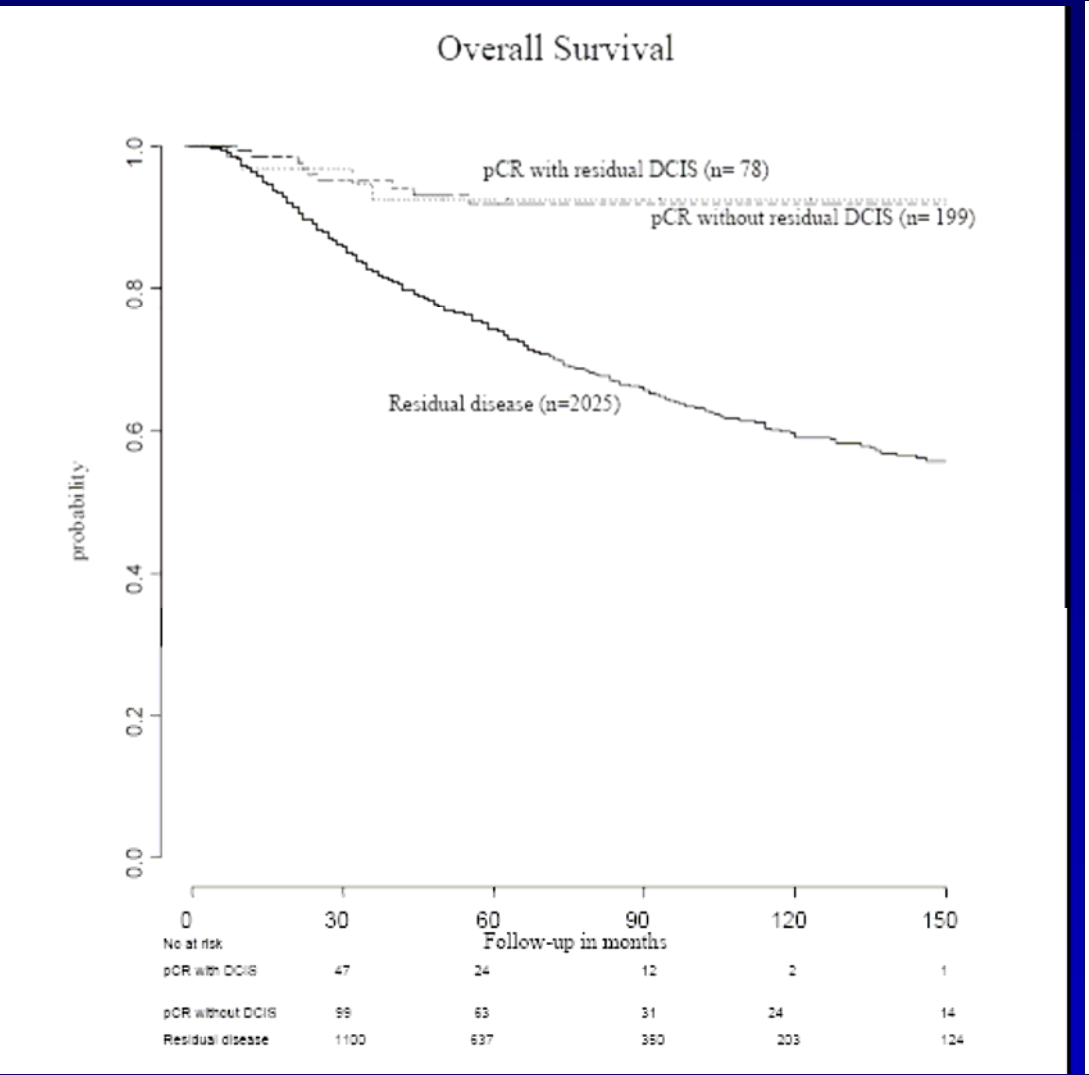
Overall survival

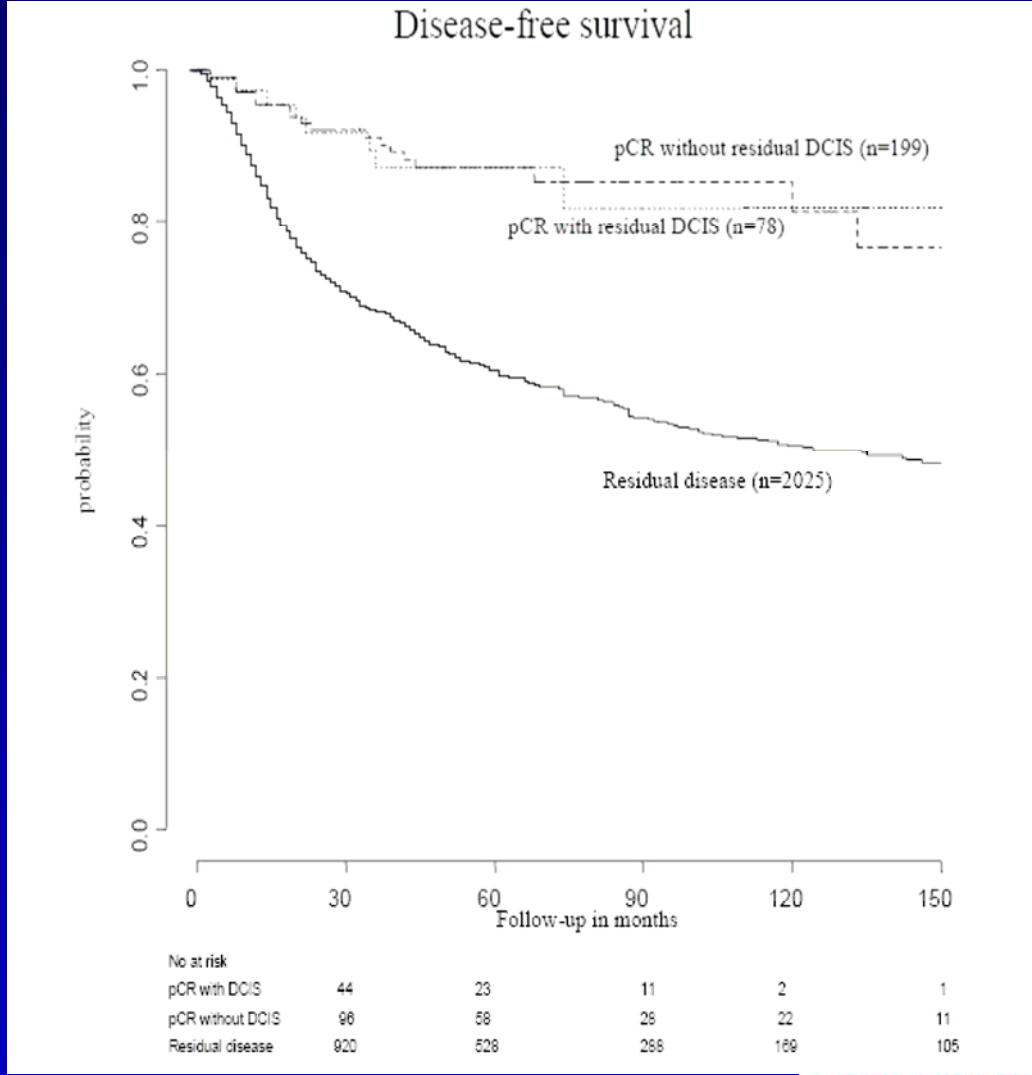




Hennessy B, et al.: *J Clin Oncol* 23:9304-11, 2005

Does Residual DCIS Influence Outcome in Patients Who Achieve pCR





Mazouni C, et al. *J Clin Oncol* 2007 (in press)

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Making Cancer History

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Is Pathological Complete Remission an Established Surrogate Marker for Survival?

- Patients who achieve pCR clearly have better survival rates than patients who do not.
  - Feldman LD, et al, *Cancer Res* 46:2578-81, 1986; Fisher B, et al, *J Clin Oncol* 16:2672-85, 1998; Kuerer HM, et al, *J Clin Oncol* 17:460-9, 1999

Questions

- If pCR rate increases will survival rate increase too?
- Is pCR of prognostic value in patients with ER+ breast cancer or those treated with endocrine therapy?
- Can patients who achieve a pCR be treated with less therapy? (surgery, RT, adjuvant systemic treatment)

Tools to Predict Response

- Individual predictive marker
  - Pathological
  - Biochemical
- Predictive Indices
- Functional Imaging (PET)
- Genetic Profiling

Factors Predictive of Higher pCR Rate

Factor	Higher pCR rate
Tumor size	Smaller size
Tumor grade	Higher grade
Histological type	Ductal > lobular
ER/PR	Negative
HER-2	Positive
Proliferative markers	Higher
MDR-1/pgp	Negative

Reported pCR Rates by Histological Type

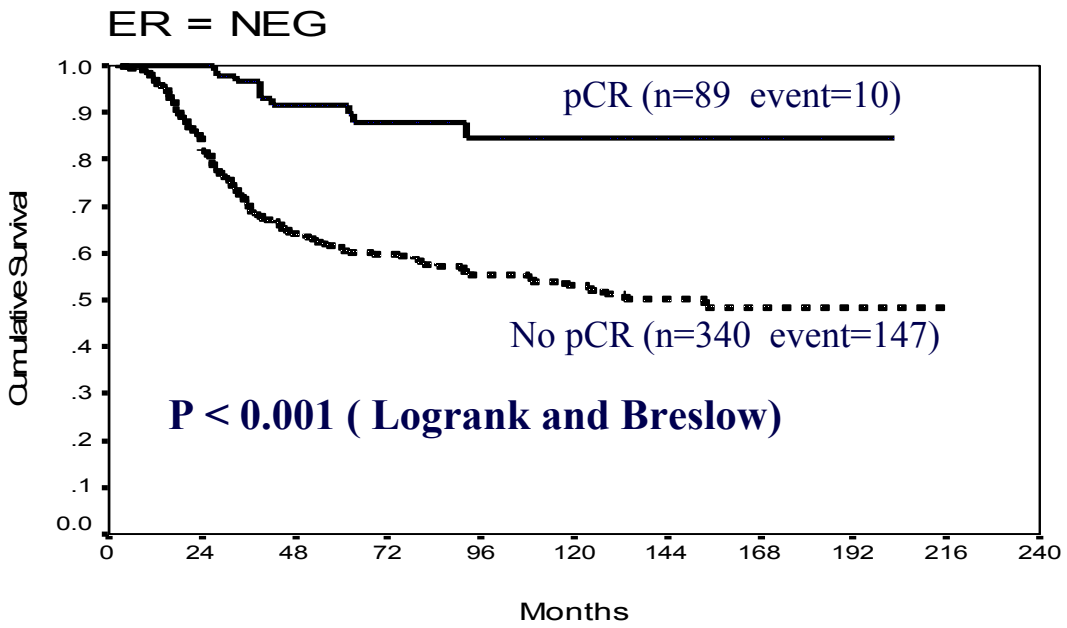
Author (year)	No. pCR/Total No.	
	Lobular	Ductal
Cocquyt (03)	0/26	15/101
Chatuverdi (04)	0/31	44/260
Pu (05)	0/5	4/41
Cristofanilli (05)	4/122	138/908
Tubiana-Hulin (05)	1/118	67/742
Vincent-Salomon (05)	1/52	32/532
Total (%)	6/354 (1.7)	300/2584 (11.6)

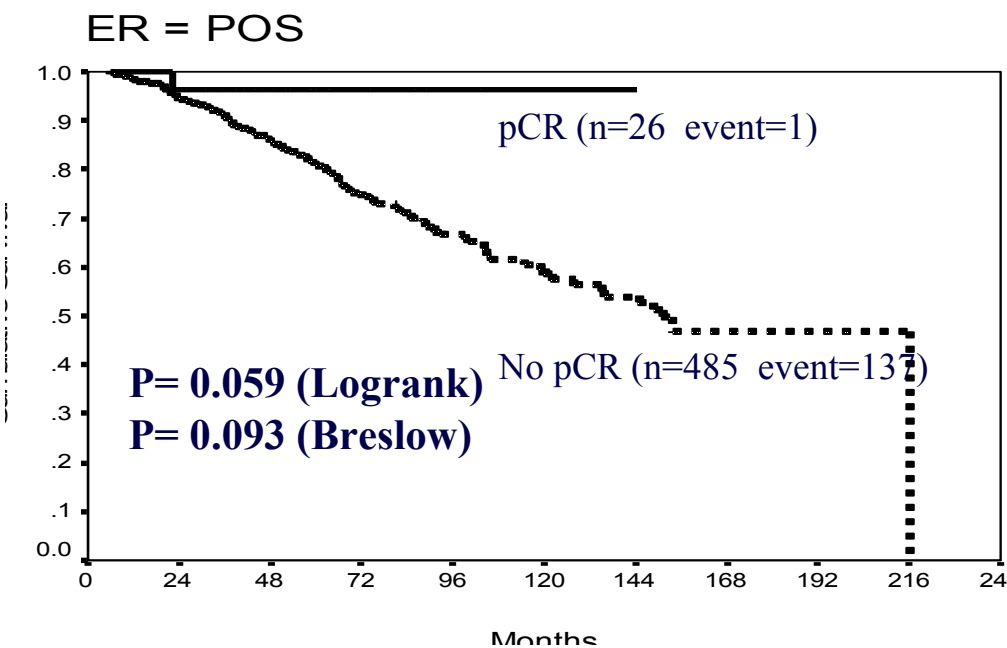
Katz A, et al. Breast Cancer Res Treat 100 (Suppl 1):S113 (2097), 2006, and *Lancet Oncol* 8(1):55-62, 2007

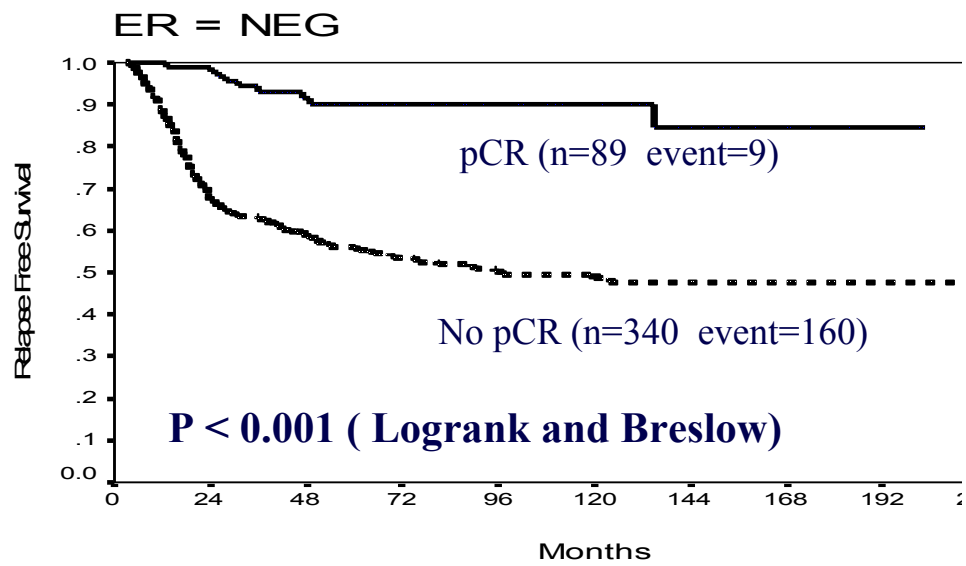
Hormone Receptor Content is a Reliable Predictor of pCR

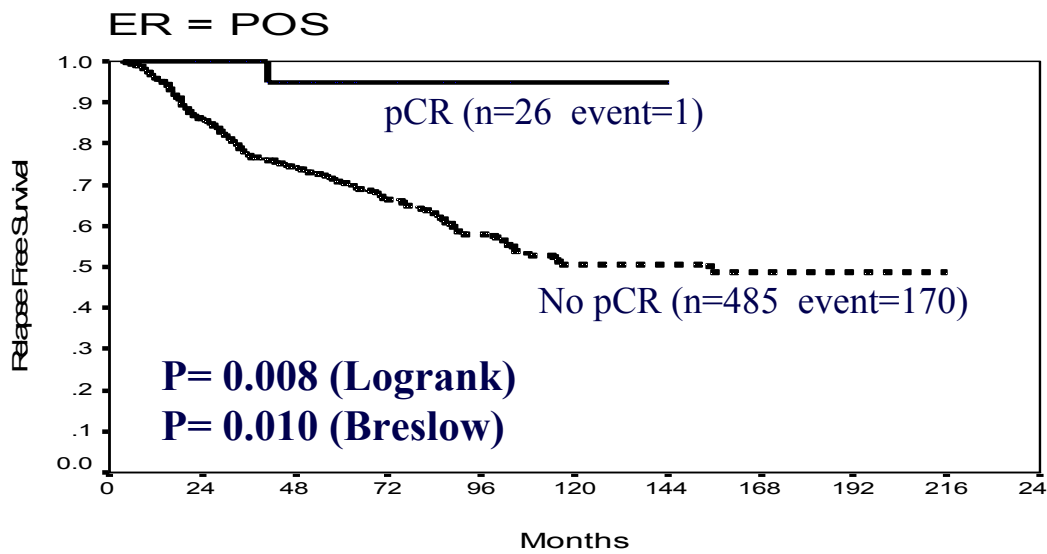
Trial/ author	No. of pts	Regimen	% HR negative	% pCR	
				HR-	HR+
Kemeny	54	FACVb	34	20.0	7.7
Ring	435	CMF, A/E	29	21.6	8.1
Bear	1211	AC	41	13.6	5.7
Bear	565	AC+T	43	22.8	14.1
GEPARDO	250	ddAD+/-T	44	15.4	1.1
GEPARDUO	913	ddAD/CA-D	26	22.8	6.2
GEPARTRIO	286	TAC/TAC-NX	32	36.6	10.1
Buzdar	1018	FAC+/-P	NA	20.6	5.6

Outcomes by pCR and ER Status





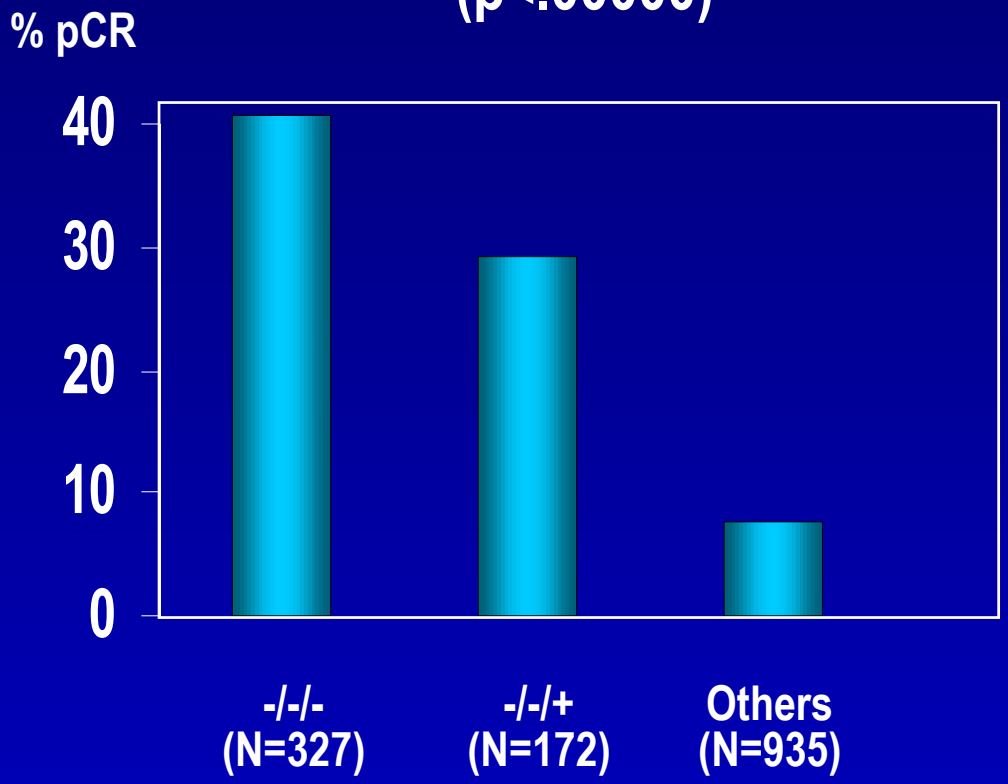




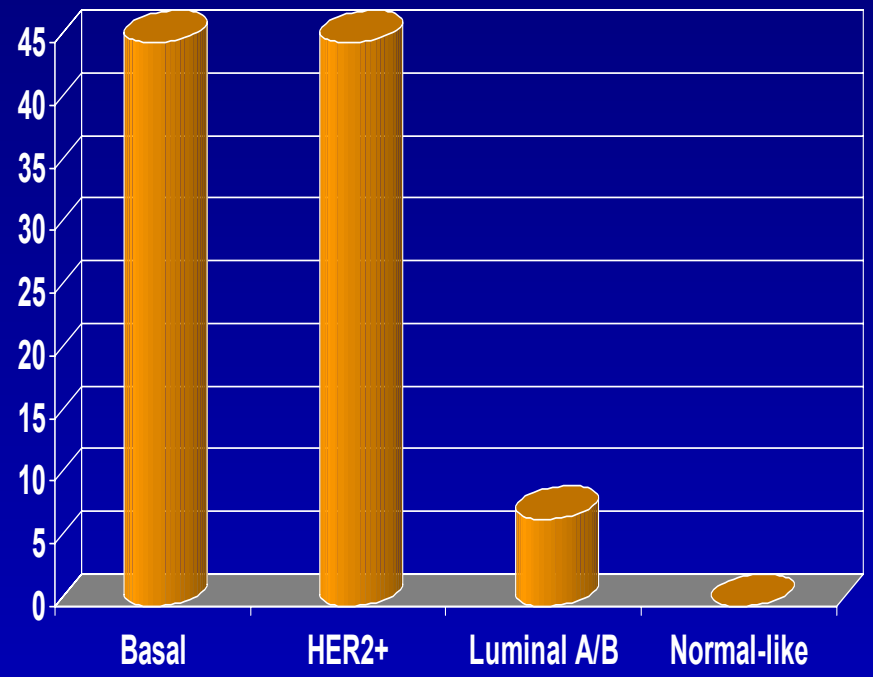
Guarneri V, et al, *J Clin Oncol* 24:1037-44, 2006

Pathological CR by Molecular Subtype

ER/PR/HER2 (p<.00000)



Gene Expression Profile (p<0.001)



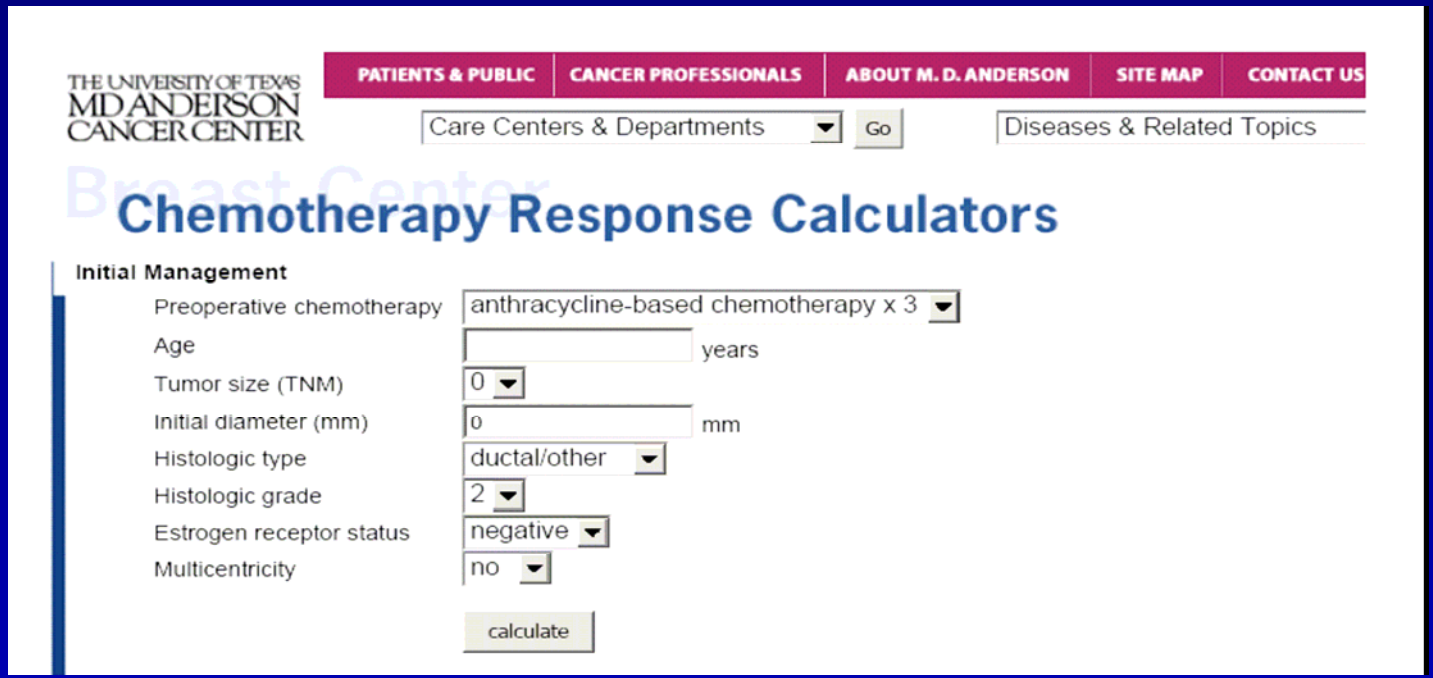
von Minckwitz G, et al.: 29th Annual SABCS; Dec 14-17, 2006; San Antonio, Tex.;
Rouzier R, et al.: *Clin Cancer Res* 11:5678-85, 2005

Individual Predictive Markers

- There is no individual pathological or molecular marker that can reliably predict response to PCT in an individual patient
- It could be hypothesized that patients with ER-negative, high-grade tumors with high S-phase fraction (or Ki-67) would be more likely to respond than tumors with the opposite characteristics

Tumor size, grade, histology and ER-status can be combined into a predictive index of pathologic CR

This pCR predictor is available at:
www.mdanderson.org/care_centers/breastcenter/dIndex.cfm?pn=448442B2-3EA5-4BAC-98310076A9553E63



Rouzier R et al: Nomograms to predict pathologic complete response and metastasis-free survival after preoperative chemotherapy for breast cancer. *J Clin Oncol, 23:8331-8339:2005.*

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Making Cancer History

Genetic Index (Oncotype Dx) to Predict pCR

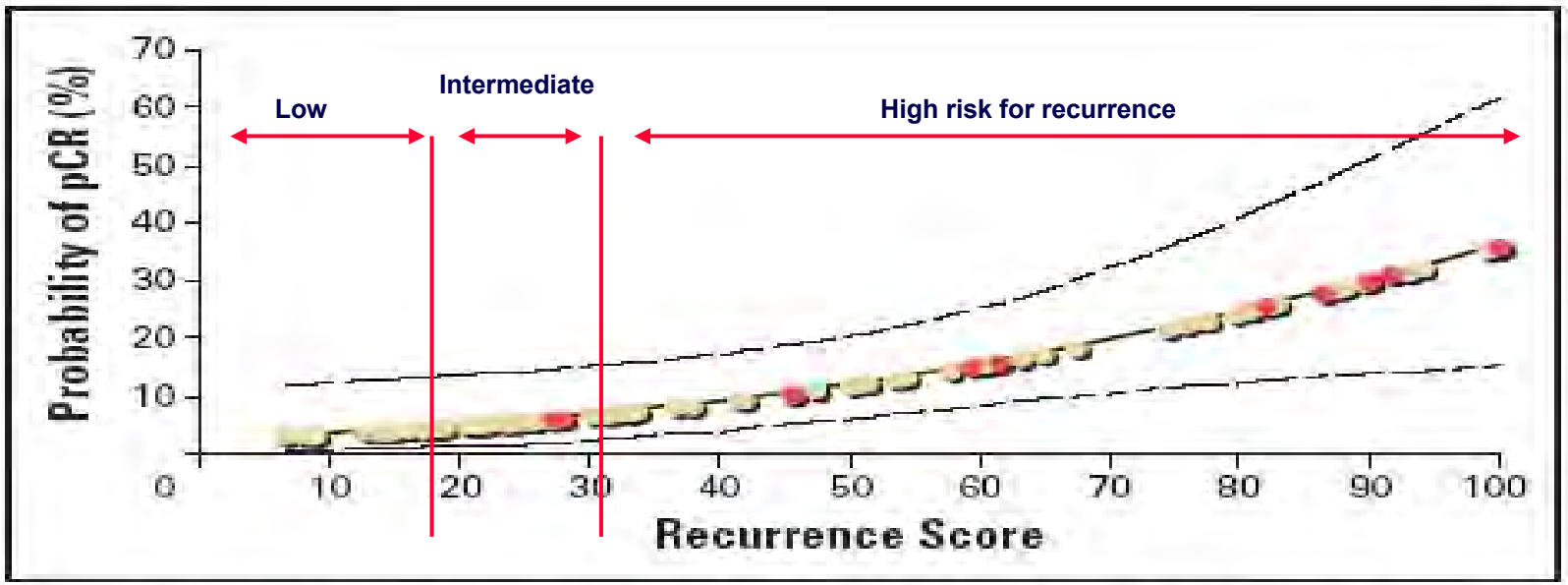
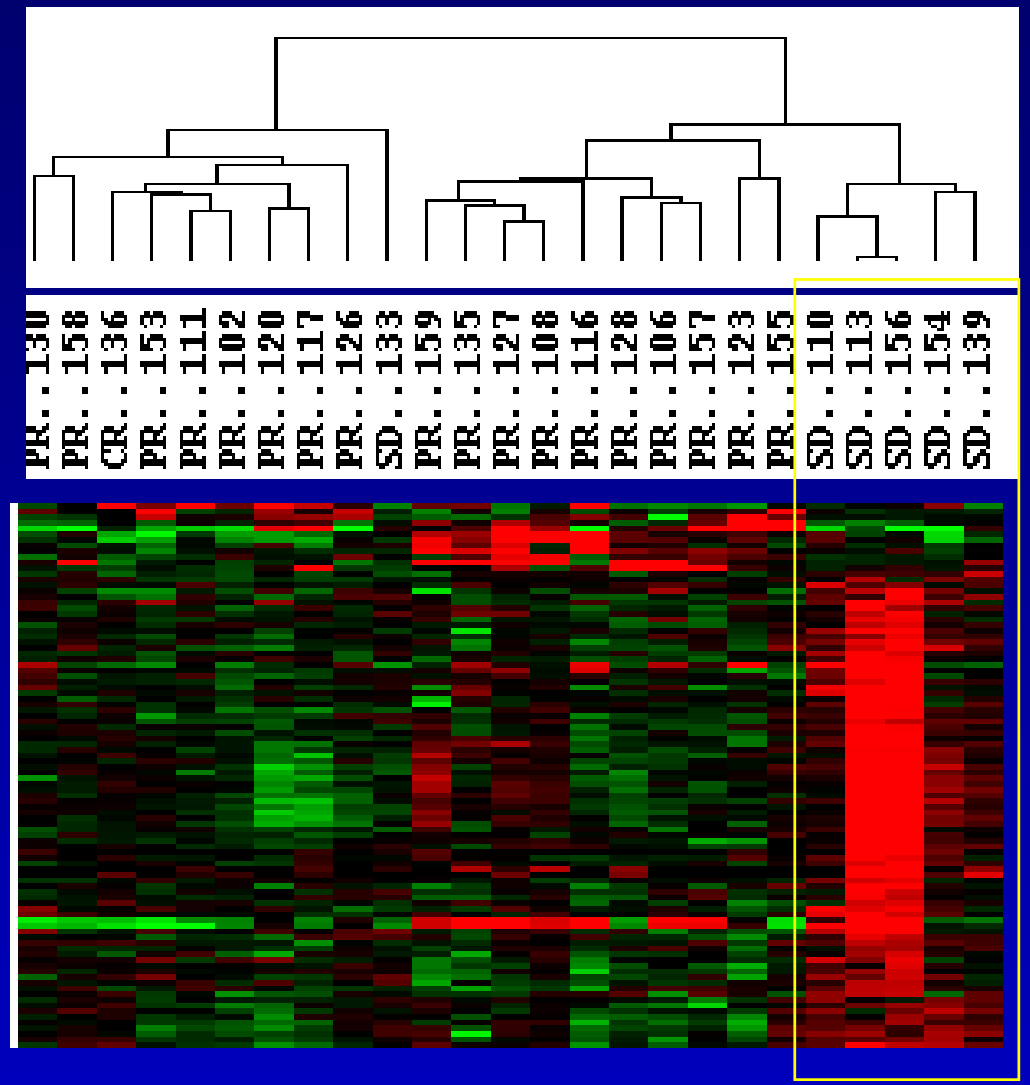


Fig 2. Probablity of pathologic complete response (pCR) as a function of Recurrence Score in the Instituto Nazionale Tumori–Milan (Italy) cohort. The Recurrence Score was calculated for each patient from the expression of 16 cancer-related genes and five reference genes. The red circles represent patients who had a pCR. The yellow circles represent patients who did not have a pCR.

L.Gianni et al. JCO, 2005; 23: 7265-7277

Supervised Cluster Analysis
Taxol® Clinical Response Markers (N=25)

- Top 100 Markers
- Ranked By AbsECombo



L. Pusztai et al., ASCO 2003 #1

Should We Switch Chemotherapy Based on Response to the Initial Regimen?

Sequential Regimens

Author (study)	Treatments	pCR rate	*P*	PFS/ RFS	*P*
Thomas (MDACC)	VACP →VACP	NA	-	26	0.162
	VACP →VbMF	NA		46	
Smith (Aberdeen)	CVAP→CVAP	15	N/A	78%	0.022
	CVAP→Doc	31		93%	
Bear (B-27)	AC	13	<0.0001	69%	0.03
	AC→Doc	26		74%	
Von Minckwitz (GEPARTRIO)	TAC→TAC	24	<0.0001	N/A	N/A
	TAC→NX	6		N/A	

Primary Systemic Therapy: Optimal for All Patients?

“All complex problems have simple answers that are invariably wrong”

H. L. Mencken

A More Complex Answer

- PST is optimal for all patients who are candidates for systemic therapy.
- If indication for systemic therapy is uncertain, surgical removal is preferable.
- PST should be tailored to the biological profile of the primary tumor:

Treatment by Molecular Class

Class	Treatment	Additional Therapies
ER and/or PR-expressors	Aromatase inhibitors SERMs	± chemotherapy
HER2-amplified	Trastuzumab, lapatinib	± chemotherapy, hormone therapy
Triple-negative (ER, PR, HER2)	Chemotherapy (Platinum salts [?])	± bevacizumab
Basaloid	EGFR-inhibitors (?)	Platinum salts (?)

Hortobagyi GN, 2007

When is PST Not Indicated

- PST is Not Indicated when:
  - Systemic Therapy is not indicated
  - Primary and or LN metastases cannot be measured
  - Patient is not compliant
  - Multidisciplinary team is not available