

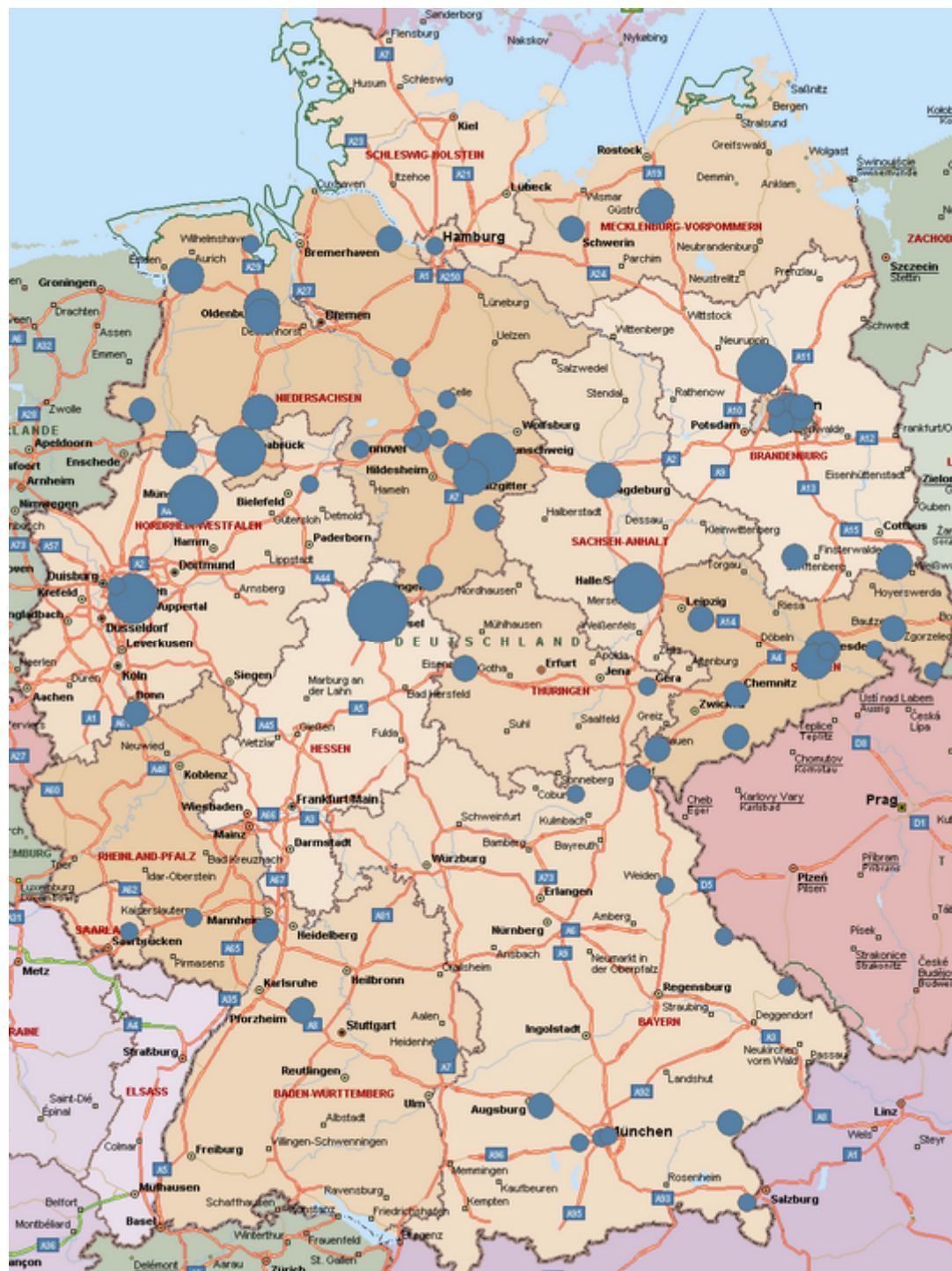
PIO Treffen Berlin 2009

Mam macarcinom

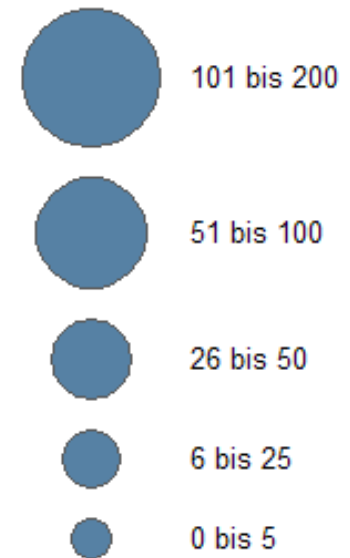


TYPVS
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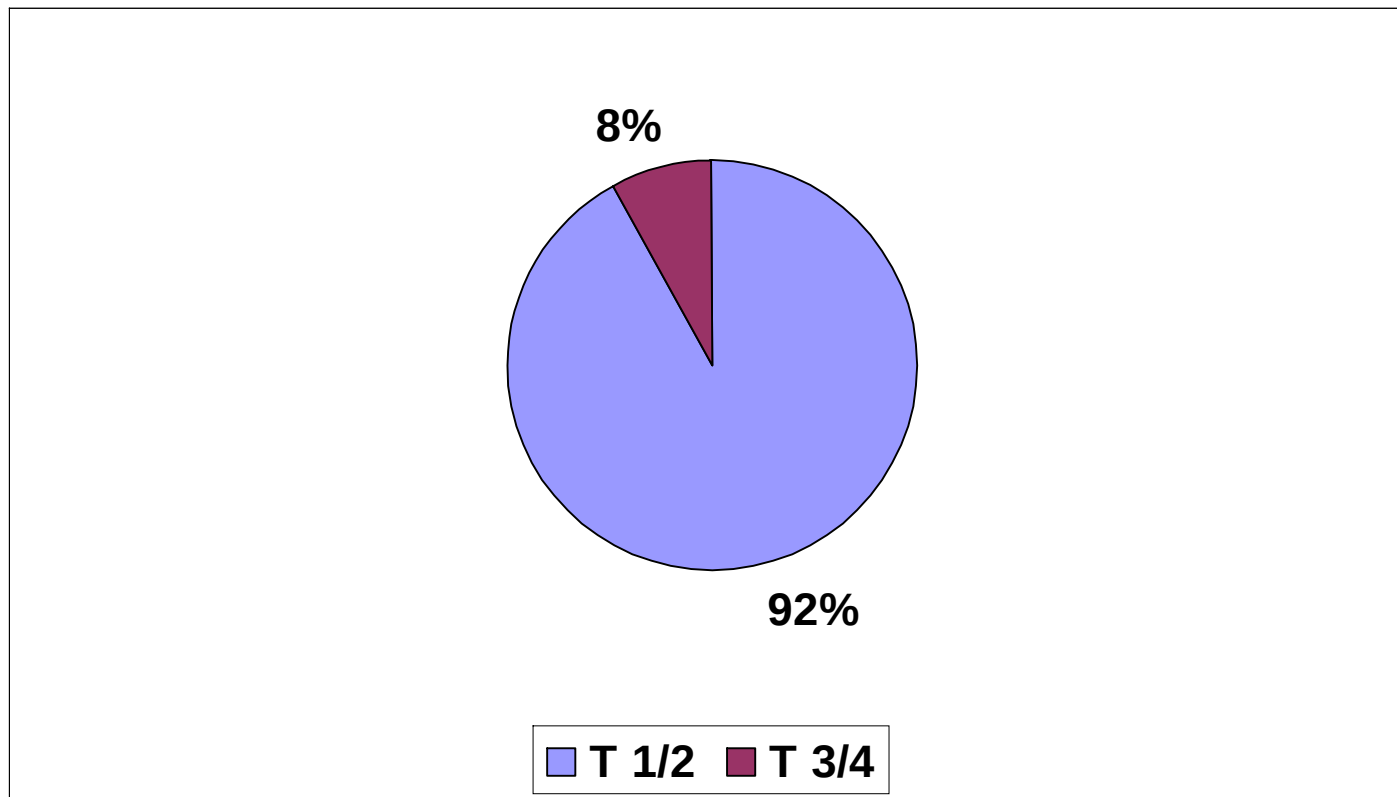
Verteilung der Patienten



Qualitätssicherungsprojekt

Adjuvante Chemotherapie

T-Status



Qualitätssicherungsprojekt

Adjuvante Chemotherapie

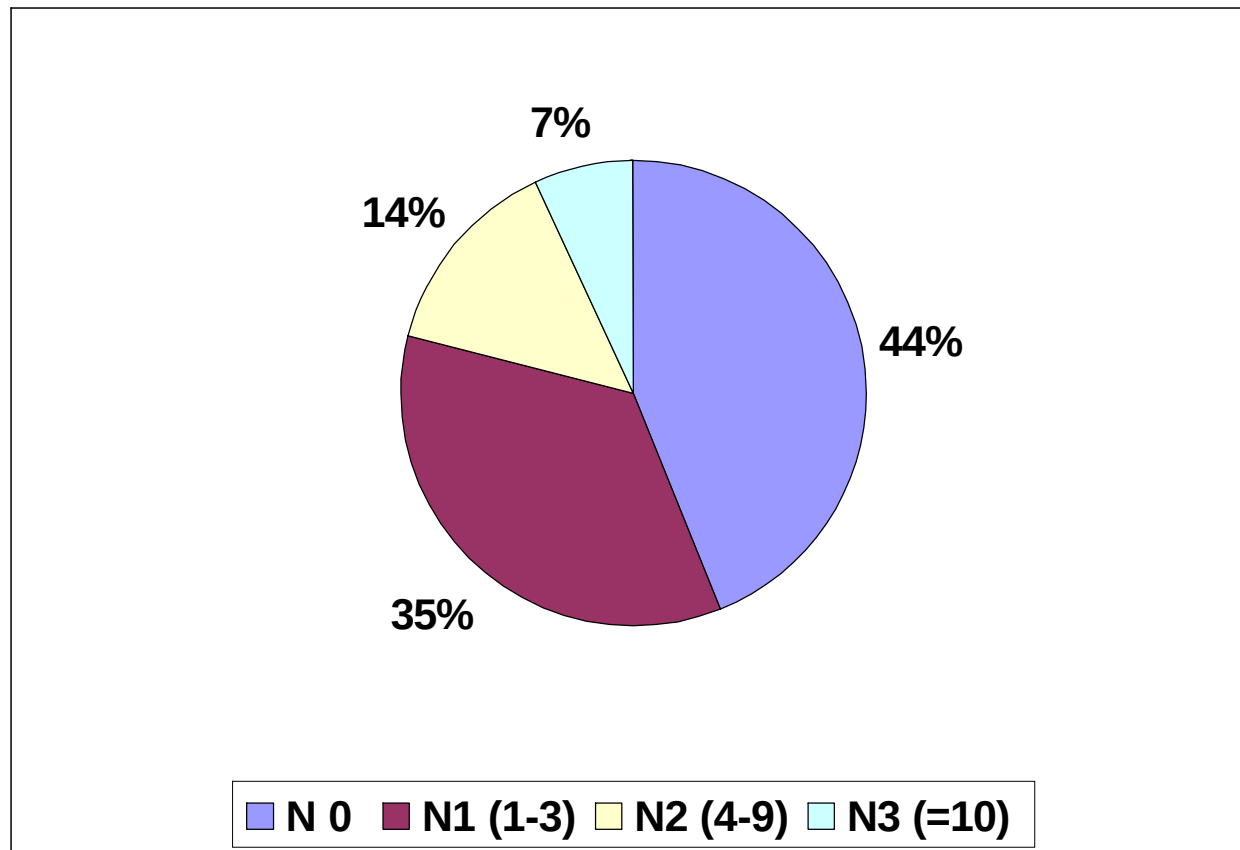
T-Status

Therapie	T 1/2 (%)	T 3/4 (%)
FEC	97	3
FEC-Docetaxel	89	11
EC-Paclitaxel	90	10
DAC	80	20
EC-Docetaxel	85	15
Gesamt	92	8

Qualitätssicherungsprojekt

Adjuvante Chemotherapie

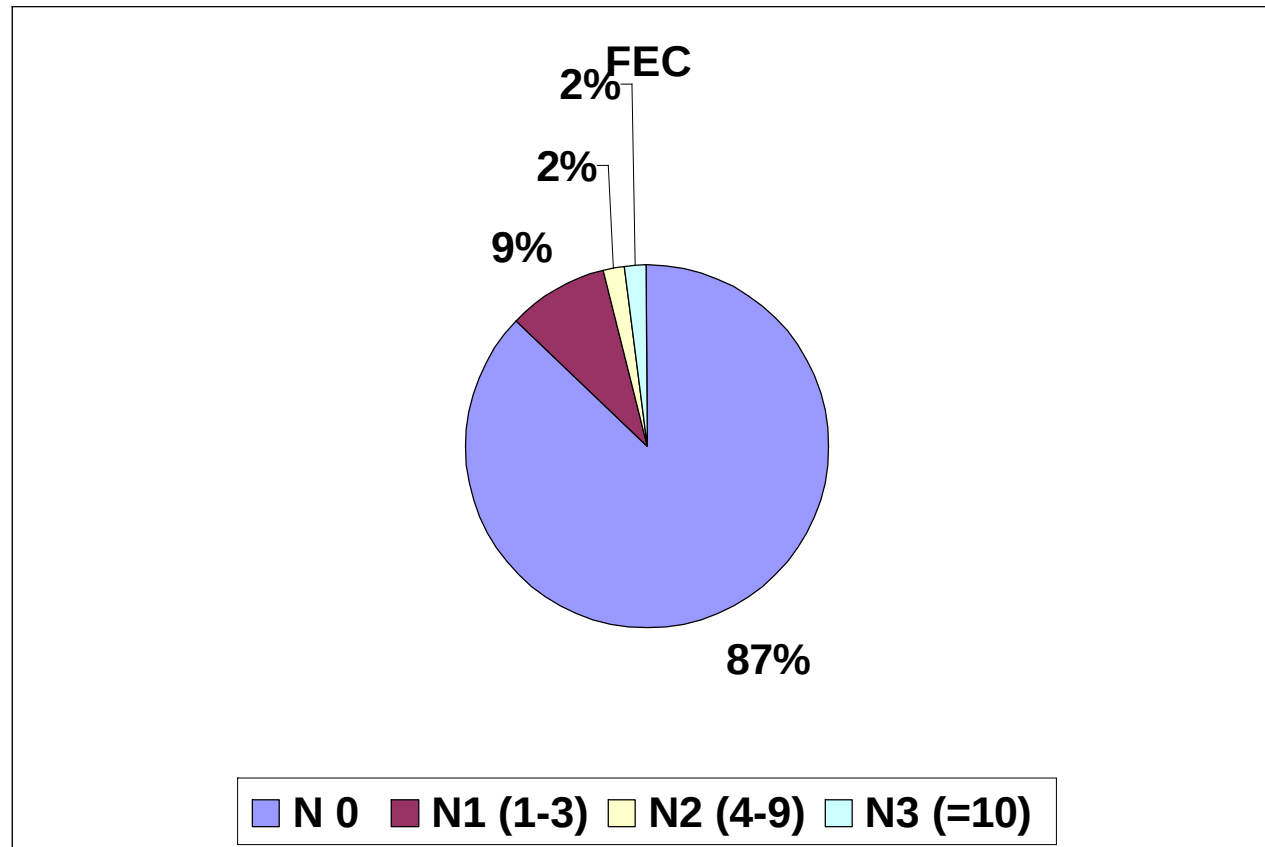
N-Status



Qualitätssicherungsprojekt

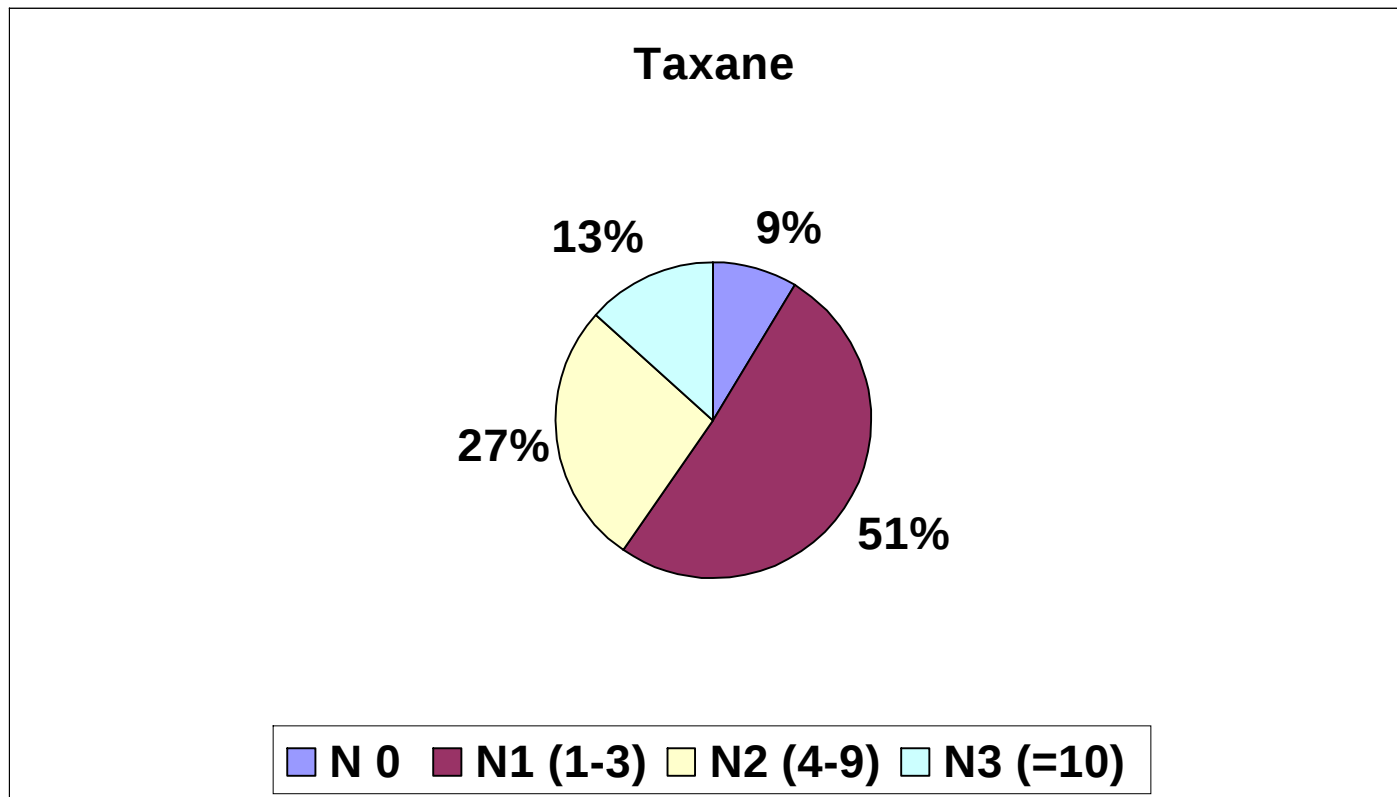
Adjuvante Chemotherapie N-Status

FEC



Adjuvante Chemotherapie N-Status

Taxane



Qualitätssicherungsprojekt

Adjuvante Chemotherapie

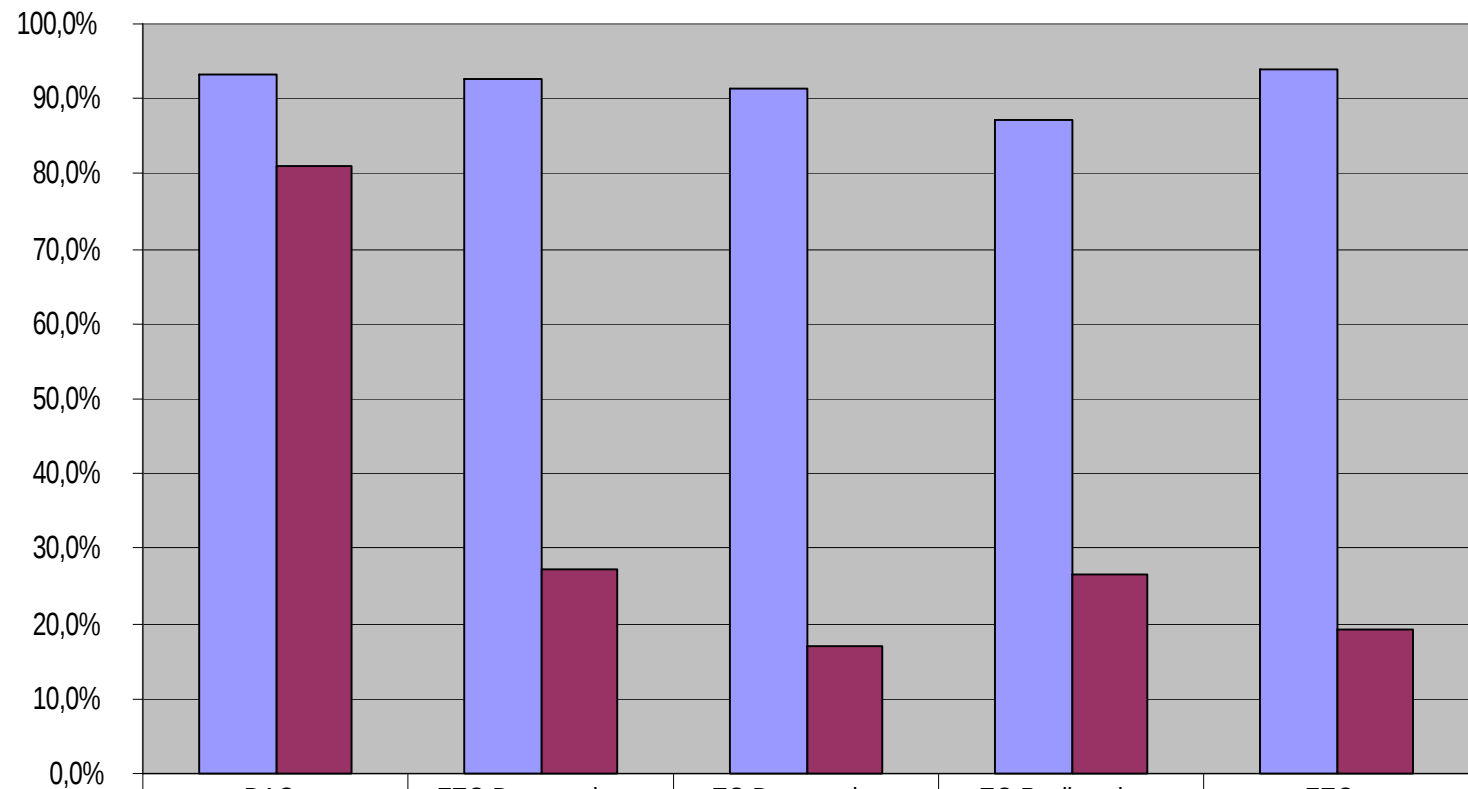
N-Status

Therapie	N 0 (%)	1-3 (%)	4-9 (%)	=10 (%)
FEC	89	9	2	2
FEC-Docetaxel	14	57	20	9
EC-Paclitaxel	9	40	26	24
DAC	9	46	33	12
EC-Docetaxel	2	61	29	8
Gesamt	44	35	14	7

Qualitätssicherungsprojekt

Adjuvante Chemotherapie

Zykluszahl

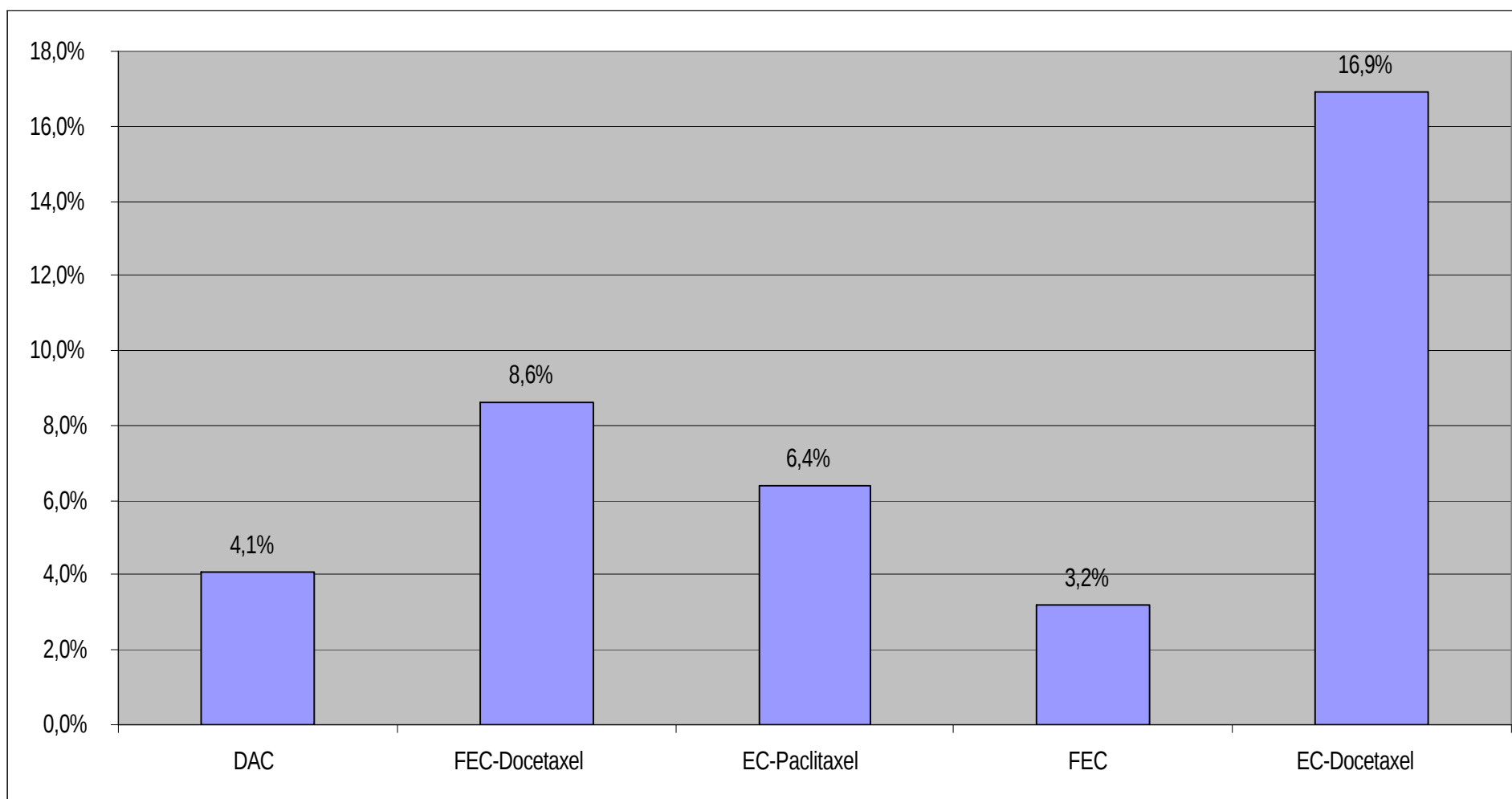


tatsächlich verabreichte Zyklenzahl	93,2%	92,7%	91,5%	87,2%	93,8%
G-CSF Gabe	81,1%	27,4%	16,9%	26,6%	19,2%

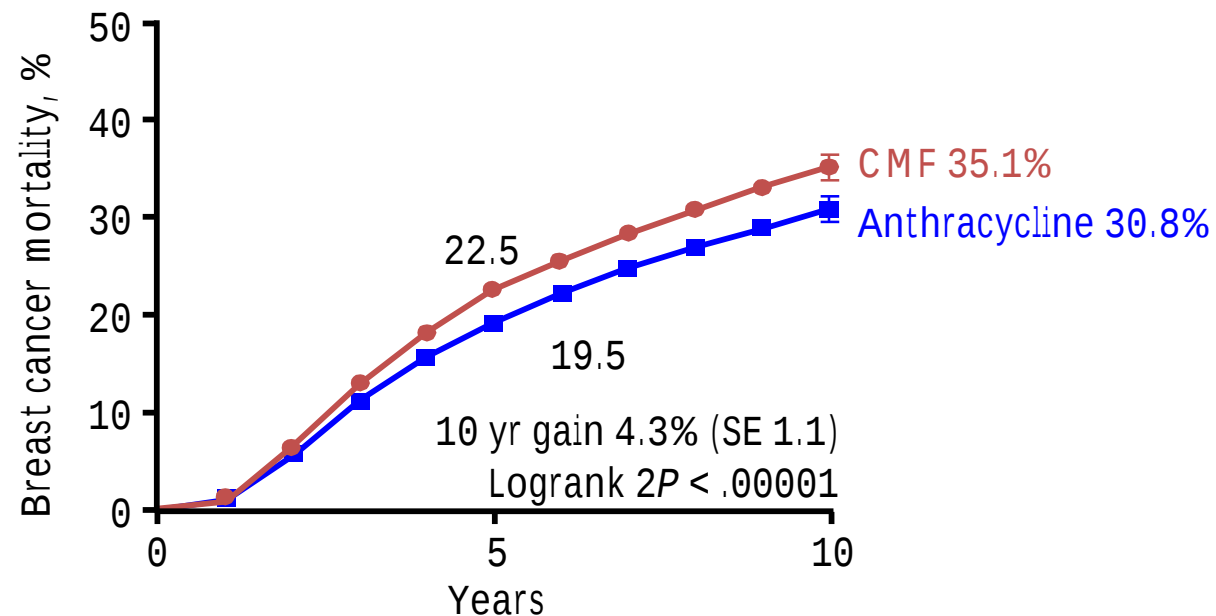
Qualitätssicherungsprojekt

Adjuvante Chemotherapie

Dosisreduktion

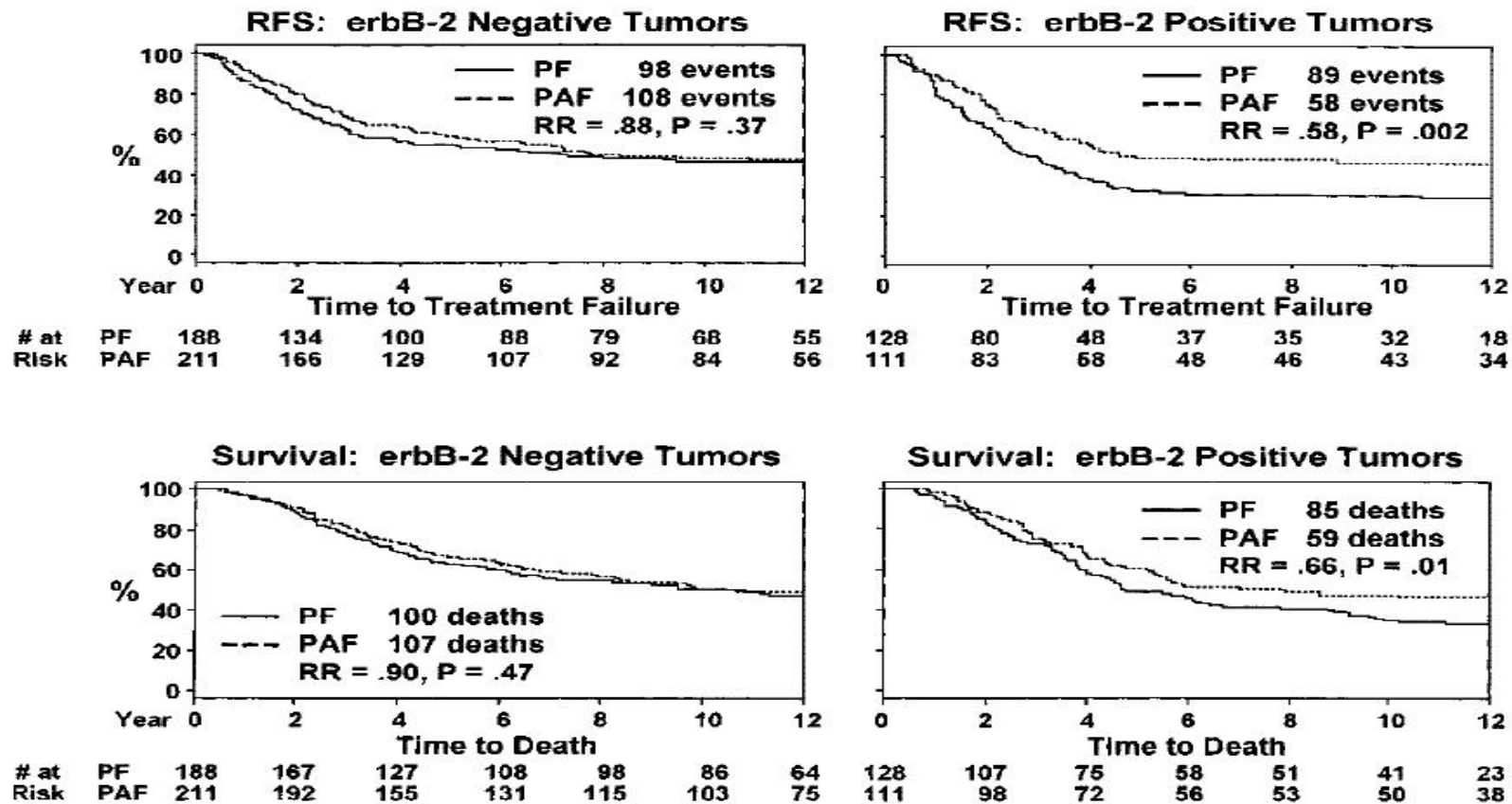


Breast Cancer Mortality

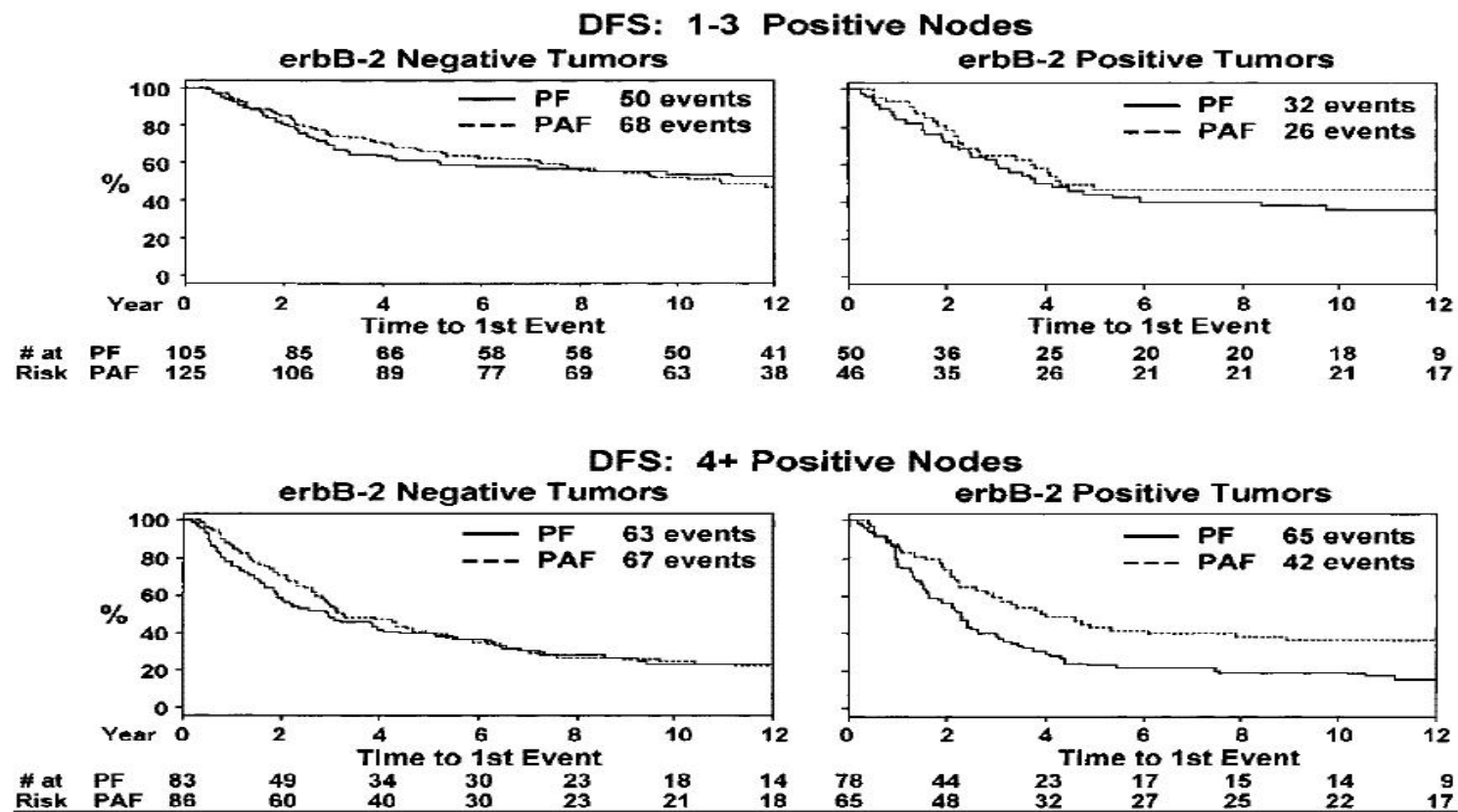


	Years 0-4	Years 5-9	Year 10+
Anthracycline	4.23 (4.44 – 0.21)	3.33 (3.67 – 0.34)	2.25 (2.88 – 0.63)
CMF	4.82 (5.01 – 0.19)	3.50 (3.86 – 0.36)	3.46 (4.27 – 0.81)
Rate ratio, from (O-E) / V	0.83 SE 0.04 -100.2 / 554.1	0.89 SE 0.07 -22.6 / 186.8	0.64 SE 0.18 -9.0 / 20.1

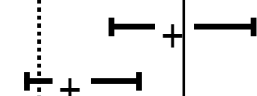
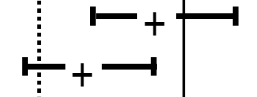
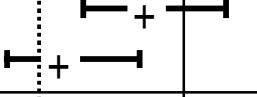
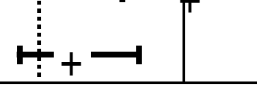
NSABP-B11



NSABP-B11

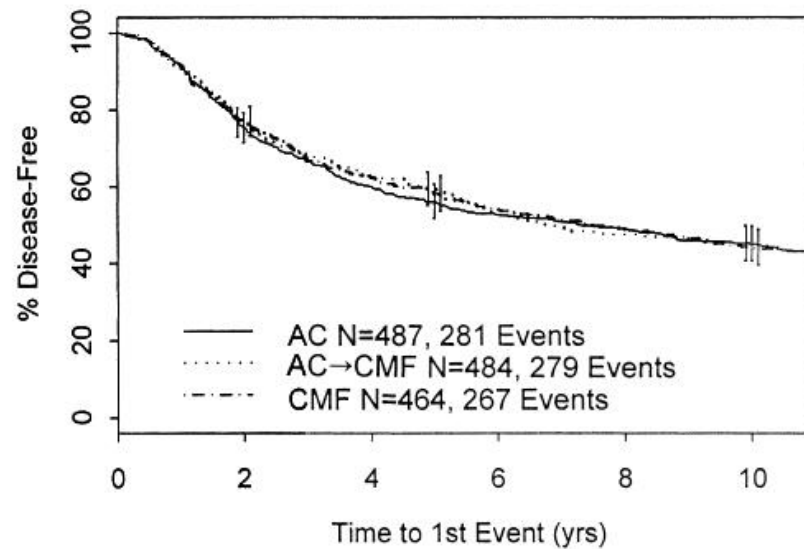


NSABP-B11

Outcome	erbB-2 Status	RR: PAF vs PF 0.05 1.00 1.50	P Value PAF vs PF	P Value Interaction
DFS	Negative Positive		.74 .001	.02
OS	Negative Positive		.47 .01	.15
RFS	Negative Positive		.37 .002	.06
DDFS	Negative Positive		.84 .003	.02

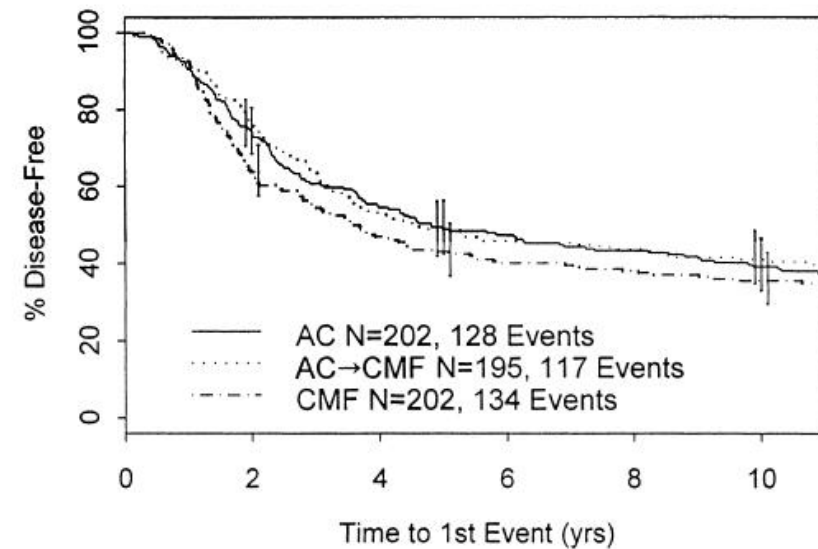
NSABP-B15

DFS, HER2 Negative



Treatment		Number at Risk					
AC	487	366	289	251	231	188	
AC→CMF	484	371	299	251	219	188	
CMF	464	356	288	249	222	176	

DFS, HER2 Positive

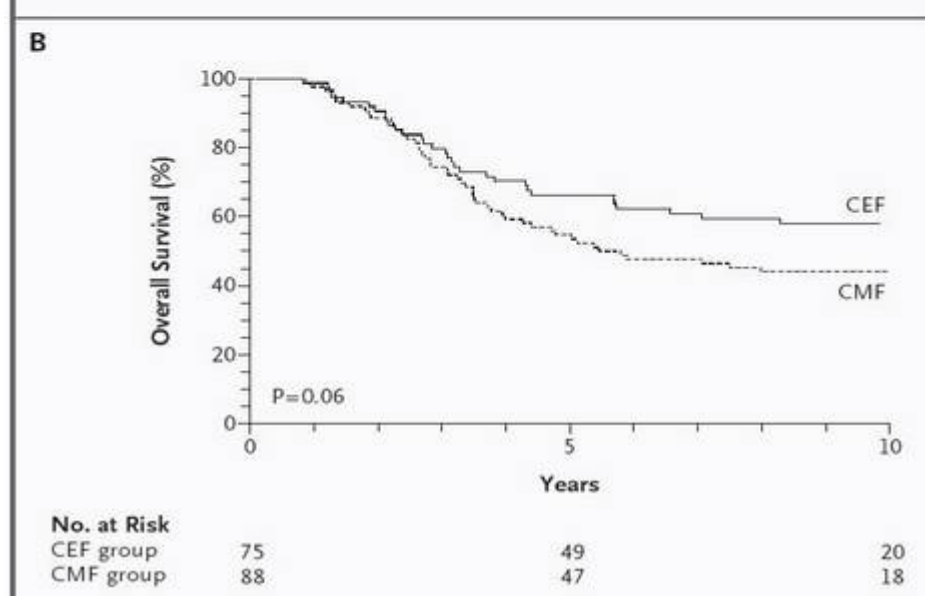
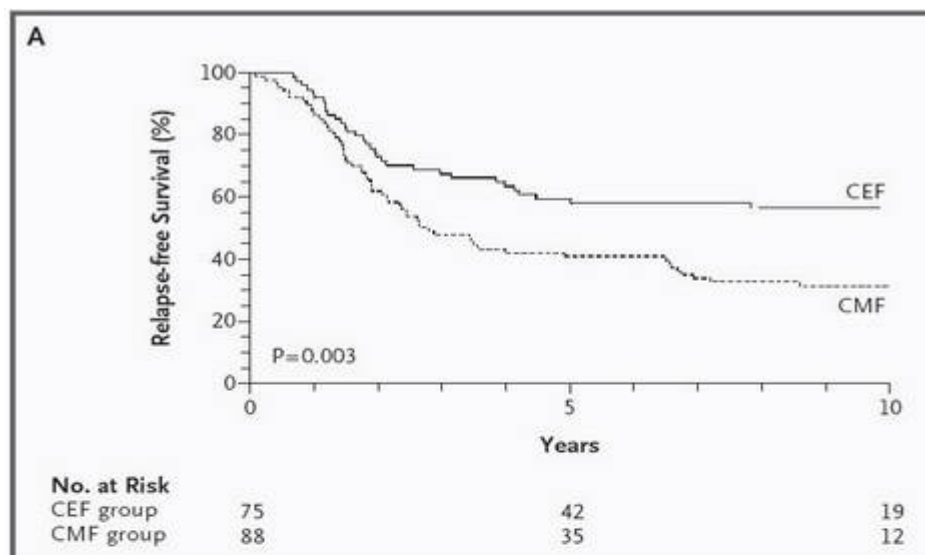
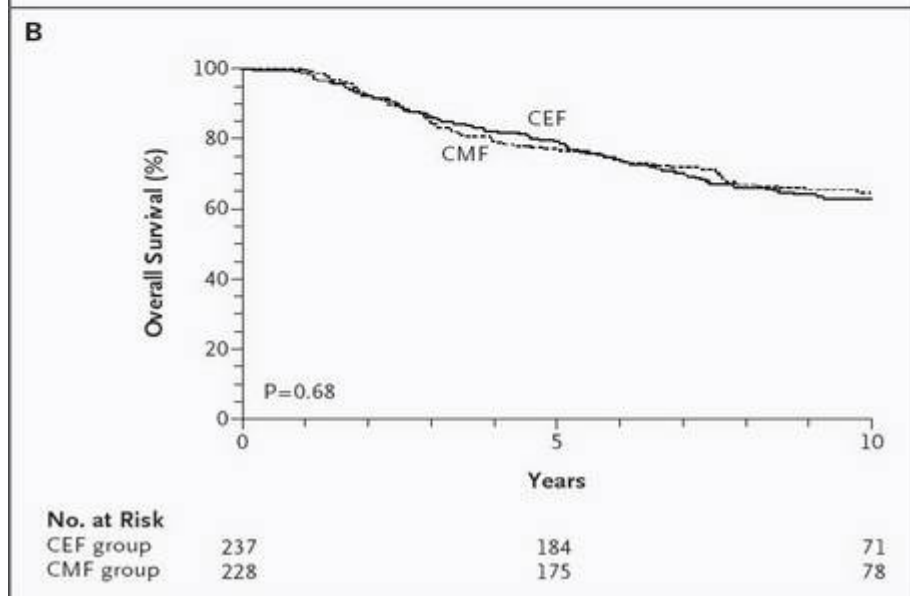
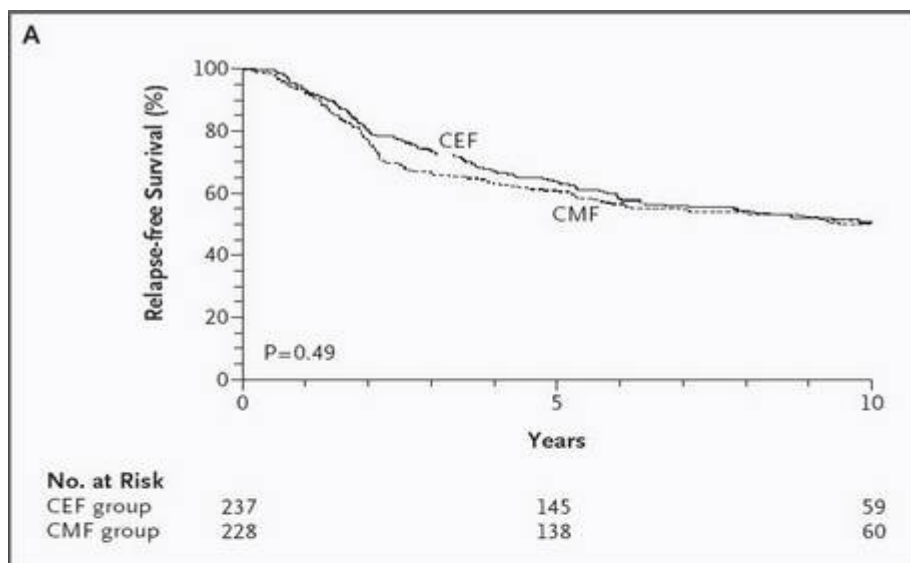


Treatment		Number at Risk					
AC	202	151	110	94	86	71	
AC→CMF	195	148	103	89	80	71	
CMF	202	129	95	81	76	64	

HER-2 Negative

MA.5 Trial

HER-2 Positive



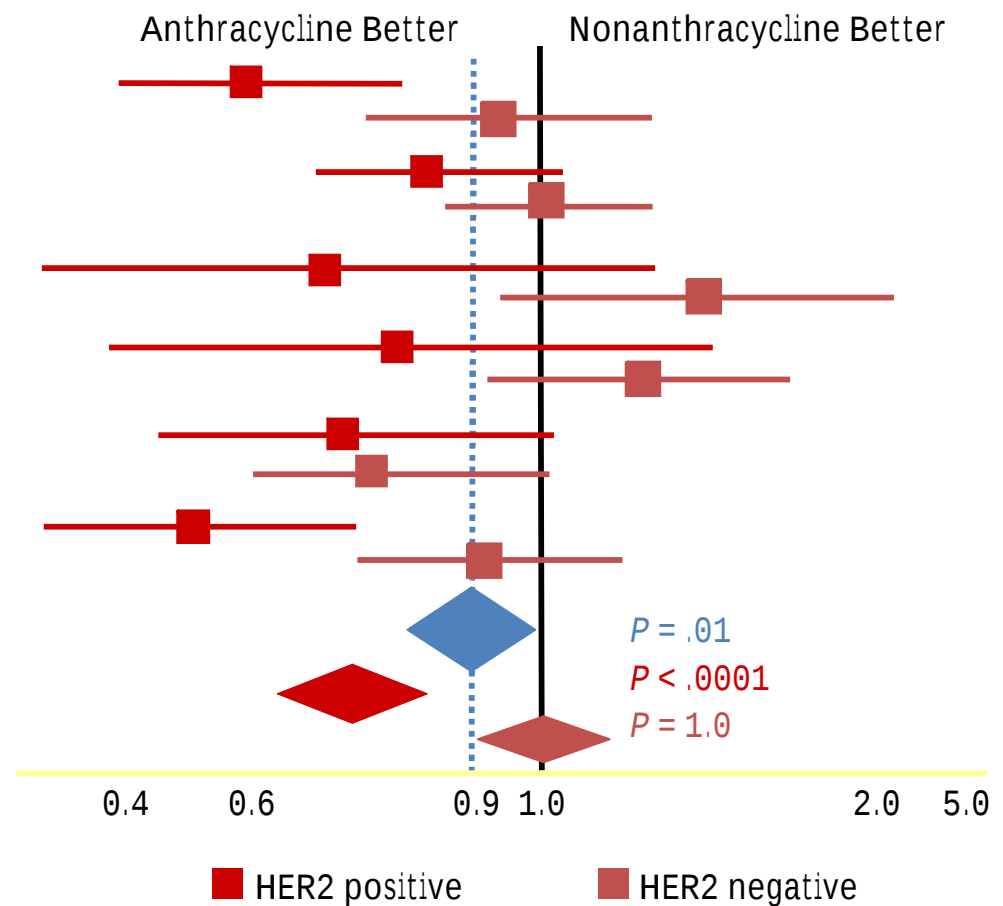
Disease-Free Survival

Study	HR	95% CI
NSABP B11	0.60	0.44-0.82
	0.96	0.75-1.23
NSABP B15	0.84	0.65-1.08
	1.02	0.86-1.20
Brussels	0.65	0.34-1.27
	1.35	0.93-1.97
Milan	0.83	0.46-1.49
	1.22	0.91-1.64
DBCCG-89-D	0.75	0.53-1.06
	0.79	0.60-1.05
NCIC MA-5	0.52	0.34-0.80
	0.91	0.71-1.17
Total	0.90	0.82-0.98
Overall	0.71	0.61-0.83
	1.00	0.90-1.11

heterogeneity $c25 = 5.3$; $P = .38$

heterogeneity $c25 = 7.6$; $P = .18$

Test for interaction $\chi^2 = 13.7$; $P < .001$



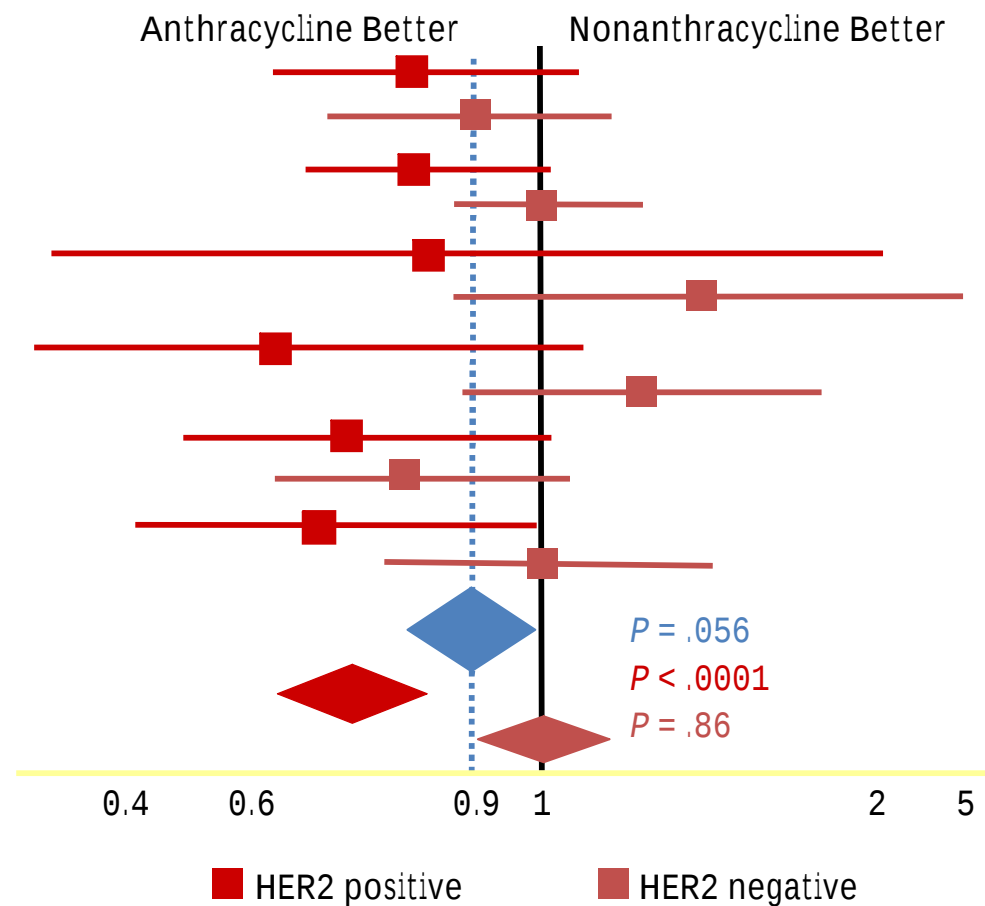
Overall Survival

Study	HR	95% CI
NSABP B11	0.66	0.47-0.92
	0.90	0.69-1.18
NSABP B15	0.82	0.63-1.06
	1.07	0.88-1.30
GUN3	0.85	0.27-2.69
	1.64	0.85-3.15
Milan	0.61	0.32-1.16
	1.26	0.89-1.79
DBCCG-89-D	0.73	0.50-1.05
	0.82	0.59-1.13
NCIC MA-5	0.65	0.42-1.01
	1.06	0.80-1.40
Total	0.91	0.83-1.00
Overall	0.73	0.62-0.85
	1.03	0.92-1.16

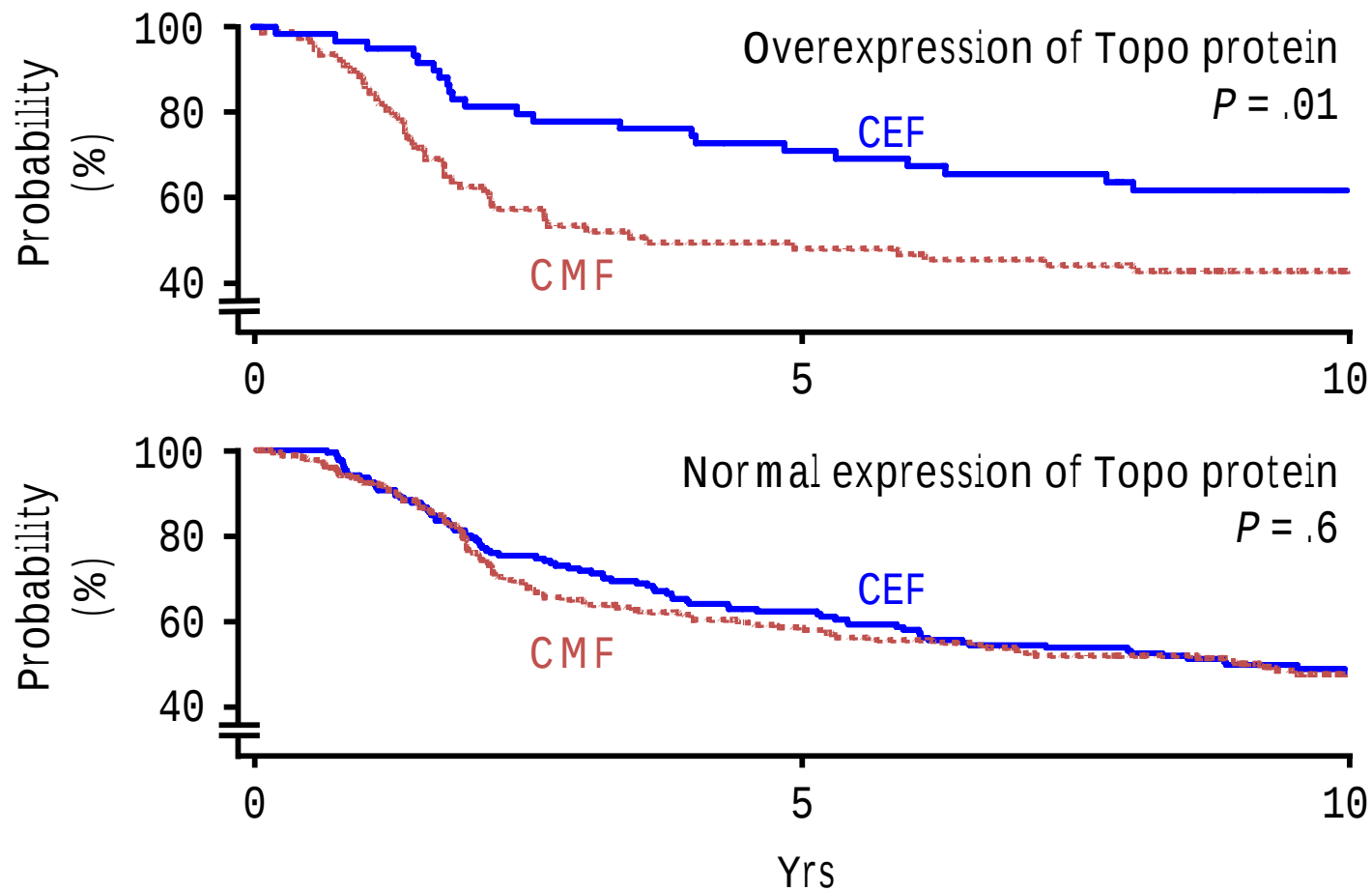
heterogeneity $c25 = 5.2$; $P = .39$

heterogeneity $c25 = 5.5$; $P = .36$

Test for interaction $\chi^2 = 12.0$; $P < .001$

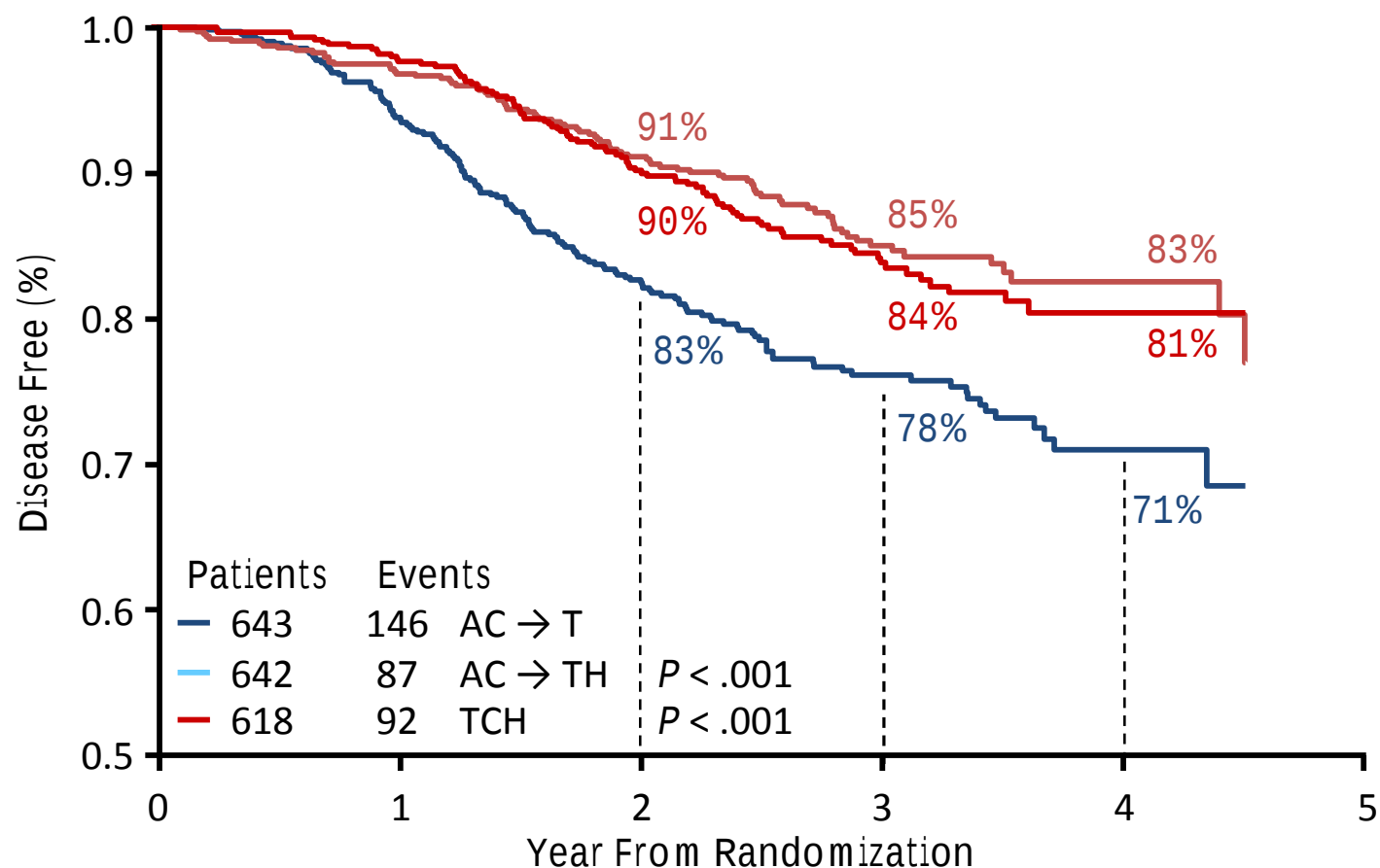


DFS by Treatment MA.5 trial



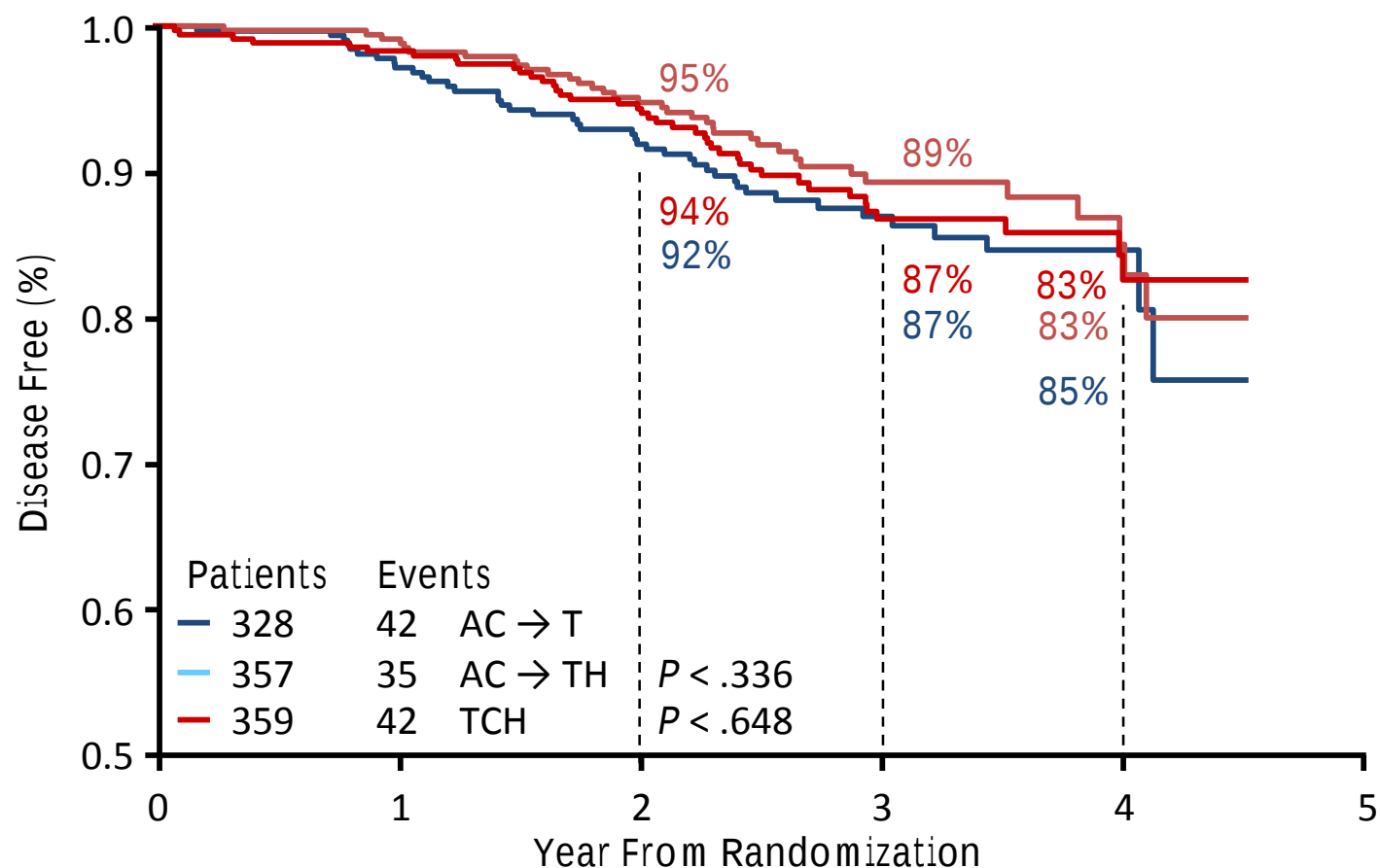
- **Topo IIa** Genamplifikation und nicht HER2 ist verantwortlich für die verbesserte Anthracyclin Sensitivität
- Die verbesserte Anthracyclin Sensitivität ist **NICHT** hervorgerufen durch HER2 Überexpression

DFS Non-coamplified Topo IIa by Arm: BCIRG 006 Second Interim Analysis

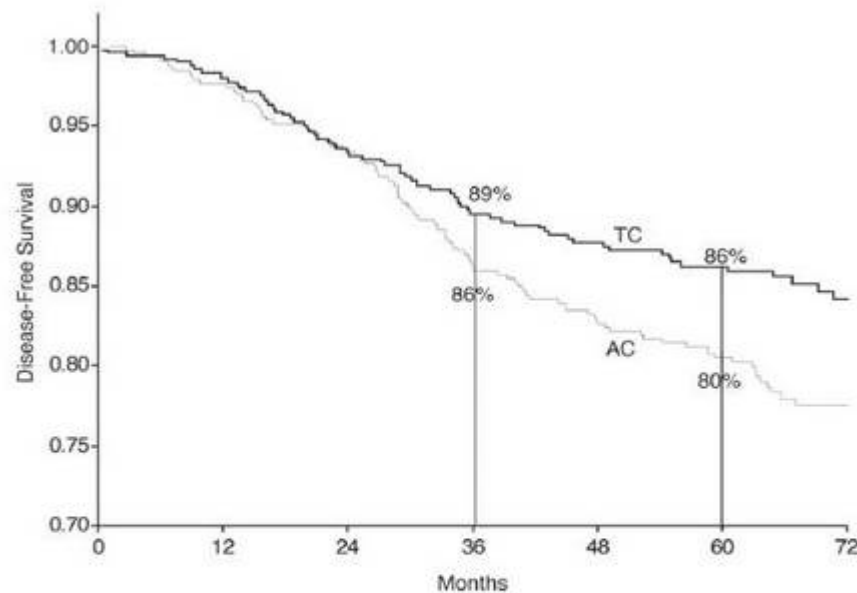


Slamon D, et al. SABCS 2006. Abstract 52.

DFS Coamplified Topo IIa by Arm: BCIRG 006 Second Interim Analysis



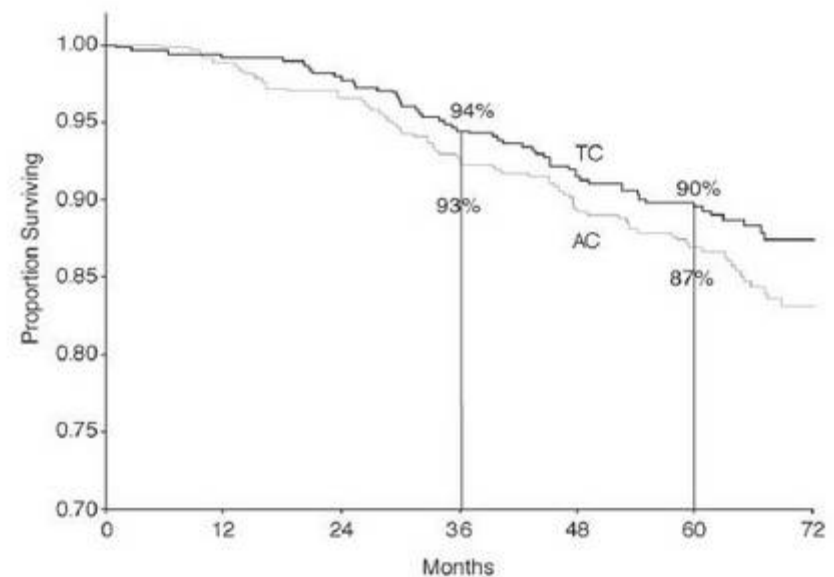
TC x 4 vs AC x 4



Arm	N	Relapse	Months	12	24	36	48	60	72	P
TC	506	71	% DFS	98	93	89	88	86	84	.015
AC	510	103	% DFS	98	93	86	83	80	78	

Patients at risk per year:

		12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
TC	506	478	440	409	374	317	
AC	510	483	450	401	369	307	



Arm	N	Deaths	Months	12	24	36	48	60	72	P
TC	506	55	% Survival	99	98	95	92	90	87	.13
AC	510	73	% Survival	99	97	93	90	87	83	

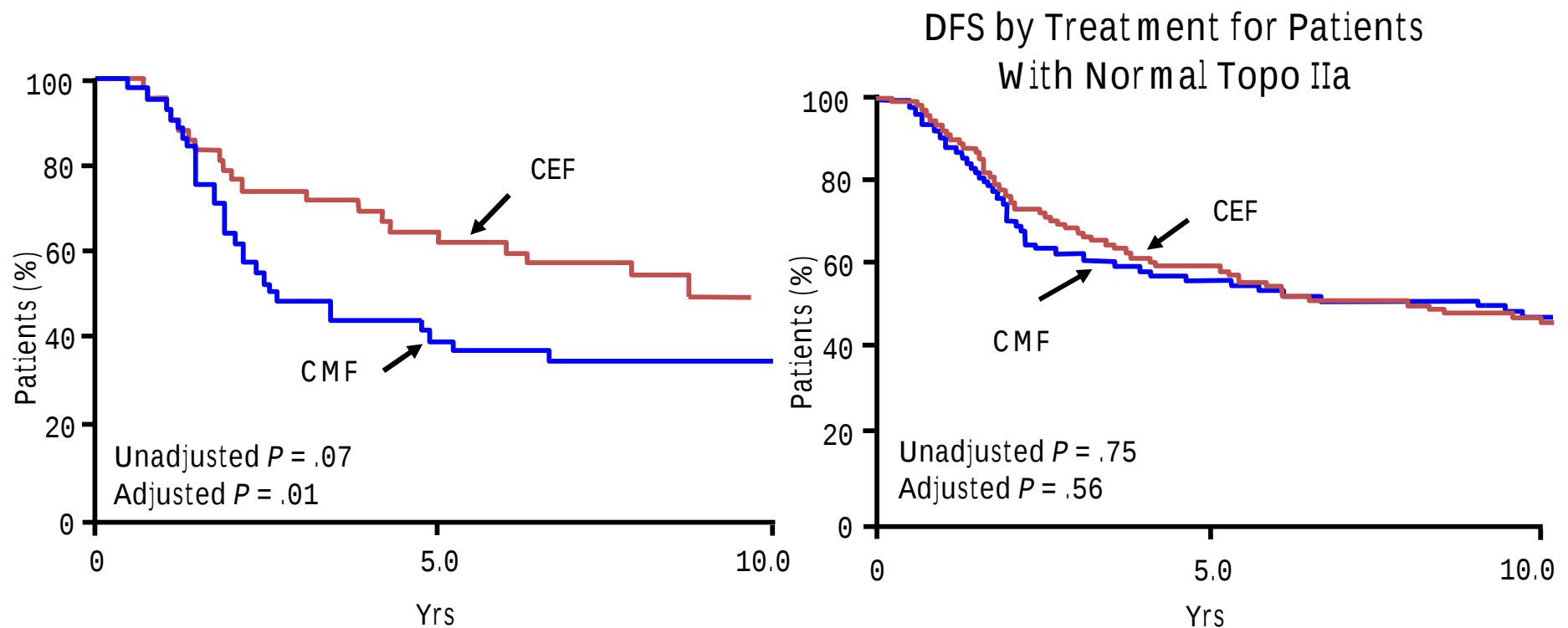
Patients at risk per year:

		12 Months	24 Months	36 Months	48 Months	60 Months	72 Months
TC	506	483	459	431	389	332	
AC	510	489	466	433	400	335	

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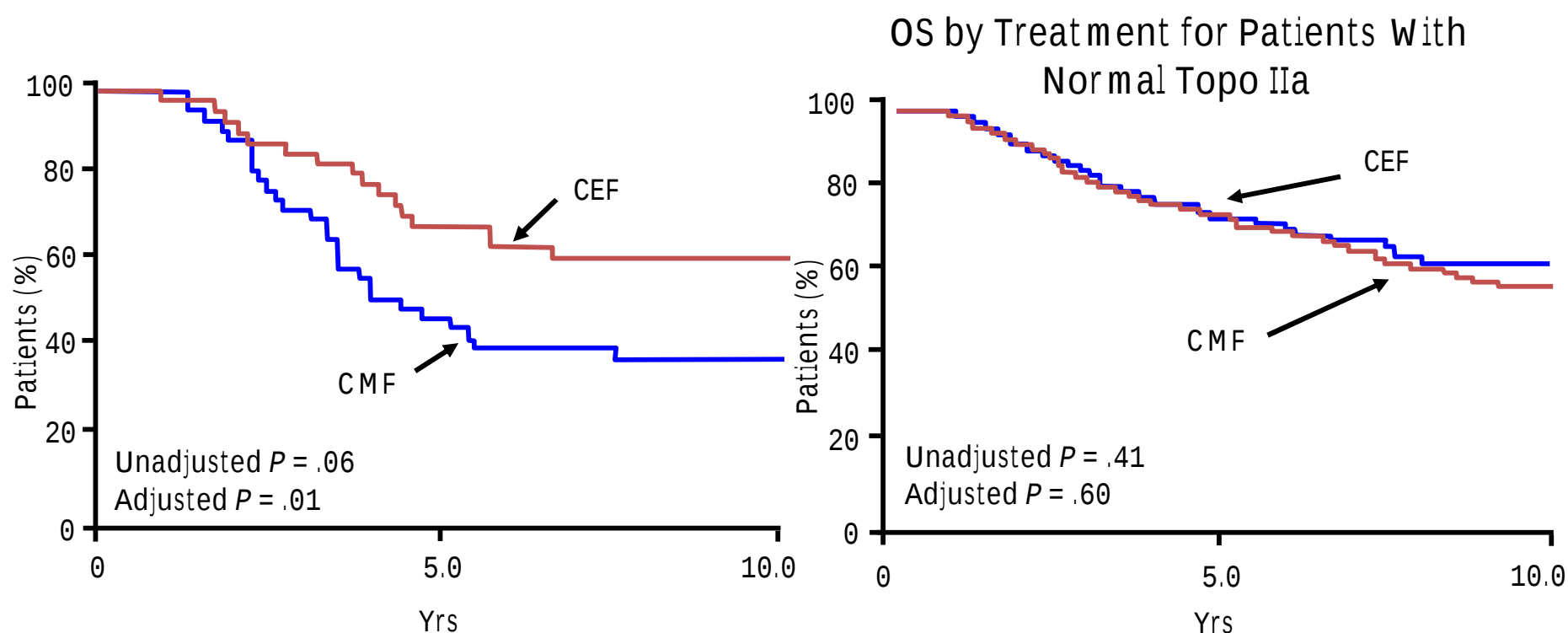
DFS by Treatment for Patients With Topo IIa Amplified or Deleted Tumors

MA.5 trial



OS by Treatment for Patients With Topo IIa Amplified or Deleted Tumors

MA.5 trial



Welches ist der beste prediktive Faktor für CEF vs CMF in MA.5?

	DFS <i>P</i> Value	OS <i>P</i> Value
HER2/neu	.01	.02
Topo IIa protein*	.04	.03
Topo IIa gene	.09	.04

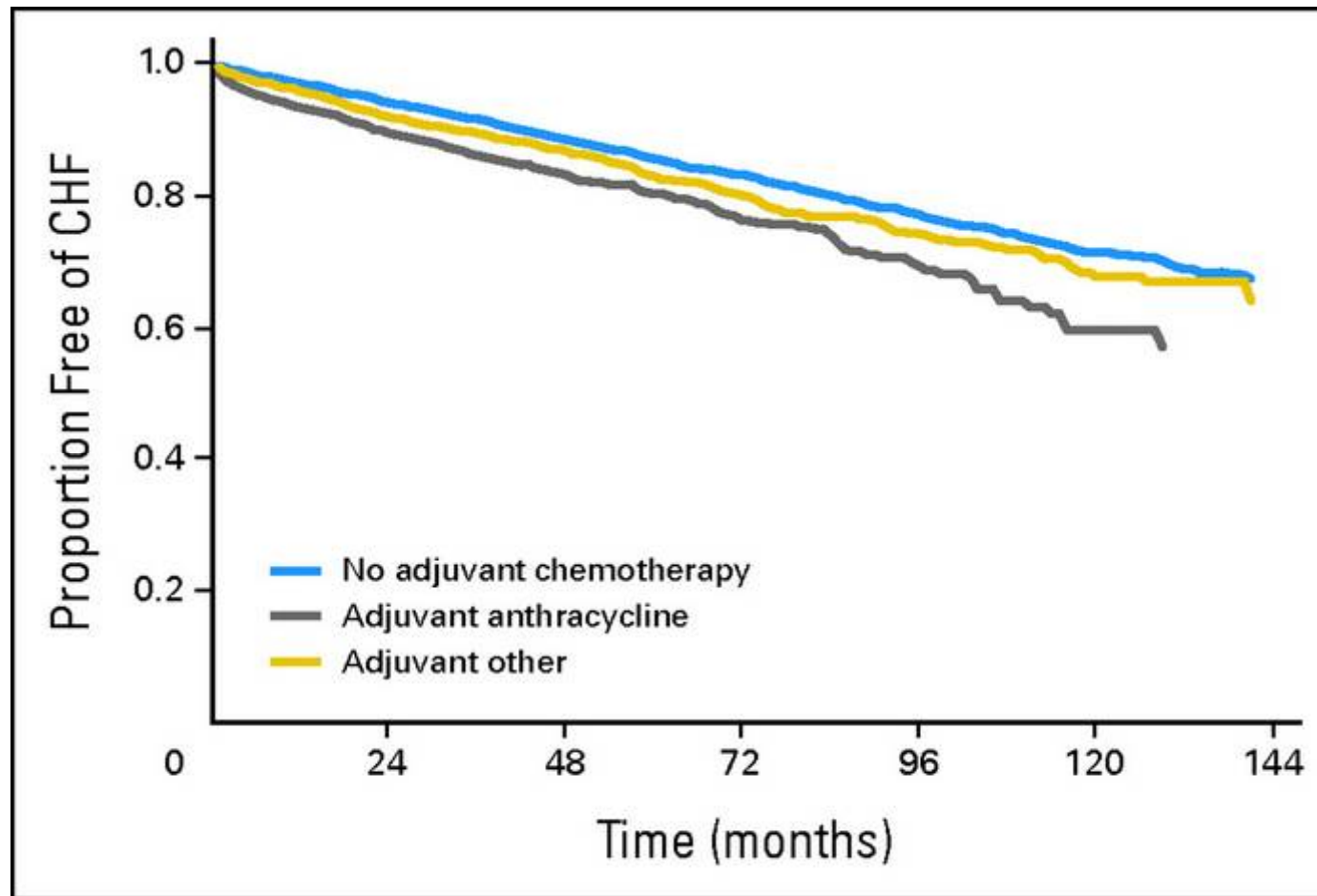
*Exploratory analysis.

Therapeutic Index: Most Recent BCIRG 006 Data

	AC → TH	TCH
Breast cancer recurrence	93	98
Breast cancer deaths	44	47
Grade 3/4 CHF	20	4
Acute leukemia	4*	0
Total	161	149

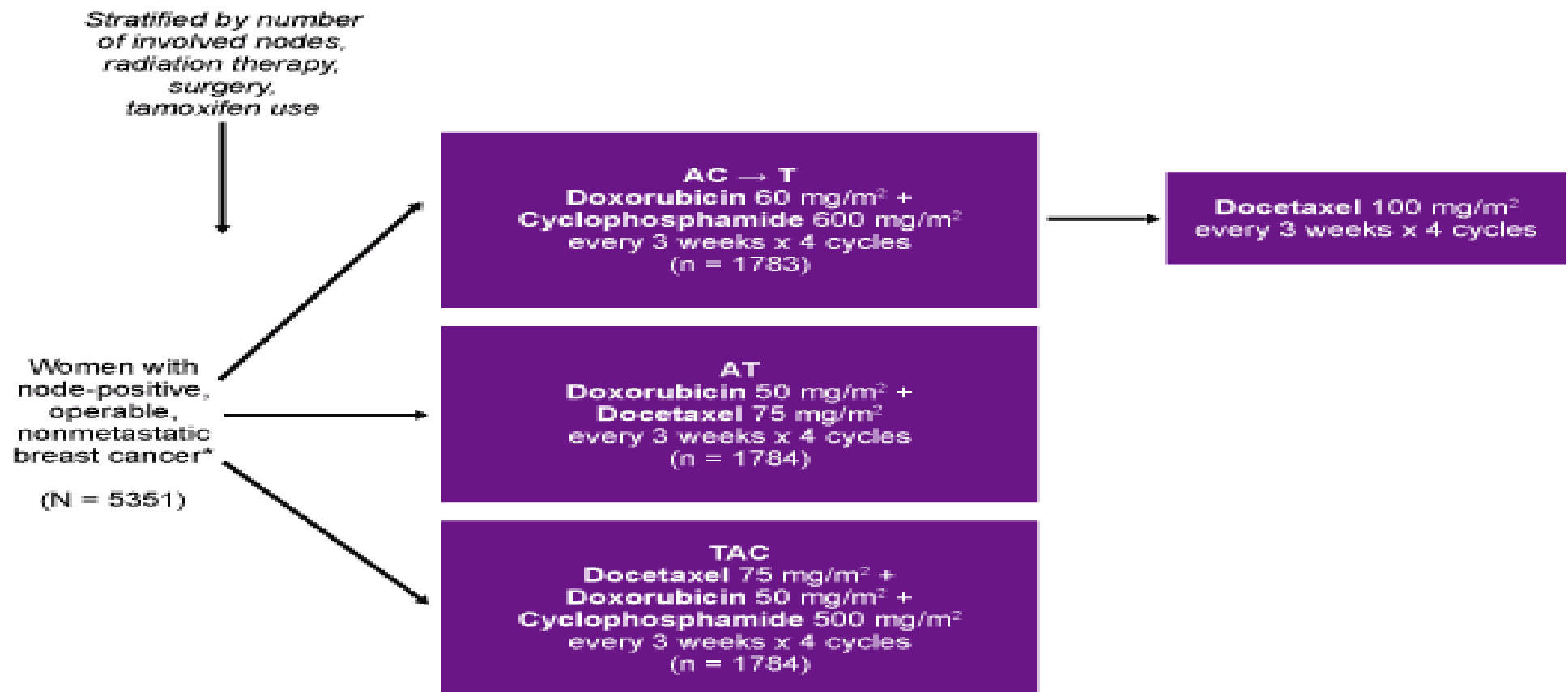
*In both anthracycline-based arms.

Fig 1. Women aged 66 to 70 years: freedom from congestive heart failure (CHF) by adjuvant chemotherapy type



Pinder, M. C. et al. J Clin Oncol; 25:3808-3815 2007

NSABP B-30: Doxorubicin and Cyclophosphamide Followed by Docetaxel Associated With Best Survival Outcomes vs Concurrent Approaches in Node-Positive EBC



*Estrogen receptor– and/or progesterone receptor–positive patients to receive tamoxifen for 5 years following chemotherapy.

NSABP B-30: Doxorubicin and Cyclophosphamide Followed by Docetaxel Associated With Best Survival Outcomes vs Concurrent Approaches in Node-Positive EBC

- Tumor size: T1-3
- Lymph node: N0-1 based on clinical exam
 - = 1 positive node determined by pathologic exam
- No distant metastases: M0
- Established estrogen receptor and progesterone receptor status
- Radiation therapy plan submitted prior to randomization

NSABP B-30: Doxorubicin and Cyclophosphamide Followed by Docetaxel Associated With Best Survival Outcomes vs Concurrent Approaches in Node-Positive EBC

I

- Main Findings
- Cycles of therapy completed
 - AC → T (n = 1748)
 - AC: 99%
 - T: 86%
 - AT (n = 1729): 97%
 - TAC (n = 1740): 97%
- Patients evaluable for OS and DFS evaluation
 - Intent-to-treat analyses
 - AC → T: n = 1753
 - AT: n = 1753
 - TAC: n = 1758
- Significant increase in OS with AC → T vs AT and in DFS with AC → T vs AT or TAC
 - Equivalent outcomes for AT and TAC

NSABP B-30: Doxorubicin and Cyclophosphamide Followed by Docetaxel Associated With Best Survival Outcomes vs Concurrent Approaches in Node-Positive EBC

- Distant recurrence most frequent first event among all 3 study arms with significant difference in cumulative incidence between arms ($P = .009$)
 - **AT: n = 280 events TAC: n = 218 events AC → T: n = 257 events**
- Significant difference in cumulative incidence of regional recurrence between treatment arms
- ($P = .02$) **AC → T: n = 16 events AT: n = 22 events TAC: n = 35 events**
- Subgroup analyses of DFS by age, endocrine receptor status, number of lymph nodes, tumor size, hormonal therapy, or menopausal status consistently favored
 - **AC → T over TAC**
 - **AC → T over AT**

	Grade 3/4 Toxicity, %			
	AC → T (n = 1749)	AT (n = 1750)	TAC (n = 1749)	P Value
• Febrile neutropenia	22	13	16	< .0001
• Infection	8	6	6	.0036

NSABP B-30: Doxorubicin and Cyclophosphamide Followed by Docetaxel Associated With Best Survival Outcomes vs Concurrent Approaches in Node-Positive EBC

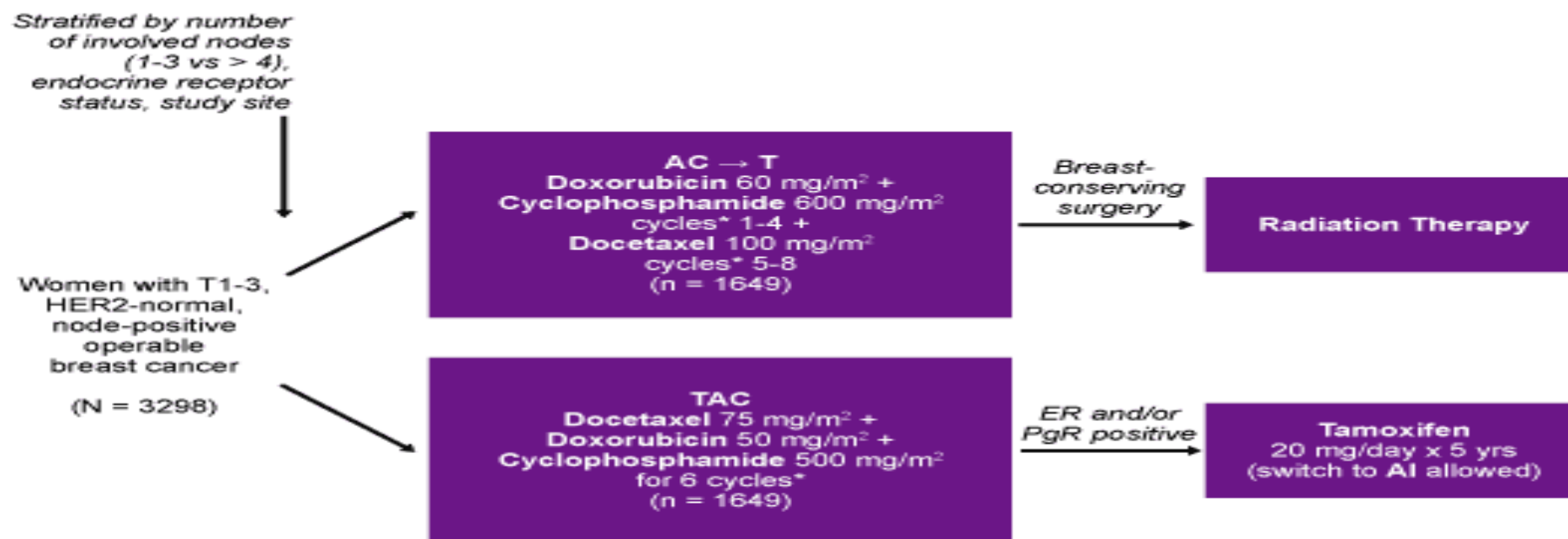
- *Among premenopausal women, OS significantly longer in patients with vs without amenorrhea
 - Risk ratio: 0.76 ($P = .038$)
 - DFS also significantly longer in patients with amenorrhea
 - Risk ratio: 0.70 ($P = .00041$)
 - Premenopausal women eligible: $n = 2445$
 - Follow-up available: $n = 2366$
 - Risk lower with amenorrhea across treatment, age, hormonal therapy subgroups

NSABP B-30: Doxorubicin and Cyclophosphamide Followed by Docetaxel Associated With Best Survival Outcomes vs Concurrent Approaches in Node-Positive EBC

III

- In women with lymph node–positive early breast cancer, OS with doxorubicin (A) plus cyclophosphamide (C) followed by docetaxel (T) treatment (AC → T)
 - Borderline superior OS compared with concurrent combination docetaxel, doxorubicin, cyclophosphamide (TAC)
 - Significantly superior to AT
- DFS with AC → T was significantly superior to TAC and AT
- Improved DFS and OS with vs without amenorrhea among premenopausal women

BCIRG-005: Similar DFS With AC → T and TAC in Patients With HER2-Normal, Node-Positive Early Breast Cancer



AI, aromatase inhibitor; ER, estrogen receptor, PgR, progesterone receptor.

*Dosing on Day 1 of 3-week cycles.

All patients received premedication with dexamethasone 8 mg twice daily for 3 days and prophylactic ciprofloxacin 500 mg twice daily on Days 5-14.

BCIRG-005: Similar DFS With AC → T and TAC in Patients With HER2-Normal, Node-Positive Early Breast Cancer

- Key eligibility criteria
 - Histologically confirmed breast cancer
 - Lymph node positive
 - Tumor stage: T1-3
 - HER2 normal by central fluorescence in situ hybridization assay
 - = 70 years of age
 - Karnofsky performance score = 80%
 - Definitive surgery with dissection of = 6 axillary lymph nodes
 - = 60 days between surgery and randomization
 - Exclusion criteria^[2]
 - Metastatic disease
 - Abnormal hematologic, renal, hepatic, or cardiac function
 - Previous therapy for breast cancer (ie, immunotherapy, hormonal treatment, gene therapy, or chemotherapy)
 - Bilateral, invasive breast cancer
 - Pregnancy
 - Concurrent ovarian hormone replacement therapy
-
- **AC → T (n = 1649) TAC (n = 1649)**
 - Median age, yrs
 - 50
 - 50
 - Median Karnofsky performance score
 - 100
 - 100

BCIRG-005: Similar DFS With AC → T and TAC in Patients With HER2-Normal, Node-Positive Early Breast Cancer

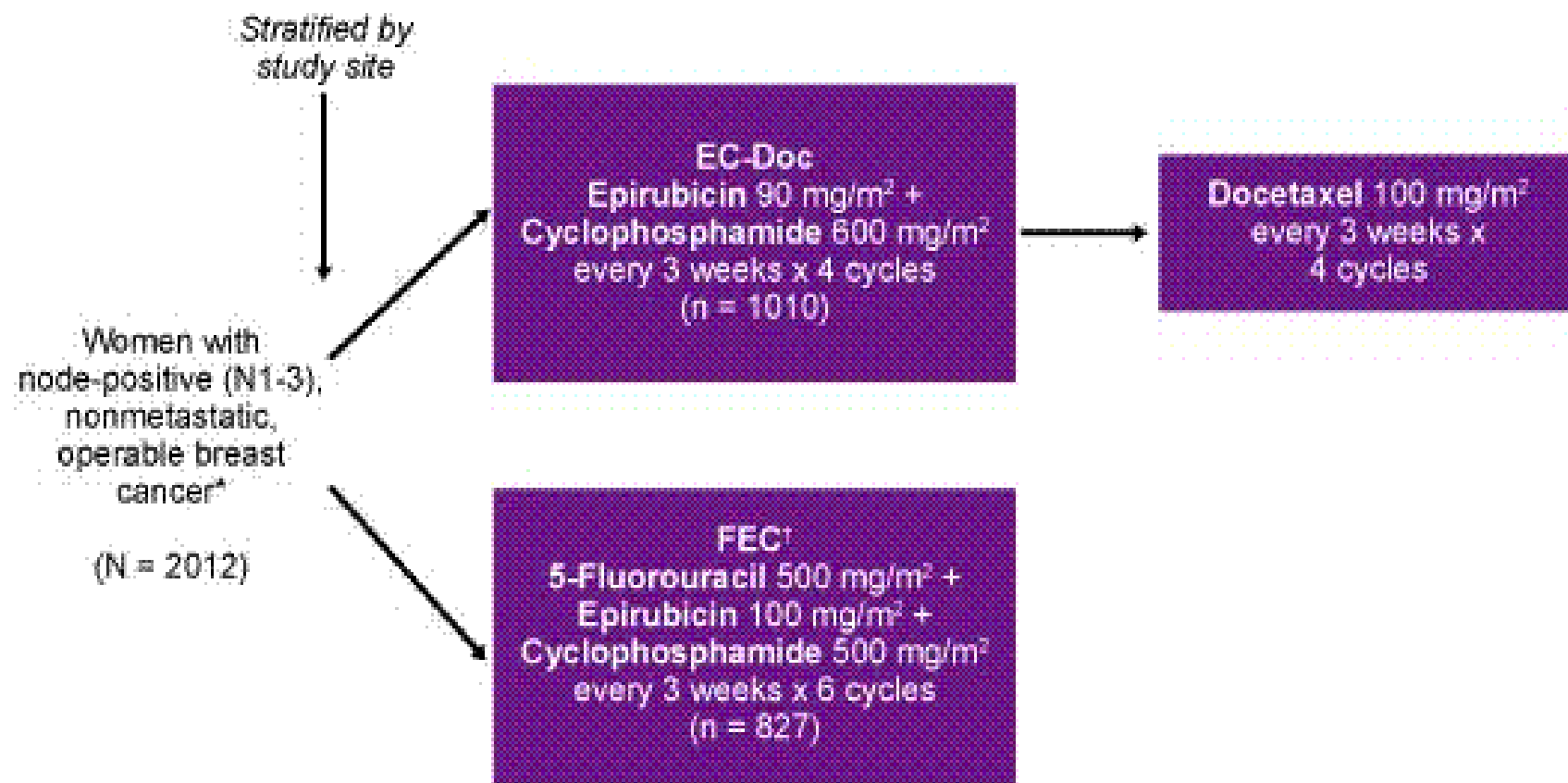
- Therapy delivery
 - Completed all planned cycles of therapy
 - AC → T: 91% TAC: 94% Median relative dose intensity: 0.99 on both arms
- DFS and OS outcomes No significant differences between study arms
- DFS with doxorubicin/cyclophosphamide followed by docetaxel (AC → T) equivalent to combination docetaxel, doxorubicin, cyclophosphamide (TAC) in patients with HER2-normal, node-positive early breast cancer
 - Despite higher-dose intensity with AC → T vs TAC
- Higher incidence of febrile neutropenia, increased use of granulocyte colony-stimulating factor with TAC
- Higher incidence of sensory neuropathy, myalgia, nail changes with AC → T

**BCIRG-005: Similar DFS With AC → T and TAC in Patients With HER2-Normal,
Node-Positive Early Breast Cancer**

	AC → T, %	TAC, %	HR (95% CI)	p
Value	(n = 1649)	(n = 1649)		
• DFS	78.6	78.9	1.002 (0.86-1.16)	.98
• OS	88.9	88.1	0.91 (0.75-1.11)	.37

- No difference in DFS among subgroups by number of involved lymph nodes or hormone receptor status (including triple-negative subgroup)

Epirubicin, Cyclophosphamide Followed by Docetaxel Improves Survival vs Concurrent 5-Fluorouracil, Epirubicin, Cyclophosphamide in Women With Intermediate Risk Breast Cancer



*Estrogen receptor-positive patients to receive tamoxifen for 5 years following chemotherapy.

†175 patients treated with alternative regimen (CMF; cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m² on Days 1, 8 every 4 weeks) not included in current analysis.

Epirubicin, Cyclophosphamide Followed by Docetaxel Improves Survival vs
Concurrent 5-Fluorouracil, Epirubicin, Cyclophosphamide in Women With
Intermediate Risk Breast Cancer

- West German Study Group (WSG) and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Mamma Intergroup Study EC-Doc (AM02): randomized, multicenter phase III trial^[1]
- 5-year OS rate 5-year EFS Overall epirubicin, cyclophosphamide followed by docetaxel treatment (EC-Doc) 90.2 vs 85.8 5-fluorouracil, epirubicin, cyclophosphamide (FEC) HR 1.514 (1.11-2.07)
- EFS rates significantly higher even among patients with hormone receptor–positive disease Hormone receptor status
 - Positive 92.5 vs 88.7 HR 1.55 (1.04-2.32) p .03
 - Negative 81.8 vs 74.9 HR 1.43 (0.86-2.39)
- EC-Doc viable treatment option for patients with early breast cancer and 1-3 involved lymph nodes

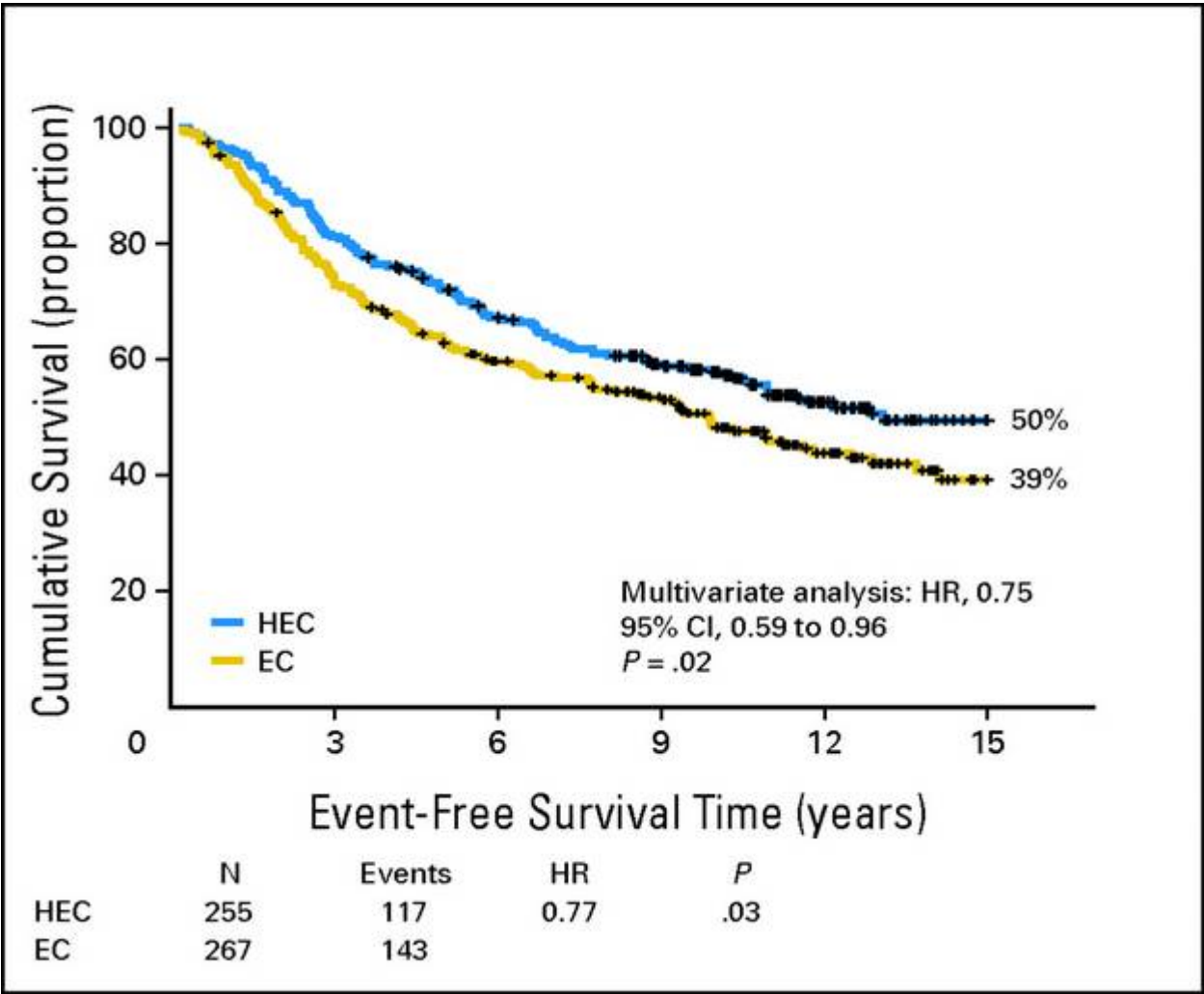
Antrazykline Hochdosis vs Normaldosis

First Author/Study	Type	No. of Patients	Median FU (years)	Treatment	DFS (%)	P	OS (%)	P
Picart (Belgian)	N+	777	12.2*	8 EC, IV	39		56	
				8 HEC, IV	50		59	
						.03		.26
Fumoleau ⁶ (FASG 01)	Premenopausal N+	621	10.9	6 FEC50, IV	53.4		64.3	
				3 FEC50, IV	42.5	.02	56.6	.10
				3 FEC75, IV	43.6	.05	59.7	.59
Bonneterr ^{e3} (FASG 05)	N+	565	9.2	6 FEC50, IV	45.3		50.0	
				6 FEC100, IV	50.7		54.8	
						.036		.038

Antrazykline Hochdosis vs Normaldosis

Budman ⁷ (CALGB 8541)	N+	1,572	9	4 FAC60, IV	58		66
				6 FAC40, IV	54		65
				4 FAC30, IV	47		58
Linden ⁹ (INT-0137)	High-risk N- or N+	3,176	7.2	6 AC	79	.0002	88
				4 A C intensified	81		89
Henderson ^{8¶} (CALGB 9344)	N+	3,121	5.8	4 AC (60, 75 or 90 mg/m ²) paclitaxel x 4	69	.20	79
					66	.79	
					67		
						.60	

Fig 1. Kaplan-Meier estimates of event-free survival (EFS) for higher-dose epirubicin and cyclophosphamide (HEC) versus lower-dose epirubicin and cyclophosphamide (EC)



de Azambuja, E. et al. J Clin Oncol; 27:720-725 2009

Vergleich Antrazykline vs C M F

First Author/Stu dy	Type	No. of Patients	Median FU (years)	Treatment	DFS (%)	P	OS (%)	P
Piccart study (Belgian)	N+	777	12.2*	6 CMF, oral	45	.39, HEC x CMF	57	NS
				8 EC, IV	39	.21; EC x CMF	56	NS
				8 HEC, IV	50	.03; HEC x EC	59	NS
Bonadonn a (BClin Oncol 22:1614-1620, 2004)	N+ (1-3)	552	17.5	2 CMF, IV q3w/1 DOX (up to 12 cycles)	49	Figures not specified		
				8 CMF, IV 4 DOX	46			
Bonadonn a (, 2004A, et al. J Clin Oncol 22:1614-1620)	N+ (> 3)	403	17.2	4 DOX 8 CMF, IV	34	.64	40	

Ejlertsen (Ejlertsen B, Mouridsen HT, Jensen MB, et al. Eur J Cancer 43:877-884, 2007)	Premenopausal N- or N+	1,224	10	9 FEC, IV	HR = 0.84		HR = 0.79	
				9 CMF, IV		< .04		< .01
Coombes, ICGG (Coombes RC, Bliss JM, Wils J, et al. J Clin Oncol 14:35-45, 1996)	Premenopausal N+	399	4.8 [¶]	6 FEC2, IV	5-year figures not specified		86.6	
				6 CMF2, IV		.03	73.8	
Poole, NEAT + BR9601 (Poole CJ, Earl HM, Hillier L, et al. N Engl J Med 355:1851-1862, 2006)		2,027	4 [¶]	4 EPI 4 CMF, oral	76 v 69	.02	82 v 75 (EPI CMF v CMF)	
			374	6 CMF, oral	EPI CMF versus CMF		< .001	
				Total, N- and N+ 4 EPI 4 CMF, IV 8 CMF q3w, IV	2,391	Or	< .001	

Fig 1. Meta-analysis of hazard ratios (HR) in trials comparing anthracycline- versus non-anthracycline-based regimens by HER-2/neu status

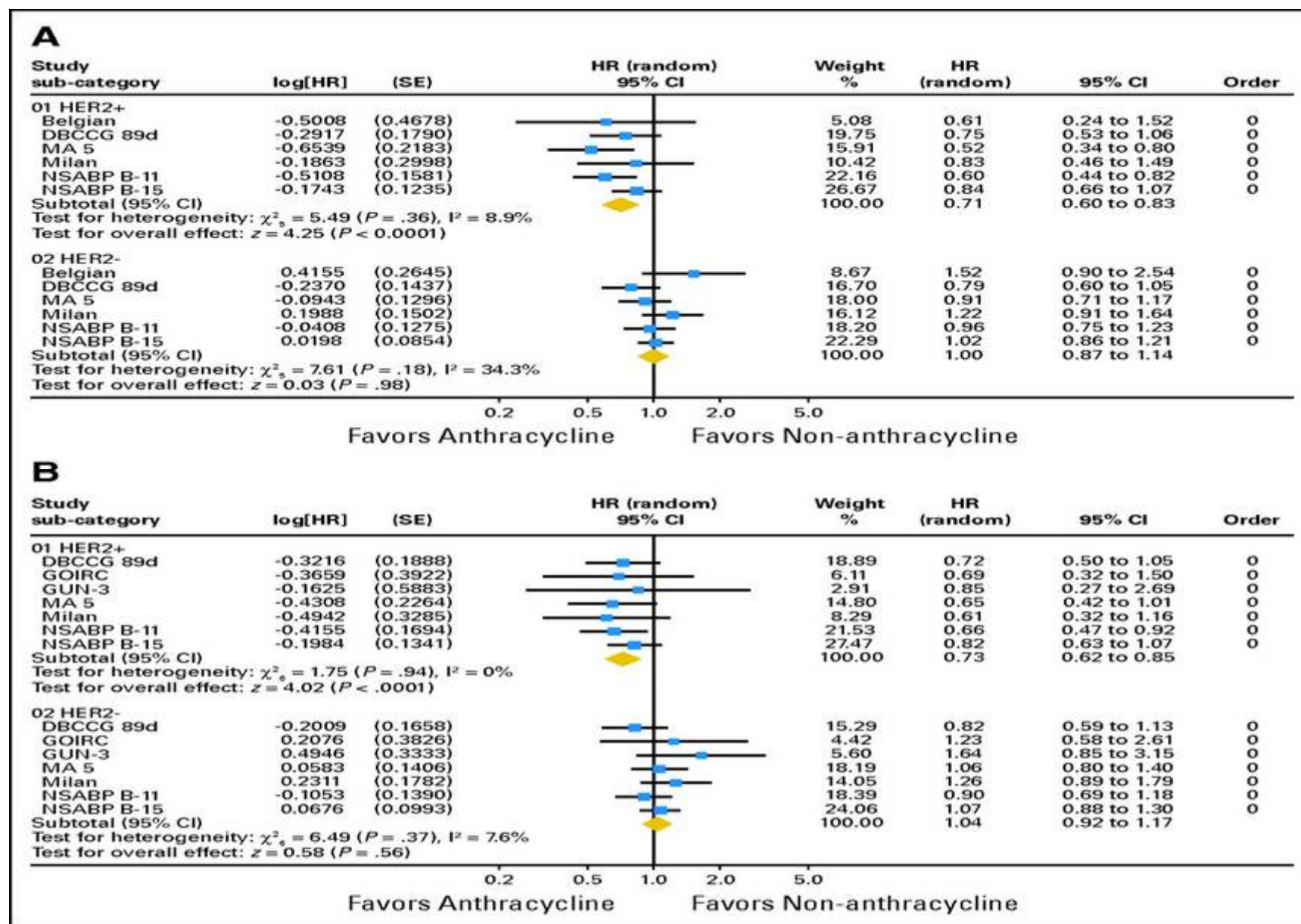
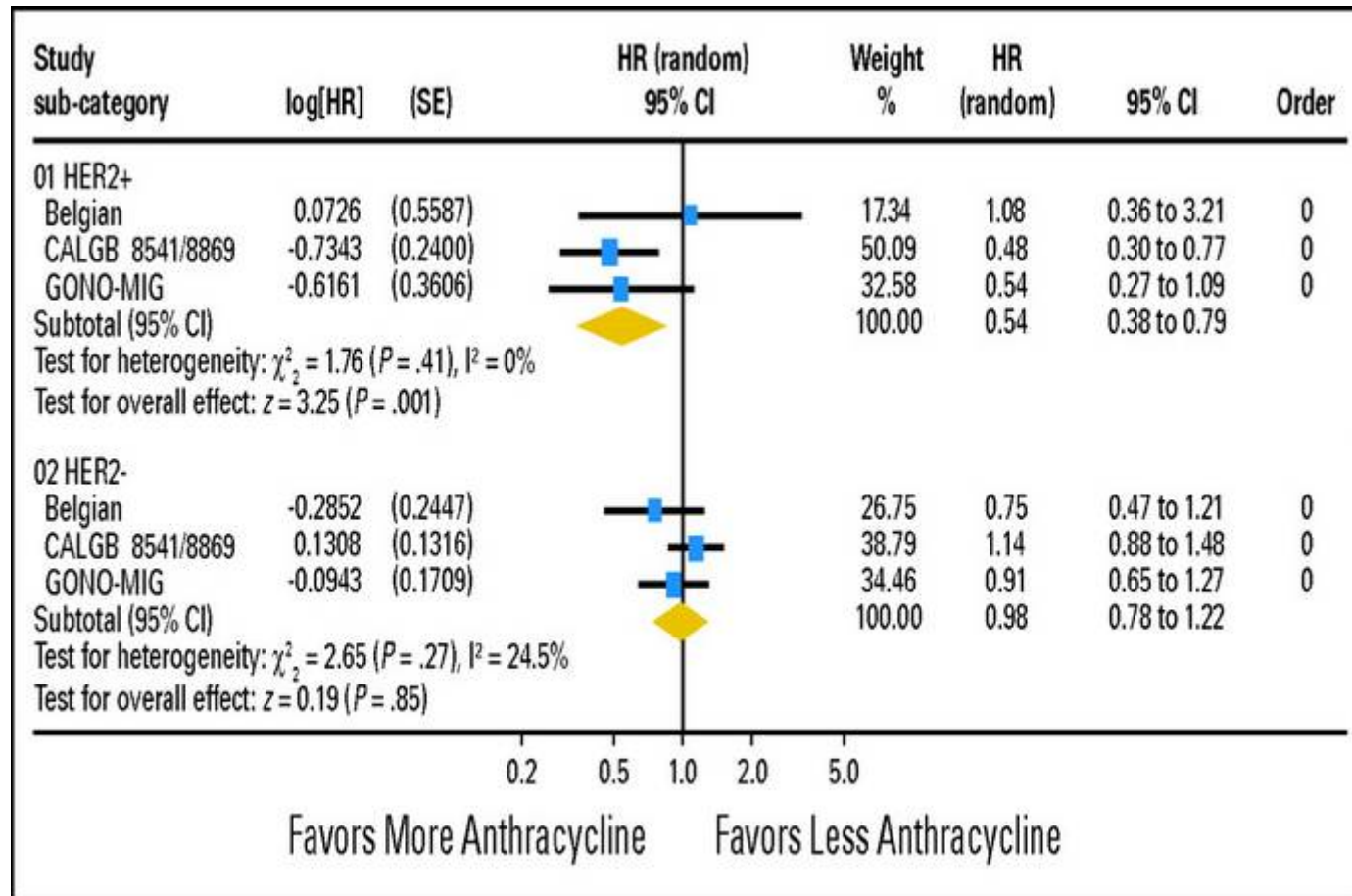
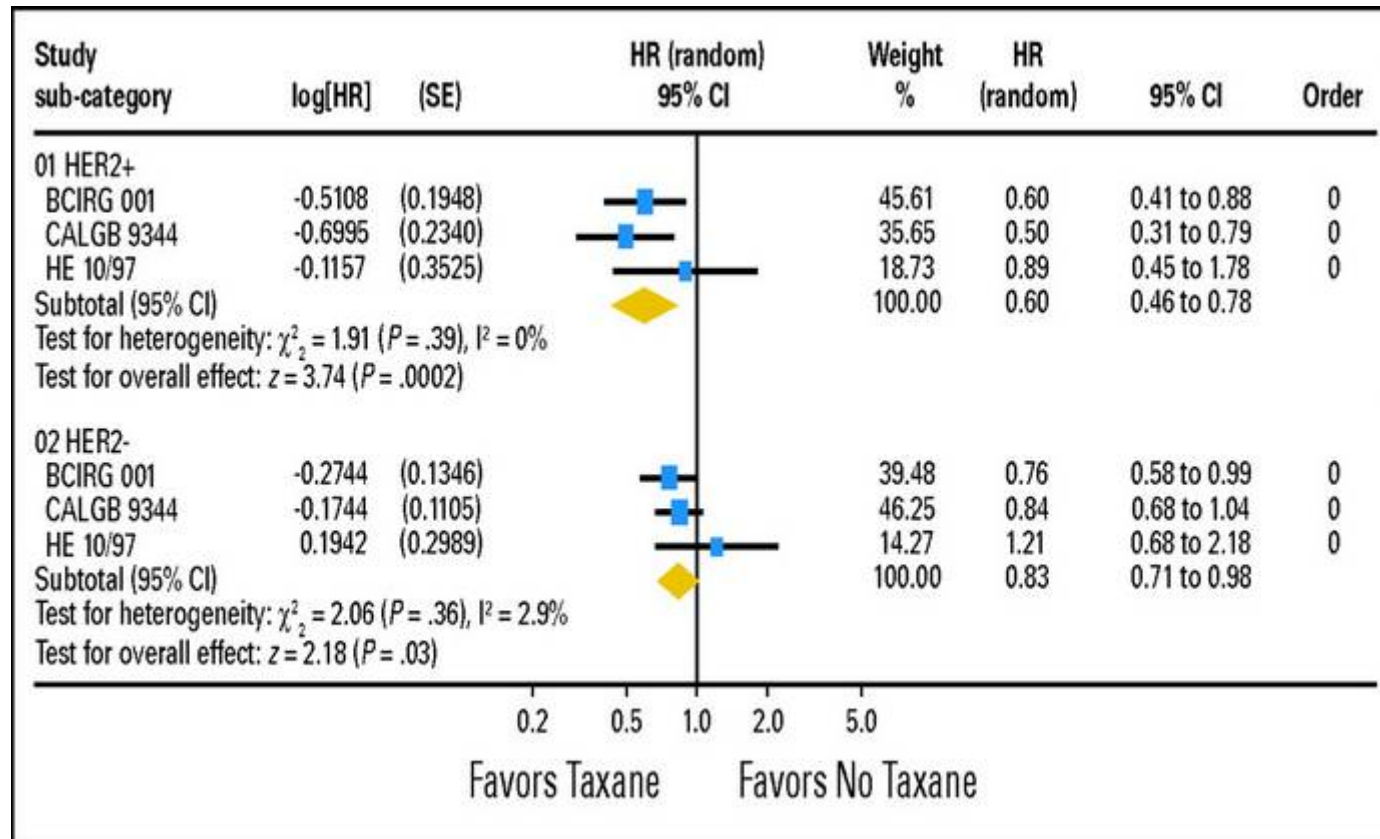


Fig 2. Meta-analysis of disease-free survival hazard ratios (HRs) in trials comparing different anthracycline-based regimens by HER-2/neu status



Pritchard, K. I. et al. J Clin Oncol; 26:736-744 2008

Fig 3. Meta-analysis of disease-free survival hazard ratios (HRs) in trials comparing taxane-containing with non-taxane-containing regimens by HER-2/neu status



Pritchard, K. I. et al. J Clin Oncol; 26:736-744 2008

HER2 Positivity Associated With Increased Risk of Recurrence Even in Patients With Small Breast Cancer Tumors Rahkit SABCS 2008

- ~ 10% of node-negative invasive breast cancers = 1 cm tested HER2 positive
- In patients with tumors = 1 cm, HER2 positivity associated with significantly shorter recurrence-free survival (RFS), distant RFS (DRFS)
 - HER2 positivity associated with 2.7-fold increased risk of recurrence in 5 years
- Suggests potential value of anti-HER2 therapy in this patient population
- Background
- HER2-positive breast cancer aggressive; associated with poor clinical outcomes
- Randomized clinical trials demonstrating clinical benefit of trastuzumab with adjuvant chemotherapy in early-stage HER2-positive breast cancer largely excluded node-negative tumors = 1 cm
- Outcomes in patients with small HER2-positive tumors not well defined
- Current study determined risk of recurrence with T stage 1a, 1b node-negative, HER2-positive breast cancer
- Summary of Study Design
- Data gathered from University of Texas M. D. Anderson Cancer Center Breast Cancer Management System database of node-negative invasive breast cancers
 - Patients diagnosed 1990-2002 with T stage 1a, 1b N0M0 breast cancer
 - Tumors = 1 cm
 - Excluded patients treated with adjuvant chemotherapy or trastuzumab
- Second data set from 2 European institutes used for validation
- Hormone receptor status assessed using standard immunohistochemistry
- HER2 status assessed by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH)
 - IHC: 3+ receptor overexpression
 - FISH: gene copy/CEP-17 ratio > 2.0

- 5-year RFS rate:
HER2-positive vs HER2-negative patients (77.1% vs 93.7%,; $P < .0001$)
 - Multiple factors significantly associated with RFS in these patients
- Factors not significantly associated with DRFS
 - Hormone receptor status (negative vs positive; $P = .111$)
 - Menopausal status ($P = .069$)
 - Histology (ductal vs other; $P = .882$)
 - T stage (1a vs 1b; $P = .576$)
 - Grade (1/2 vs 3; $P = .188$)
- Data from 350 European patients analyzed for validity
 - Patient characteristics
 - Median age: 60 years (range: 29-88)
 - HER2 positive: 6%
 - T stage 1b: 86%
 - Grade 3: 14%
 - 5-year RFS significantly lower in HER2-positive vs HER2-negative patients (87.4% vs 97.0%; $P = .043$)
 - No significant difference in 5-year DRFS with HER2-positive vs HER2-negative disease (92.3% vs 97.0%; $P = .449$)
- Overall 5-year RFS in University of Texas M. D. Anderson Cancer Center patient group: 92.0%
 - Overall 5-year DRFS: 96.2%
- Reference
- Rakhit R, Broglio K, Peintinger F, et al. Significant increased recurrence rates among breast cancer patients with HER2-positive tumors 1 cm or smaller. Program and abstracts of the 31st Annual San Antonio Breast Cancer Symposium; December 10-14, 2008; San Antonio, Texas. Abstract 701.

- doch behandeln? Wie – keine Daten
- *Matthew Ellis, MD, PhD:*
At our center, we have a single-arm study of **12 treatments of weekly paclitaxel plus trastuzumab** as a treatment for the lower-risk spectrum of HER2-positive disease.
- This important question is not likely to be answered anytime soon because it would take approximately 6000 lower-risk patients to be randomized to treatment with or without trastuzumab, which is nearly impossible to achieve because of lack of funding to conduct such a trial, as well as potential difficulties with acceptance of randomization to no anti-HER2 therapy (E. Perez)

Tau Expression Correlates With Survival Outcomes in Early Breast Cancer: Analysis of NSABP-B28 SABCS 2008

Retrospective analysis^[1] of tissue microarray data from the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B28 randomized phase III trial

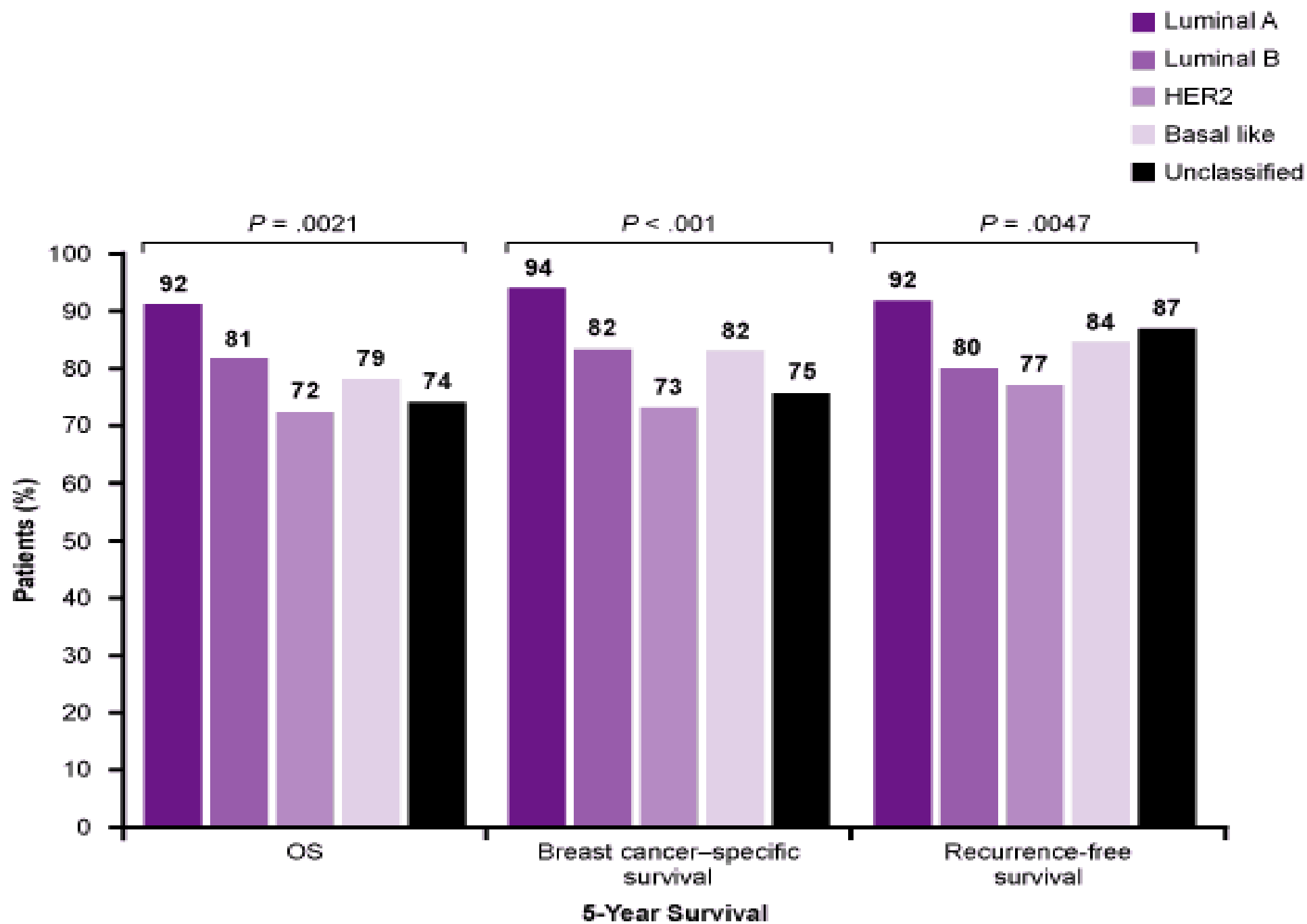
- Summary of Key Conclusions
- High levels of Tau protein expression correlate with longer DFS and OS in patients with early-stage breast cancer treated with adjuvant anthracycline, paclitaxel, and hormonal therapy
 - No significant interaction between Tau expression and paclitaxel outcomes
- Background
- Results on the predictive and prognostic value of Tau inconsistent^[2-4]
- Low Tau protein expression may be associated with decreased responsiveness of estrogen receptor (ER)-positive tumors to endocrine therapy
- Current study sought to evaluate the association of Tau protein expression with survival outcomes in patients with early-stage, node-positive breast cancer receiving adjuvant therapy
- Summary of Study Design
- 3060 previously untreated patients with node-positive breast cancer randomized to receive
 - 4 courses of doxorubicin/cyclophosphamide (AC) or
 - AC followed by 4 additional courses of paclitaxel (ACT)
 - Patients with hormone receptor-positive tumors also received adjuvant hormonal therapy (tamoxifen)
- Current study included patients from NSABP-B28 with tissue microarray data (n = 1942; 63%)
 - Tau immunohistochemistry (IHC) results correlated with survival outcomes
- Main Findings
- Lack of consensus in results from 2 pathologists
 - 32% of overall IHC results conflicted
 - 8% of Tau-only results conflicted
- Final consensus scoring indicated that 43% of cancers Tau positive
- Tau expression significantly more common in ER-positive, progesterone receptor (PgR)-positive, HER2-negative, and low-grade tumors
 - No correlation between Tau positivity and lymph node positivity, age of patient, or tumor size

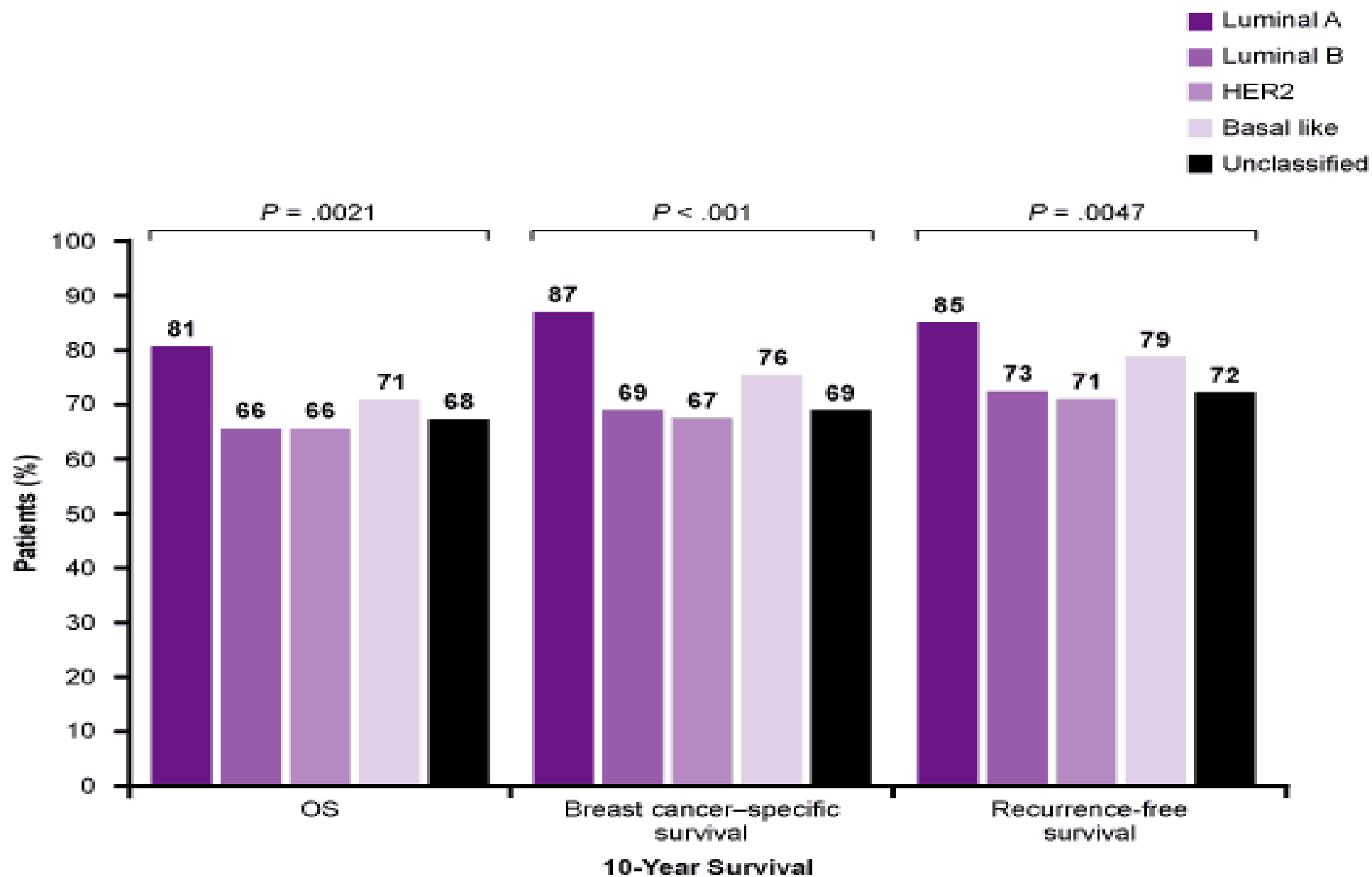
- Survival 10 years after randomization significantly higher in Tau-positive compared with Tau-negative tumors
 - OS: $P < .0001$
 - DFS: $P < .0001$
 - No significant effect of paclitaxel on Tau outcomes
- In univariate analyses, Tau, ER, HER2 expression, grade, tumor size, nodal status independently and significantly associated with DFS and OS ($P < .003$)
- Several factors associated with survival on multivariate analysis
 - DFS
 - Treatment: ACT vs AC ($P = .032$)
 - Tumor size: < 2 vs > 4 cm ($P = .011$)
 - Tumor grade: low vs high ($P = .0077$)
 - Lymph node involvement: $= 3$ vs > 3 ($P < .0001$)
 - ER expression: positive vs negative ($P = .00047$)
 - Tau expression: positive vs negative ($P = .018$)
 - OS
 - Age: $= 49$ vs > 60 years ($P = .0046$)
 - Tumor size: < 2.0 vs $2.1-4.0$ cm ($P = .014$)
 - Tumor grade: low vs intermediate or high ($P = .0016$)
 - Lymph node involvement: $= 3$ vs > 3 ($P < .0001$)
 - ER expression: positive vs negative ($P = .0001$)
 - Tau expression: positive vs negative ($P = .0001$)
- Tau remained significant predictor of survival after adjusting for age, nodal status, histological grade, tumor size
 - Increased survival in Tau-positive patients may have resulted from favorable prognosis for Tau-positive, ER-positive cancers
- Of Tau-positive cancers, 88% ER positive
- ~ 40% of ER-positive cancers Tau negative
 - In ER-positive patients, Tau-positive patients had improved survival
 - DFS: $P = .0018$
 - OS: $P = < .0001$
- No significant interaction between low Tau expression and Paclitaxel efficacy overall or based on ER status

Luminal A Molecular Subtype Associated With Better Prognosis in Invasive, Nonmetastatic Breast Cancer

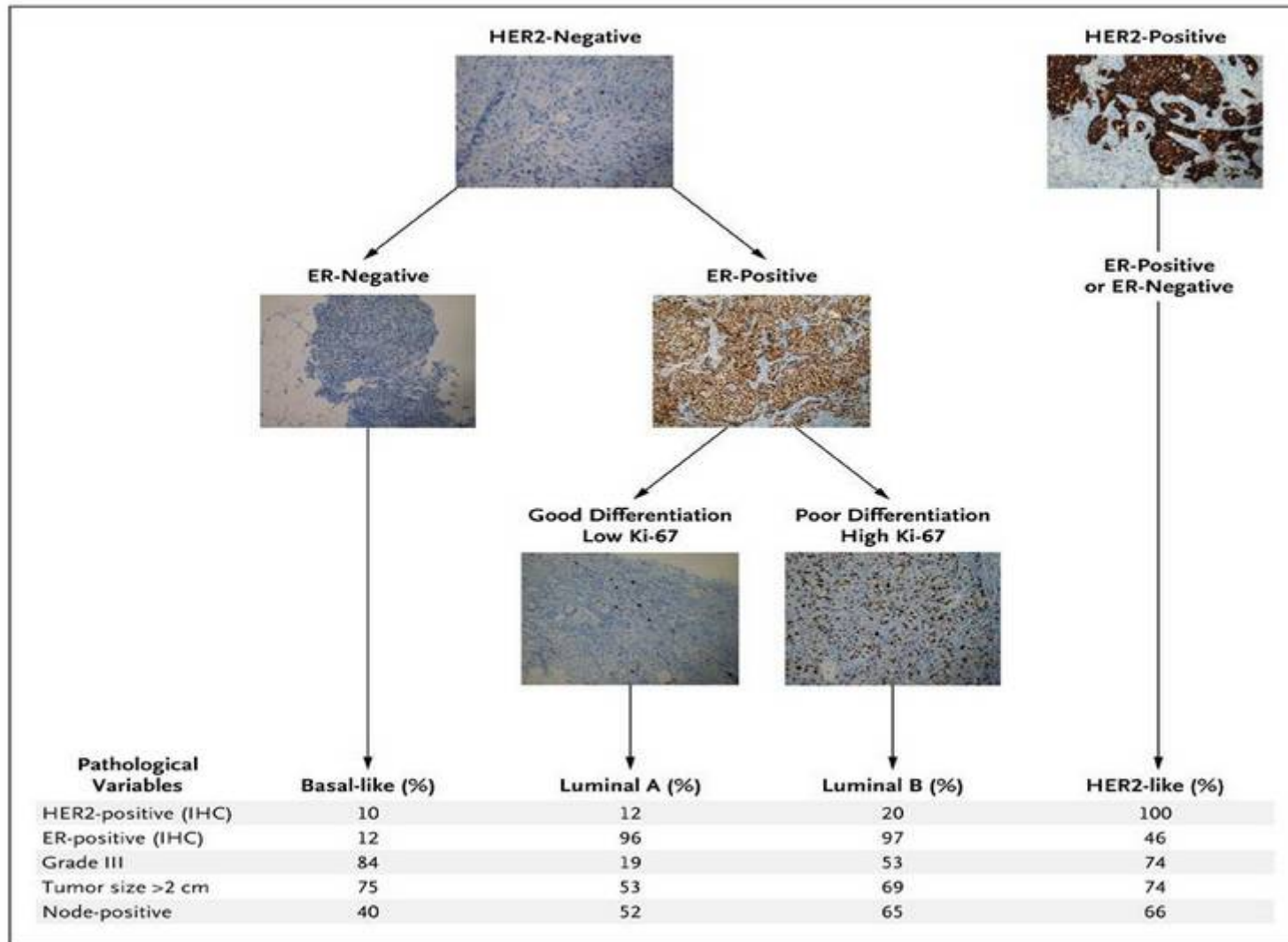
Retrospective molecular analysis of samples from the Nurses' Health Study

- In women with invasive, nonmetastatic breast cancer, luminal A tumors associated with better prognosis than luminal B, HER2 subtype, and basal-like tumors
 - Additional unclassifiable subset comparable to basal-like tumors in survival outcomes and may represent additional subtype of basal-like tumors
-
- Background
 - Molecular analysis of tumor types and correlation with clinical outcomes could help better tailor therapy to patients
 - Current study compared survival outcomes among various molecular phenotypes in women with invasive, nonmetastatic breast cancer
 - Summary of Study Design
 - Patients (N = 2021) with invasive, nonmetastatic breast cancer from the Nurses' Health Study
 - Diagnosed between 1976 and 1996
 - Tissue samples available for microarray and immunohistochemical analysis
 - Samples classified into 5 subgroups based on molecular characteristics: 1) Luminal A, 2) luminal B, 3) HER, 4) basal like, and 5) not classified
 - Disease
 - Risk of death/recurrence higher for subtypes other than luminal A according to multivariate analysis (adjustments: age, diagnosis time, body mass index, node status, and tumor grade, stage, size)
 - Total deaths: n = 725
 - Breast cancer deaths: n = 435
 - Recurrences: n = 463
 - Reference
 - Dawood S, Collins LC, Connolly JL, et al. Defining breast cancer prognosis based on molecular phenotypes: results from a large cohort study. Program and abstracts of the 31st Annual San Antonio Breast Cancer Symposium; December 10-14, 2008; San Antonio, Texas. Abstract 1068.





Clinicopathological Features



Sotiriou C and Pusztai L. N Engl J Med 2009;360:790-800

Table 1. Commercially Available Genomic Assays for the Prediction of Clinical Outcome in Patients with Breast Cancer.*

Variable	MammaPrint	Oncotype DX	Theros	MapQuant Dx
Provider	Agendia	Genomic Health	Biotheranostics	Ipsogen
Type of assay	70-Gene assay	21-Gene recurrence score	2-Gene ratio of HOXB13 to IL17R (H/I) and molecular-grade index	Genomic grade
Type of tissue sample	Fresh or frozen	Formalin-fixed, paraffin-embedded	Formalin-fixed, paraffin-embedded	Fresh or frozen
Technique	DNA microarrays	Q-RT-PCR	Q-RT-PCR	DNA microarrays
Centrally certified laboratory†	Yes	Yes	Yes	Yes
Indication	To aid in prognostic prediction in patients <61 yr of age with stage I or II, node-negative disease with a tumor size of ≤5 cm	To predict the risk of recurrence in patients with ER-positive, node-negative disease treated with tamoxifen; to identify patients with a low risk of recurrence who may not need adjuvant chemotherapy	To stratify ER-positive patients into groups with a predicted low risk or high risk of recurrence and a predicted good or poor response to endocrine therapy	To re-stratify grade 2 tumors into low-risk grade 1 or high-risk grade 3 tumors, specifically for invasive, primary, ER-positive grade 2 tumors
Level of evidence (I–V)‡	III	II	III	III
FDA clearance	Yes	No	No	No
Availability	Europe and United States	Europe and United States	United States	Europe

* ER denotes estrogen receptor, FDA Food and Drug Administration, and Q-RT-PCR quantitative reverse-transcriptase–polymerase chain reaction.

† Laboratories were certified according to the criteria of the Clinical Laboratory Improvement Amendments or by the International Organization for Standardization.

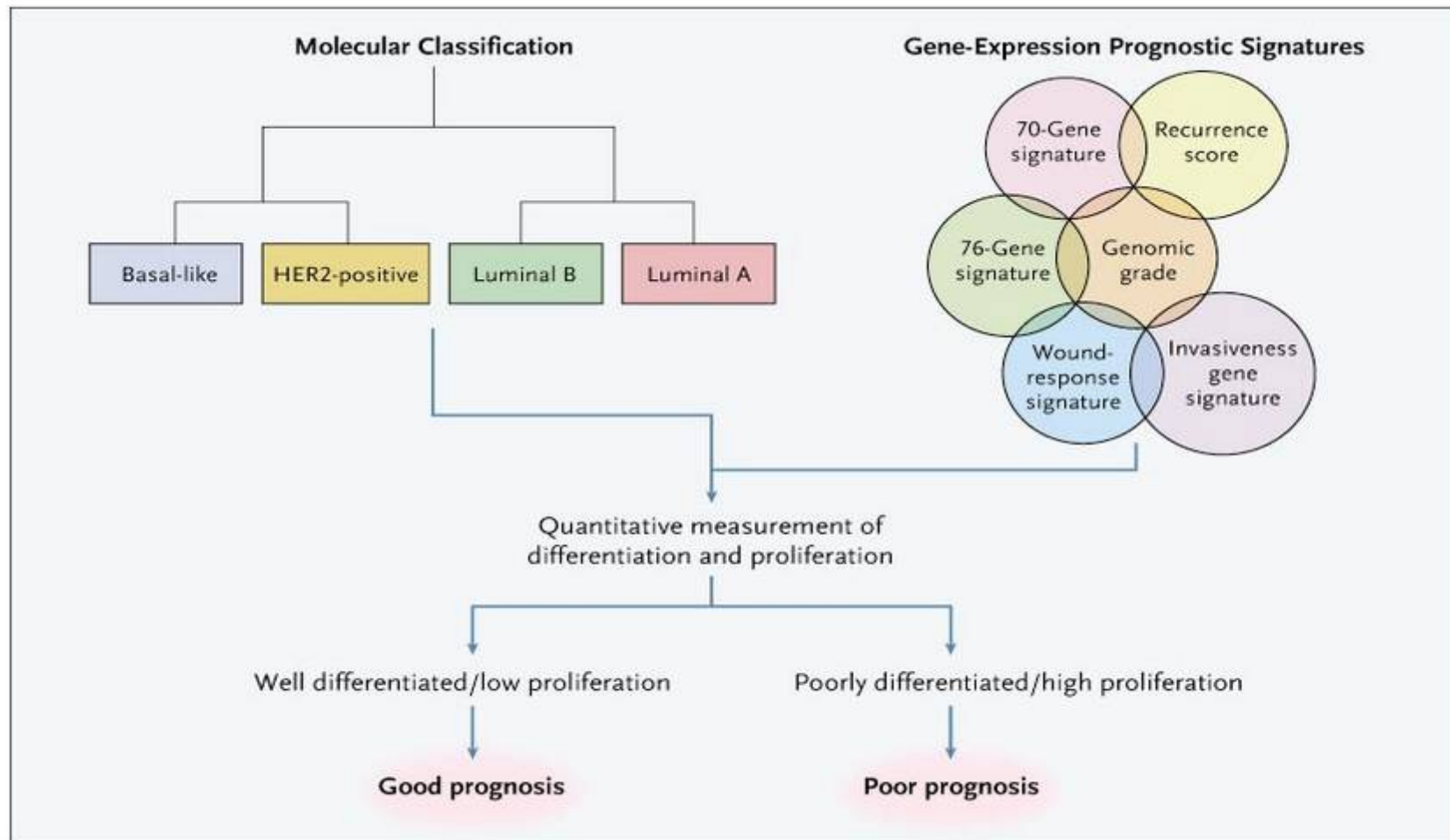
‡ Levels of evidence are measured on a scale ranging from I (strongest) to V (weakest).⁵⁴

Sotiriou C and Puztai L. *N Engl J Med* 2009;360:790-800



The NEW ENGLAND
JOURNAL of MEDICINE

Classification, Gene-Expression Signatures, and Clinical Outcome



Sotiriou C and Puztai L. N Engl J Med 2009;360:790-800

Vorhersage der Wirksamkeit von Chemotherapie

This 30-gene predictor showed higher sensitivity than a clinical predictor that included age, nuclear grade, and ER status (92% vs. 61%). It also correctly identified 92% of the patients who achieved a pathologic complete response. The positive predictive value of the pharmacogenomic signature was a modest 52%, but its negative predictive value was 96%.



GERLAND.

TYPVS
FRISIAE
ORIENTALIS.
Autore
Vbbone Emmio.



