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COMPREHENSIVE CANCER CENTER VIENNA

ESMO 2012
Abstracts #320 and #321

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Abstracts to be discussed

→ **Abstract #320; Chen XS et al.**
Significantly Superior Outcome after Neoadjuvant Chemotherapy with Docetaxel, Anthracycline and Cyclophosphomide versus TC:
Results from the NATT Trial in Triple Negative or HER2 positive Breast Cancer

→ **Abstract #321; Ataseven B et al.**
Impact of multifocal or multicentric disease on surgical, locoregional, and distant survival after neoadjuvant chemotherapy in 3562 breast cancer patients

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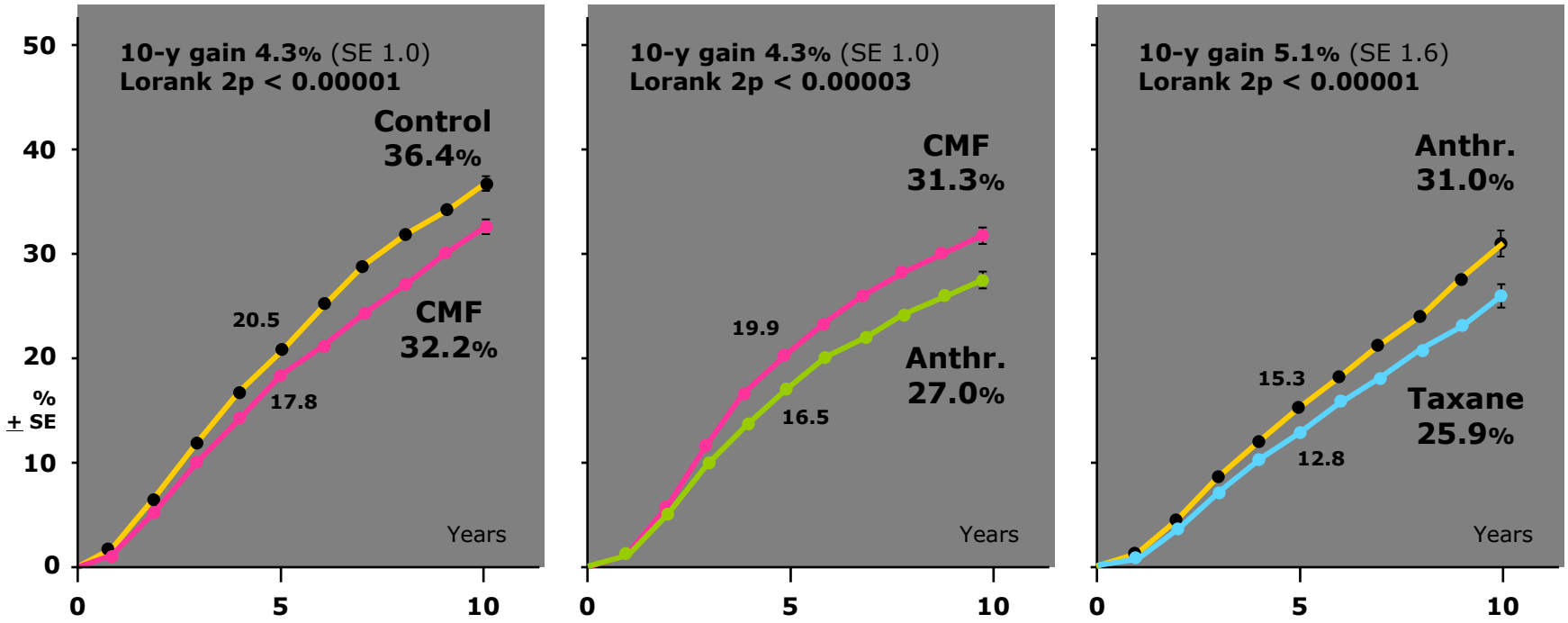
Improvement of adjuvant chemotherapy? [1]



Death rates (% / year: total – rate in women without recurrence) & logrank analyses

1 Peto R on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Presented at SABCS 2007, December 13, 2007. San Antonio, TX.

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Doubts concerning anthracyclines?

- Relative benefit of anthracyclines to CMF might be restricted to Her2-positive cancers with topo-IIα overexpression [1,2]
- ACs inhibit topoisomerase-IIα (topo-IIα); Gene coding for topo-IIα is located in close proximity to the Her2/neu-gene (17q12-q21)
- Her2-amplification may be accompanied by amplification of the topo-IIα as well
- Isolated amplification of the topo-IIα is rare [2,3]
- Cardiotoxicity; secondary MDS, AML [3,4]

1 Di Leo A et al. Clin Cancer Res 2002;8:1107-1116.
2 Press MF et al. J Clin Oncol 2011;29:859-867.
3 .Mano MS et al. Cancer Treat Rev 2007;33:64-77.
3 Jones S et al. J Clin Oncol 2009,27:1177-1183.
4 Slamon D et al. N Engl J Med 2011;365:1273-1283

Evidence for anthracycline-free regimens

→ **BCIRG006** [1]
AC-TH *versus* AC-T:
DFS HR 0.64; *p*<.001; OS HR 0.63; *p*<.001
TCH *versus* AC-T:
DFS HR 0.75; *p*=.04; HR 0.75; *p*=.04
No significant difference between the AC-TH and TCH

→ **US Oncology 9735** [2]
TC x 4 *versus* AC x 4
OS (7 years follow-up):
87% (TC) *versus* 82% (AC)
HR 0.69; 95% CI 0.50 to 0.97; *p*=.032

1 Slamon D et al. N Engl J Med 2011;365:1273-1283.
2 Jones S et al. J Clin Oncol 2009,27:1177-1183.

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A novel treatment standard? [1]

- Prescription practice of anthracycline-free regimens at the UCSF 2000-2005;2006-2010
- 1,116 patients from the UCSF Cancer Registry database
- 50% HR-positive, 25% Her2-positive, 17% TNT
- Overall, 80% received anthracyline-based chemotherapy
- Use of anthracyclines decreased from 95% to 65%, while the use of non-anthracyline-based chemo increased from 5% to 35%

1 Serrurier KM et al. J Clin Oncol 2012;30(Suppl.27):Abstr.#141.

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Trials in favour of anthracyclines?

→ **M.21** [1]
Canadian CEF *versus* AC-P q3w (and DD AC-P)
Benefit in terms of RFS in favour of CEF

→ **GOIM 9902** [2]
EC120 x 4 *versus* EC120-Docetaxel
Five year DFS:
73.4% in both arms; HR 0.99; 95% 0.75-1.31; *p*=.95

1 Burnell M et al. Presented at: 29th Annual San Antonio Breast Cancer Symposium; December 14-17, 2006; San Antonio, TX.
2 Vici P et al. Ann Oncol 2012;23:1121-1129.

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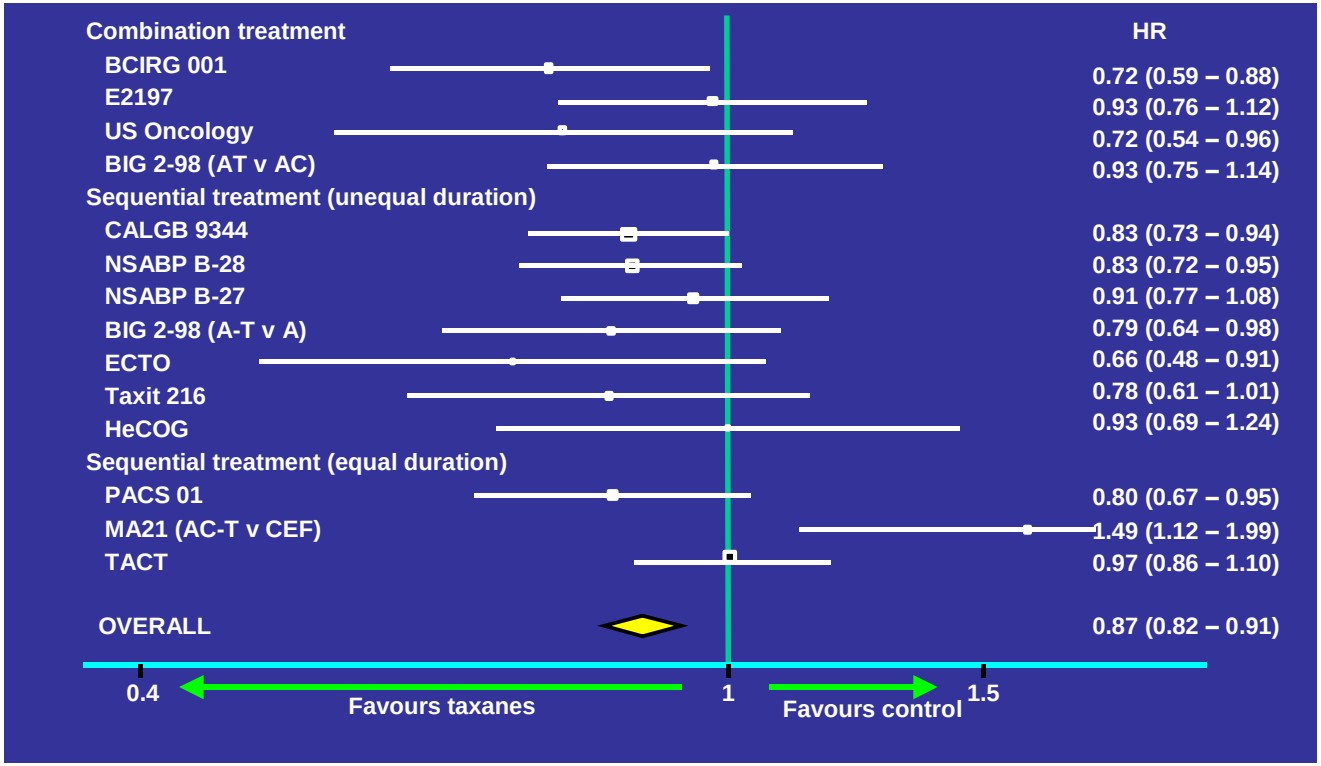
Taxanes *versus* no Taxanes [1]



1 Peto R on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Presented at SABCS 2007, December 13, 2007. San Antonio, TX.

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Significantly Superior Outcome after Neoadjuvant Chemotherapy with Docetaxel, Anthracycline and Cyclophosphomide versus TC: Results from the NATT Trial in Triple Negative or HER2 positive Breast Cancer

Xiao-song Chen [1], Guo-lin Ye [2], Chen-fang Zhang [3], Xin-zheng Li [4], Yi-ding Chen [5], Kun-wei Shen [1]

for the NATT Study Group

[1] Ruijin Hospital Shanghai Jiaotong University School of Medicine, Shanghai; [2]The First People's Hospital of Foshan, Guangdong; [3]Guangzhou General Hospital of Guangzhou Military Area, Guangdong; [4]Shanxi Provincial Cancer Hospital, Shanxi; [5]Obstetrics and Gynecology Hospital affiliated to Zhejiang University, Zhejiang

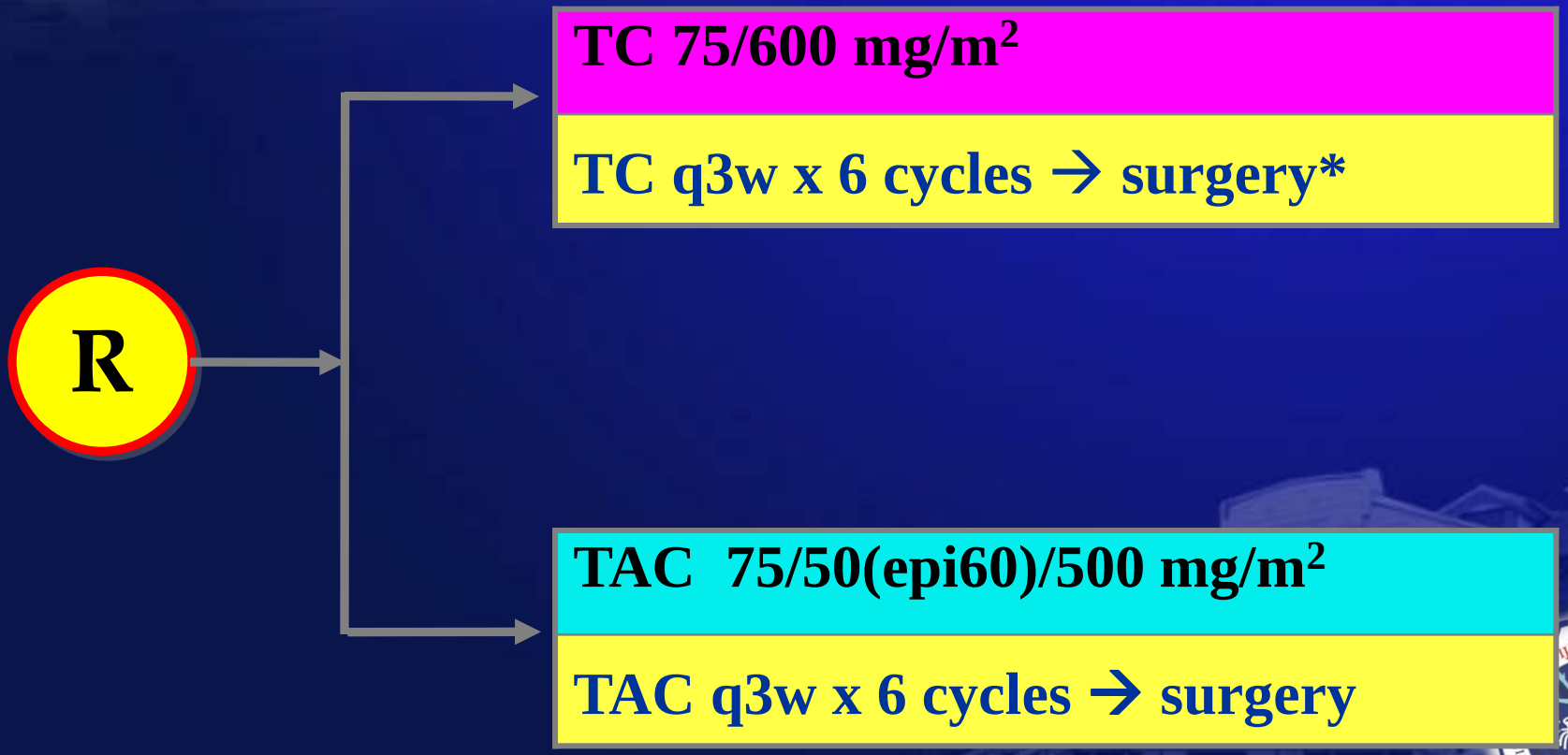
Vienna, Austria Sep. 29, 2012

VIENNA 2012 ESMO congress

2012 ESMO ; Abstract 320PD

Study Design

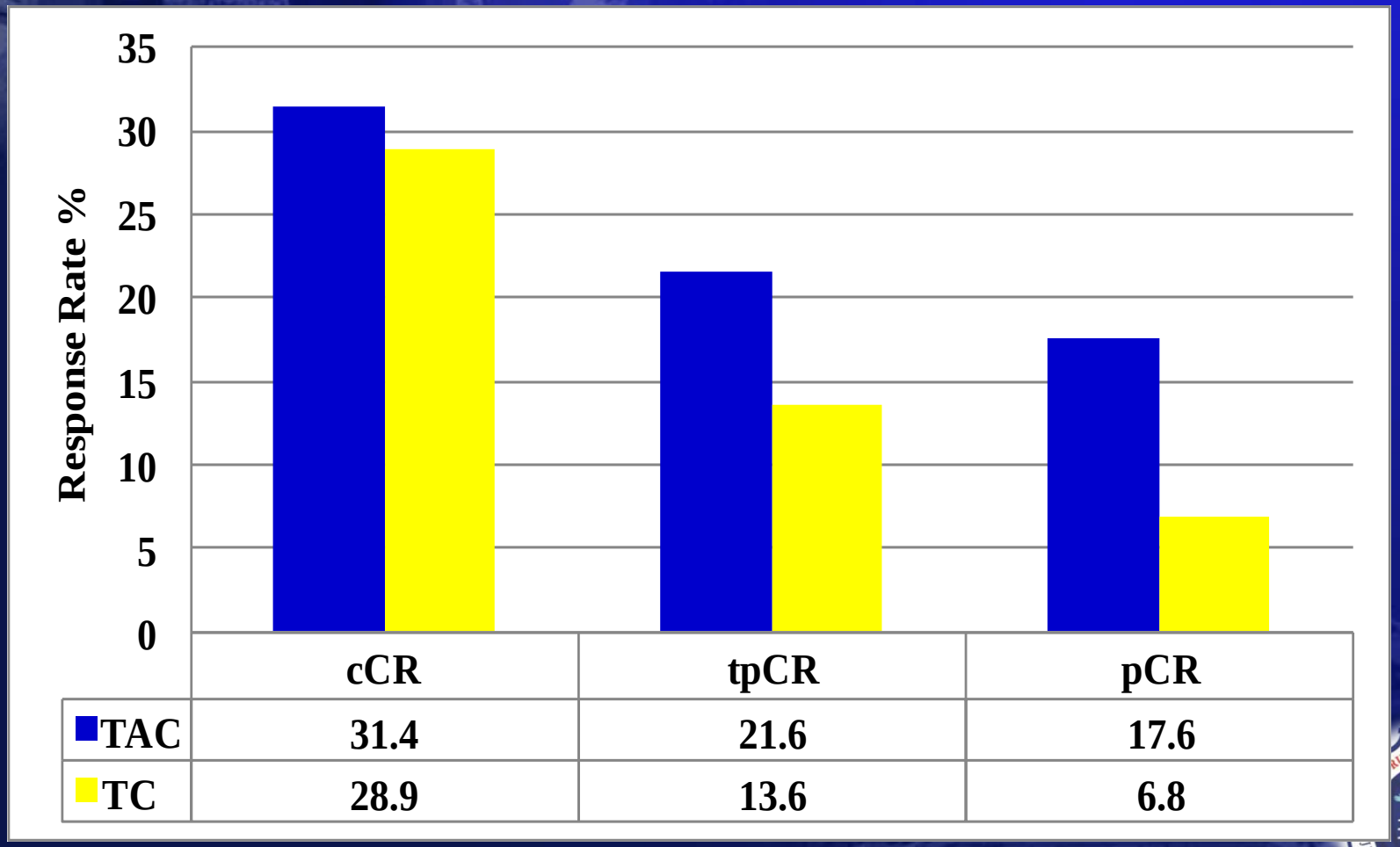
Triple Negative or HER2 positive breast cancer



Endpoints

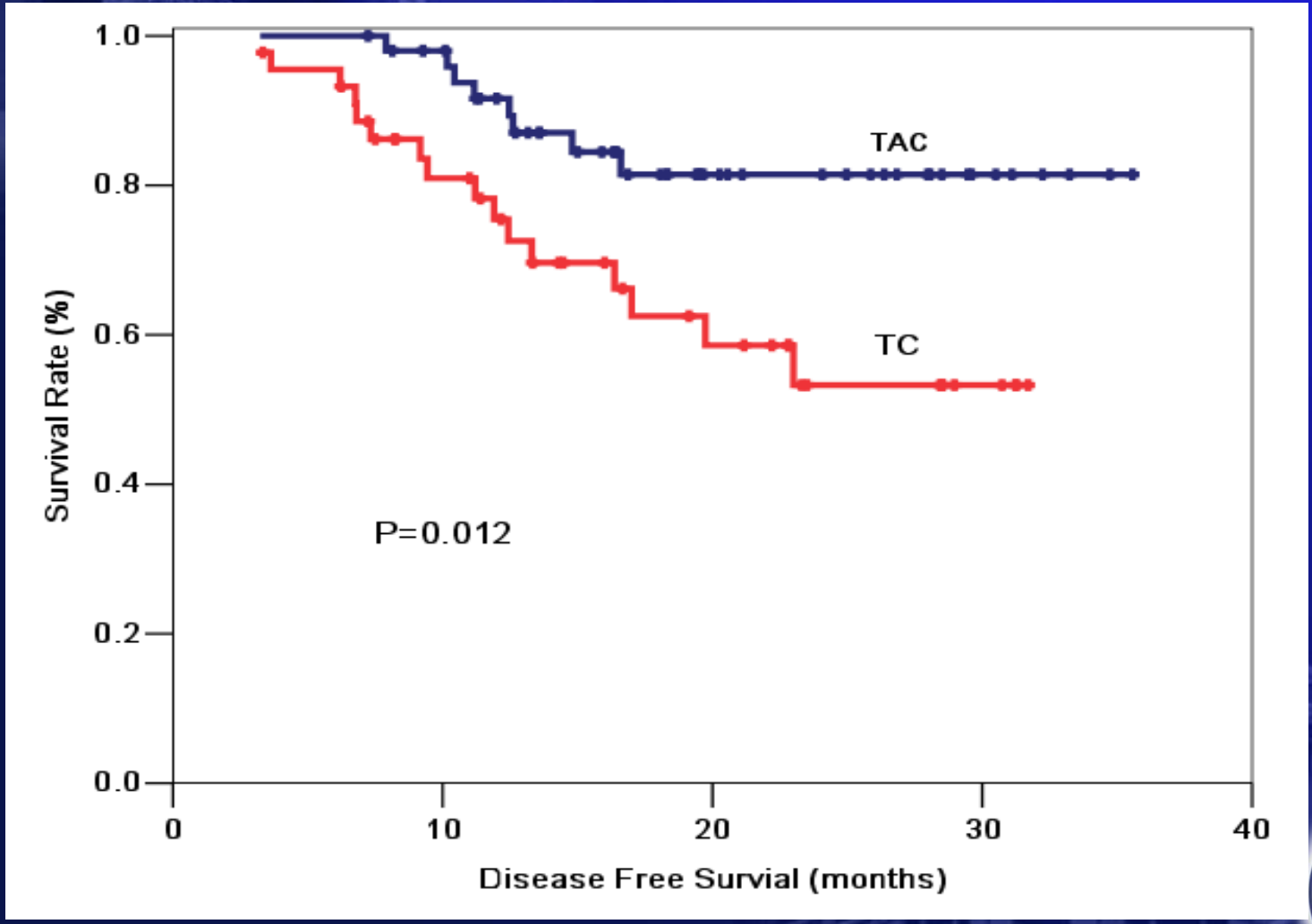
- **Primary endpoint: pCR rate among two groups**
  - Definition of pCR: no invasive tumor in breast and axillary
- **Secondary endpoints:**
  - DFS, EFS and OS
  - Breast conservation surgery rate
  - Clinical response rate
  - Safety and toxicity
  - pCR predictive factors

Tumor response in 95 breast cancer patients

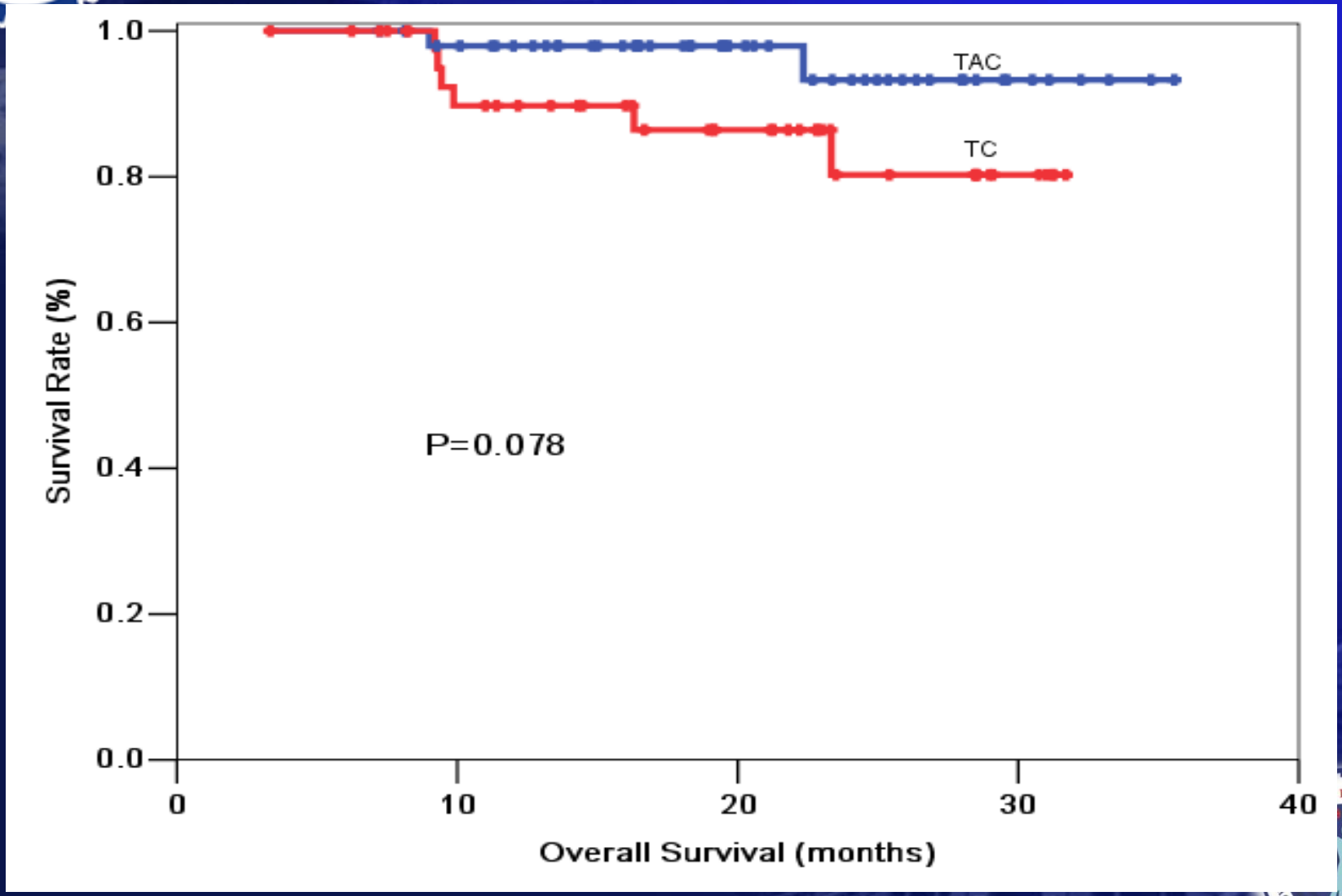


	cCR	tpCR	pCR
TAC	31.4	21.6	17.6
TC	28.9	13.6	6.8

DFS in TC & TAC Group



OS in TC & TAC Group



Conclusions

- pCR rate was not significantly differentbetween TAC and TC in NCT of TNBC or HER2 positive breast cancer;

- Adding anthracycline to TC can significantly improve outcome (EFS and DFS);

- Anathracycine should be considered as a necessary and effective drug in neoadjuvant treatment in this trial setting.

Results: pts Characteristics

Characteristics	TAC (51 pts)	TC (45 pts)	*P* value*
Age			0.204
Mean（ages）	47.2（26-62）	48.0（25-69）	
≤ 35	4	5	
35-55	40	28	
>55	7	12	
BMI Index			0.723
≤25	39	33	
>25	12	12	
Menstrual status			0.428
Pre/peri-menopausal	30	30	
Postmenopausal	21	15	
Pathological Status			0.645
Invasive ductal carcinoma	45	41	
Others	6	4	
Tumor stage			0.969
0-2	24	21	
3-4	27	24	

Characteristics	TAC (51 pts)	TC (45 pts)	*P* value*
Lymph node stage			0.055
0	12	4	
1-3	39	41	
AJCC Stage			0.413*
II	24	15	
IIIA	21	25	
IIIB	5	3	
IIIC	1	2	
ER Status			0.267
Negative	45	36	
Positive	6	9	
PR Status			0.744
Negative	43	39	
Positive	8	6	
HER2 Status			0.990
Negative	26	23	
Positive	25	22	

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The role of anthracyclines finally clarified?

- Implication of anthracycline activity
- Low overall patient number
- Nearly 50% of all patients accrued Her2-positive
- Anthracyclines active – but what about the Her2-negative population?
- Results of NSABP B-49 (NCT01547741) to be awaited!
  TC x 6 *versus* TAC x 6 [1]

1 NSABP B-49. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01547741?term=NSABP+B-49&rank=1.

Changing perceptions

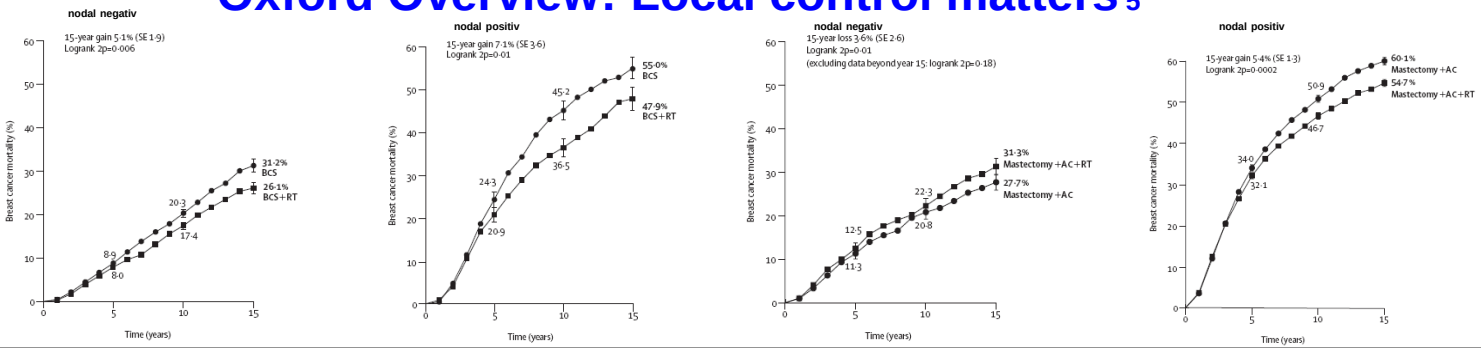
Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

→ **William Halsted (Johns Hopkins) suggests radical mastectomy including the large pectoral muscule in 1894** [1,2]

→ **Bernie Fisher: Breast cancer as systemic disease from the onset** [3,4]

→ **Oxford Overview: Local control matters** [5]



1 Halsted WS. The Johns Hopkins Hospital Reports 1894-1895;4: 297.
2 Halsted WS. Ann Surg 1907;46:1-19.
3 Rabinovitch R and Kavanagh B. J Clin Oncol 2009;27:2422-2423.
4 Fisher B. Cancer 1977;40(Suppl. 1):574-587.
5 EBCTCG. The Lancet 2005;366:2087-2106.

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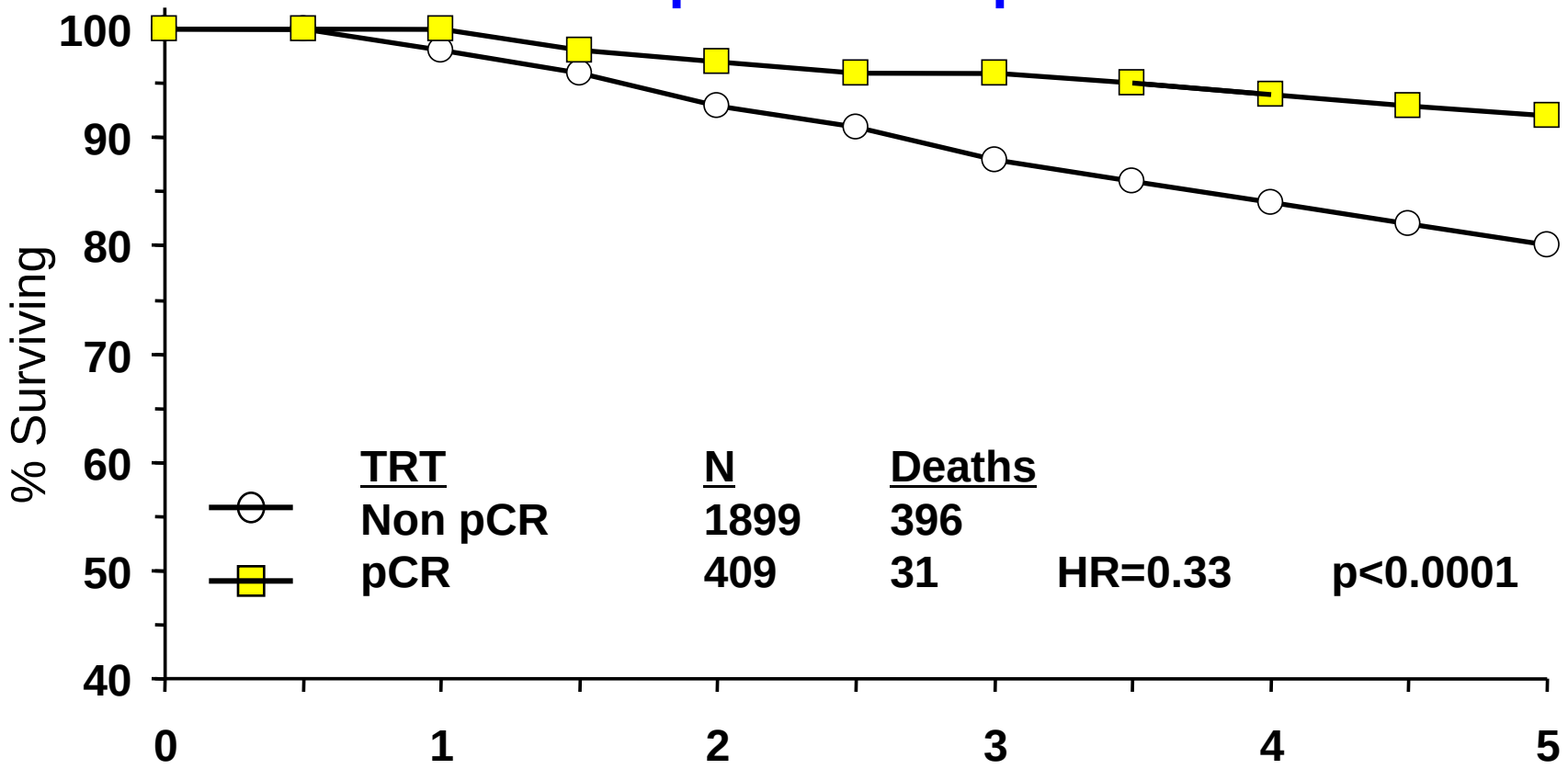
Neoadjuvant chemotherapy [1]

- Mandatory in inflammatory and ulcerated BC
- Increases the rate of breast conserving surgeries in patients with primarily operable breast cancer not amendable to BCT
- pCR may serve as surrogate for OS [2]
- Increased rate of local recurrences? [3]

1 Kaufmann M et al. J Clin Oncol 2007;25:2664-2670
2 Bear HD et al. J Clin Oncol 2007;24:2019-2027.
3 Mauri D et al. J Natl Cancer Inst 2005;97:188-194.

NSABP B-27 – OS pCR *vs.* no pCR[1]

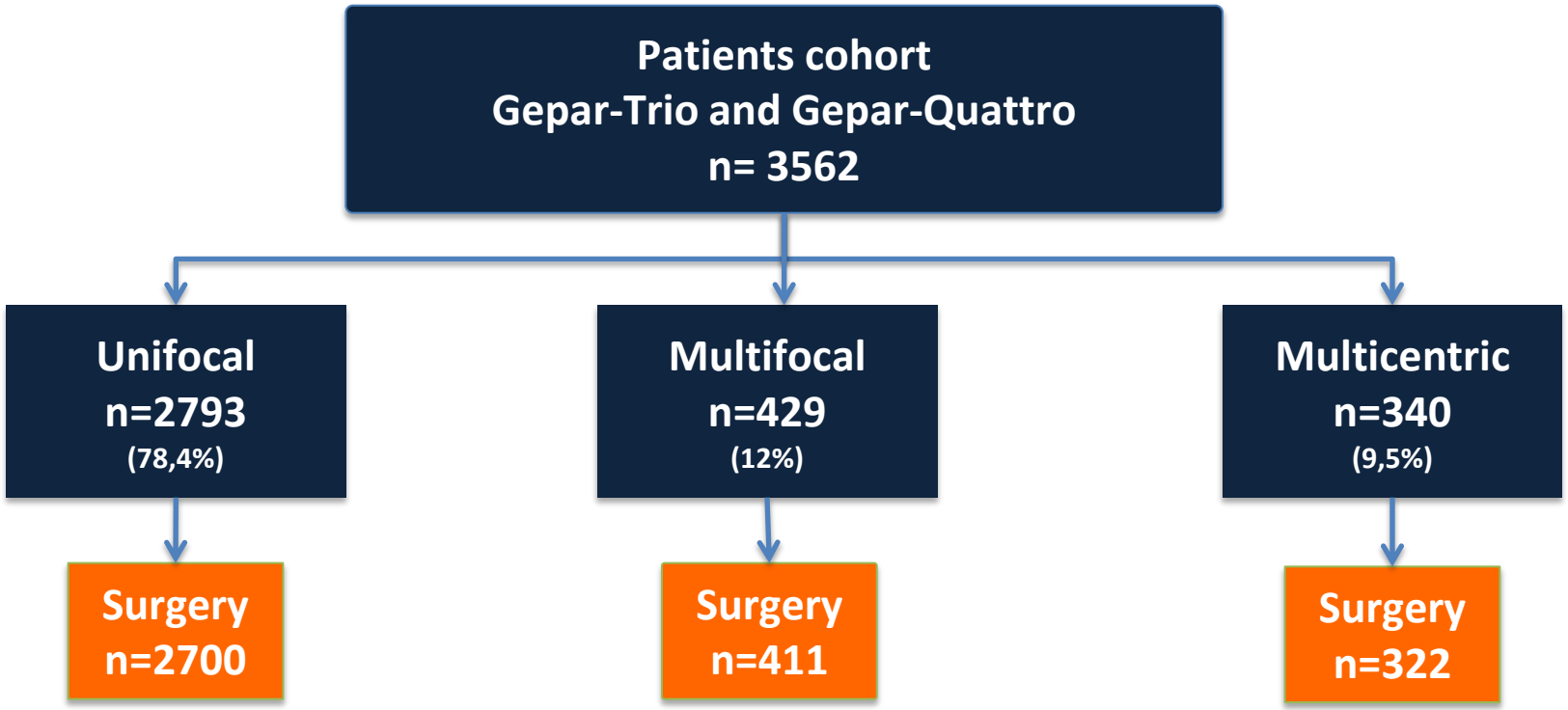


1 Bear HD et al. J Clin Oncol 2006;24:2019-2027.

Impact of multifocal or multicentric disease on surgical, locoregional, and distant survival after neoadjuvant chemotherapy in 3562 breast cancer patients

B. Ataseven, J.U. Blohmer, C. Denkert, B. Gerber, J. Heil, T. Kühn, S. Kümmel, M. Rezai, S. Loibl, G. von Minckwitz;

Study population



Unifocal	Multifocal	Multicentric
pCR (%)	pCR (%)	pCR (%)
18,7	14,1	14,9
BCS %	BCS %	BCS %
71,7 (n=1936)	56,2 (n=231)	35,1 (n=113)
ME %	ME %	ME %
28,3 (n=764)	43,8 (n=180)	64,9 (n=209)

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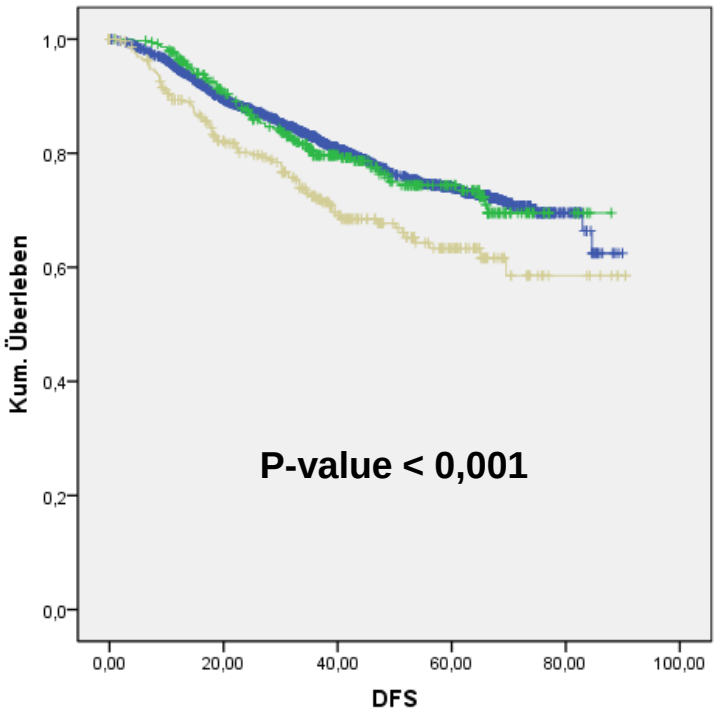
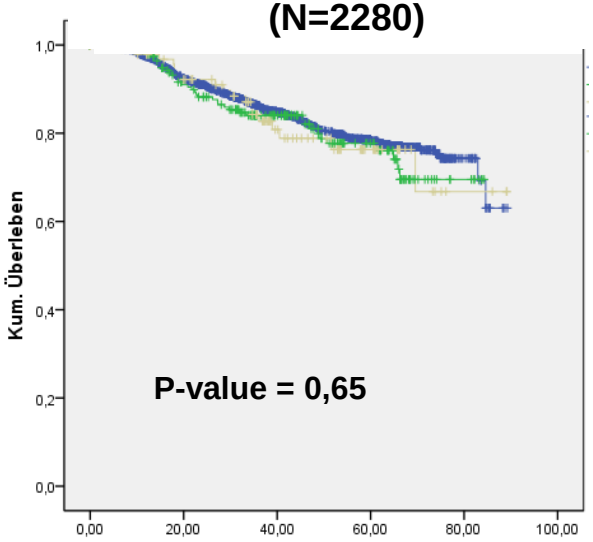
Disease-Free Surival

All patients (N=3562)

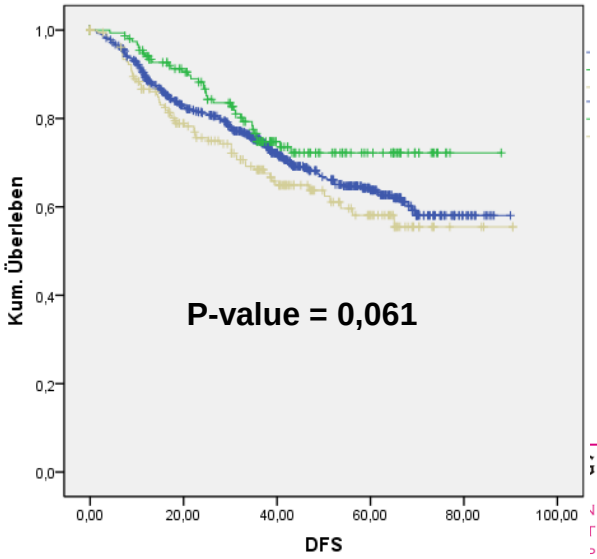


single
multifocal
multicentric

Breast Conservation (N=2280)



Mastectomy (N=1153)



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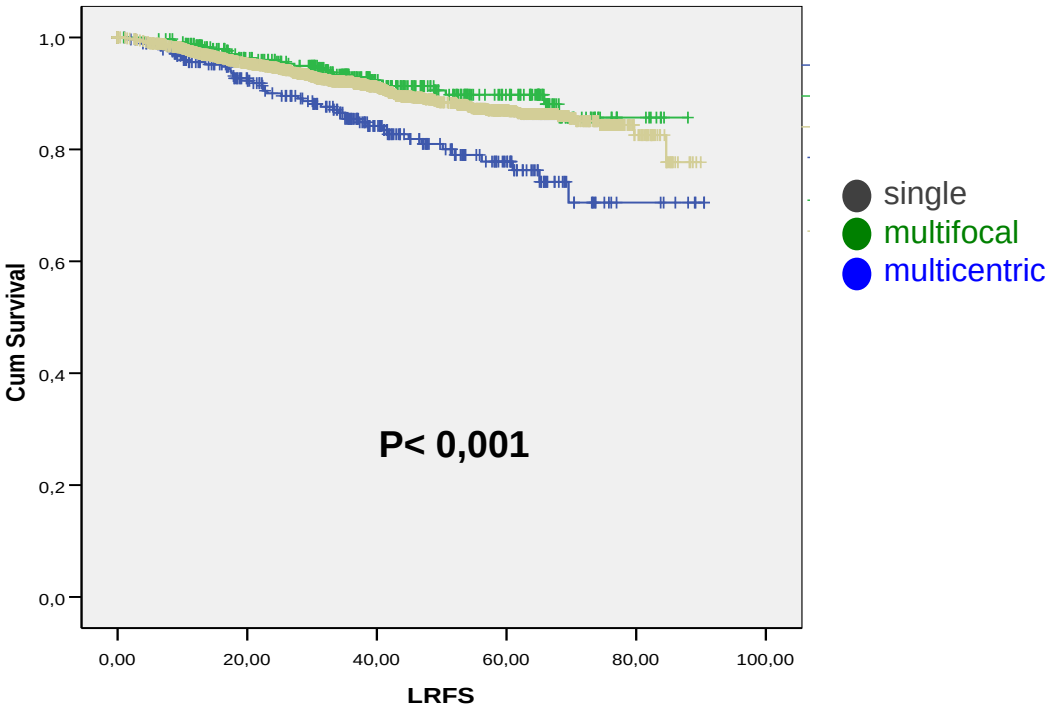
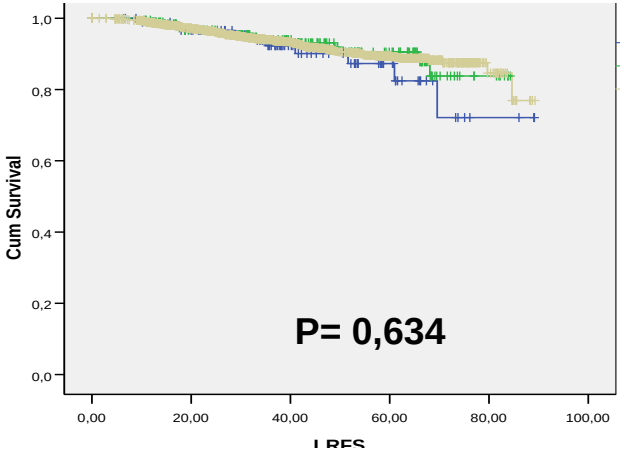
Local-Recurrence Free Survival

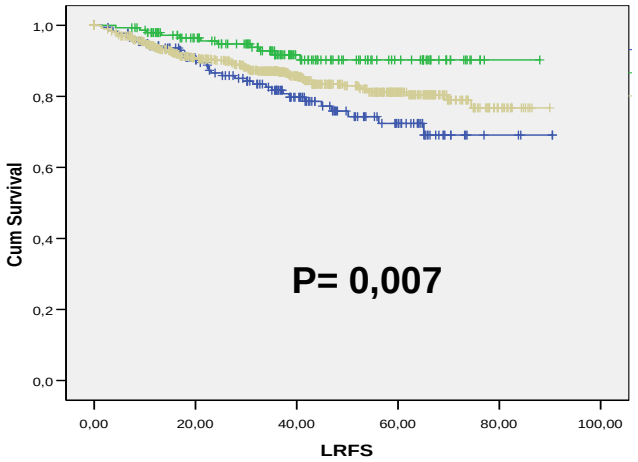
All patients
(N=3502)



Breast Conservation
(N= 2245)



Mastectomy
(N= 1131)



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Outcome

- Low locoregional relapse rate in patients with pCR irrespective of focality (p=.713)
- Prognostic factors for locoregional recurrence in multivariate analysis:
  Tumour and nodal status (at surgery), grading, HR status, and type of surgery, but not focality of the tumour
- Overall survival was not statistically different through all focality groups

Conclusion

- Tumor focality and type of surgery did not show an impact on overall survival.
- Multifocal or multicentric disease were unfavorable prognostic factors for LRFS and DFS overall and in mastectomized patients, but not in patients treated by breast conservation.
- LRFS was low in patients with pCR, irrespective of focality or type of surgery.
- DFS was impaired in patients after multicentric disease despite a pCR: it might be questionable in how far pCR was correctly diagnosed in this subgroup. Patients with multicentric disease and pCR should be followed up closely
- Breast conservation (with tumor-free margins) for multifocal or multicentric breast cancer is feasible after neoadjuvant chemotherapy and seems not to impair outcome

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Reassuring data?

- → **Current guidelines are reluctant to recommend BCT in patients with multicentric carcinoma** [1]
- → **Clinical data suggest the feasibility of BCT in MC** [2-4]
- → **Multicentric tumours associated with worse prognosis**
- → **Not true in patients with BCT, potentially due to excellent tumour repsonse**
- → **Aim: Improvement of optimal reponse to neoadjuvant chemotherapy**

1 Leitlinienprogramm Onkologie | S3-Leitlinie Brustkrebs | Juli 2012; p80. Available at http://www.senologie.org/fileadmin/downloads/S3-Brustkrebs-v2012-OL-Langversion.pdf
2 Bauman L et al. Ann Surg Oncol 2010;17(Suppl. 3):325-329.
3 Gentilini O et al. Breast Cancer Res Treat 2009;113:577-583.
4 Oh JL J Clin Oncol 2006;24:4971-4975.

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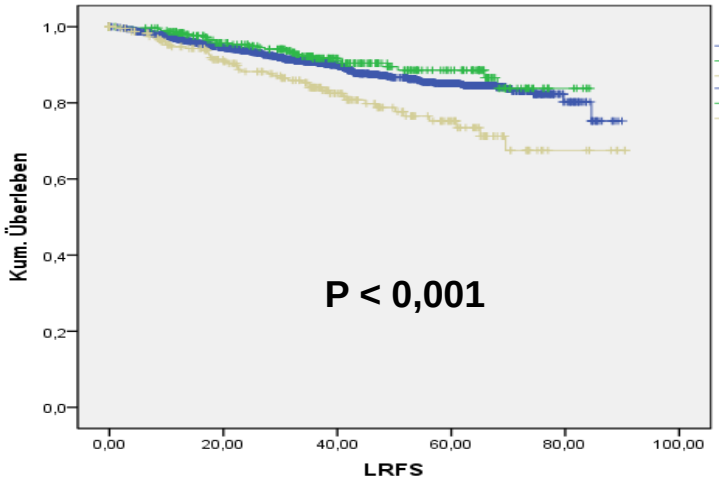
Acknowledgments

Catharina de Vries
Anna Berghoff
Peter Dubsky
Florian Fitzal
Karin Dieckmann
Andrea Rottenfusser
Arik Galid
Robert Mader
Thomas Hofmann-Bachleitner
Ursula Pluschnig
Zsuzsanna Bago-Horvath
Christoph Minischdorfer
Katja Pinker
Martin Filipits
Flora Zaghouri
Marharetha Rudas
Raimund Jakesz
Michael Gnant
Alexander de Vries
Günther G. Steger
Christoph C. Zielinski

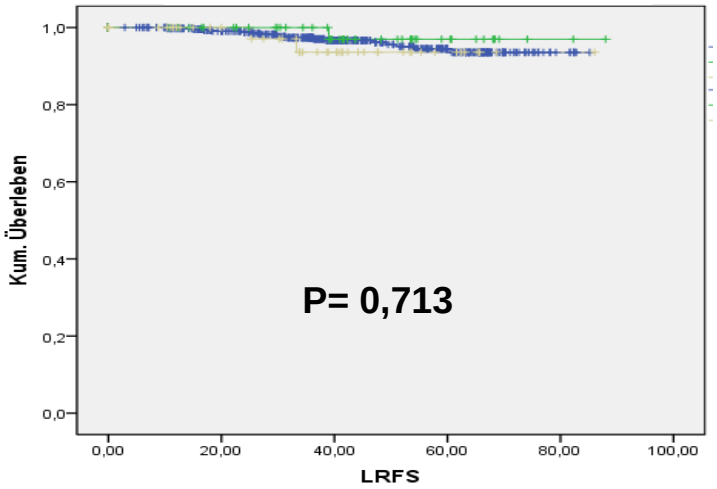
LRFS in Patients with/without pCR

No pCR (n= 2886)

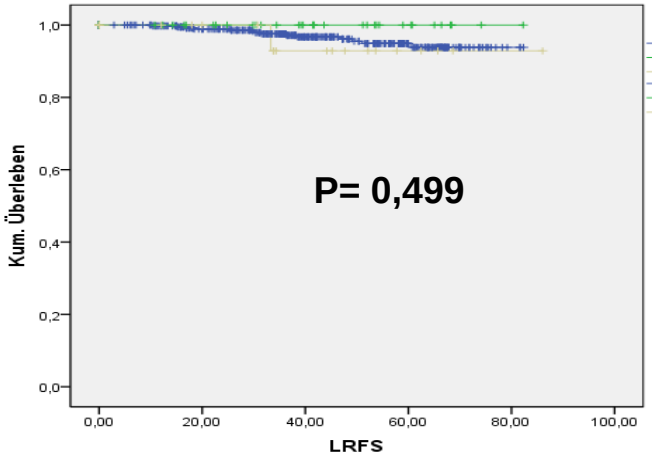


single
multifocal
multicentric

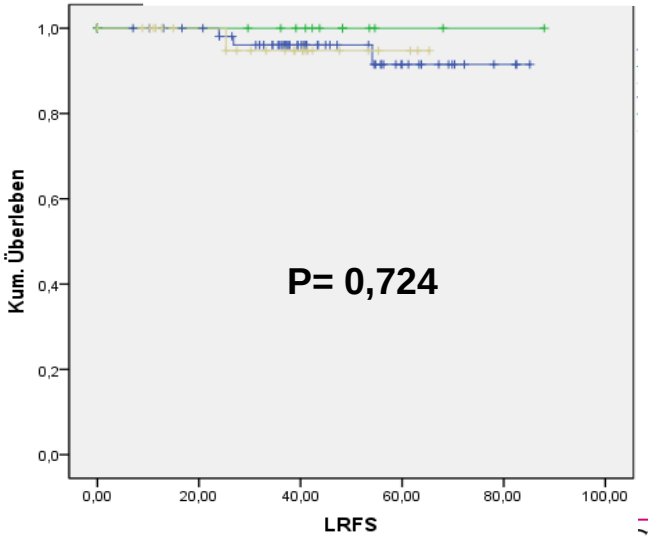
pCR (n=616)



Breast Conservation + pCR (n=503)



Mastectomy + pCR (n=102)



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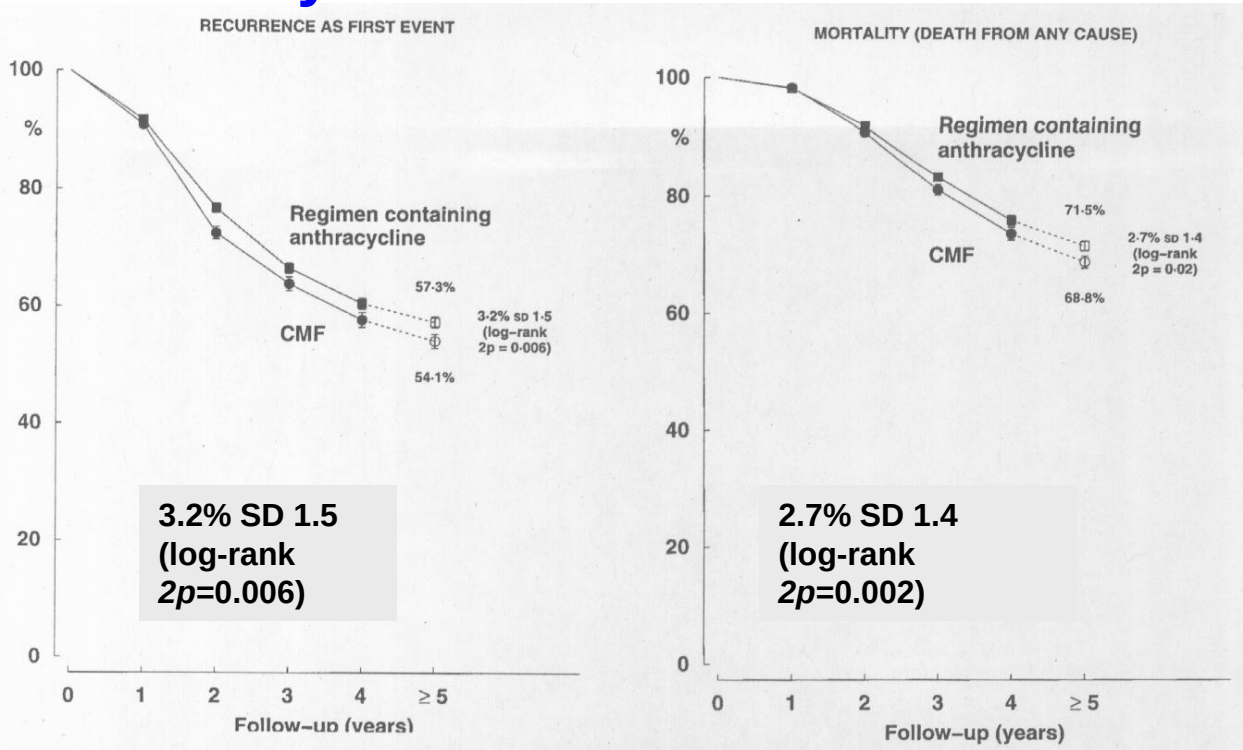
Anthracyclines *versus* CMF [1]



3.2% SD 1.5 (log-rank *2p*=0.006)

2.7% SD 1.4 (log-rank *2p*=0.002)

1 EBCTCG. The Lancet 2005;366:2087-2106.

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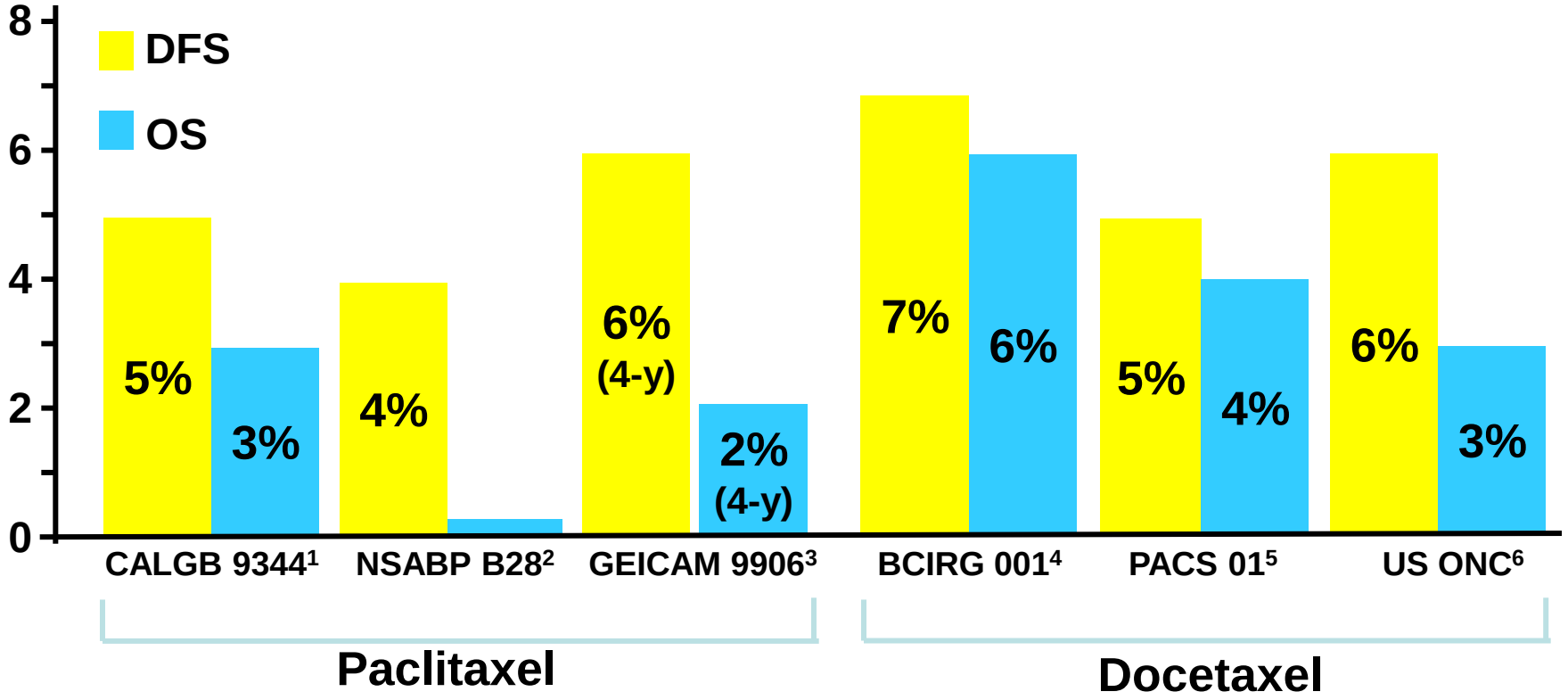
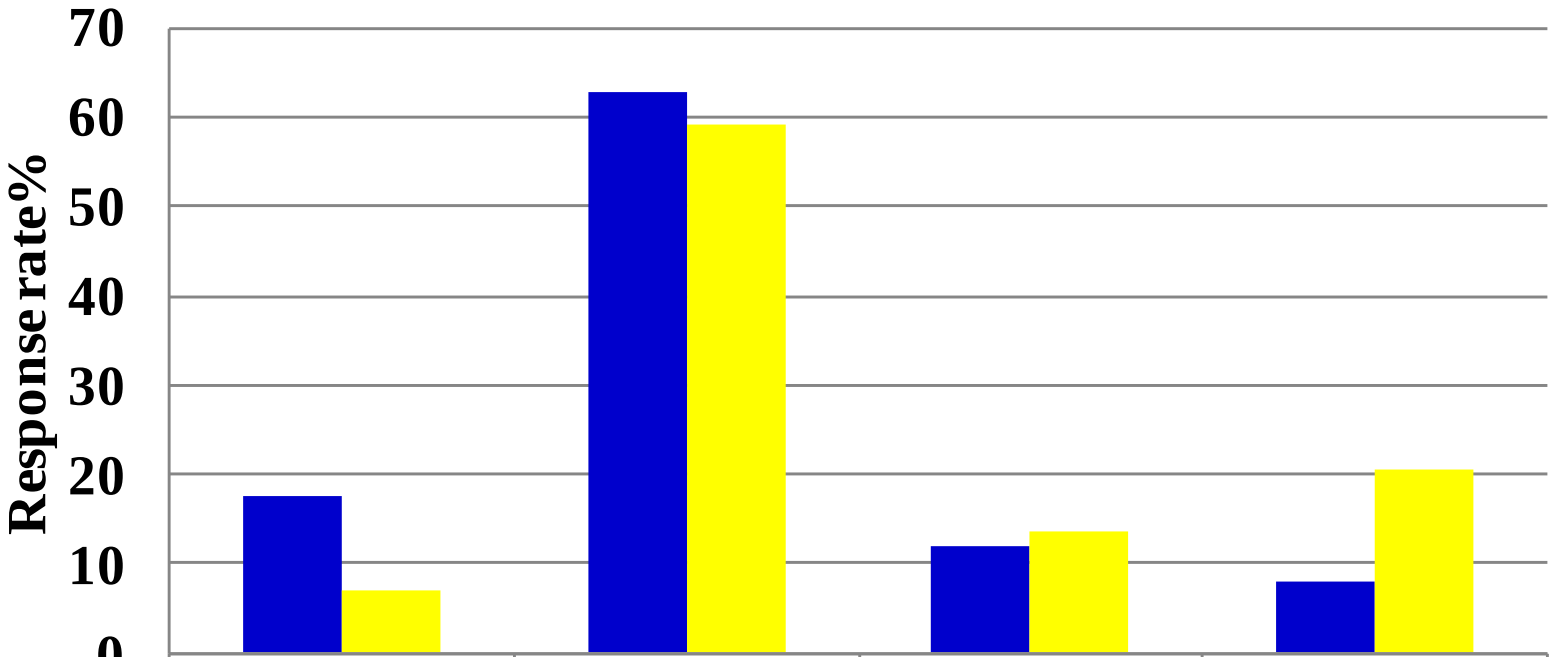
Differential effects of different taxanes [1-6]



1 Henderson IC et al. J Clin Oncol 2003;21:976–983.
2 Mamounas EP et al. ASCO 2005. Abst 12.
3 Martin M et al. SABCS 2005. Abstr.39..
4 Martin M et al. N Engl J Med 2005;352:2302–2313
5 5.Roché H et al. SABCS 2004.Abst27.
6 Jones S et al. J Clin Oncol 2006;24:5381–5387.

Results: pathological response

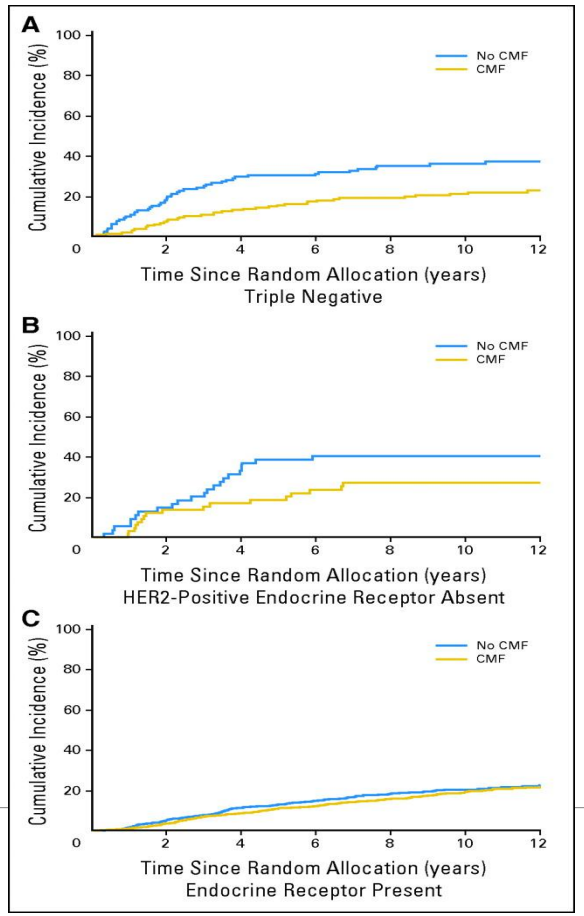
Pathological tumor and axillary response in 95 breast cancer patients



	CR	PR	SD	PD
TAC	17.6	62.8	11.8	7.8
TC	6.8	59.1	13.6	20.5

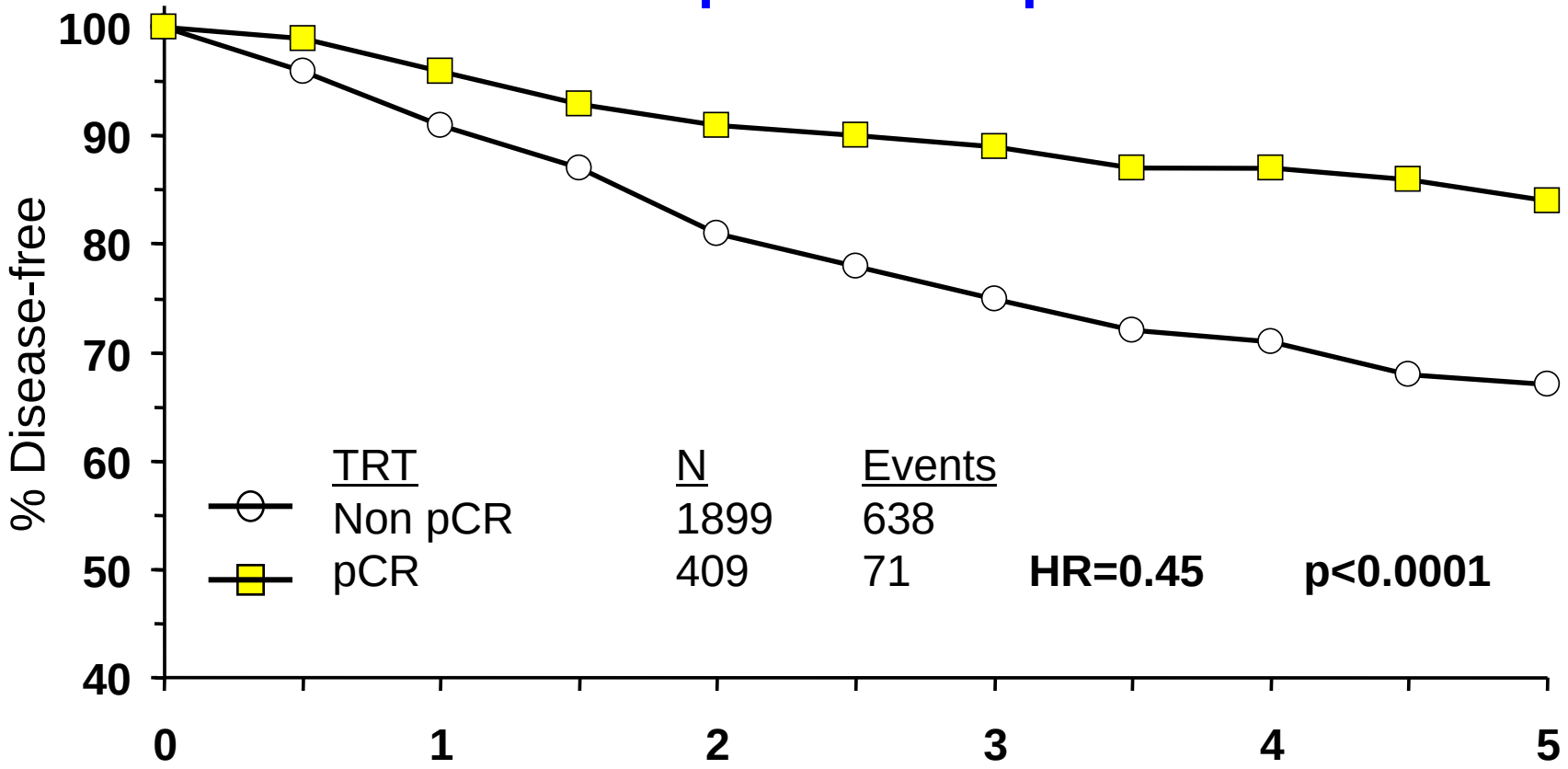
Activity of chemotherapy depends on BC subtype [1]

→ **Estimated subtype-specific cumulative incidence of relapse over time according to treatment group (CMF v no CMF) for patients with**
(A) triple-negative,
(B) Her2 -positive, HR-negative
(C) HR-positive tumours



1 Colleoni, M. et al. J Clin Oncol 2010;28:2966-2973.

NSABP B-27 – DFS pCR *vs.* no pCR



1 Bear HD et al. J Clin Oncol 2006;24:2019-2027.

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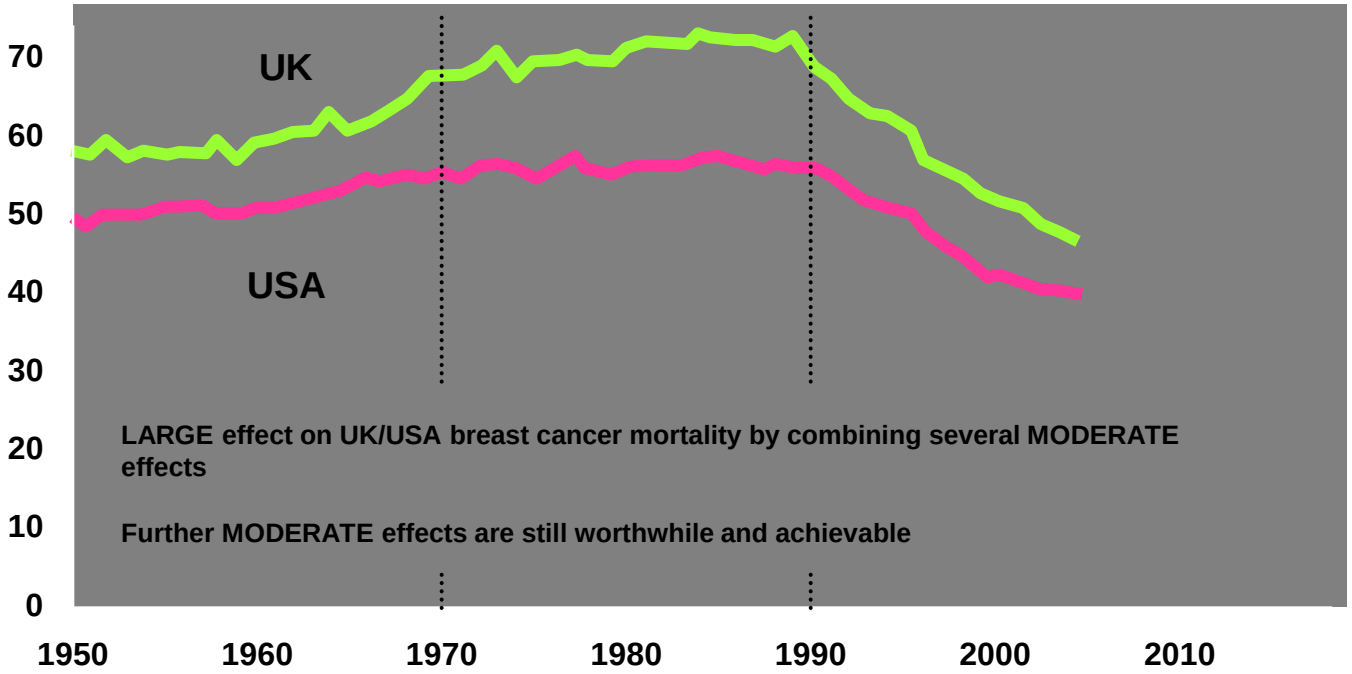
Conclusion [1]

Death rate/100 000 women, age standardised*



1 Peto R on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Presented at SABCS 2007, December 13, 2007. San Antonio, TX.