PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

When to consider mid-course changes of therapy based on early response?

Gunter von Minckwitz, M.D., Ph.D., German Breast Group

Topics

Early response:

- As predictor of pathologic response
- As predictor of long-term outcome
- As a decision aid to switch therapy
- To identify patients who might (not) benefit from a switch

Royal Marsden Hospital
n = 198 pts. with operable b.c.

Predictors of pCR/pINV after a variety of therapies	univariate p-value
T1/T2 tumors	0.004
Young age	0.008
Response after 2nd cycle	0.001*

*best predictor in multi-variate analysis

Verrill MV et al. Breat Cancer Res Treat 50:328 1998

Prediction of pCR by response evaluation after 2-4 cycles

Study	Treatment	N pts.		pCR (%)	
		R	NR	R	NR
• GeparD*uo*	ddAT	350	348	17	3
• GeparDuo	AC-T	300	148	17	7
• GeparTrio	TAC	1390	622	21	5
Total		2040	1118	19.6	4.6
		(65%)	(35%)	p<0.001	

R=Responder (cCR or cPR); NR=Non-responder (cNC); dd=dose-dense; T=Docetaxel

Multivariate analysis for pCR in GeparTrio (N=2190)

group with highest chance for pathCR	All	Odds ratio*	
		Responder	Non-Responder
< 40 yrs	2.0	-	6.3
High grade	2.7	2.2	-
ductal	2.2	2.1	-
ER/PR neg	3.7	4.3	2.5
Complete Response after 2 cycles	10.4	2.3	n.a.

* Odds ration against group with lowest pCR rate

Predictors of pCR in GeparTrio

% pCR

ER/PR
(P<0.00000)

- / -
(N=629)

+ / -
(N=266)

+ / +
(N=900)

% pCR

Response after 2 cycles
(P<0.00000)

CR
(N=108)

PR
(N=1257)

NC
(N=627)
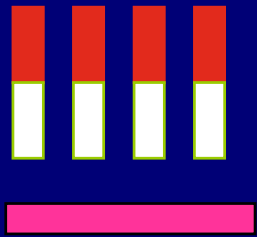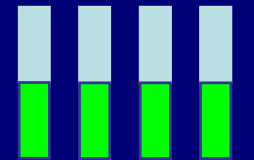
PD
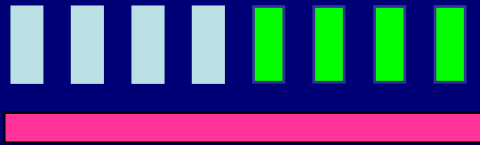(N=12)
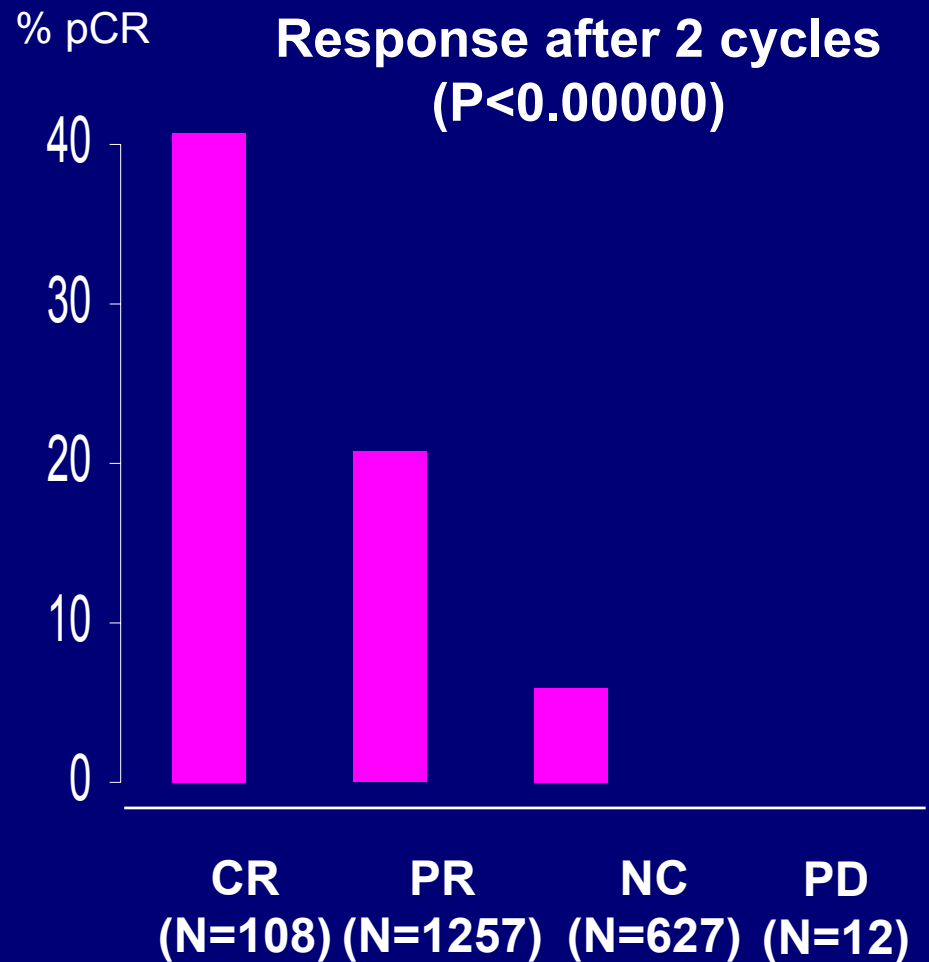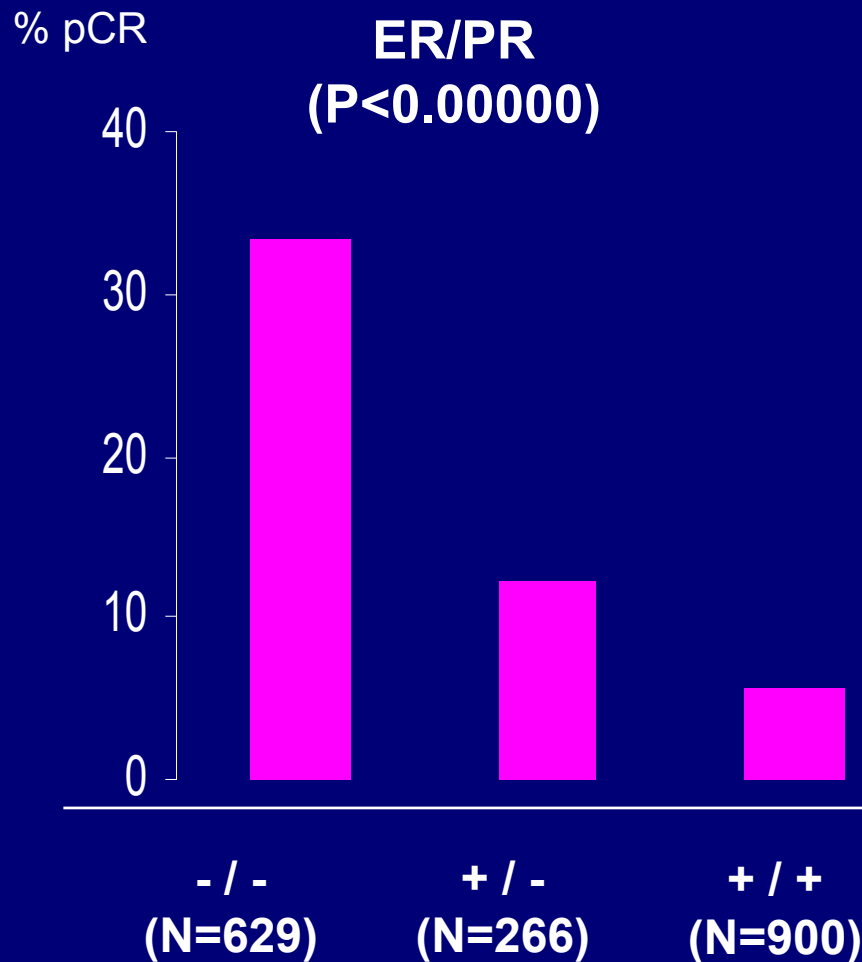
GeparQuattro

N=1500

R

Stratified acc. to Early Response

OP

OP

OP

| Epirubicin 90 mg/m² | Cyclophosphamide 600 mg/m² | Docetaxel 100 mg/m² (A) 75 mg/m² (B,C) | Capecitabine 1800 mg/m² | If Her2 pos: Trastuzumab 6 mg/kg q3w 1y | If endocrine responsive Tam/AIs |

AGO

GBG
GERMAN BREAST GROUP

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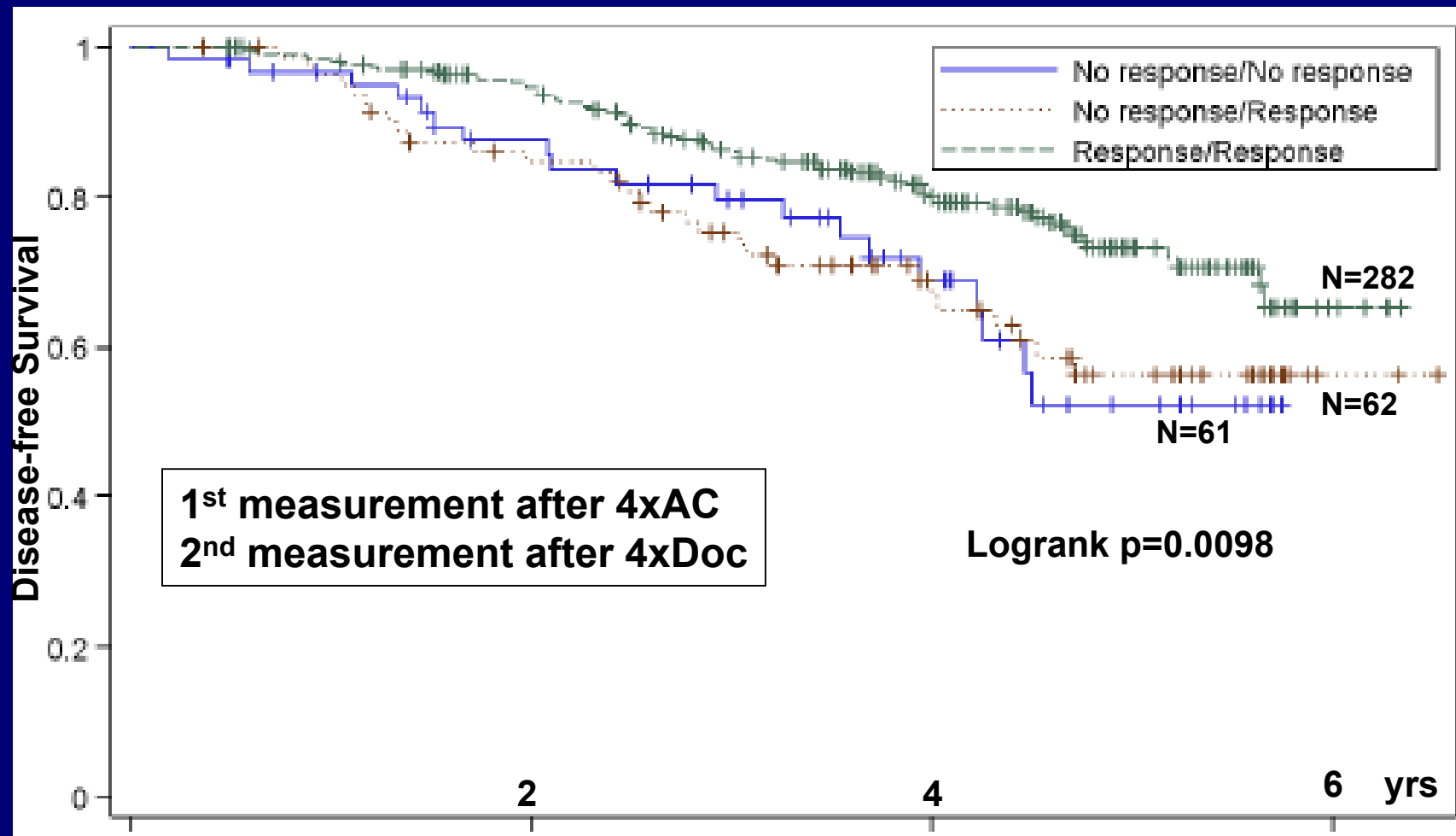# Long Term Prognosis according to Early Response to 4xAC(+Tam)

Response to 4x AC(+Tam)	N Pts.	Event rate at 78 months (after nil or Docetaxelx4)
cCR	906	24.7%
cPR	1079	35.1%
cNC	324	49.1%

$p < 0.0001$

Bear D, NSABP B-27, JCO 2006
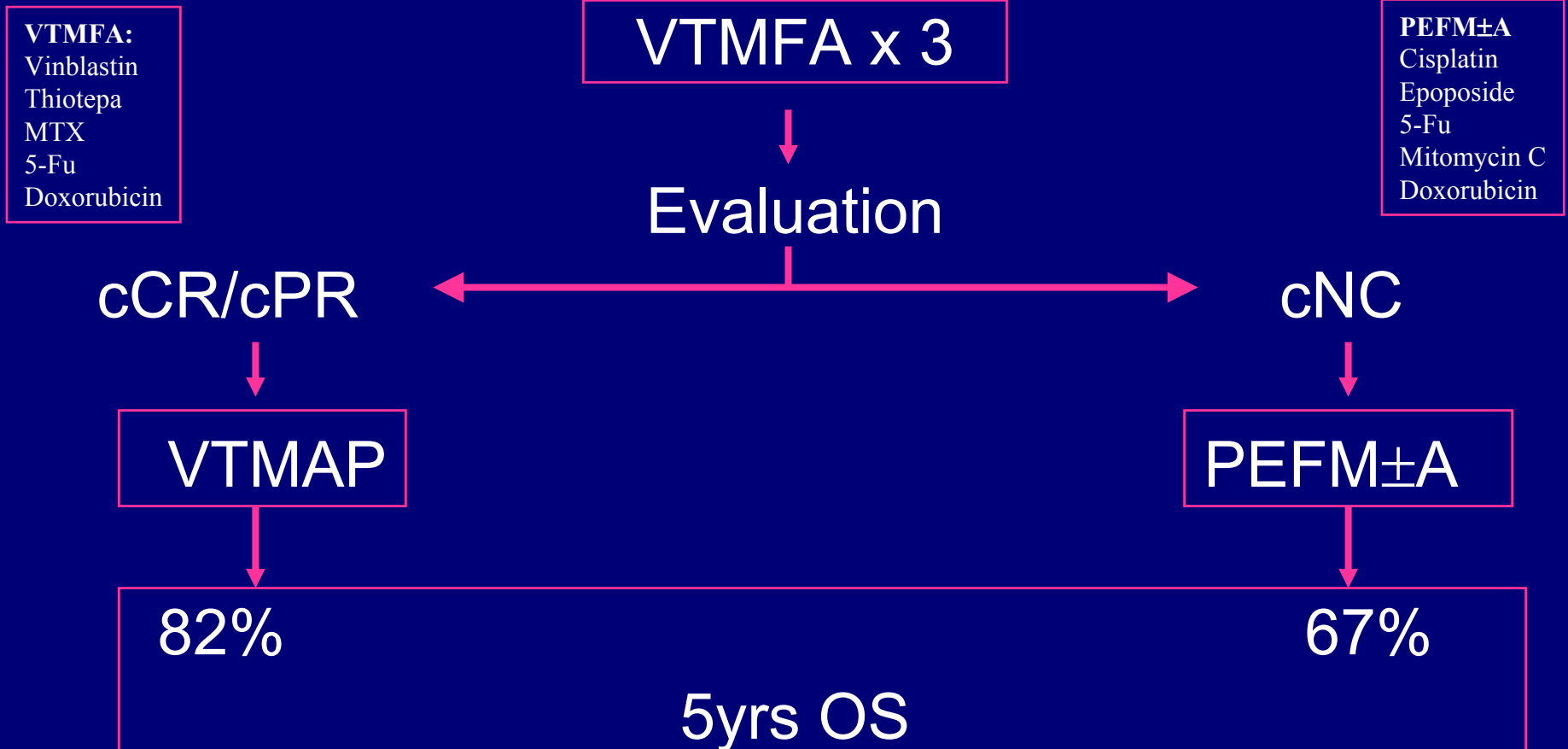
GeparDuo
425 Pts. receiving AC-Doc

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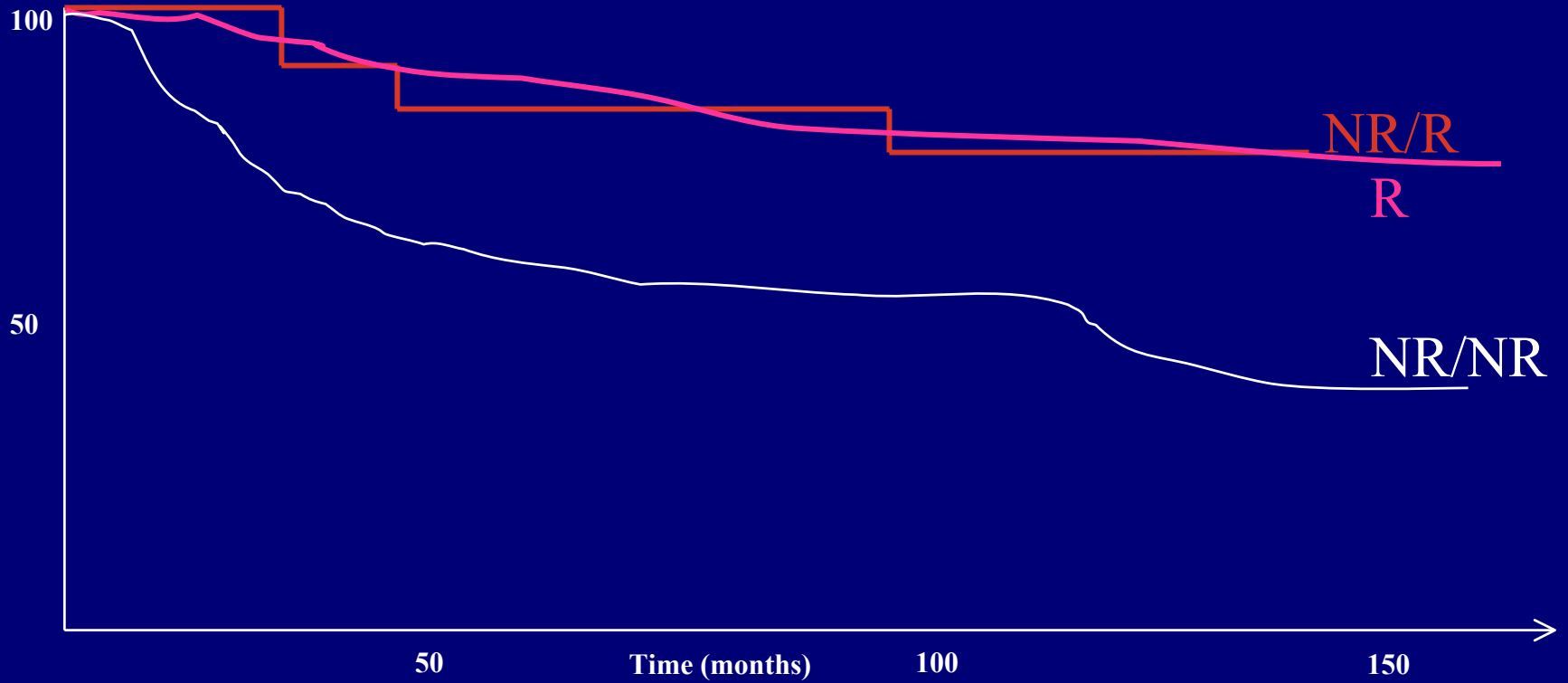
02SR 86 French Phase II Trial
n = 272 Patients Stage I-IIIB

VTMFA:
Vinblastin
Thiotepa
MTX
5-Fu
Doxorubicin

VTMFA x 3

↓

Evaluation

cCR/cPR ←—————————————→ cNC

PEFM±A
Cisplatin
Epoposide
5-Fu
Mitomycin C
Doxorubicin

↓   ↓

VTMAP   **PEFM±A**

↓   ↓

82%   67%

5yrs OS

D. Khayat, ASCO 2001 Educational Book

02SR 86 French Phase II Trial
n = 272 Patients Stage I-IIIB

survival

100

50

NR/R

R

NR/NR

50   Time (months)   100   150

Aberdeen Trial
n = 133 Patients T>3cm or IIIB

CVAP x 4

CVAP:
Cyclophospamide
Vincristine
Doxorubicin
Prednisolone

Evaluation

cCR/cPR (n=97)   cNC (n=45)

R

CVAP x 4	T x 4		T x 4
16%	34%		2%

pCR

Eremin O et al. Breast Cancer Res Treat 57:29 1999
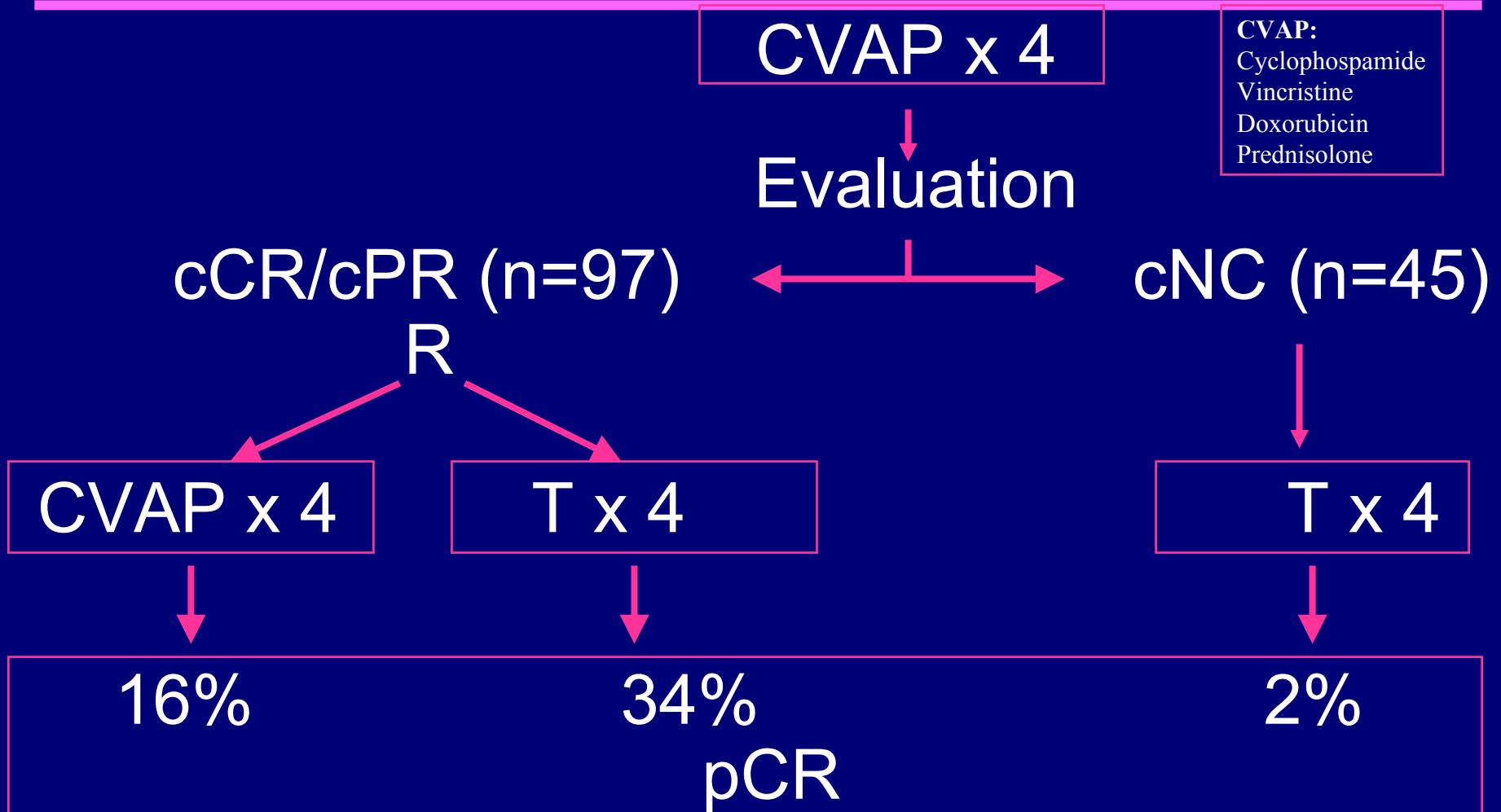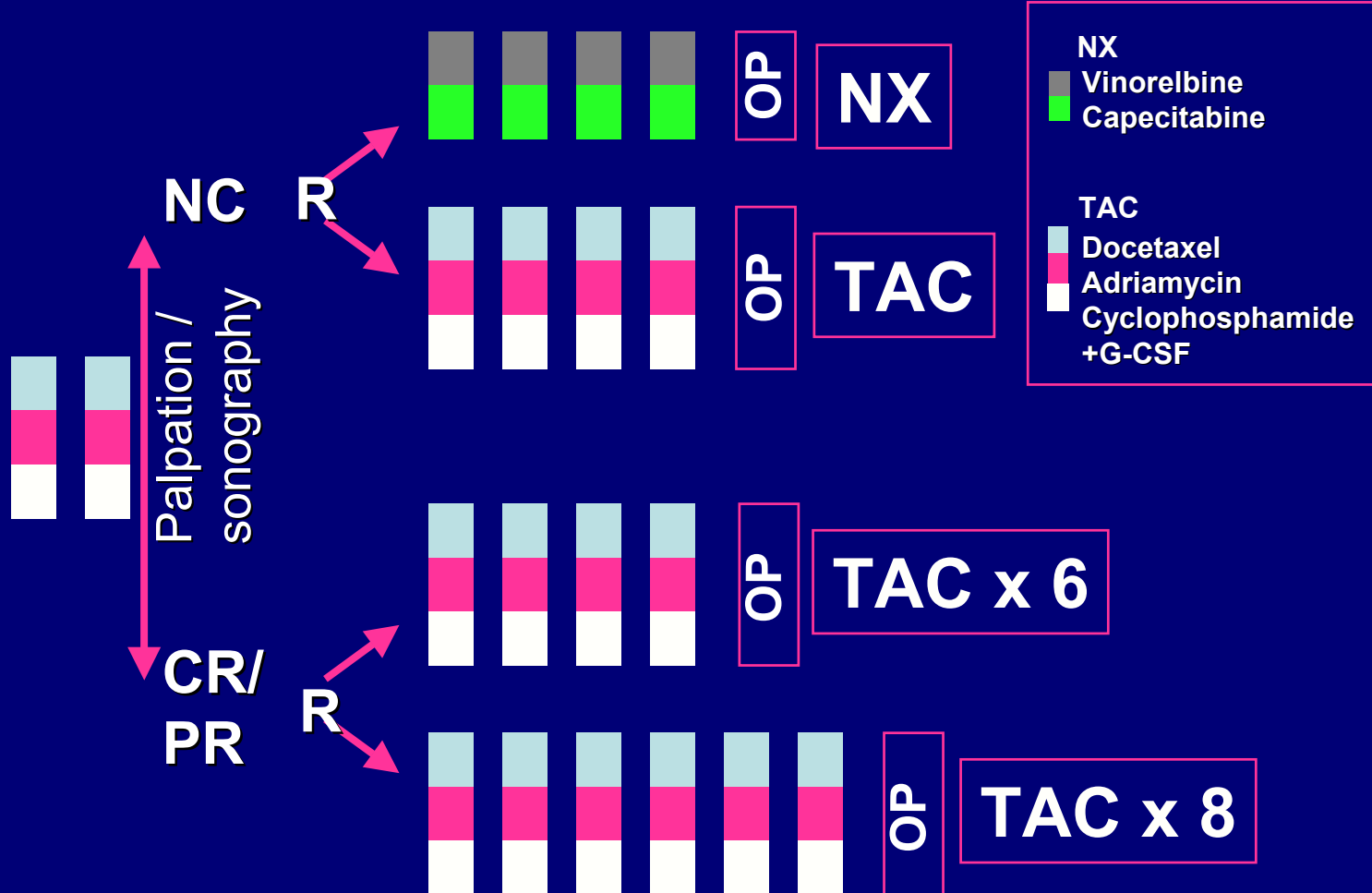
Progression-free Survival in the Aberdeen-Study (median F-up: 104 wks)
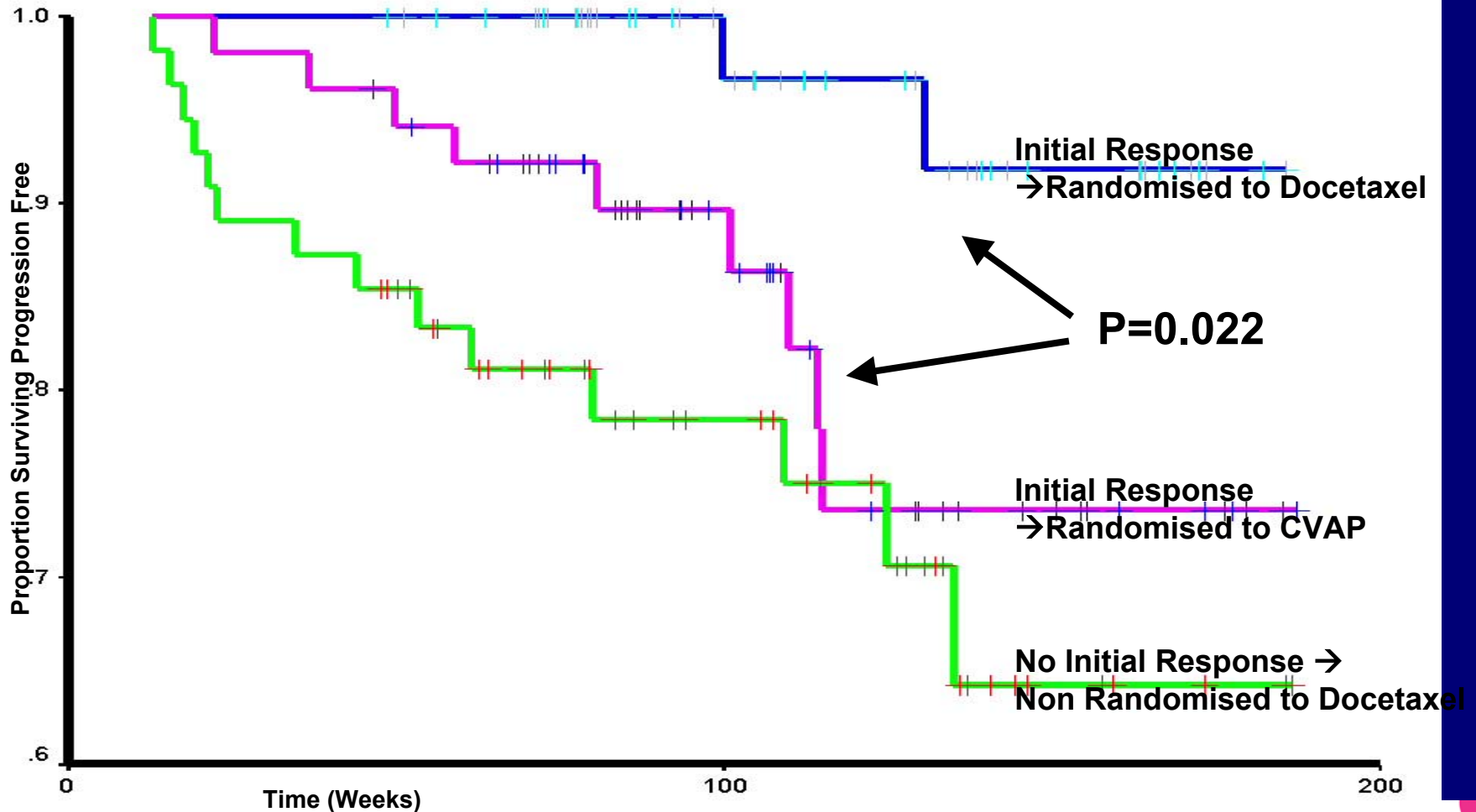
Gepartrio

Core biopsy:
uni/bilateral
cT2-4
cN0-3
size ≥ 2 cm

Palpation / sonography

NC

CR/ PR

R

R

OP NX

OP TAC

OP TAC x 6

OP TAC x 8

NX
Vinorelbine
Capecitabine

TAC
Docetaxel
Adriamycin
Cyclophosphamide
+G-CSF

Von Minckwitz, SABCS 2006

pCR Rates in GeparTrio Study
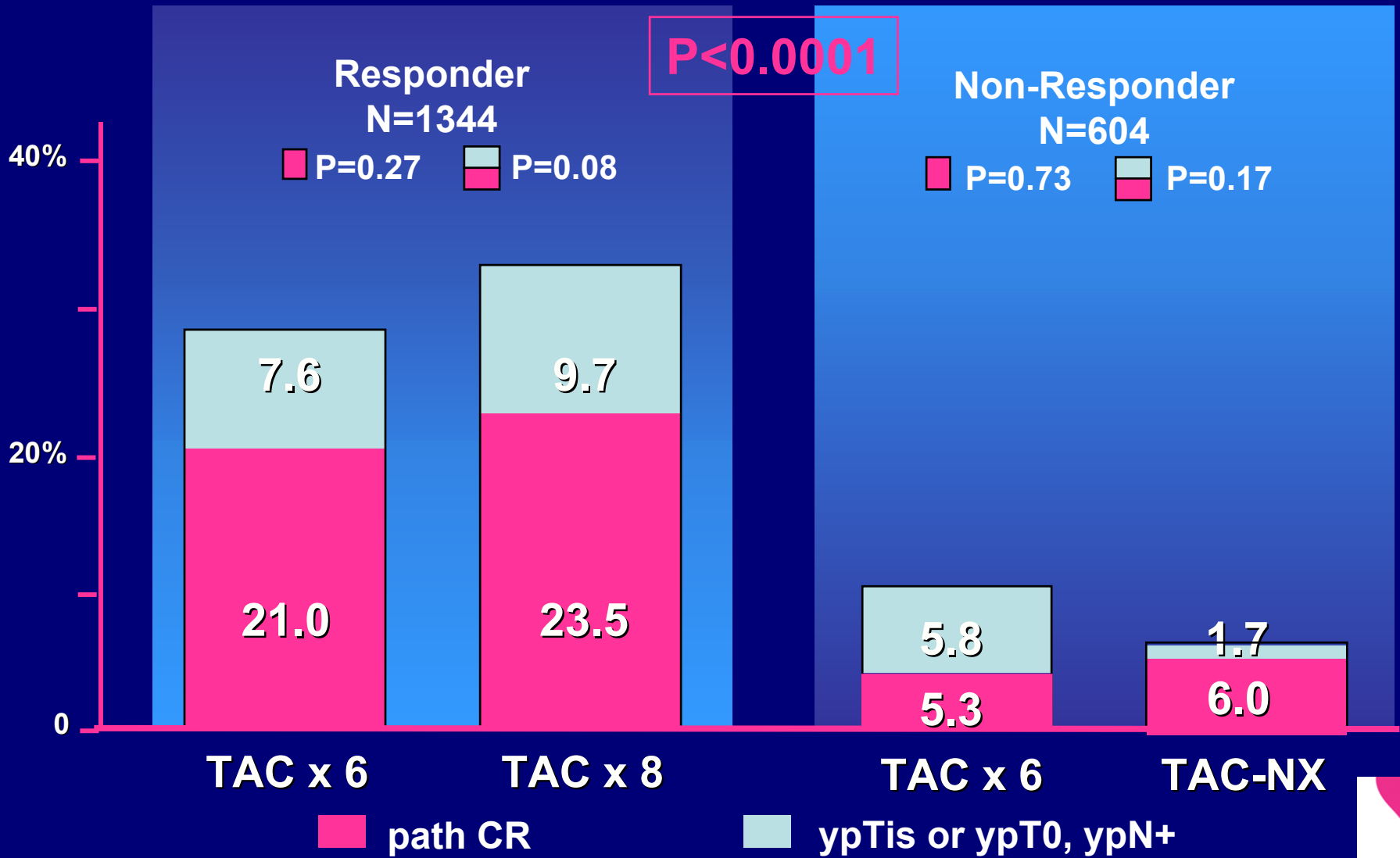
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Predictive Factors in GeparTrio for pCR by Therapy

%path CR	Responder		Non-Responder	
	TACx6	TACx8	TACx6	TAC/Nx
ER+ and PR+	11.7	18.3 P=0.03	9.5	2.5 P=0.01
Partial Response after 2 cycles	25.5	31.4 P=0.02		n.a.

Adding a Taxan to FAC
(Experience from 7 MD Anderson Trials)

N=1079   pCR (%)

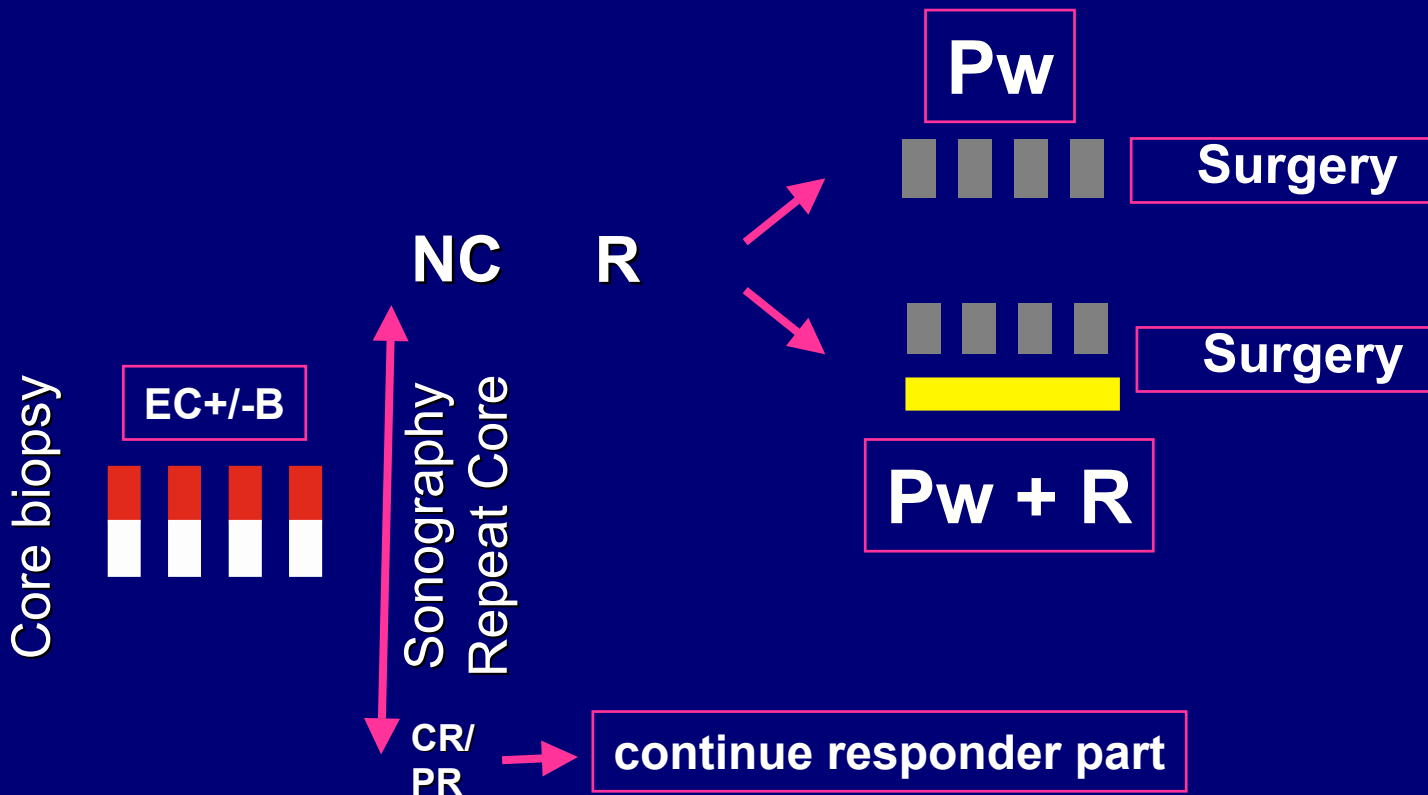|	- Taxane	+ Taxane
ER neg	15	29
ER pos	2	9

Mazouni C, Ann Oncol 2007

Patients with a Partial Response after AC might benefit from Preop Doc
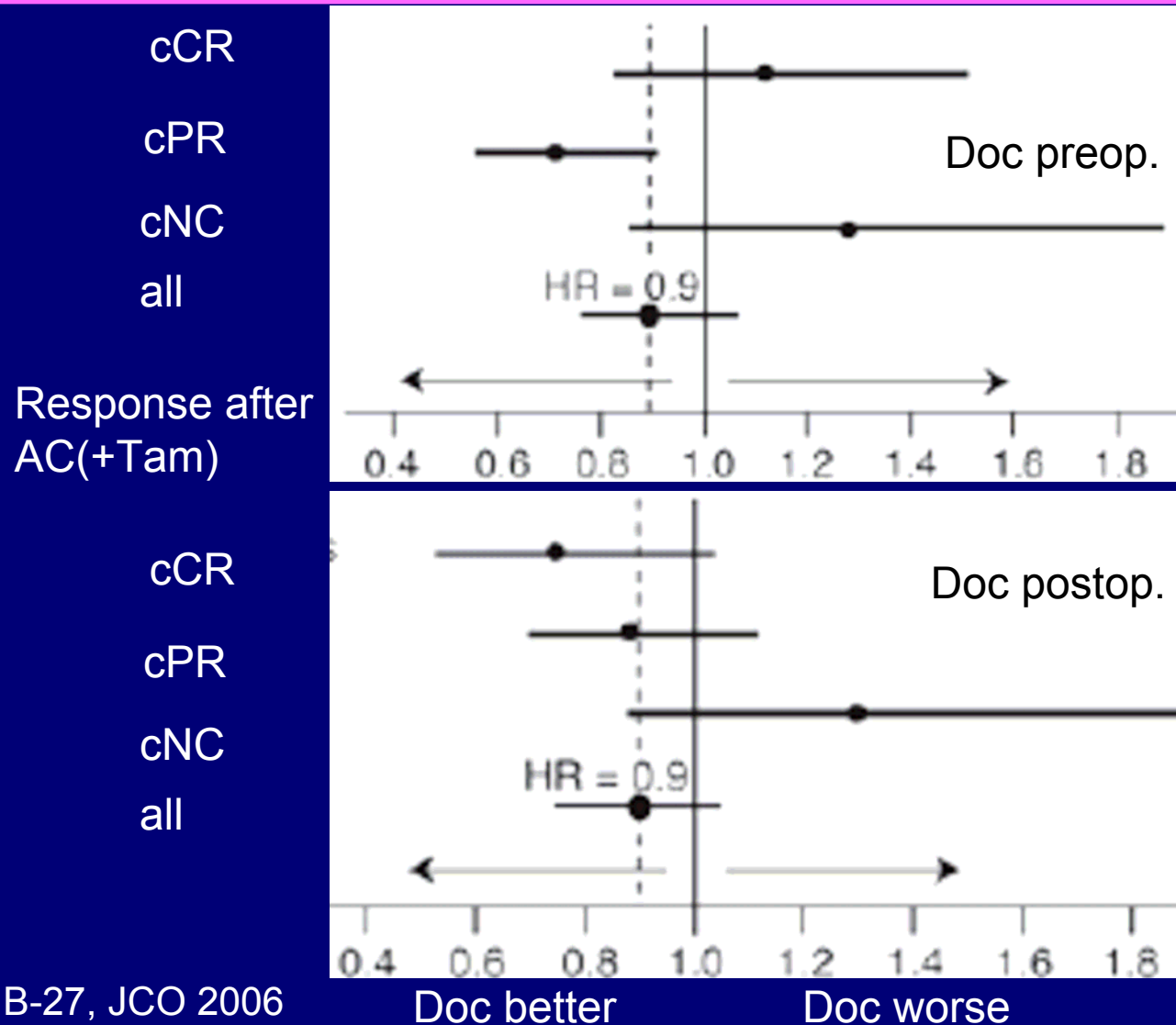
Bear D, NSABP B-27, JCO 2006

Decision Tree

N=2500

In/Exclusion criteria fulfilled → no → **No participation possible**

yes

Her-2 Status positive → no **N=1900** → **Her2- Setting: EC vs EC + Bevacizumab**

yes **N=600**

Her2+ Setting: EC-Doc/Cap Trastuzumab vs. Lapatinib

Response after 4xEC+/-B → no **N=540** → **Non-Responder Setting: Pw +/- RAD 001**

N=1360 yes

Continue Doc/Cap +/- Bev.
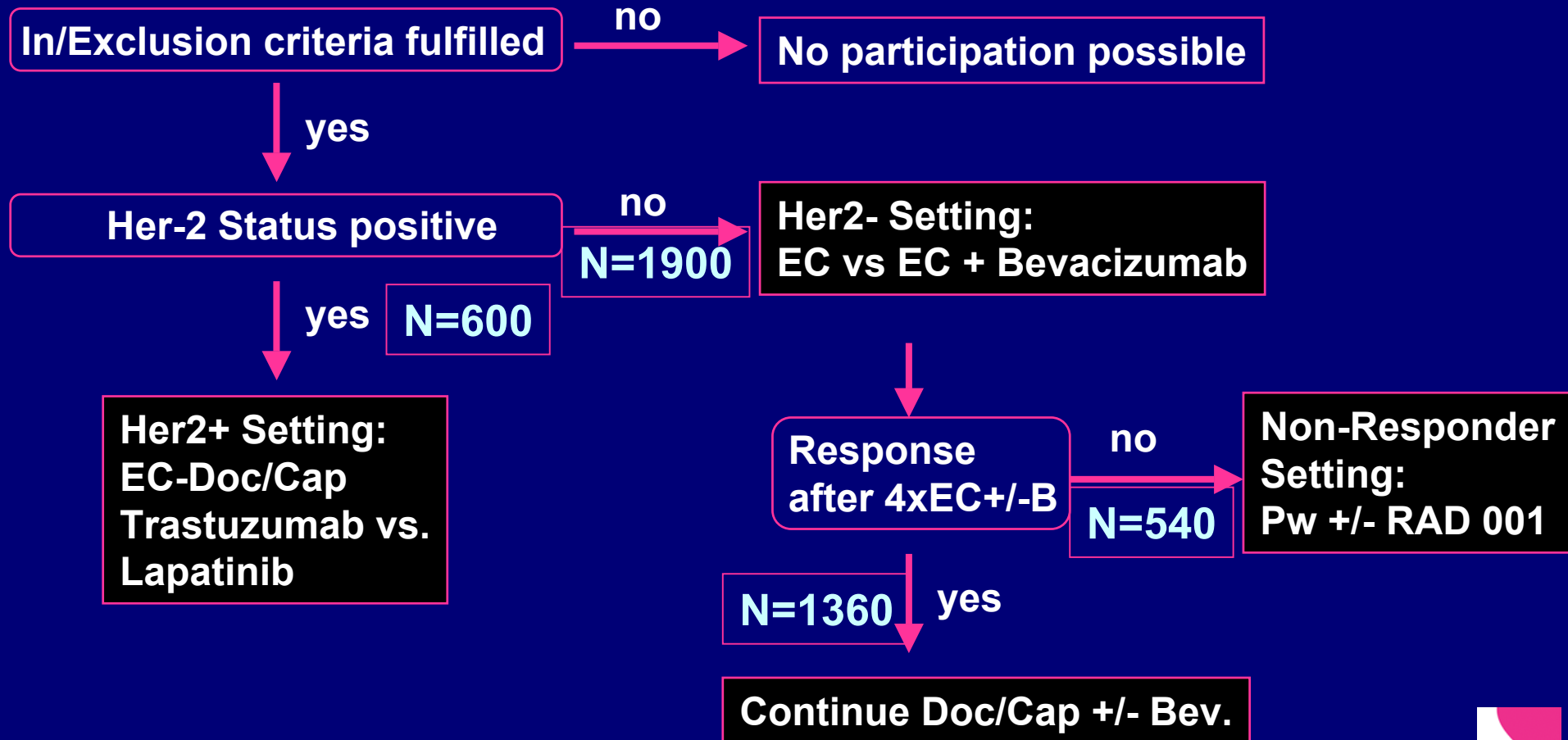
Conclusion

- Early response is an independent predictor of pCR and long term outcome (CR>PR>NC>PD).

- Benefit of a late response after switching of treatment is unclear

- Patients with an early cCR might not need further treatment intensification

- Patients with an early cPR (incomplete chemoresistance due to e.g. ER+) might benefit from more intense treatment.

- Patients with an early cNC or cPD are at high medical need for new treatment options.