

# Chemotherapy

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DBCG's 30 years experience

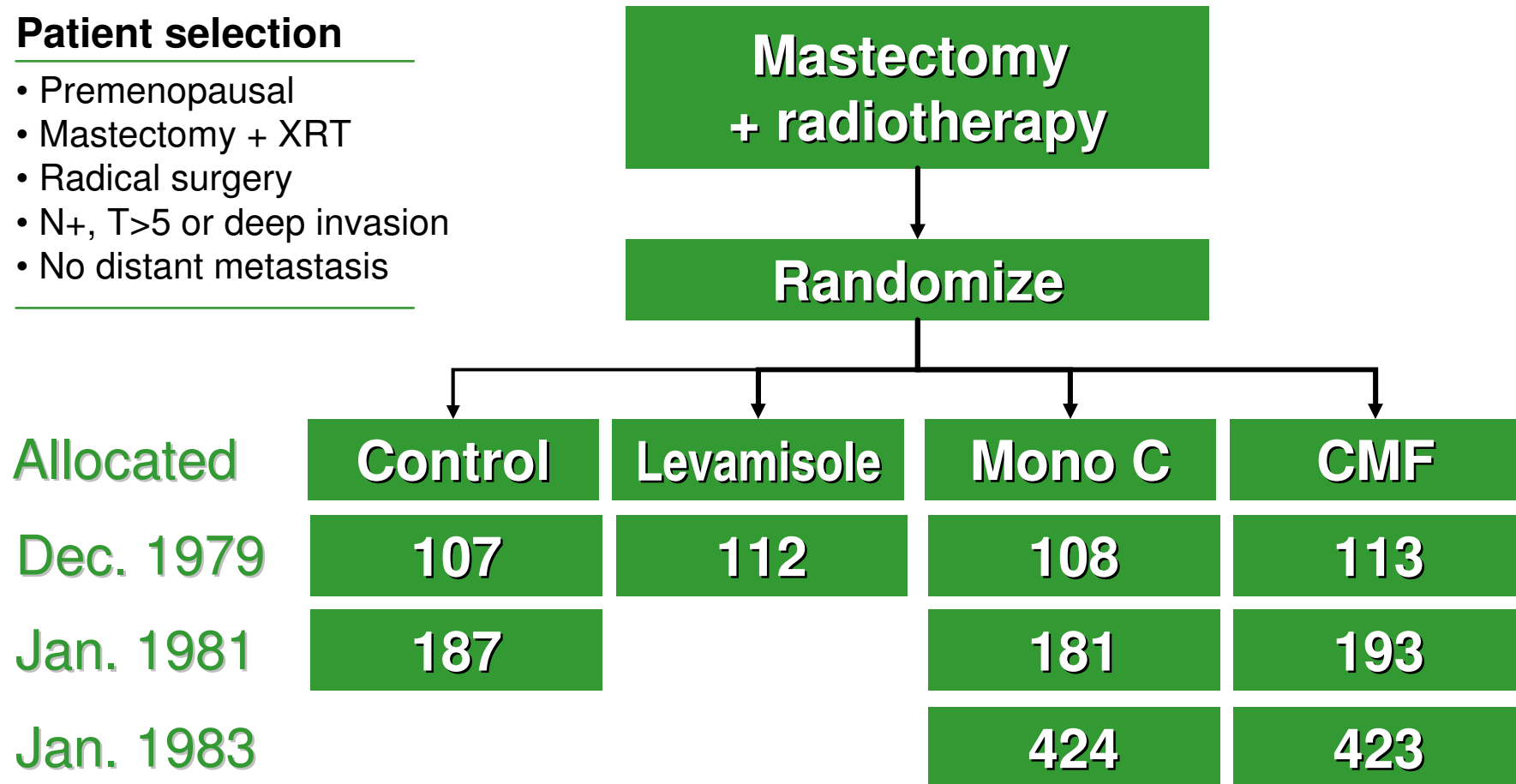
On behalf of the subcommittee for medical therapy.

Bent Ejlertsen, May 23, 2008.

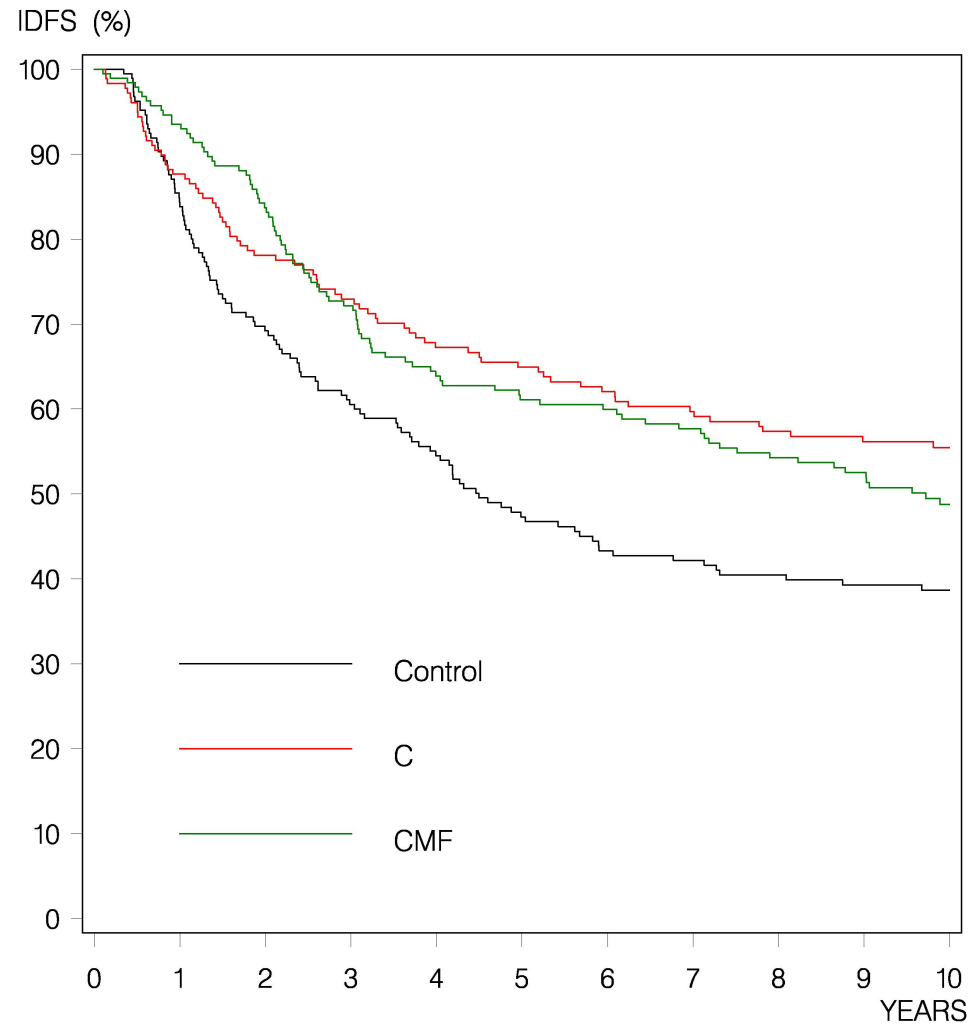
# DBCG 77B

## Patient selection

- Premenopausal
- Mastectomy + XRT
- Radical surgery
- N+, T>5 or deep invasion
- No distant metastasis

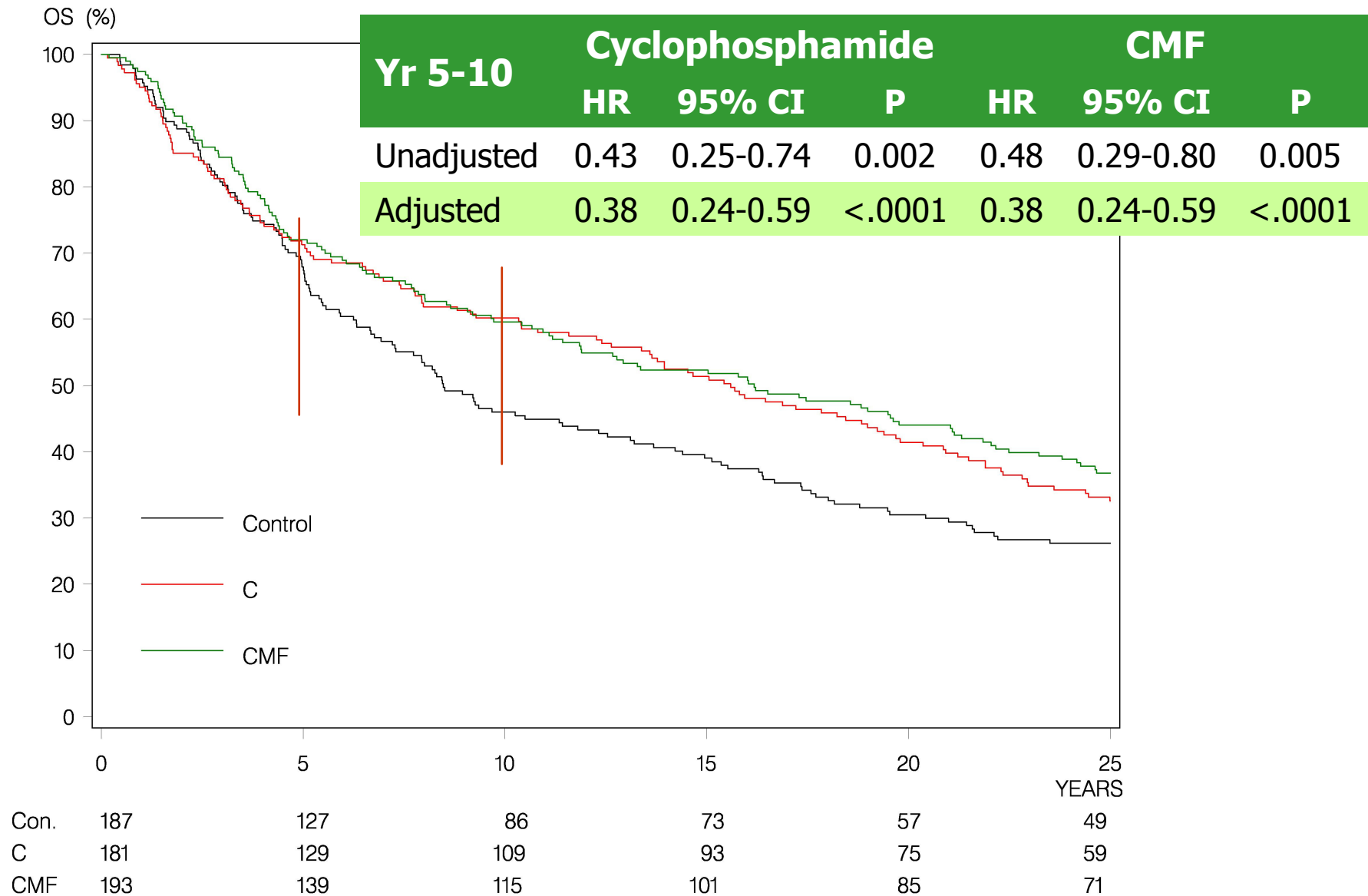


# DBCG 77B, IDFS

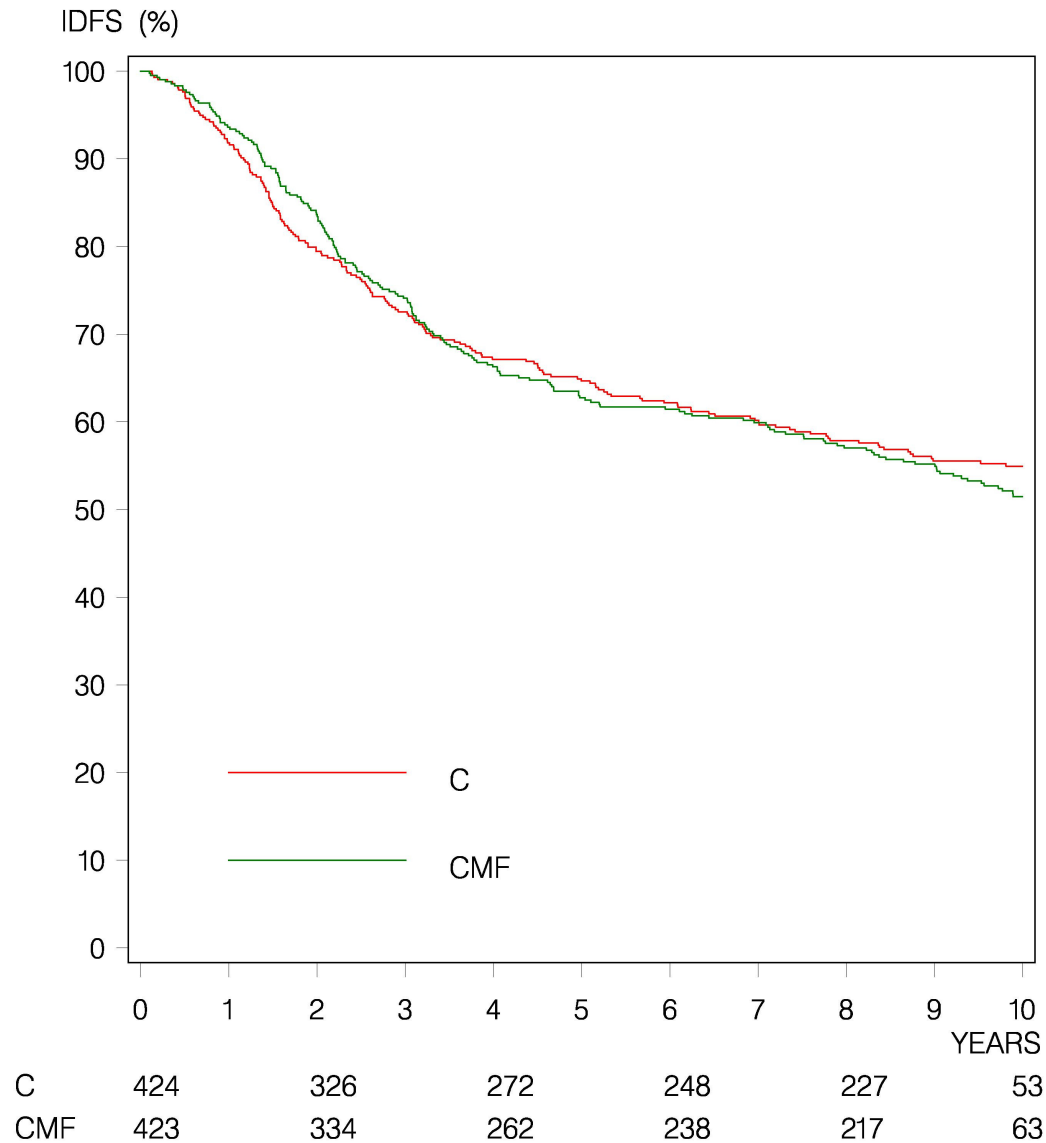


Con.	187	128	99	76	71	25
C	181	138	117	106	97	31
CMF	193	153	115	106	94	37

# DBCG 77B, Survival

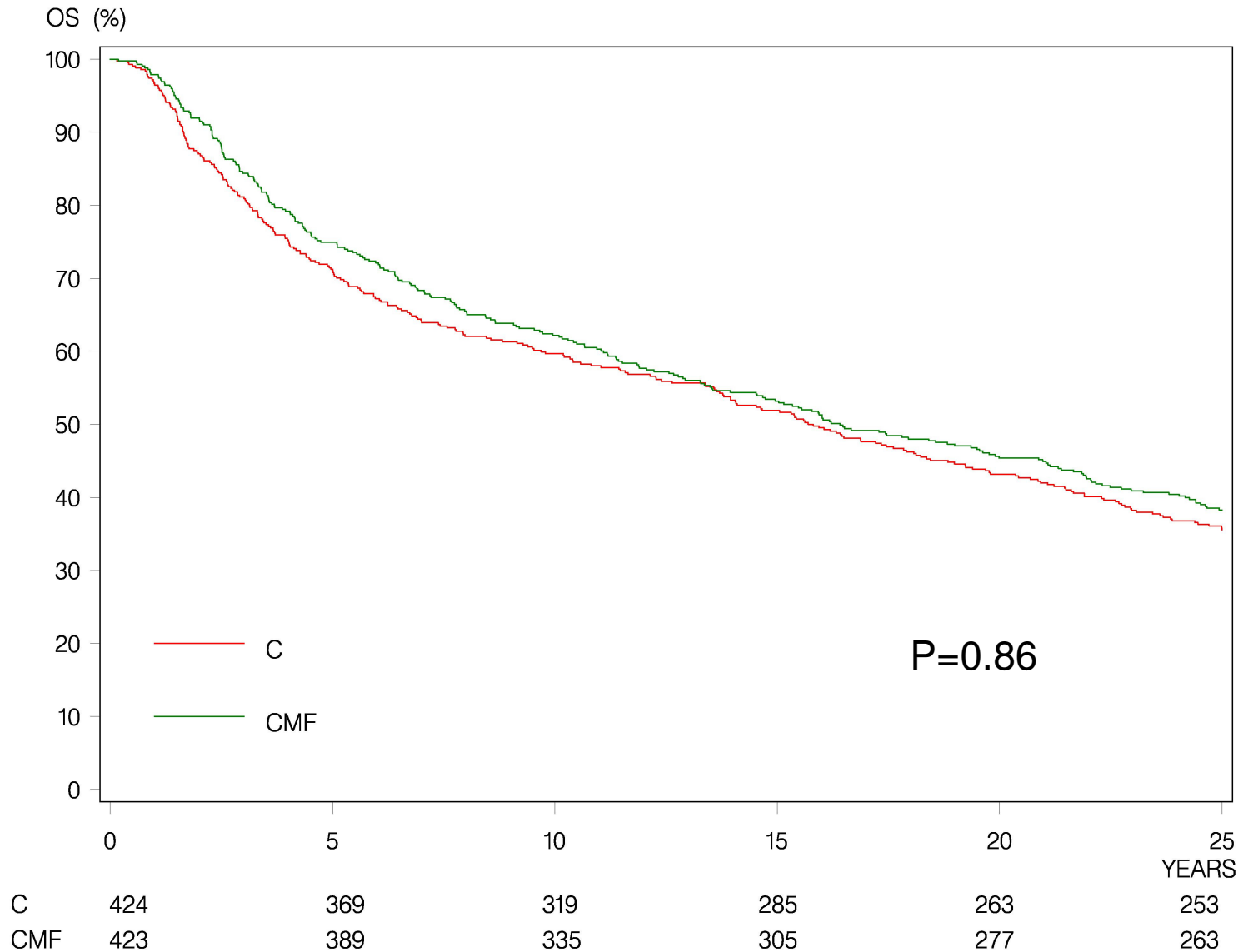


# DBCG 77B, IDFS

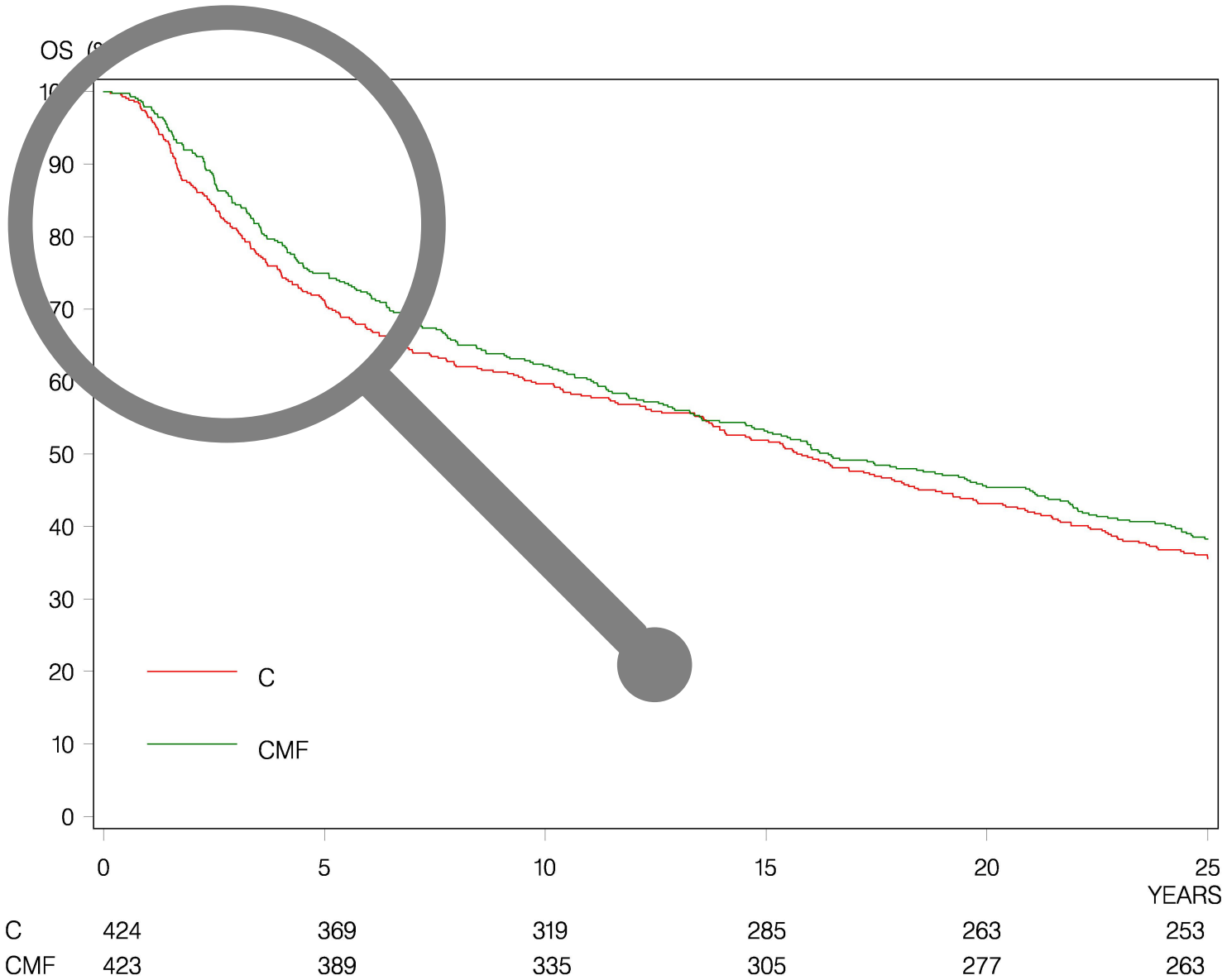


P=0.59

# DBCG 77B, Survival



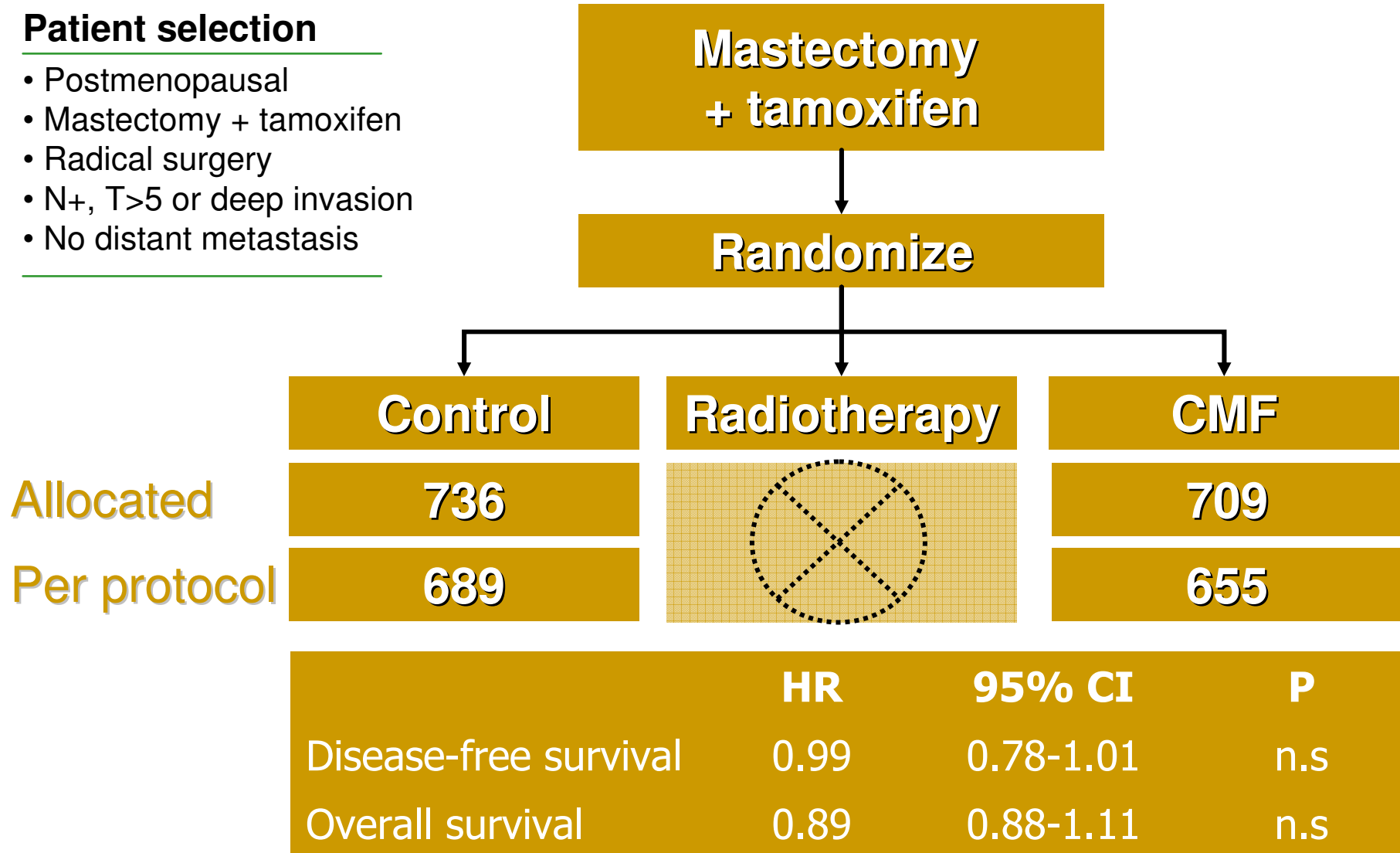
# DBCG 77B, Survival



# DBCG 82C

## Patient selection

- Postmenopausal
- Mastectomy + tamoxifen
- Radical surgery
- N+, T>5 or deep invasion
- No distant metastasis





# Possible explanations

- Chemotherapy regimen
  - Dose and schedule
- Patient selection
  - Age
  - Menopause
- Interaction
  - With tamoxifen
  - Hormone receptor status

# CMF in DBCG trials 77, 82 and 89

N=2,213

	<b>DBCG 77B</b>	<b>DBCG 82B</b>	<b>DBCG 89B+D</b>
<b>Registered</b>	<b>323</b>	<b>982</b>	<b>908</b>

## Patient selection

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- Premenopausal
  - Radical surgery for breast cancer
  - Postoperative radiotherapy
  - Node positive
  - No distant metastasis
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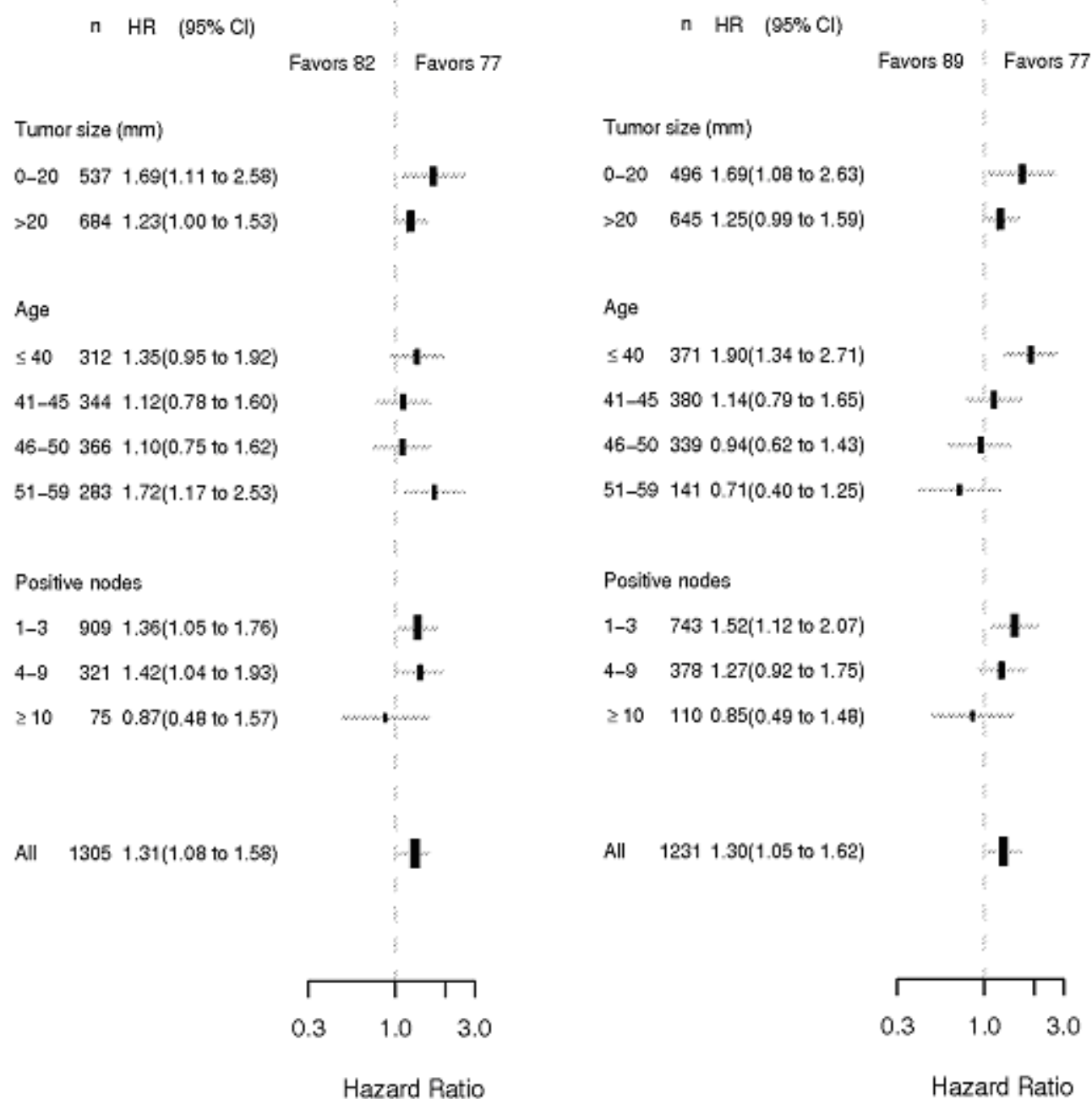
# CMF in DBCG trials 77, 82 and 89

	<b>DBCG 77B</b>	<b>DBCG 82B</b>	<b>DBCG 89B+D</b>
<b>C</b> (mg/m <sup>2</sup> )	80 po d 1-14	600 iv d 1	600 iv d 1
<b>M</b> (mg/m <sup>2</sup> )	30 d 1+8	40 iv d 1	40 iv d 1
<b>F</b> (mg/m <sup>2</sup> )	500 d 1+8	600 iv d 1	600 iv d 1
	every 4 weeks	every 4 weeks	every 3 weeks

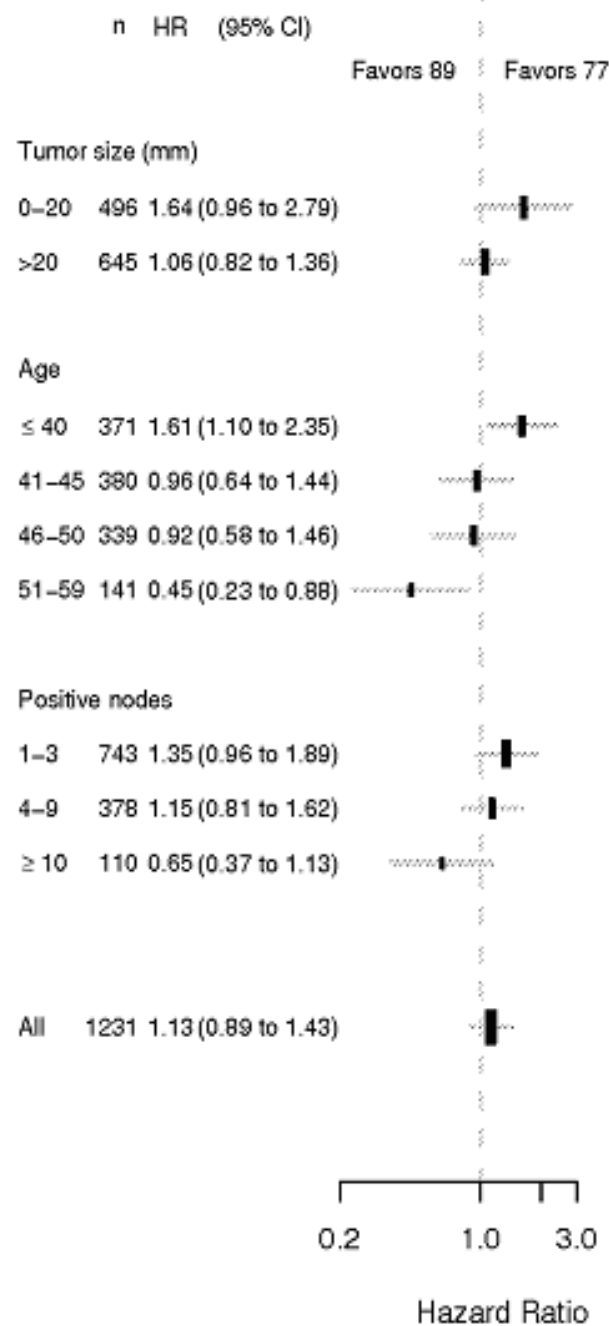
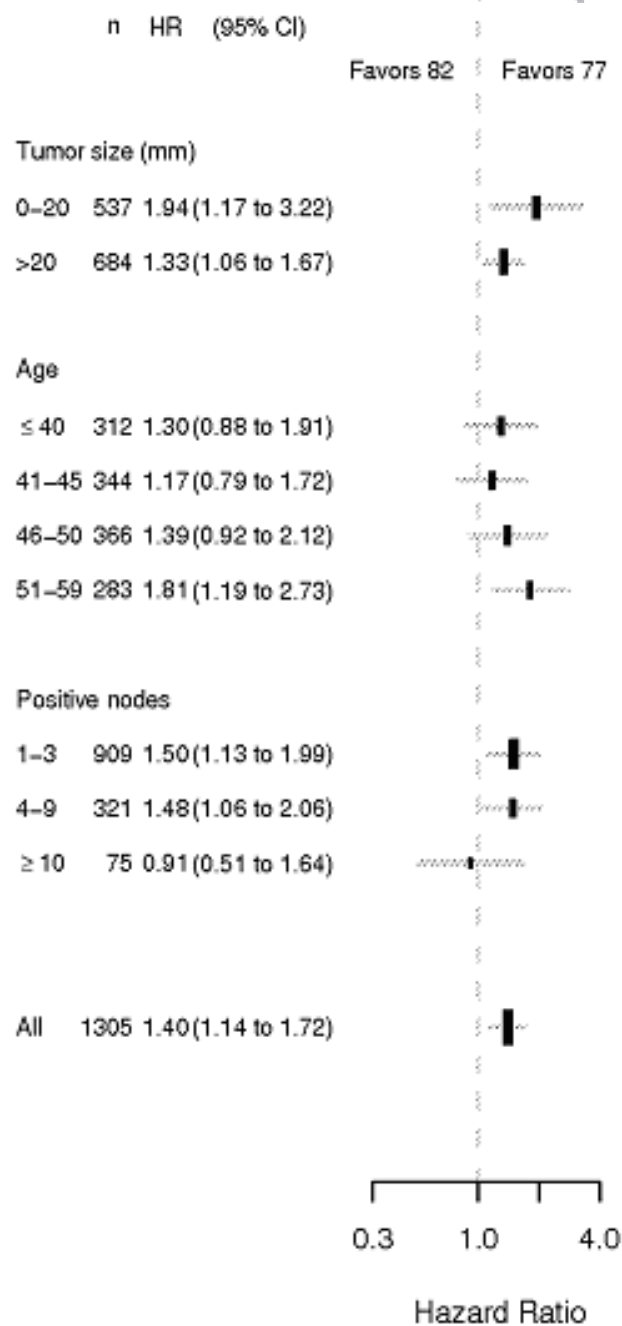
## Patient Characteristics

		DBCWG 77	DBCWG 82	DBCWG 89
No. (Col. %)		N=323	N=982	N=908
Age	≤ 45 yr.	171 (53)	485 (49)	580 (63)
	> 45 yr.	152 (47)	497 (51)	328 (36)
Surgery	BCS	0 -	114 (12)	321 (35)
	Mastectomy	323 (100)	868 (88)	587 (65)
Pos. nodes	1-3	207 (64)	702 (71)	536 (59)
	4-9	97 (30)	224 (23)	281 (31)
	≥10	19 (6)	56 (6)	91 (10)
Tumor size	0-20 mm	88 (27)	449 (46)	408 (45)
	21-50 mm	127 (39)	446 (45)	390 (43)
	> 50 mm	41 (13)	70 (7)	87 (10)
	Missing	67 (21)	17 (2)	23 (3)

# Forest plot; DFS

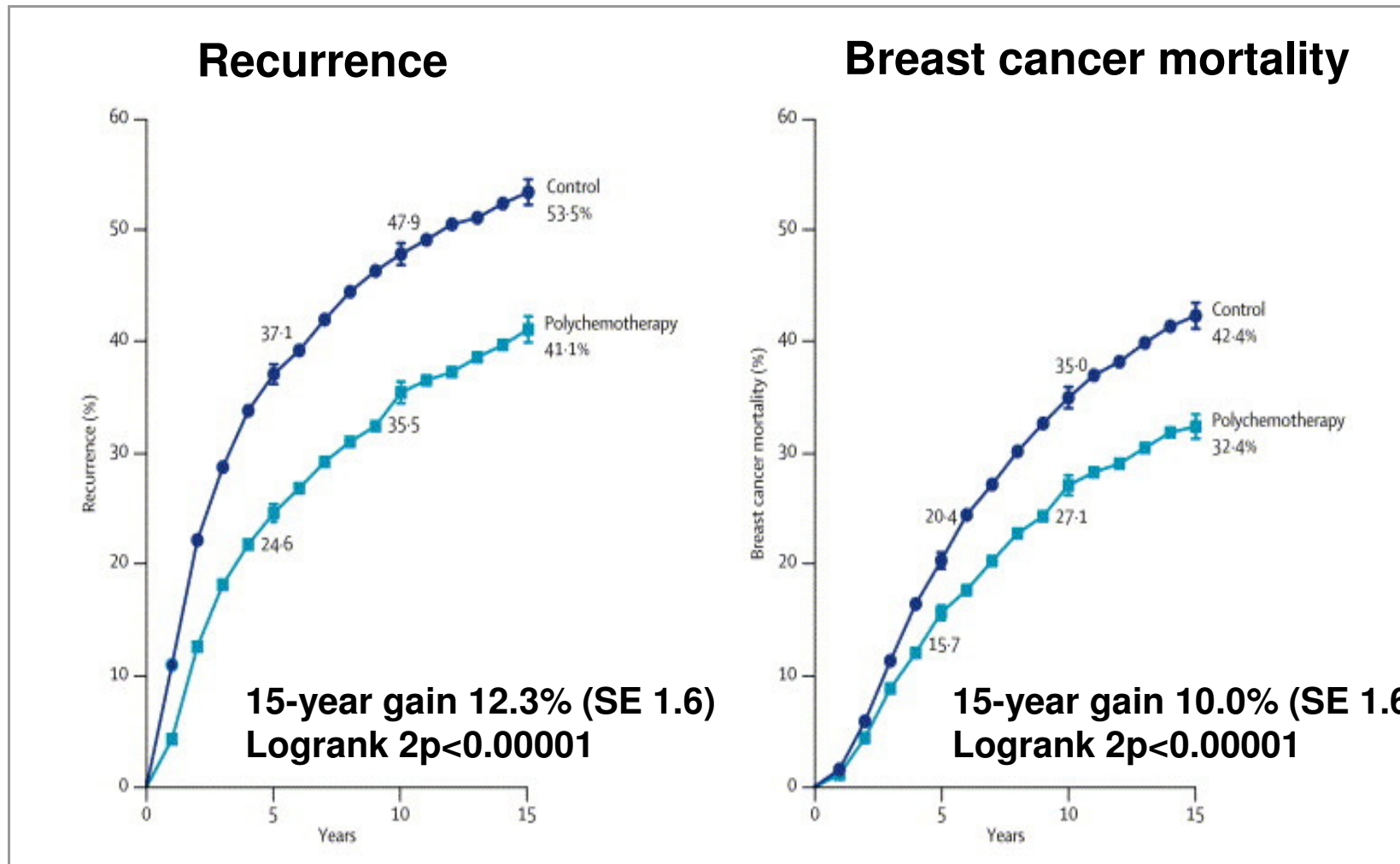


# Forest plot; Survival



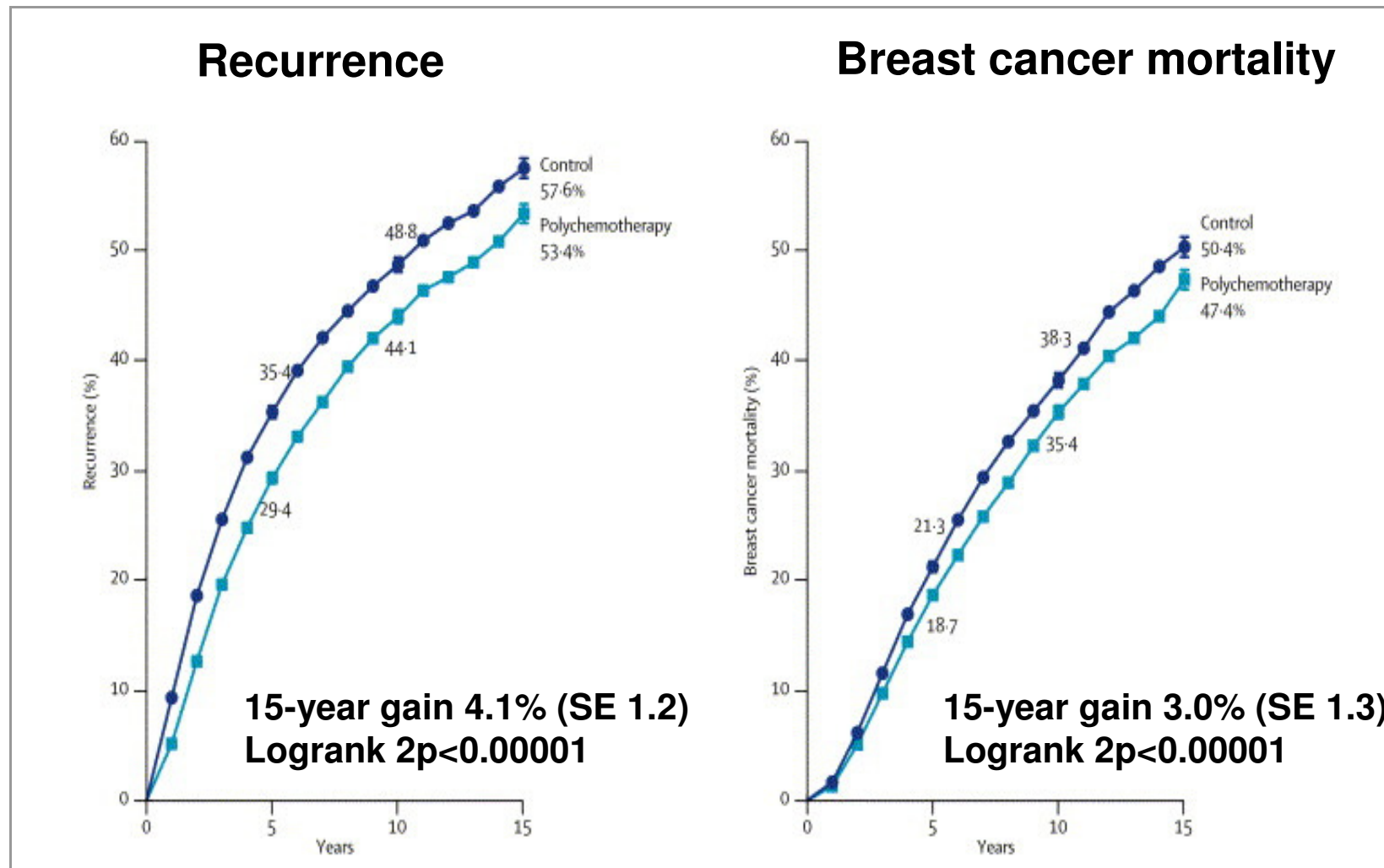
# Primary breast cancer before 50 years

## Polychemotherapy versus control



# Primary breast cancer age 50-69 years

## Polychemotherapy versus control

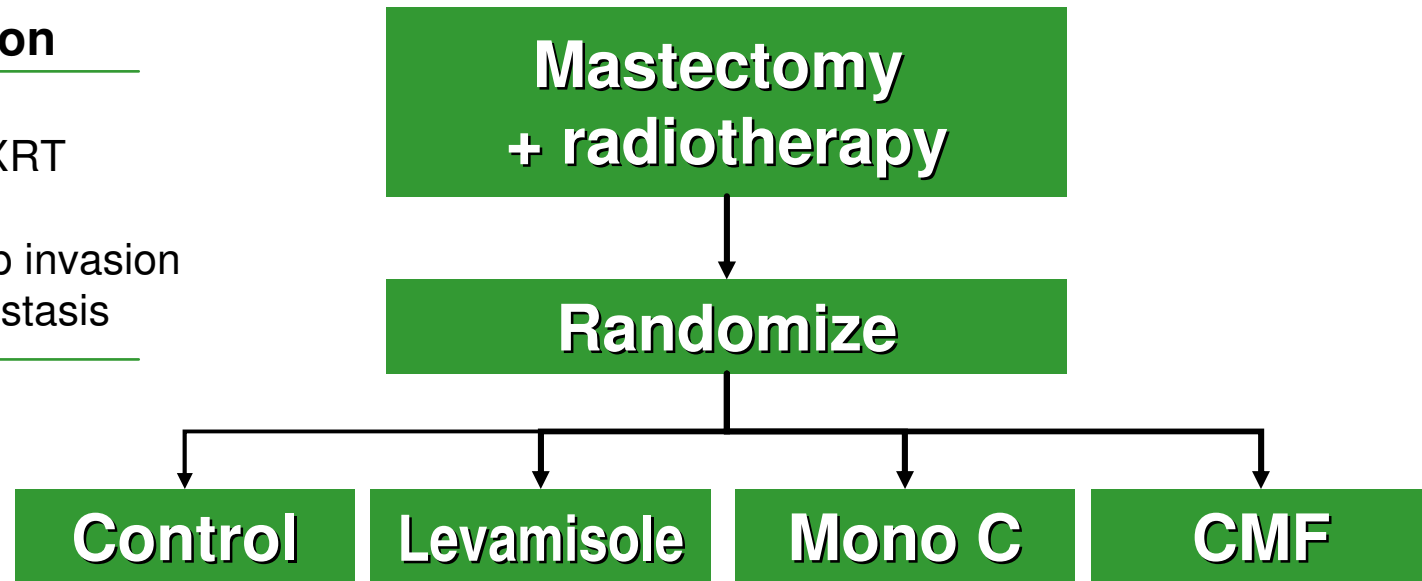




# DBCG 77B

## Patient selection

- Premenopausal
- Mastectomy + XRT
- Radical surgery
- N+, T>5 or deep invasion
- No distant metastasis



A retrospective analysis in DBCG trial 77B suggested a prognostic impact of chemotherapy induced amenorrhea.

# DBCG 89B; Design

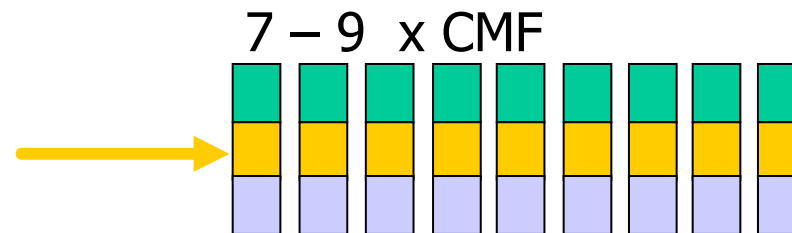
N=762

## Patient selection

- Premenopausal
- Mastectomy or BCT
- Radical surgery
- N+ or T>5
- ER+ or PgR+
- No distant metastasis

R  
A  
N  
D  
O  
M  
I  
Z  
E

Ovarian ablation



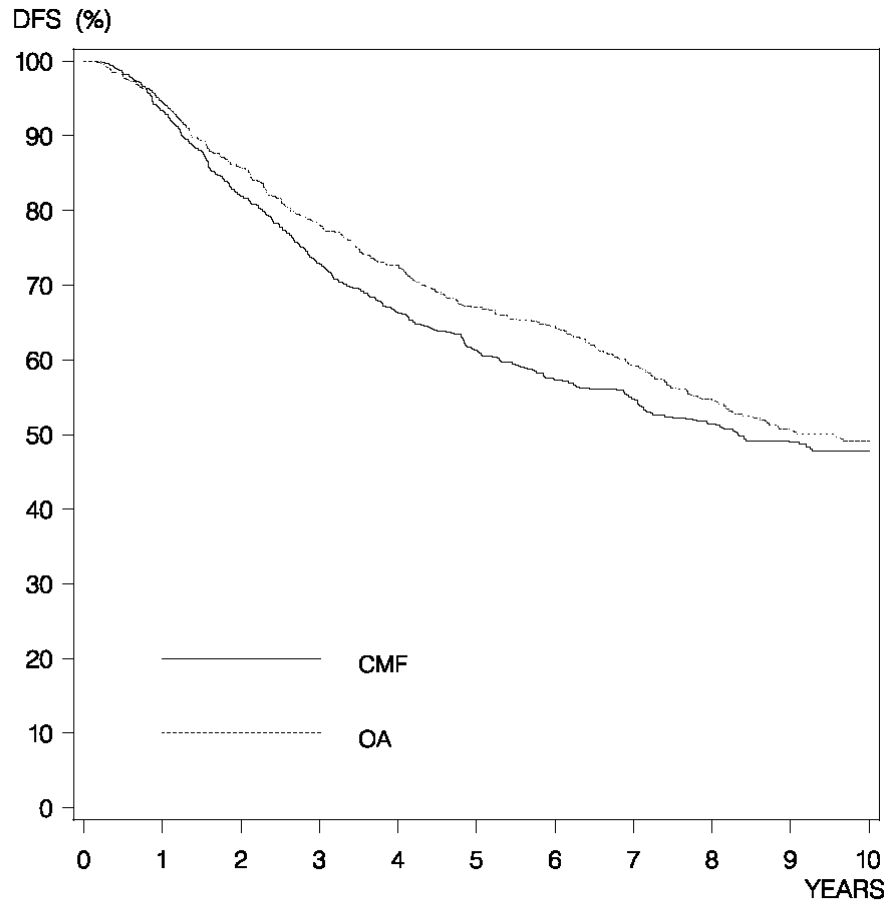
C: cyclophosphamide 600 mg/m<sup>2</sup>  
M: methotrexate 40 mg/m<sup>2</sup>  
F: 5-fluorouracil 600 mg/m<sup>2</sup>

# DBCG 89B program

	CMF	OA	All
Randomized	222	271	493
Non-enrolled	583	387	970
All	805	658	1463

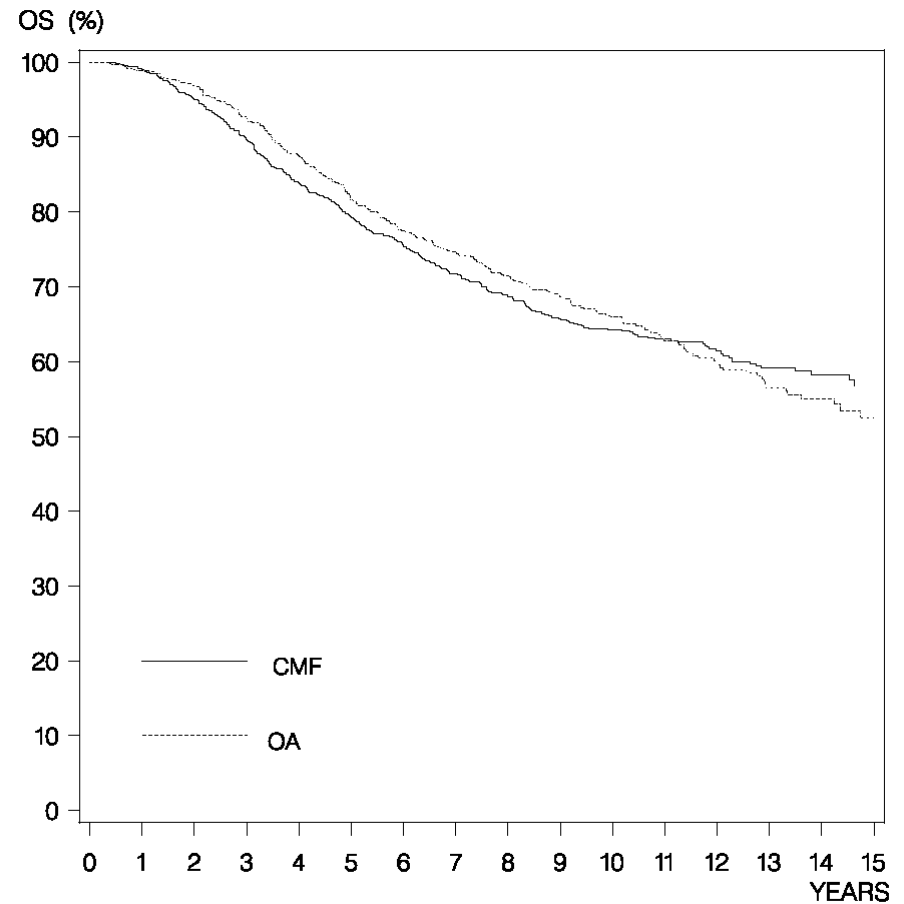
# DBCG 89B-cohort

## Recurrence-free survival (%)



CMF	805	647	514	398	303	128
OA	658	559	462	374	264	130

## Overall survival (%)



CMF	805	765	676	609	548	382	266	110
OA	658	638	575	510	455	298	189	82

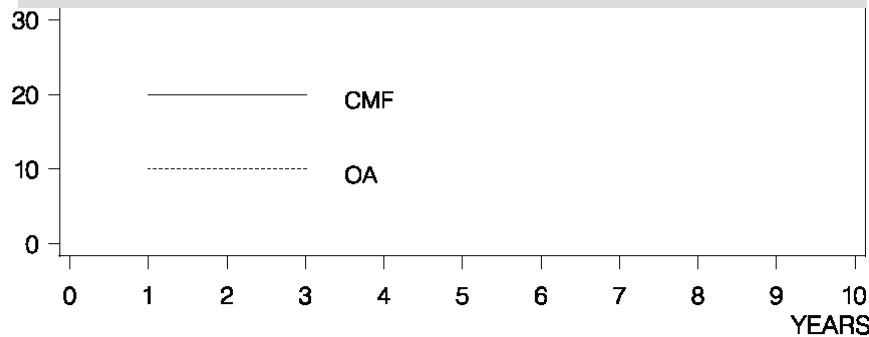
# DBCG 89B-cohort

## Recurrence-free survival (%)



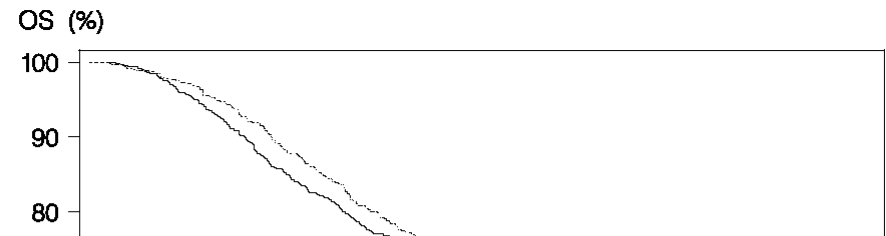
Adjusted analysis of DFS

	HR	95% CI	P
≤ 5 years	0.93	0.78-1.11	0.43
> 5 years	1.37	1.02-1.83	0.04



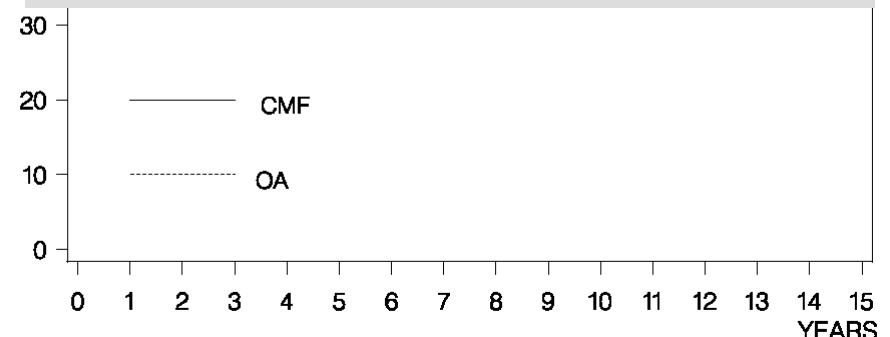
CMF	805	647	514	398	303	128
OA	658	559	462	374	264	130

## Overall survival (%)



Adjusted analysis of OS

	HR	95% CI	P
≤ 10 years	1.01	0.85-1.21	0.90
> 10 years	2.29	1.39-3.75	0.04



CMF	805	765	676	609	548	382	266	110
OA	658	638	575	510	455	298	189	82

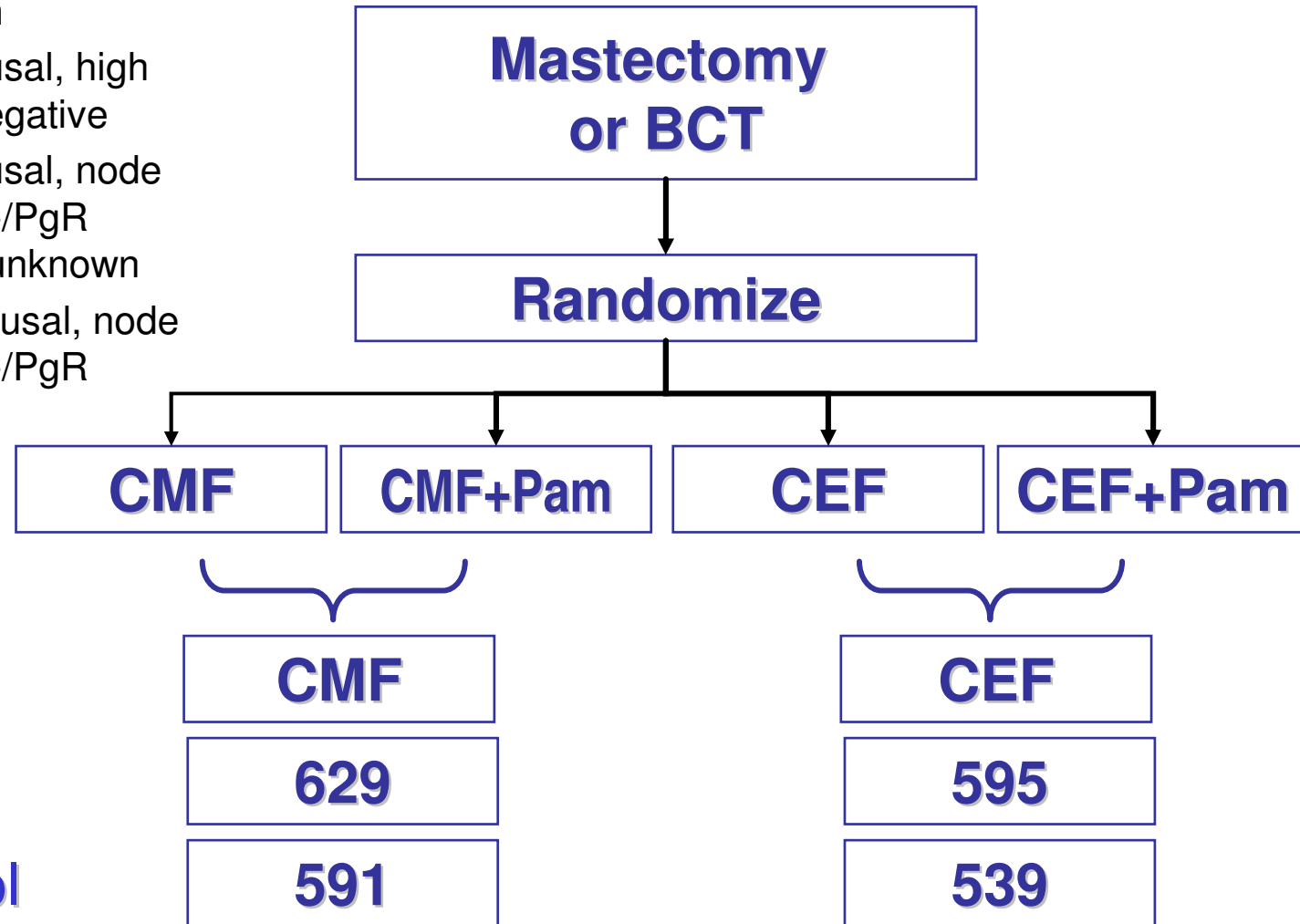
**Anthracyclines**

**Taxanes**

# DBCG 89D

## Patient selection

- Premenopausal, high risk, node negative
- Premenopausal, node positive, ER-/PgR negative or unknown
- Postmenopausal, node positive, ER-/PgR negative



Allocated

Per protocol

# DBCG 89D; Design

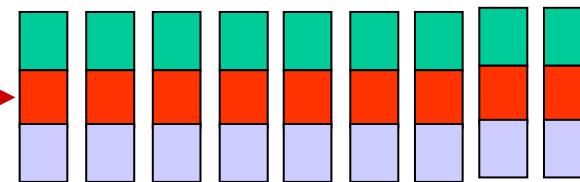
**N=1224**

## Patient selection

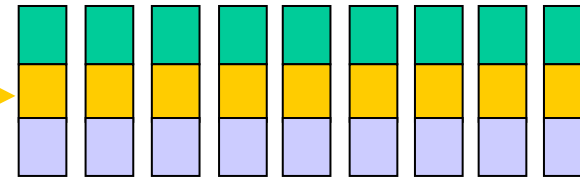
- Premenopausal, high risk, node negative
- Premenopausal, node positive, ER-/PgR negative or unknown
- Postmenopausal, node positive, ER-/PgR negative

**R  
A  
N  
D  
O  
M  
I  
Z  
E**

7 – 9 x CEF



7 – 9 x CMF

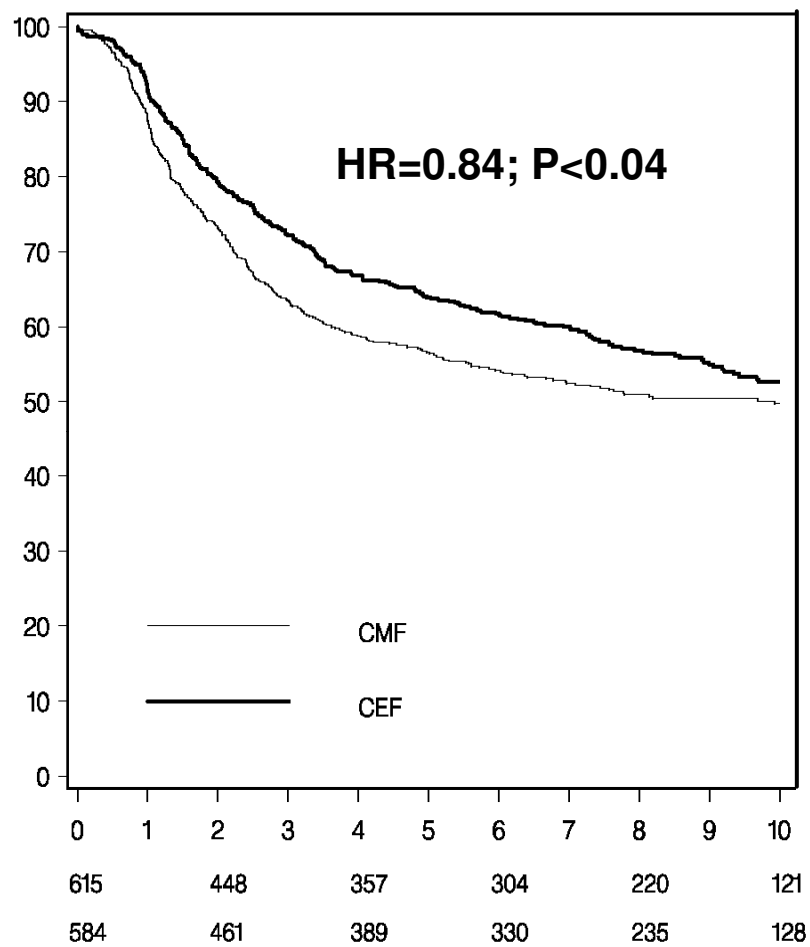


C: cyclophosphamide 600 mg/m<sup>2</sup>  
F: 5-fluorouracil 600 mg/m<sup>2</sup>  
M: methotrexate 40 mg/m<sup>2</sup>  
E: epirubicin 60 mg/m<sup>2</sup>

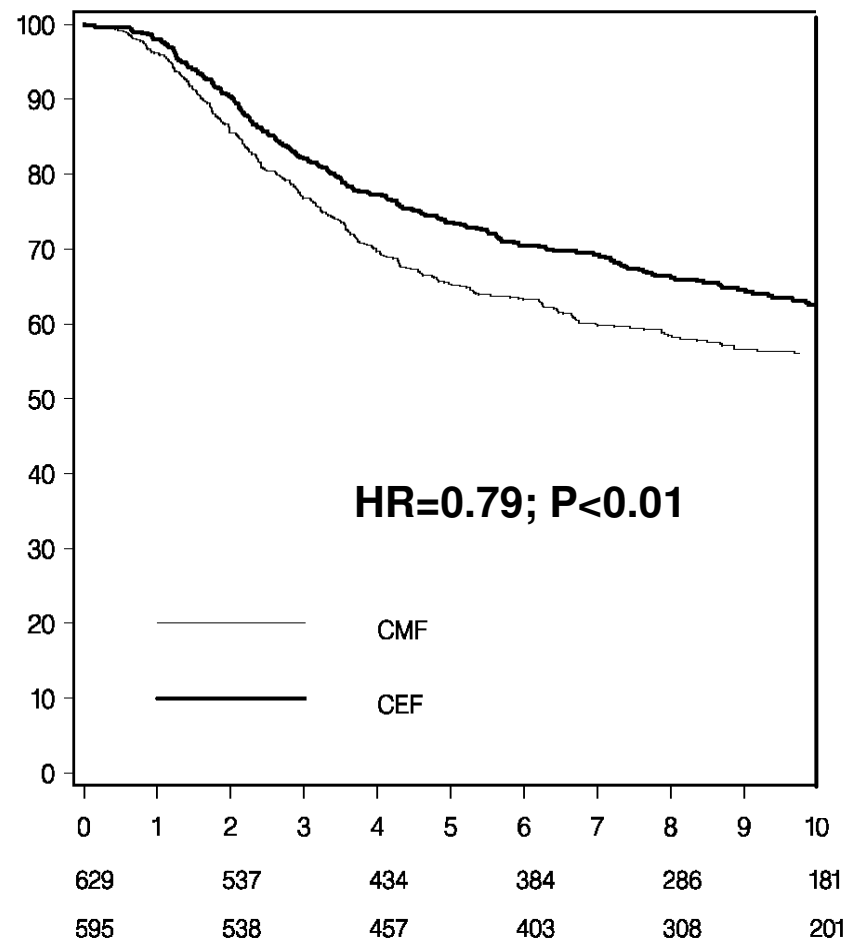


# DBCG-89D

**Recurrence-free survival (%)**

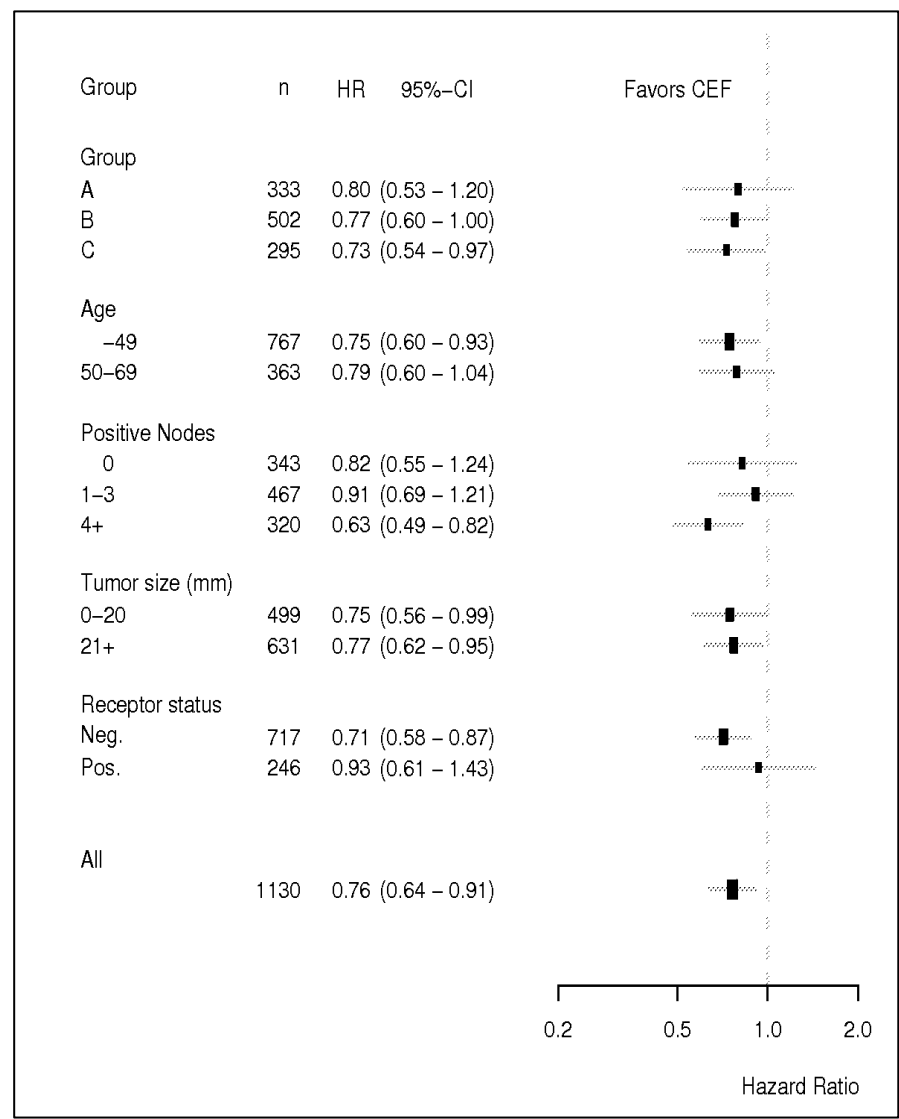


**Overall survival (%)**

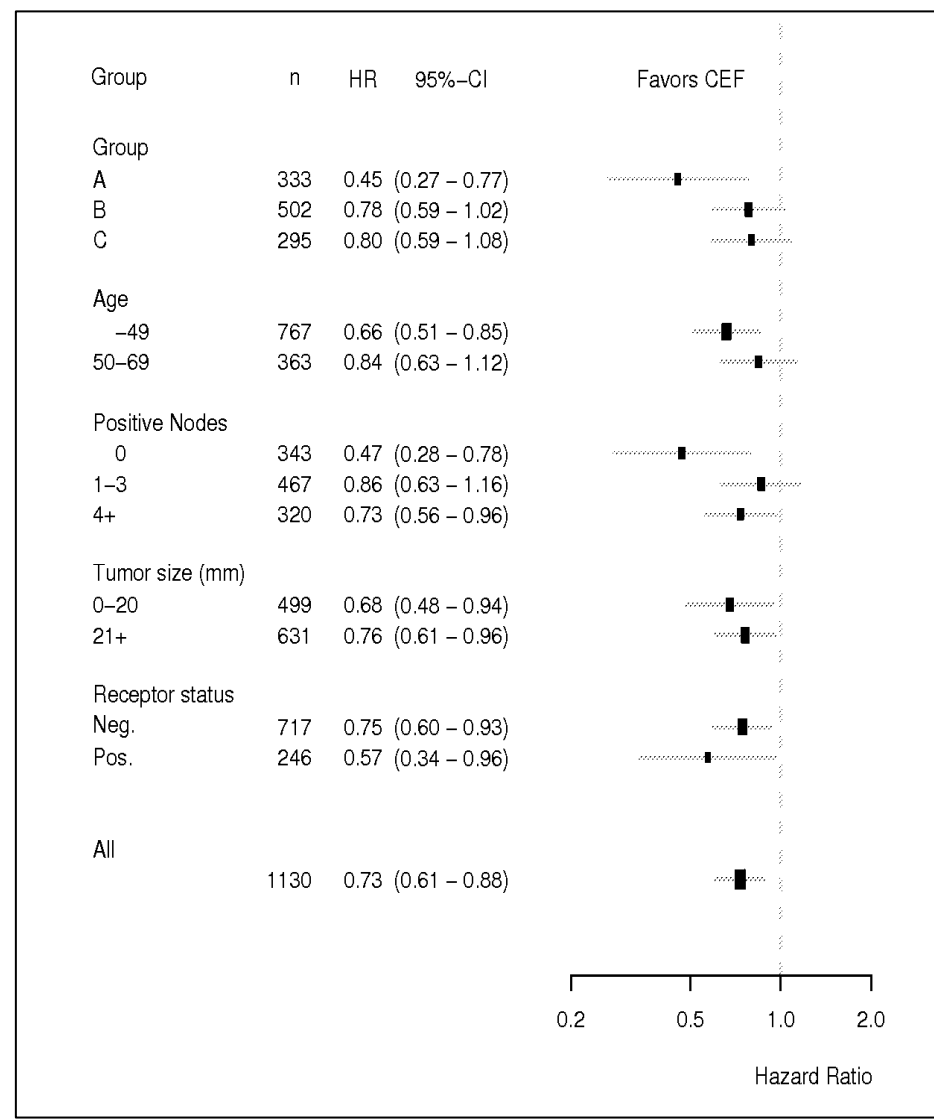


# DBCG-89D

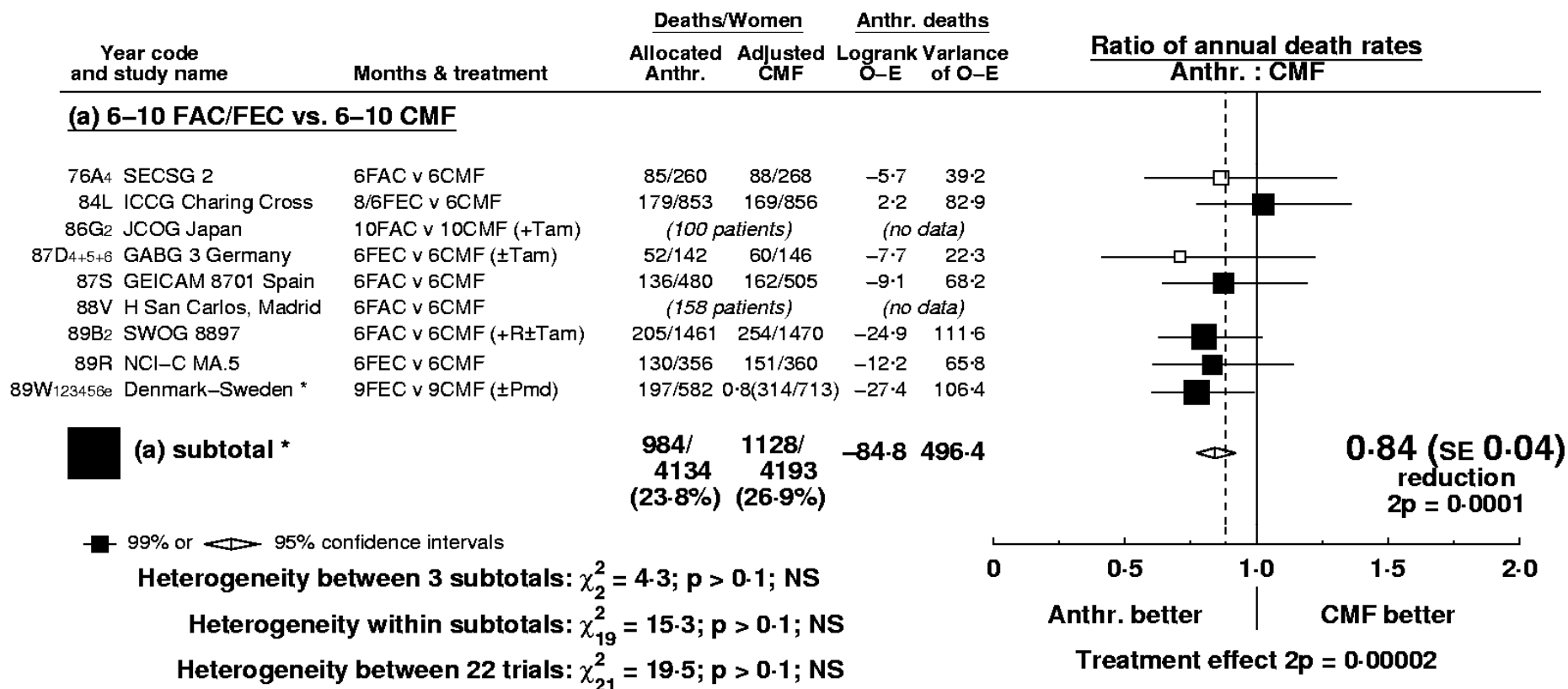
## Disease-free survival



## Overall survival



# Anthracycline-based regimen vs. CMF BREAST CANCER MORTALITY

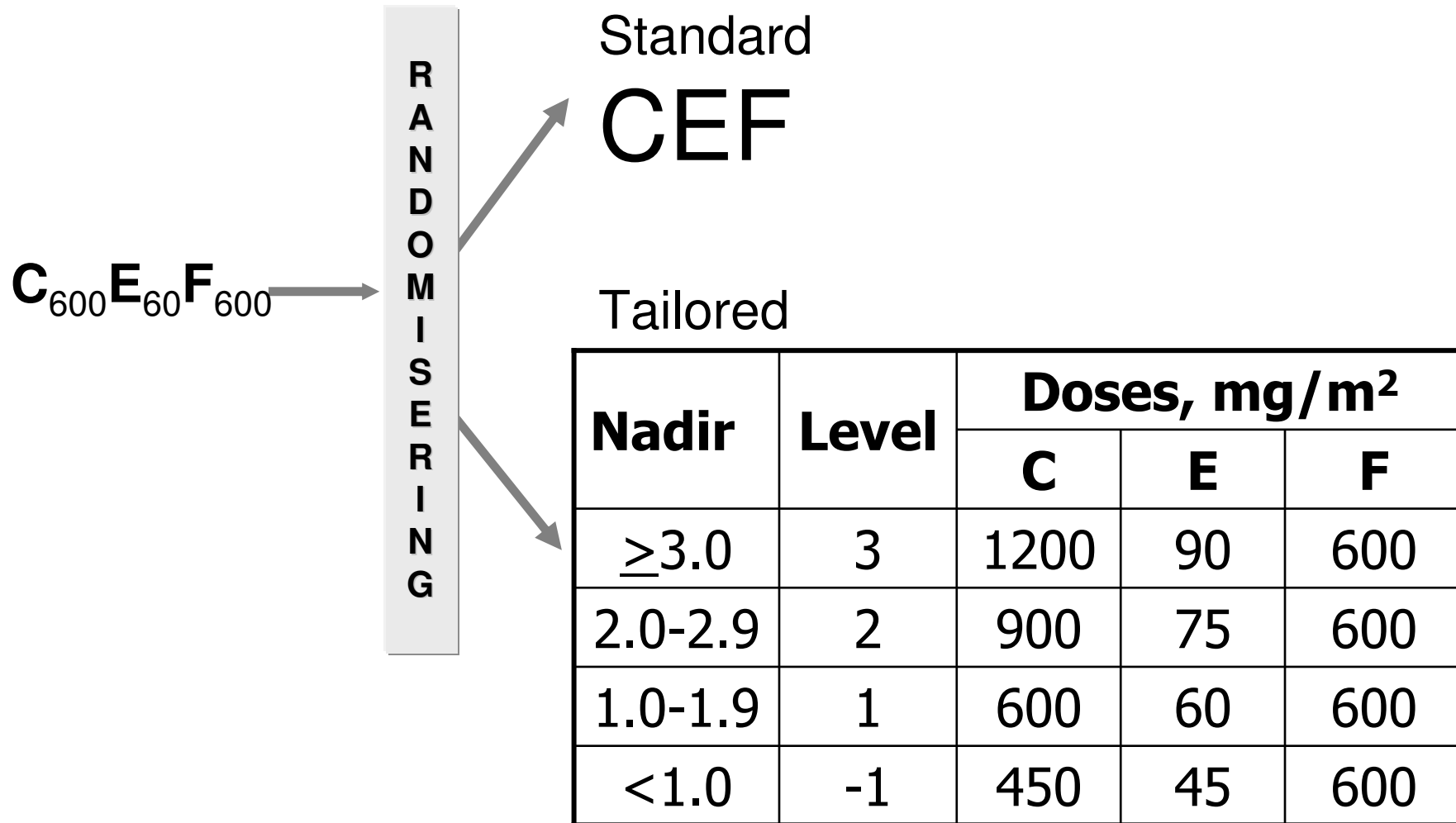


§ 1 trial with no data does not contribute to subtotals or to the overall total (allocated Anthr.: 335; allocated CMF: 337)

\* For balance, control patients in 3-way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/women.

23:41:44 10 September 2006  
Not for publication or citation

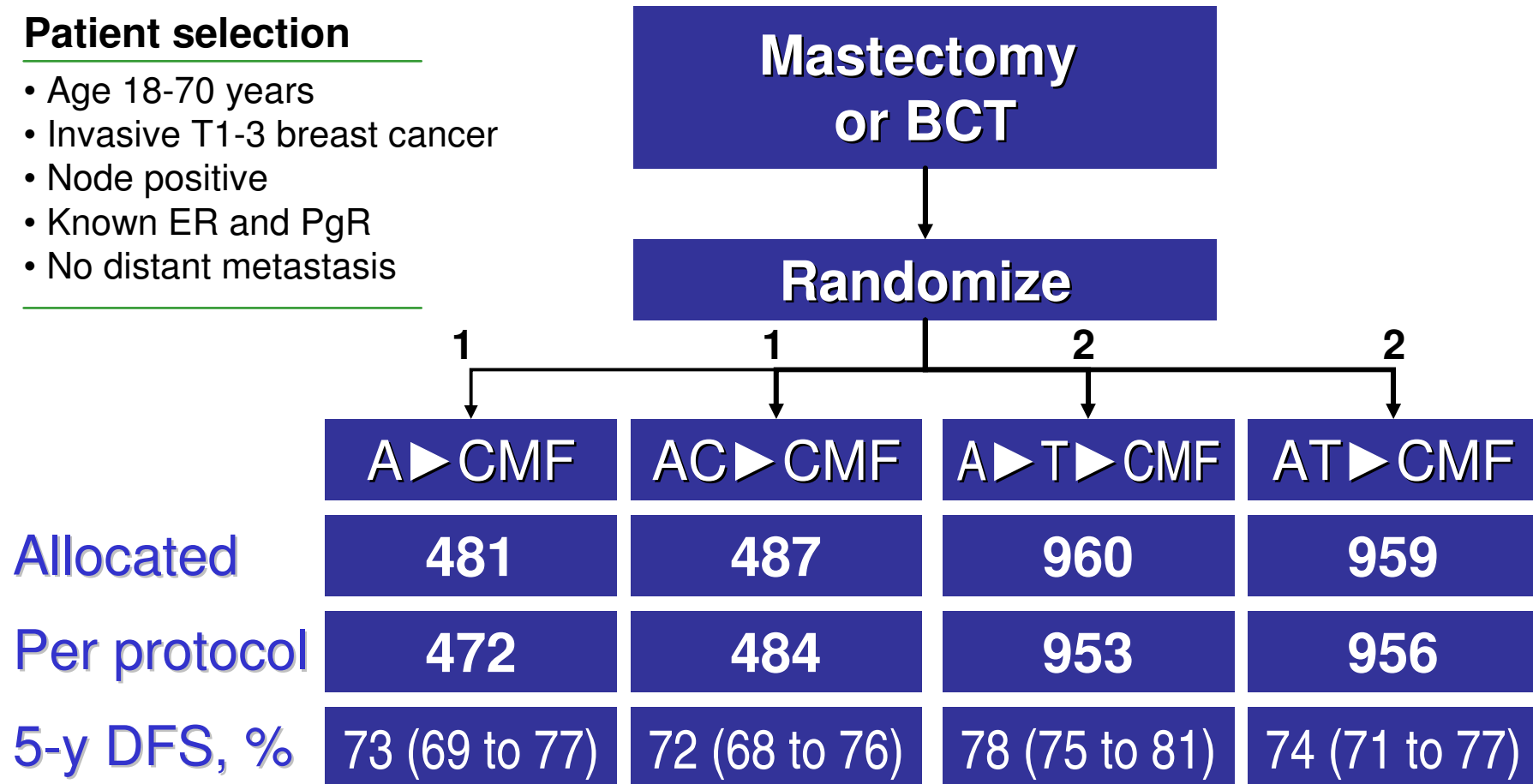
# SBG 2000-1



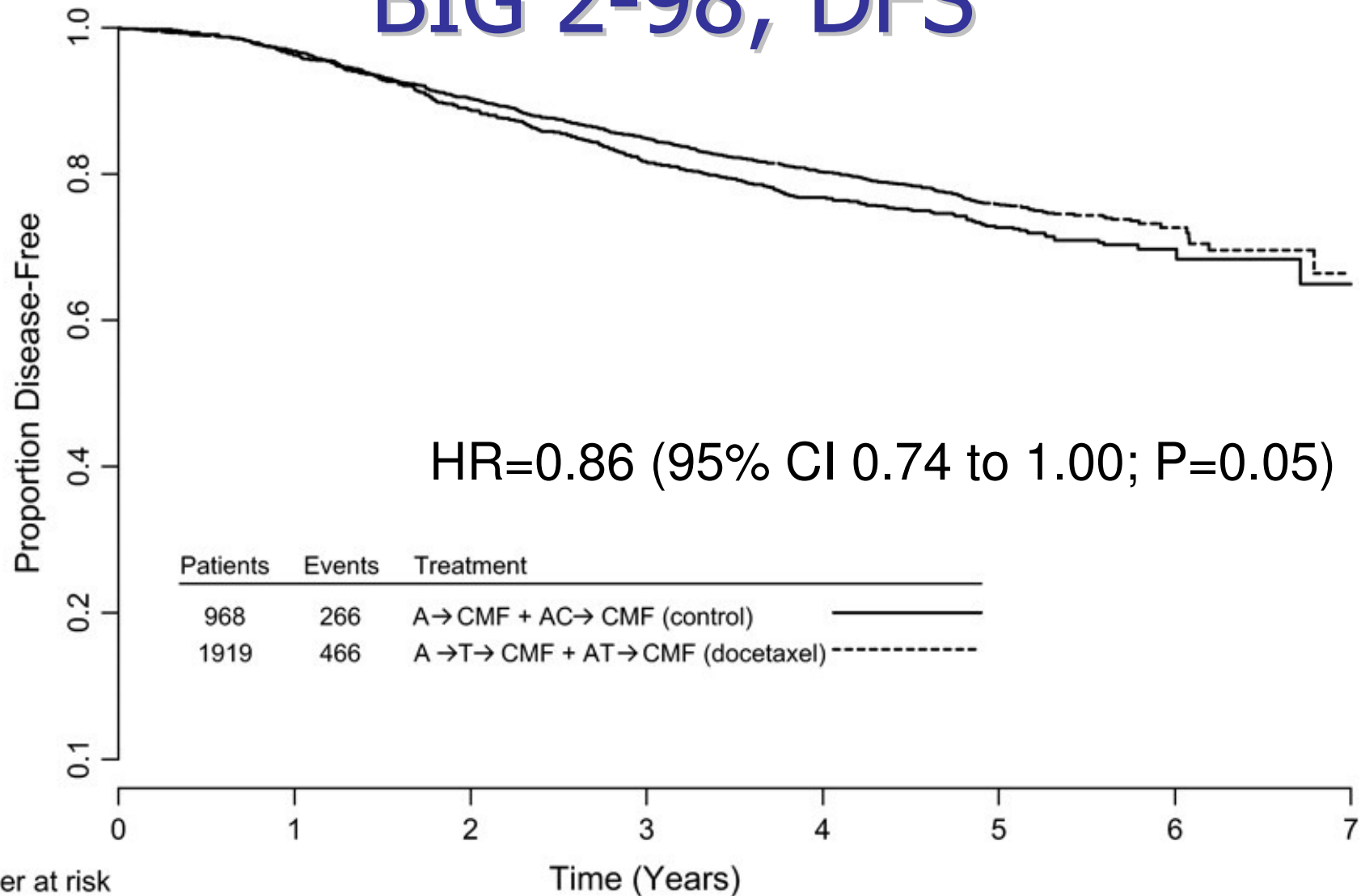
# DBCG 99F – BIG 2-98

## Patient selection

- Age 18-70 years
- Invasive T1-3 breast cancer
- Node positive
- Known ER and PgR
- No distant metastasis



# BIG 2-98; DFS



Number at risk

	0	1	2	3	4	5	6	7
A+AC	968	926	850	780	724	390	54	5
A->T+AT	1919	1850	1715	1596	1482	806	107	5

# Taxane vs no chemotherapy (Age < 50)

	Recurrence rate ratio (se)		Mortality rate ratio (se)	
CMF vs none	0.56	(0.06)	0.68	(0.05)
Antra vs CMF	0.84	(0.05)	0.81	(0.05)
Tax vs Anthra	0.84	(0.04)	0.86	(0.05)
<b>Tax vs none</b>	<b>0.38</b>	<b>(0.07)</b>	<b>0.46</b>	<b>(0.08)</b>

2p<0.00001

2p<0.00001

# Taxane vs no chemotherapy (Age 50-69)

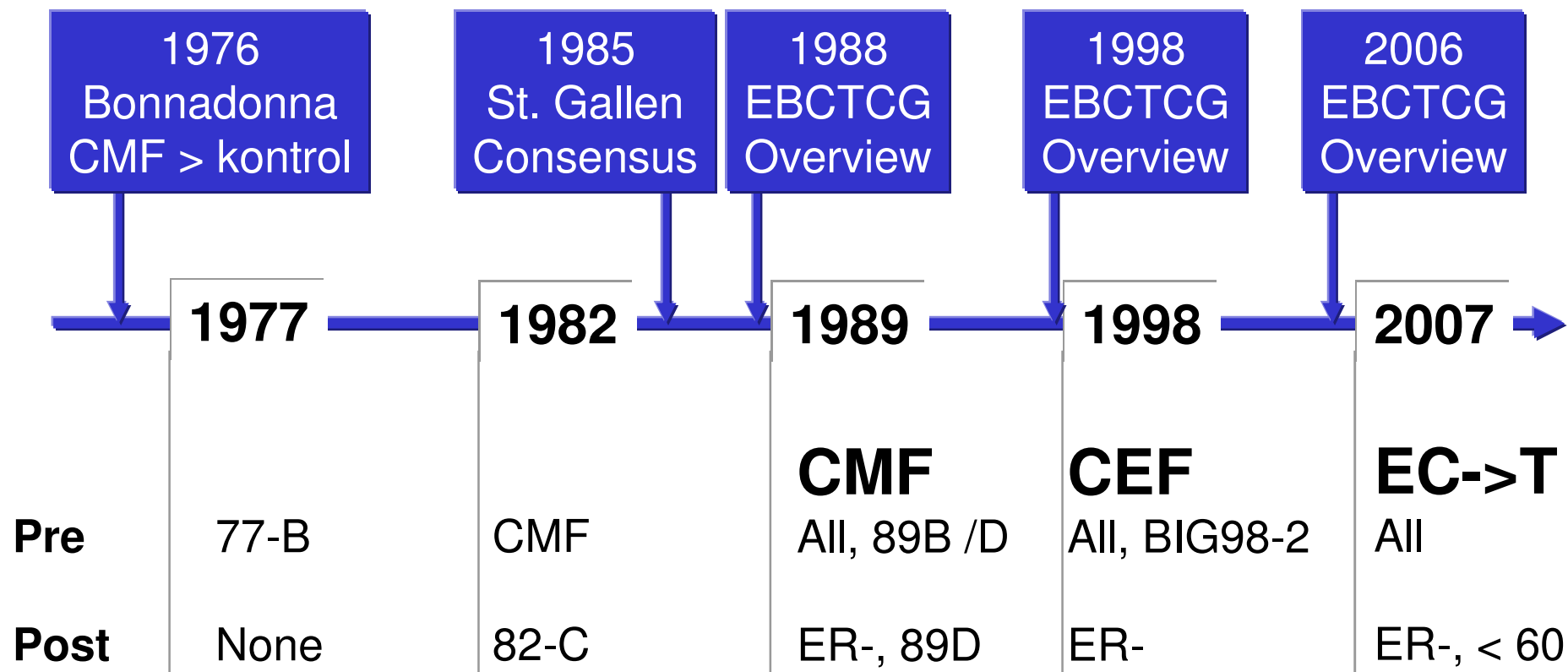
	Recurrence rate ratio (se)		Mortality rate ratio (se)	
CMF vs none	0.75	(0.03)	0.91	(0.03)
Antra vs CMF	0.89	(0.06)	0.90	(0.06)
Tax vs Anthra	0.82	(0.04)	0.85	(0.05)
<b>Tax vs none</b>	<b>0.52</b>	<b>(0.07)</b>	<b>0.66</b>	<b>(0.08)</b>

2p<0.00001

2p=0.00002



# DBCGs guidelines on chemotherapy



# Conclusions

In patients with early breast cancer, chemotherapy:

- Prolongs disease-free and overall survival
- Dose and schedule are important
- Should include alkylating agents, anthracyclines and taxanes

In addition the following might be considered:

- DNA synthesis inhibitors
- Chemical castration
- Age
- Interaction with tamoxifen
- Hormone receptor status and other biomarkers

# Participating Institutions

DBCG

The Registry

Henning Mouridsen

Susanne Møller

Maj-Britt Jensen

Oncology

Sydvestjysk Sygehus Esbjerg

Brita Bjerregaard

Departments

Herlev Hospital

Dorte Nielsen

Regionshospitalet Herning

Knud Aage Møller

Nordsjællands Hospital Hillerød

Ellen Borck

Sygehus Syd Næstved

Preben Philip

Odense Universitetshospital

Ann Knoop

Rigshospitalet

Bent Ejlersen

Sygehus Øst Roskilde

Peter Grundtvig

Bornholms Hospital

Ditte Nielsen

Vejle Sygehus

Erik Jakobsen

Regionshospitalet Viborg

Vera Haarh

Sønderborg Sygehus

Ebbe Lindegaard

Ålborg Sygehus

Lars Stenbygaard

Århus Sygehus

Jørn Andersen