DBCG

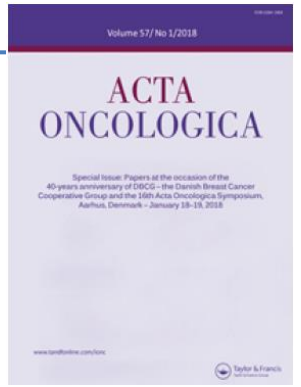
Det videnskabelige bidrag

Bent Ejlertsen

1977
40
2017
DBCG

16th ACTA ONCOLOGICA SYMPOSIUM

ACTA ONCOLOGICA, 2018 VOL. 57, NO. 1, 3–12



Forty years of landmark trials undertaken by the Danish Breast Cancer Cooperative Group (DBCG) nationwide or in international collaboration

Bent Ejlertsen, Birgitte Vrou Offersen, Jens Overgaard, Peer Christiansen, Maj-Britt Jensen, Niels Kroman, Ann Søgaard Knoop & Henning Mouridsen

ABSTRACT

Background: Over the past 40 years the Danish Breast Cancer Cooperative Group (DBCG) has made significant contributions to improve outcome and to make treatment of patients with early breast cancer more tolerable through nationwide and international trials evaluating loco-regional and systemic treatments. These trials have been instrumental to establish standards for the treatment of early breast cancer.

Methods: The DBCG 82 trials had a global impact by documenting that the significant gain in loco-regional recurrence from postmastectomy radiation added to systemic therapy was associated with a reduction in distant recurrence and mortality in high-risk pre- and postmenopausal patients. The DBCG trials comparing breast conserving surgery and radiotherapy with mastectomy and more recently the trial of internal mammary node irradiation also had a major impact of practice. The trials initiated by the DBCG 40 years ago on tamoxifen and cyclophosphamide based chemotherapy became instrumental for the development of adjuvant systemic therapy not only due to their positive results but by sharing these important data with other members of the Early Breast Cancer Trialist' Collaborative Group (EBCTCG). Trials from the DBCG have also been important for highlighting the relative importance of anthracyclines and taxanes in the adjuvant setting. Furthermore, DBCG has made a major contribution to the development of aromatase inhibitors and targeted adjuvant treatment for human epidermal growth factor receptor 2 positive breast cancers.

Results: The substantial impact of these treatment improvements is illustrated by a 46.7% 10-year overall survival of early breast cancer patients treated in 1978–1987 compared to 71.5% for patients treated 2008–2012.

Conclusions: The trials conducted and implemented by the DBCG appear to have a major impact on the substantial survival improvements in breast cancer.

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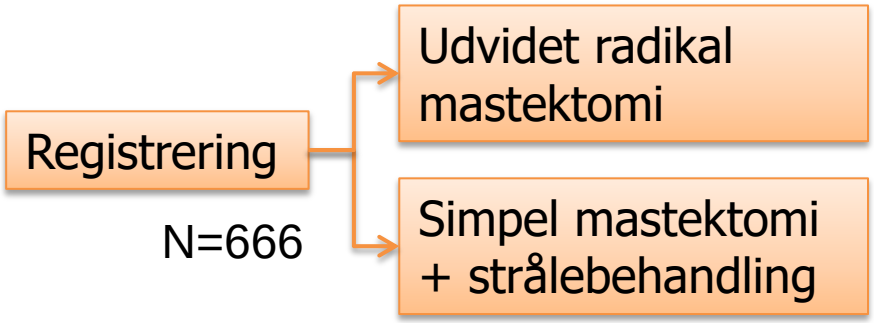
1977 40 2017 DBCG

- DBCG's 40 års jubilæumsmøde
- 16th ACTA ONCOLOGICA SYMPOSIUM
- Kliniske forsøg udført af DBCG
  - Kirurgi
  - Strålebehandling
  - Endokrin behandling
  - HER2 rettet behandling
  - Kemoterapi
- Behandlingen af brystkræft er i fire successive dekader koblet til bedre overlevelse


Inden DBCG var der ingenting?
Eller var der?

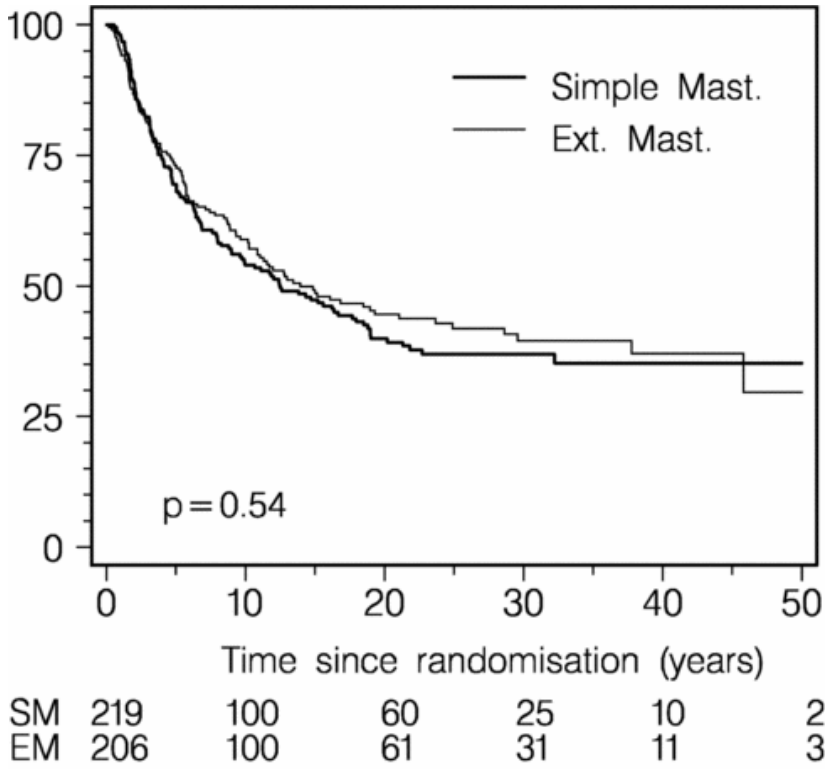
Copenhagen Breast Cancer Trials

Radikal vs simpel mastektomi



- Åbent randomiseret fase 3 forsøg
- Alle blev registreret når henvisningen var modtaget
- Åben fra november 1951 til udgangen af december 1957

Cause*-specific survival (%)



*Breast cancer specific survival

Johansen & Kaae et al. Acta Oncol 2008;47:633

Locoregional treatment

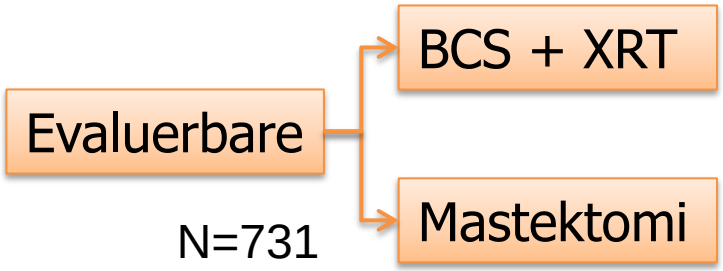
10 year disease-free and overall survival

Study	Regimens	N	DFS; 95% CI	OS; 95% CI
CBCT 01	Radical mastectomy	334	*41% (34;47)	37% (32,42)
Johansen[4]	Mastectomy + RT	332	*40% (33;46)	36% (31,41)
DBCG 82B	Mastectomy + RT	852	48% (45;52)	54% (51;58)
Overgaard[10]	Mastectomy	856	34% (30;37)	45% (42;48)
DBCG 82C	Mastectomy + RT	686	36% (32;40)	45% (41;49)
Overgaard[11]	Mastectomy	689	24% (21;28)	36% (33;40)
DBCG 82TM	Lumpectomy + RT	381	60% (55;64)	73% (68;77)
Blichert-Toft[16]	Mastectomy	350	61% (56,66)	71% (66;76)
DBCG IMN	IMN + RT	1492	#27% (25;30)	#76% (74;78)
Thorsen[31]	IMN (no RT)	1597	#30% (27;32)	#72% (70;75)

*Analysis restricted to 425 patients with surgery at two certified institutions. # DFS and OS at 8 years follow-up. RT: radiotherapy; DFS: disease-free survival; OS: overall survival; CI: confidence interval.

DBCG 82TM; BCS vs mastectomy

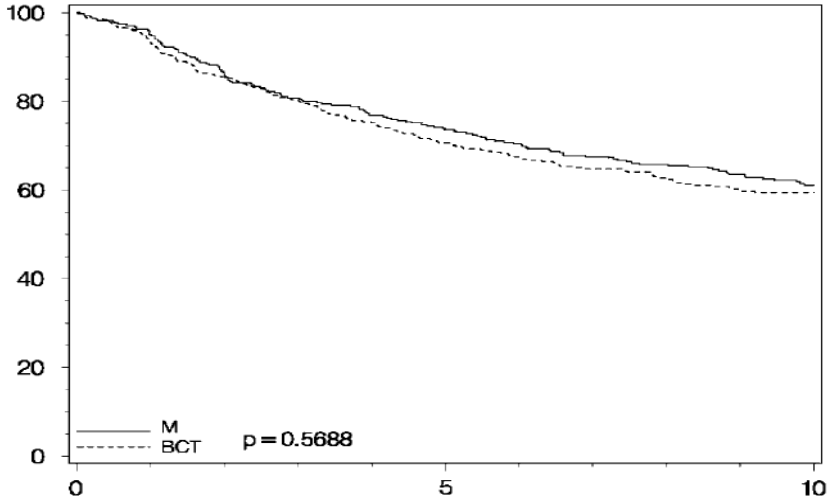
Radikal vs simpel mastektomi



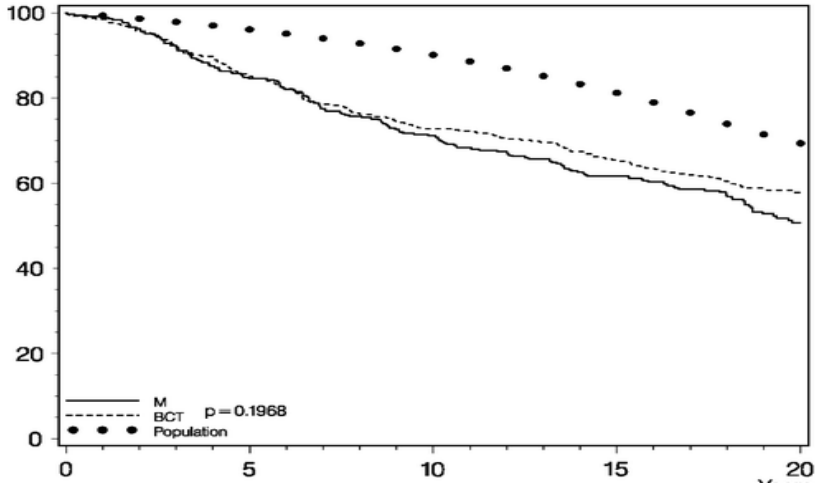
- Åbent randomiseret fase 3 forsøg
- Randomisation før samtykke efter Zelen's princip.
- Åben fra januar 1983 til udgangen af marts 1989

Blichert-Toft et al. Acta Oncol 2008;47:672

Recidivfri overlevelse (%)



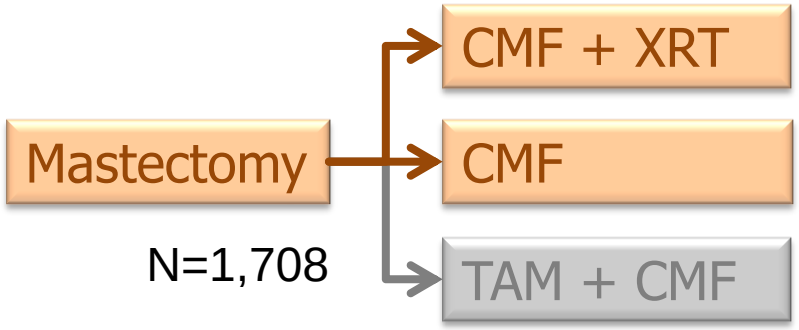
Overlevelse (%)



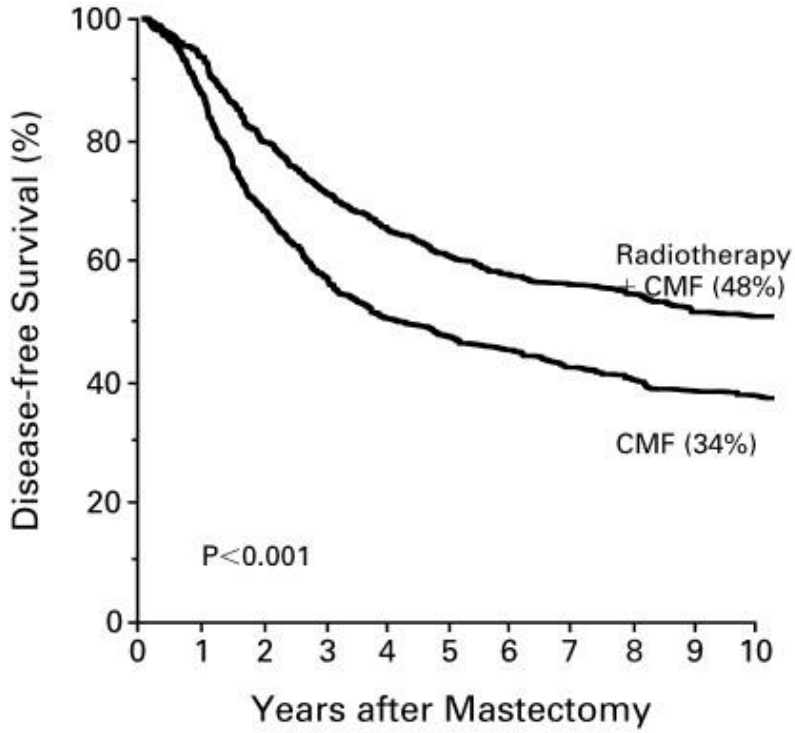
POSTOPERATIVE RADIOTHERAPY IN HIGH-RISK PREMENOPAUSAL WOMEN WITH BREAST CANCER WHO RECEIVE ADJUVANT CHEMOTHERAPY

MARIE OVERGAARD, M.D., PER S. HANSEN, M.D., JENS OVERGAARD, M.D., CARSTEN ROSE, M.D., MICHAEL ANDERSSON, M.D., FLEMMING BACH, M.D., MOGENS KJAER, M.D., CARL C. GADEBERG, M.D., HENNING T. MOURIDSEN, M.D., MAJ-BRITT JENSEN, M.SC., AND KARIN ZEDELER, M.SC., FOR THE DANISH BREAST CANCER COOPERATIVE GROUP 82b TRIAL

82B: præmenopausal



- Højrisiko, dvs. N+, T>5 cm og/eller invasion i hud eller fascie.
- Total mastektomi med partiel aksildissektion.
- CMF (600, 40, 600 mg/m^2).



Radiotherapy + CMF	852	643	505	429	308	102
CMF	856	537	382	327	216	74

Overgaard et al. NEJM 1997;337:949

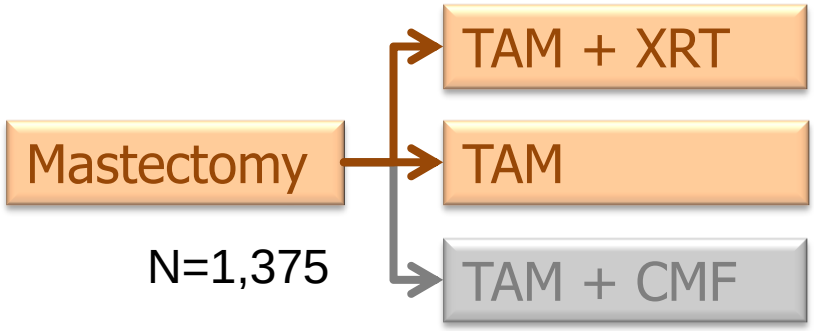
THE LANCET
Volume 353, Issue 9165, 15 May 1999, Pages 1641-1648

Articles

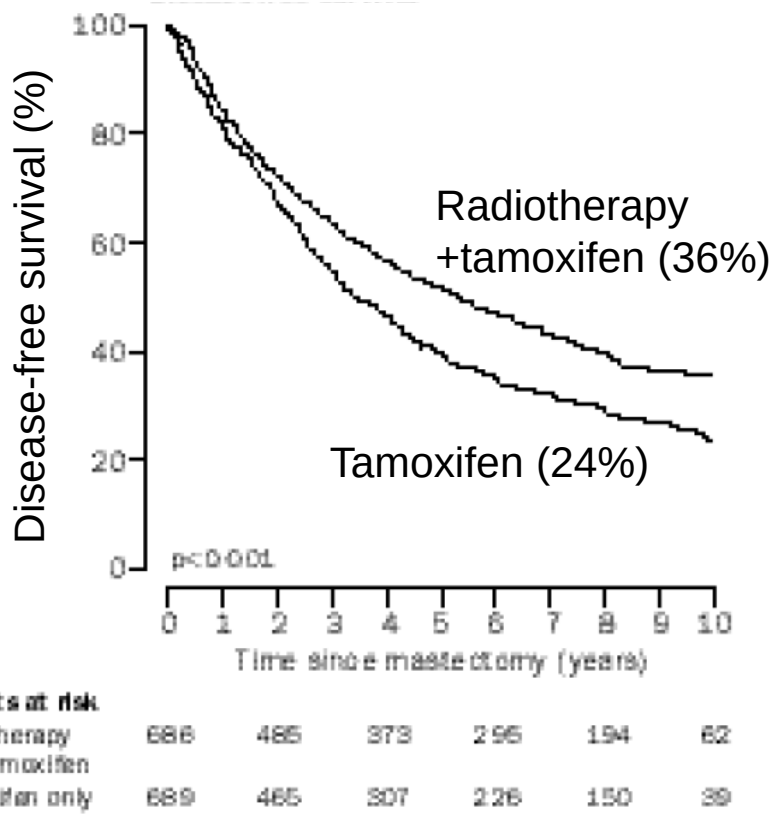
Postoperative radiotherapy in high-risk potsmenopausal breastcancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group 82c randomised trial

Marie Overgaard, Maj-Britt Jensen, Jens Overgaard, Per S Hansen, Carsten Rose, Michael Andersson, Claus Kamby, Mogens Kjær, Carl C Gadeberg, Birgitte Bruun Rasmussen, Mogens Blichert-Toft, Henning T Mouridsen

82C: postmenopausal



- Højrisiko, dvs. N+, T>5 cm og/eller invasion i hud eller fascie.
- Total mastektomi med partiel aksildissektion.
- Tamoxifen 30 mg dag. i 1 år.



VOLUME 34 · NUMBER 4 · FEBRUARY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

Lise Bech Jellesmark Thorsen, Birgitte Vrou Offersen, Hella Danø, Martin Berg, Ingelise Jensen, Anders Navrsted Pedersen, Sune Jürg Zimmermann, Hans-Jürgen Brodersen, Marie Overgaard, and Jens Overgaard

Concern of radiation-induced heart disease led to a different strategy for including the internal mammary nodes (IMN) in loco-regional RT after left and right sided breast cancer.

In patients who received loco-regional RT

- INM was included in the RT fields following right sided bc
- INM was not included in the RT fields following right sided bc

The IMN target generally included the nodes in caudal direction to the intercostal space (IC) IV (cranial border of the 5th rib).

DBCG assessed the effect of internal mammary node irradiation (IMNI) in patients with early stage node-positive breast cancer.

VOLUME 34 · NUMBER 4 · FEBRUARY 1, 2016

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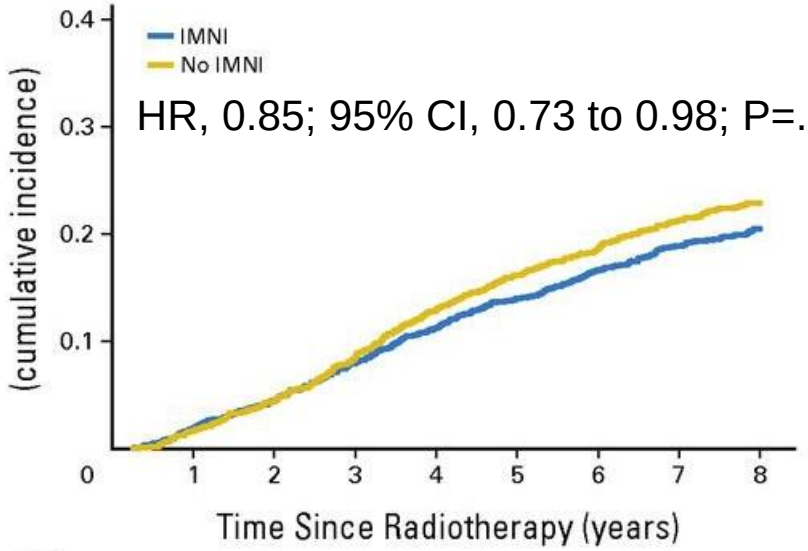
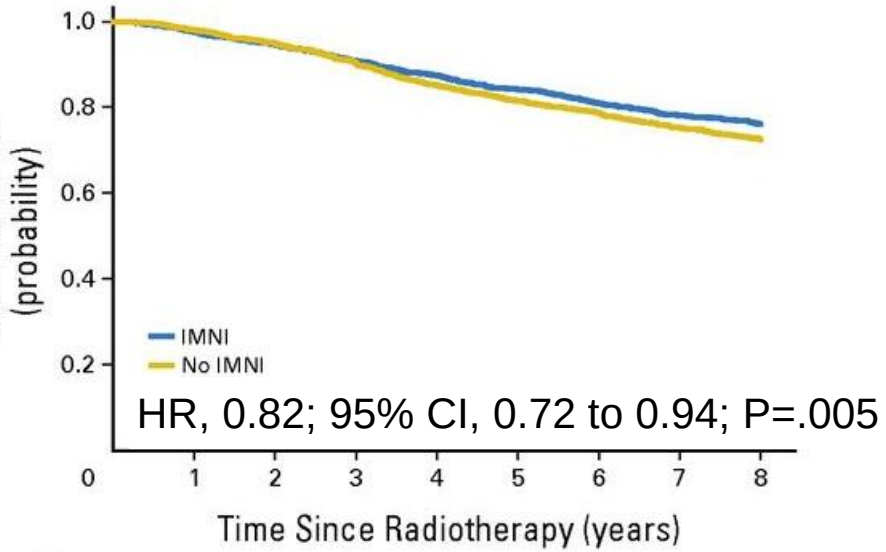
Breast Cancer Mortality



Overall Survival



IMNI	1,492	1,410	1,301	1,205	783	1,492	1,410	1,301	1,205	783
No IMNI	1,597	1,410	1,301	1,205	791	1,597	1,410	1,301	1,205	791

Adjuvant endocrine treatment

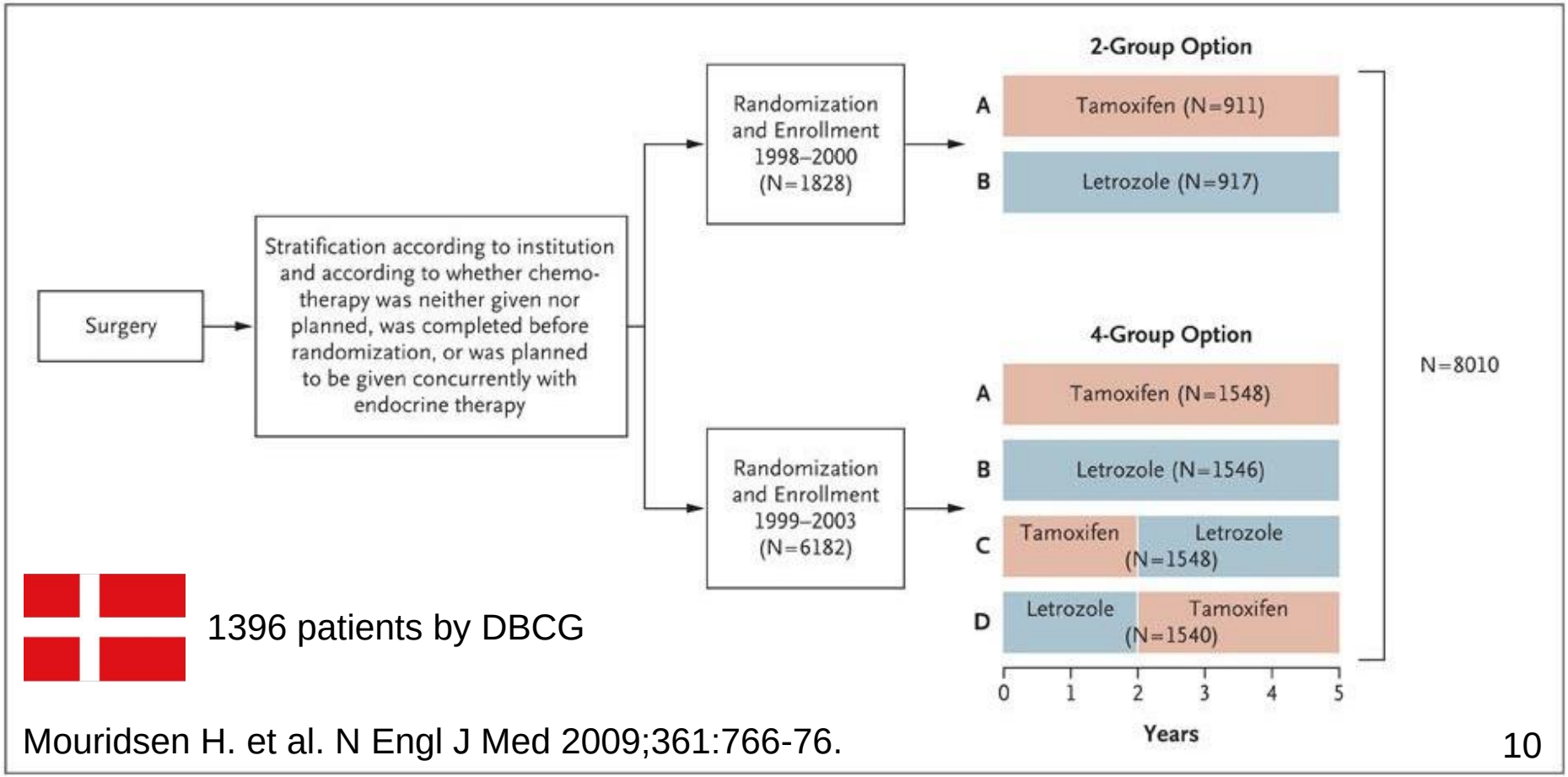
Study	Regimens	N	DFS; 95% CI	OS; 95% CI
CBCT 02 Jensen[51]	Tamoxifen Placebo	164 153	0.74; 0.53-1.05	0.79; 0.63-0.99
DBCG 77C Knoop[52]	Tamoxifen Control	868 848	0.87; 0.77-0.98	0.83; 0.73-0.94‡
DBCG 82B Andersson[56]	CMF+Tamoxifen CMF	320 314	0.93; 0.76-1.15	1.05; 0.85-1.30
DBCG 89C Andersen[54]	TAM 1 year TAM 2 years TAM→Megace	554 535 526	1.04; 0.89-1.22 1.11; 0.94-1.30	0.99; 0.85-1.15 1.05; 0.90-1.23
IES / 89CX Bliss[73]	Tamoxifen Exemestane	615 584	0.84; 0.71-0.99	0.79; 0.66-0.94
BIG 1-98 Mouridsen[70] Regan[71]	Tamoxifen Letrozole TAM→Letrozole# Letrozole→TAM#	2459 2463 1548 1540	0.86; 0.78-0.96 1.07; 0.92-1.25 1.06; 0.91-1.23	0.87; 0.77-0.999 1.10; 0.90-1.33 0.97; 0.80-1.19
FACE Smith[76]	Anastrozole Letrozole	2075 2061	0.93; 0.80-1.07	0.98; 0.82-1.17
SOLE Colleoni[78]	Cont. letrozole With breaks	2441 2443	1.08; 0.93-1.26	0.85; 0.68-1.07

DFS: disease-free survival; OS: overall survival; CI: confidence interval; TAM: tamoxifen; #: total duration of 5 years
NA: non-available; NS: non-significant. #: versus letrozole; ‡breast cancer mortality

The NEW ENGLAND JOURNAL of MEDICINE

Letrozole Therapy Alone or in Sequence with Tamoxifen in Women with Breast Cancer

The BIG 1-98 Collaborative Group*



1396 patients by DBCG

Mouridsen H. et al. N Engl J Med 2009;361:766-76.

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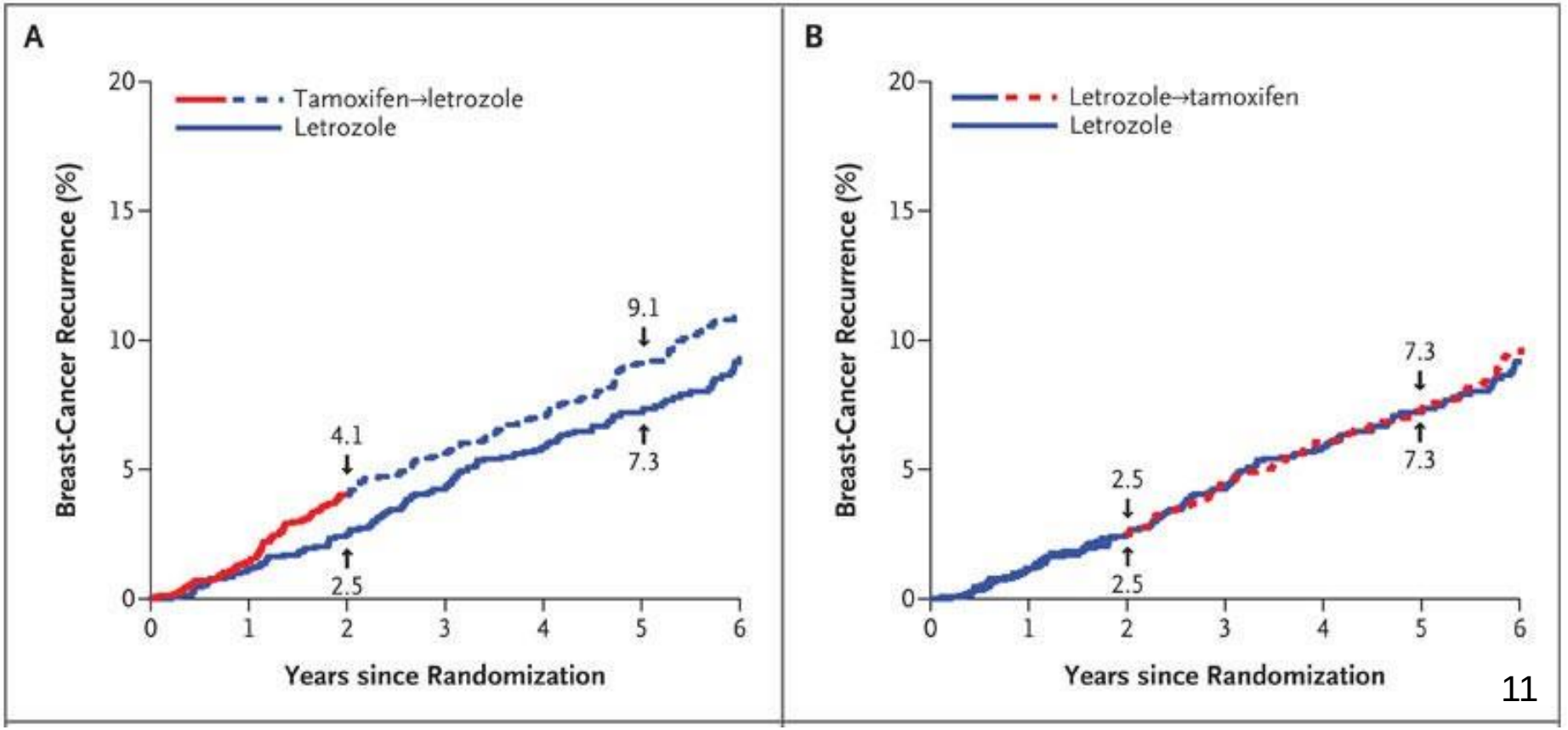


Mouridsen H. et al. NEJM 2009;361:766-76.

Adjuvant HER2 targeted treatment

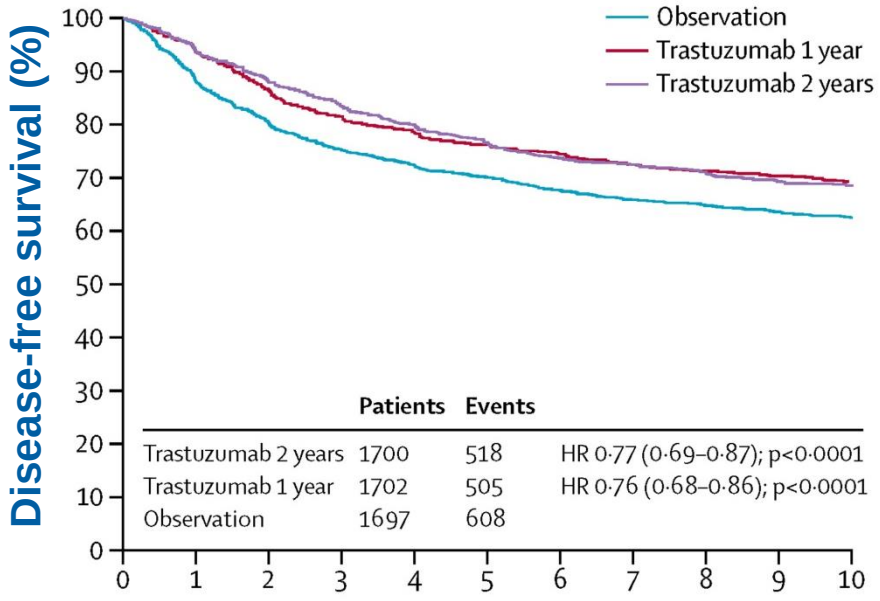
Study	Regimens	N	DFS; 95% CI	OS; 95% CI
HERA	Trastuzumab 2 yr	1700	0.77; 0.69-0.87	NA
Cameron[83]	Trastuzumab 1 yr	1702	0.76; 0.68-0.86	0.74; 0.64-0.86
	Control	1697		
ALTTO	Lapatinib + T	2093	0.84; 0.70-1.02	0.80; 0.62-1.03
Piccart[84]	T → lapatinib	2091	0.96; 0.80-1.15	0.91; 0.71-1.16
	Lapatinib	2100	1.34; 1.13-1.60	1.36; 1.09-1.72
	Trastuzumab	2097		
APHINITY	Pertuzumab	2400	0.81; 0.66-1.00	0.89; 0.66-1.21
Minckwitz[85]	Control	2404		
ExteNet	Neratinib	1420	0.67; 0.50-0.91	NA
Chan[86]	Control	1420		

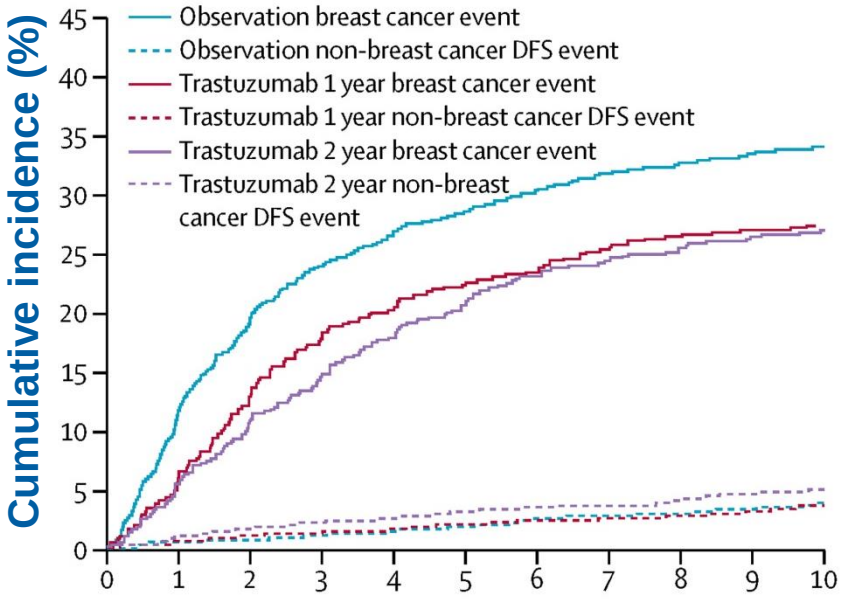
DFS: disease-free survival; OS: overall survival; CI: confidence interval; NA: non-available; NS: non-significant.

THE LANCET
Volume 389, Issue 10075, 25–31 March 2017, Pages 1195-1205

Articles

11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial





Number at risk

Observation	1697	1438	1296	1201	1140	1095	1038	990	946	911	831
Trastuzumab 1 year	1702	1552	1413	1319	1265	1213	1179	1131	1099	1069	996
Trastuzumab 2 years	1700	1553	1442	1361	1291	1222	1156	1125	1087	1045	965

	1697	1438	1296	1201	1140	1095	1038	990	946	911	831
	1702	1552	1413	1319	1265	1213	1179	1131	1099	1069	996
	1700	1553	1442	1361	1291	1222	1156	1125	1087	1045	965

Adjuvant chemotherapy

Study	Regimens	N	DFS; 95% CI	OS; 95% CI
DBCG 77B	Ctx	181	0.62; 0.46-0.83	0.70; 0.52-0.95
Ejlertsen[89]	Oral CMF	193	0.70; 0.53-0.93	0.70; 0.52-0.94
	Control	187		
DBCG 77B	Ctx	424	0.95; 0.77-1.16	1.09; 0.92-1.29
Ejlertsen[89]	Oral CMF	423		
DBCG 82C	TAM+ CMF	709	0.82; 0.71-0.93	0.95; 0.85-1.08
Ejlertsen[93]	TAM	736		
DBCG 89D	CEF	615	0.84; 0.71-0.99	0.79; 0.66-0.94
Ejlertsen[95]	CMF	584		
DBCG READ	EC→D	1001	1.00; 0.78-1.28	1.15; 0.83-1.59
Ejlertsen[101]	DC	1011		
BIG 2-98	4A→3CMF	481	0.81; 0.67-0.99	0.85; 0.67-1.11
Oakman[103]	3A→3D→4CMF	960		
	4AC→4CMF	487	1.02; 0.84-1.23	0.96; 0.76-1.21
	4AD→4CMF	959		

DFS: disease-free survival; OS: overall survival; CI: confidence interval; NA: non-available; NS: non-significant. Ctx: oral cyclophosphamide; C: cyclophosphamide; F: fluorouracil; M: methotrexate; A: doxorubicin; E: epirubicin; D: docetaxel TAM: tamoxifen.

Baggrund; adjuverende kemoterapi

- Biologien
  - I 1950'er blev der beskrevet cirkulerende tumorceller efter mastektomi.
  - I 1971 beskrev Skipper at tidlig, men ikke sen, kemoterapi kunne give komplet tumorsvind.
- Perioperativ kemoterapi
  - Fisher et al. 1968; thiothepa i NSABP-B01
  - Nissen-Meyer et al. 1971; enkeltstof cyclofosfamid
- Adjuverende kemoterapi
  - Bonadonna et al. 1976; CMF i første Milano trial

DBCG 77B

Patienter

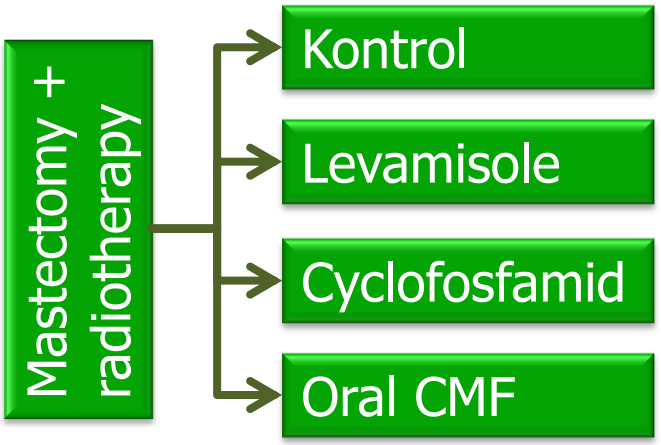
- Præmenopausale
- Mastektomi og RT
- Ingen fjernmetastaser
- Højrisiko
  - Lymfeknude positive
  - Tumor > 5 cm
  - Invasion i hud /fascie

Levamisol 5 mg/kg 2 dage ugentlig*

Oral cyclofosfamid 130mg/m^2 dag 1-14*

CMF: Oral cyclofosfamid 80mg/m^2 dag 1-14; methotrexat 30mg/m2 iv. dag 1+8; og 5-fluorouracil 500mg/m2 iv. d. 1+8*

*every 4 weeks for 48 weeks

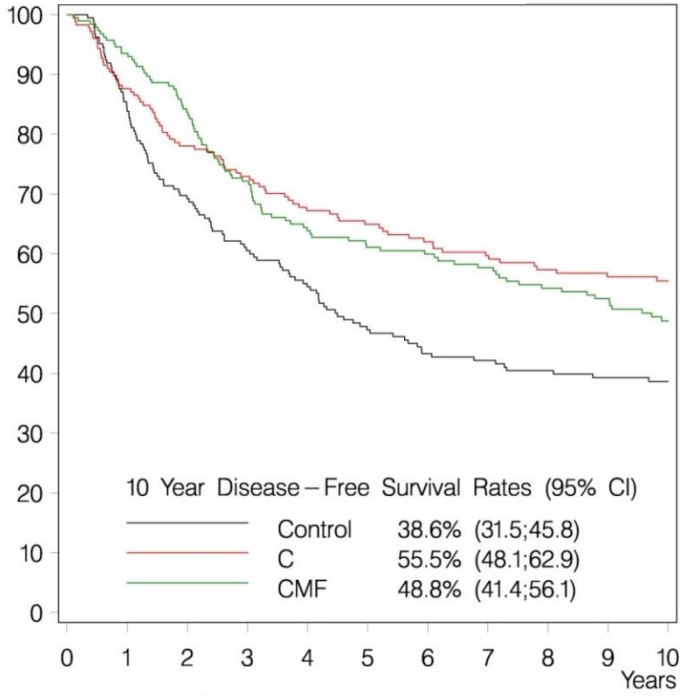


	1979	1981	1983	
Kontrol	107	187		Tidlig effektanalyse
Levamisole	112			Lukkes pga. bivirkninger
Cyclofosfamid	108	181	424	
Oral CMF	113	193	423	

Cancer (2010) 116, 2081-2089

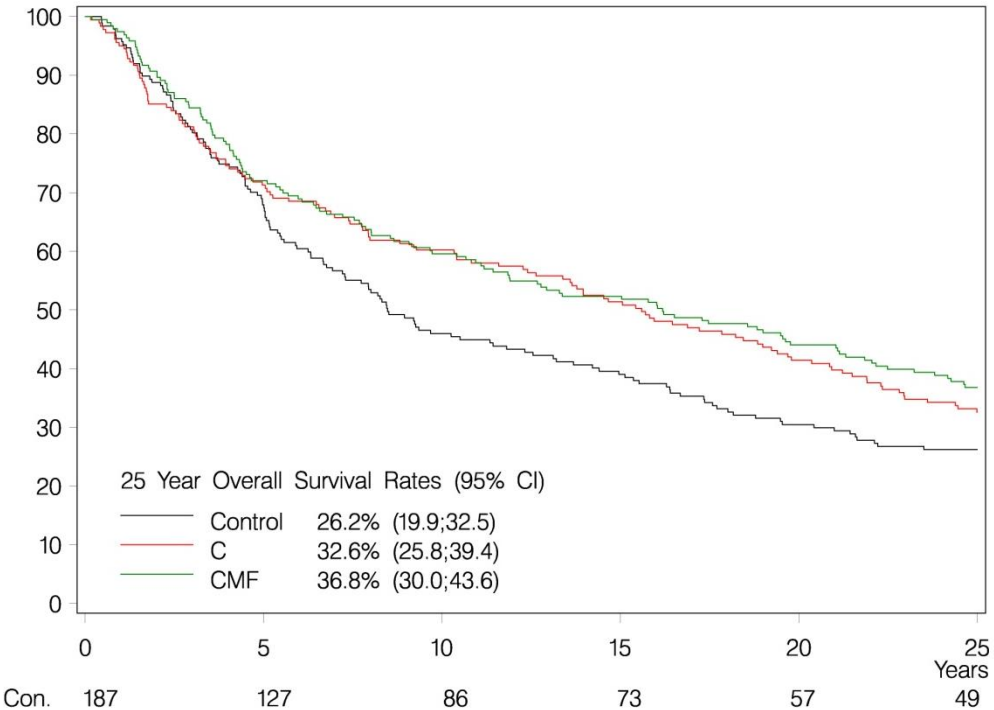
Cyclophosphamide, Methotrexate, and Fluorouracil; Oral Cyclophosphamide; Levamisole; or No Adjuvant Therapy for Patients With High-Risk, Premenopausal Breast Cancer

Disease-Free Survival (%)



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

Overall Survival (%)



Con.	187	127	86	73	57	49
C	181	129	109	93	75	59
CMF	193	139	115	101	85	71

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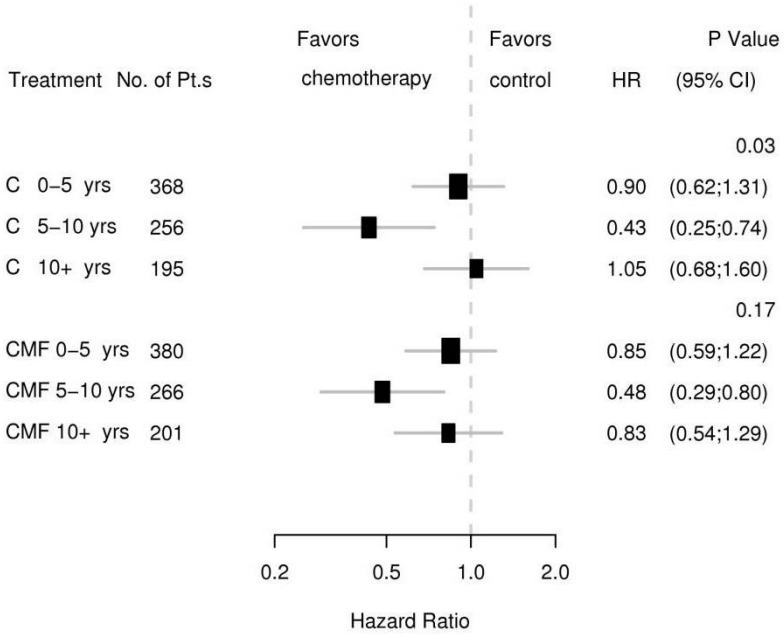

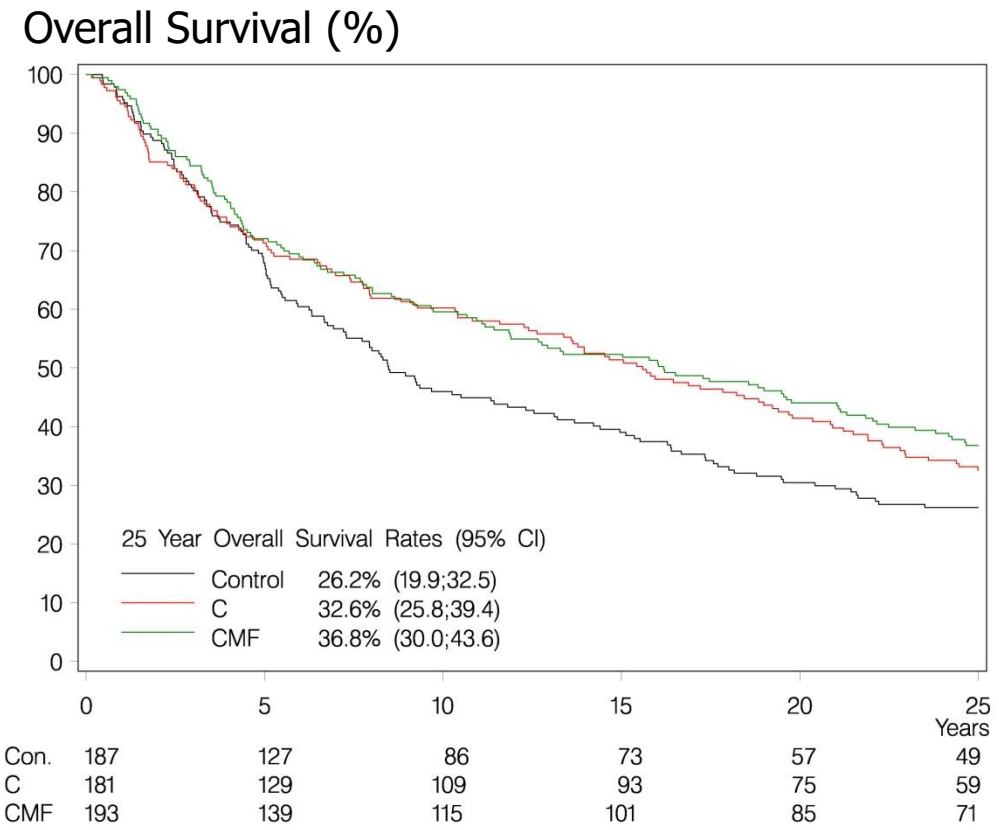

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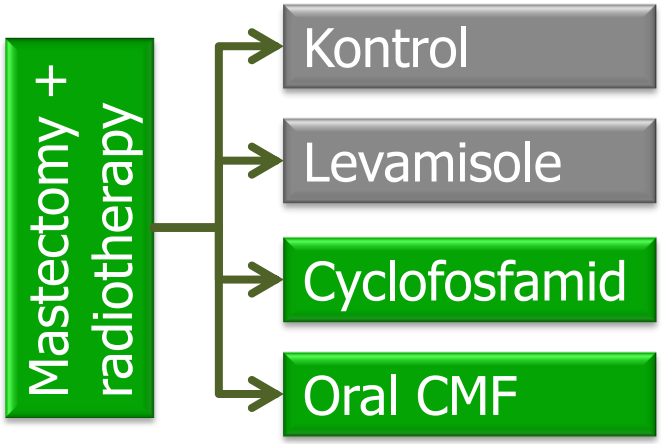
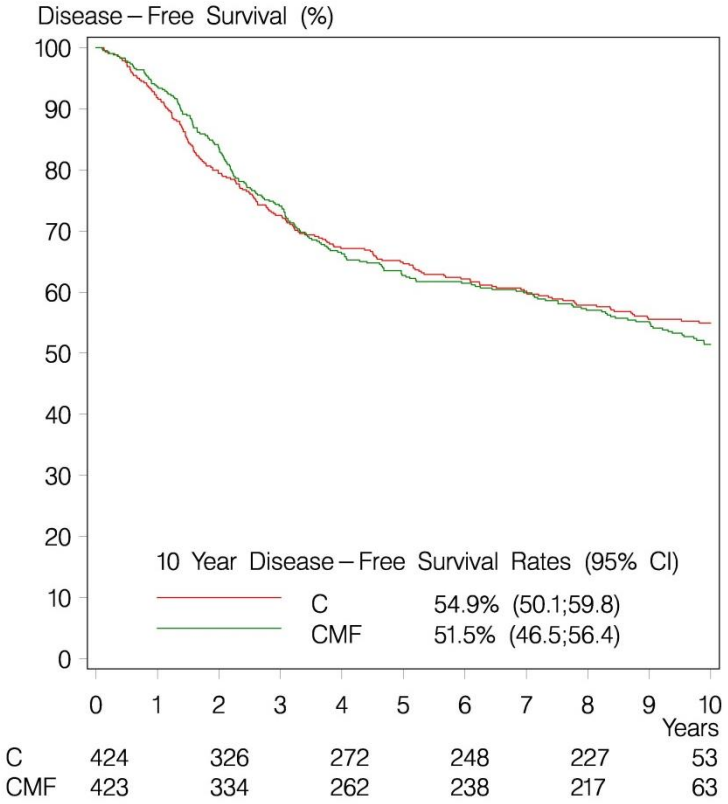


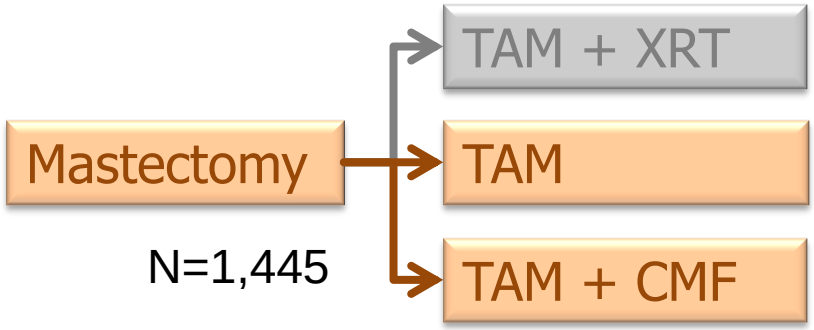


European Journal of Cancer (2013) 49, 2986–2994

ELSEVIER

One year of adjuvant tamoxifen with chemotherapy and tamoxifen in postmenopausal patients with stage II breast cancer

82C: postmenopausal



C : cyclophosphamide 600 mg/m^2 day 1 *
M: methotrexate 40 mg/m^2 day 1 *
F : 5-fluorouracil 600 mg/m^2 day 1 *

*every 4 weeks for 9 cycles

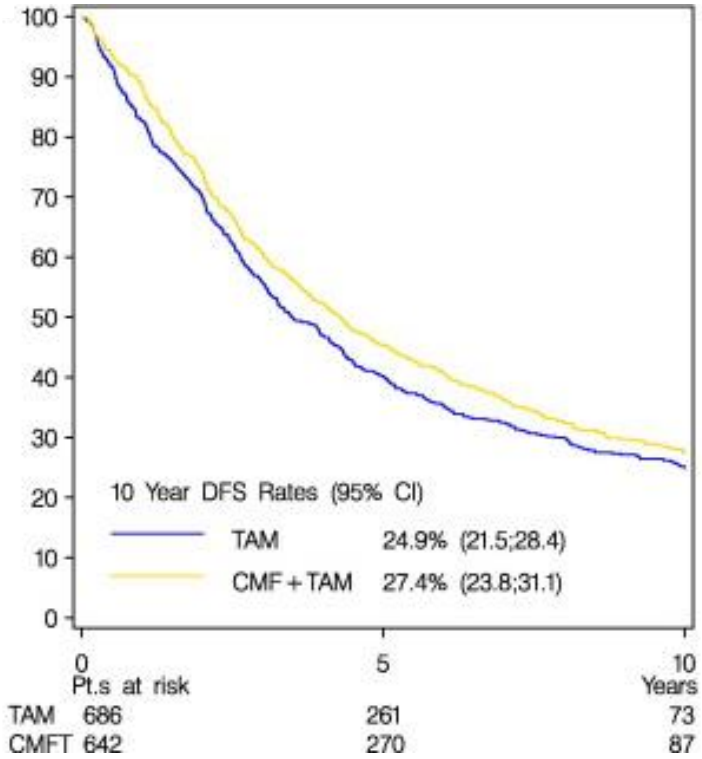
- Højrisiko, dvs. N+, T>5 cm og/eller invasion i hud eller fascie.
- Total mastektomi med partiel aksildissektion.
- Tamoxifen 30 mg dag. i 1 år.

European Journal of Cancer (2013) 49, 2986–2994

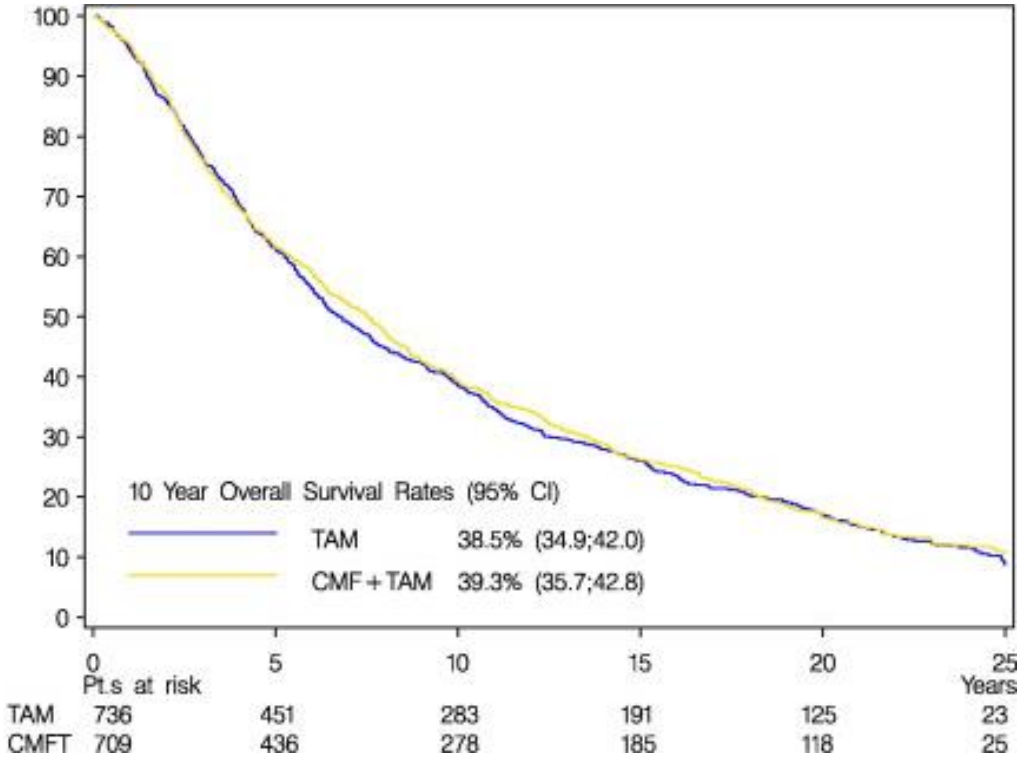
ELSEVIER

One year of adjuvant tamoxifen with chemotherapy and tamoxifen in postmenopausal patients with stage II breast cancer

Disease-Free Survival (%)



Overall Survival (%)



EUROPEAN JOURNAL OF CANCER 43 (2007) 877–884

Improved outcome for substituting methotrexate with epirubicin: Results from a randomised comparison of CMF versus CEF in patients with primary breast cancer

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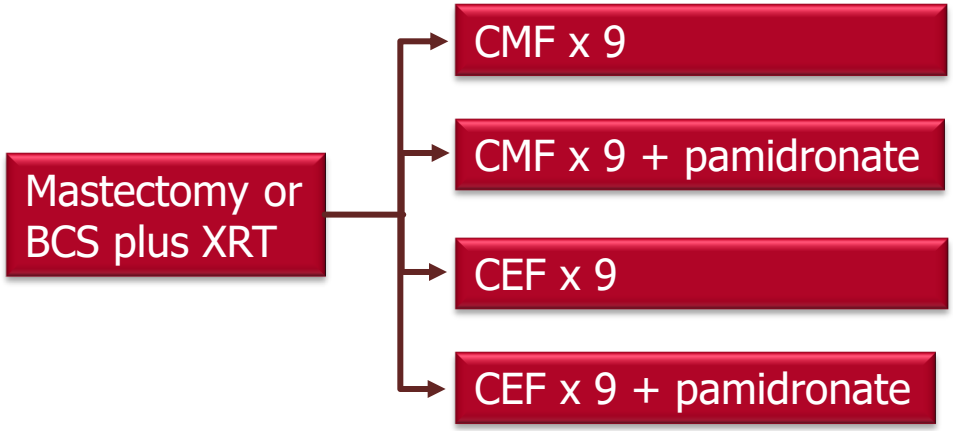
DBCG 89D Trial Schema

Patient selection

A. Premenopausal, high risk, node negative
B. Premenopausal, node positive, ER-/PgR negative or unknown
C. Postmenopausal, node positive, ER-/PgR negative



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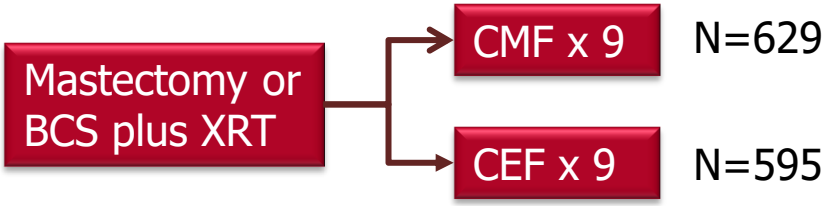

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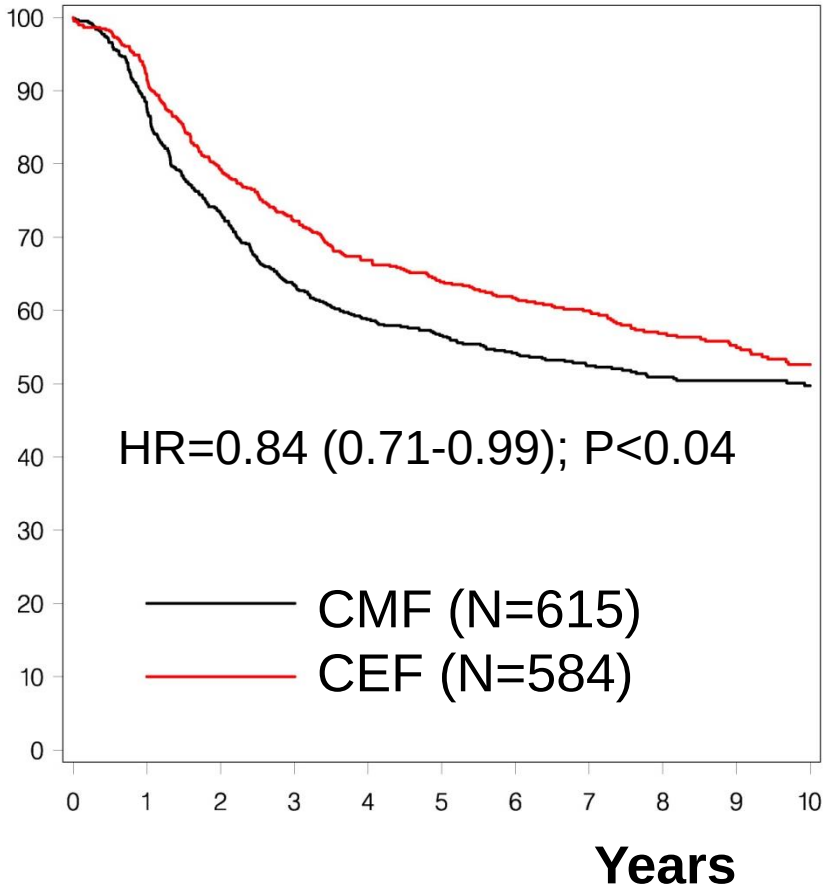
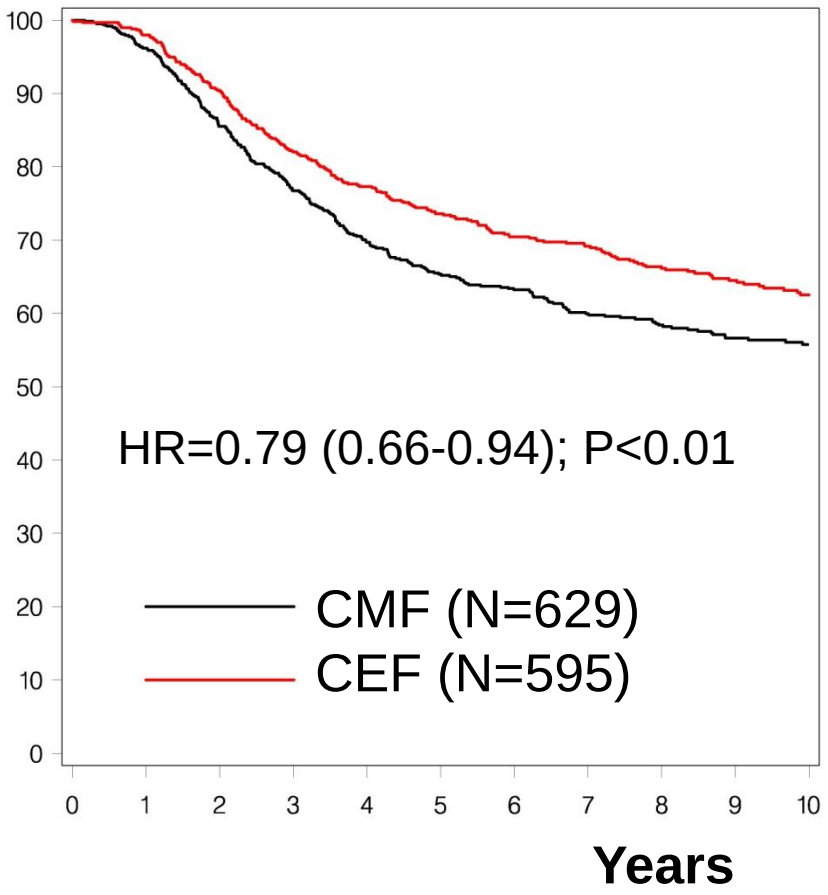
DBCG 89D Main Trial Results

Disease-Free Survival (%)



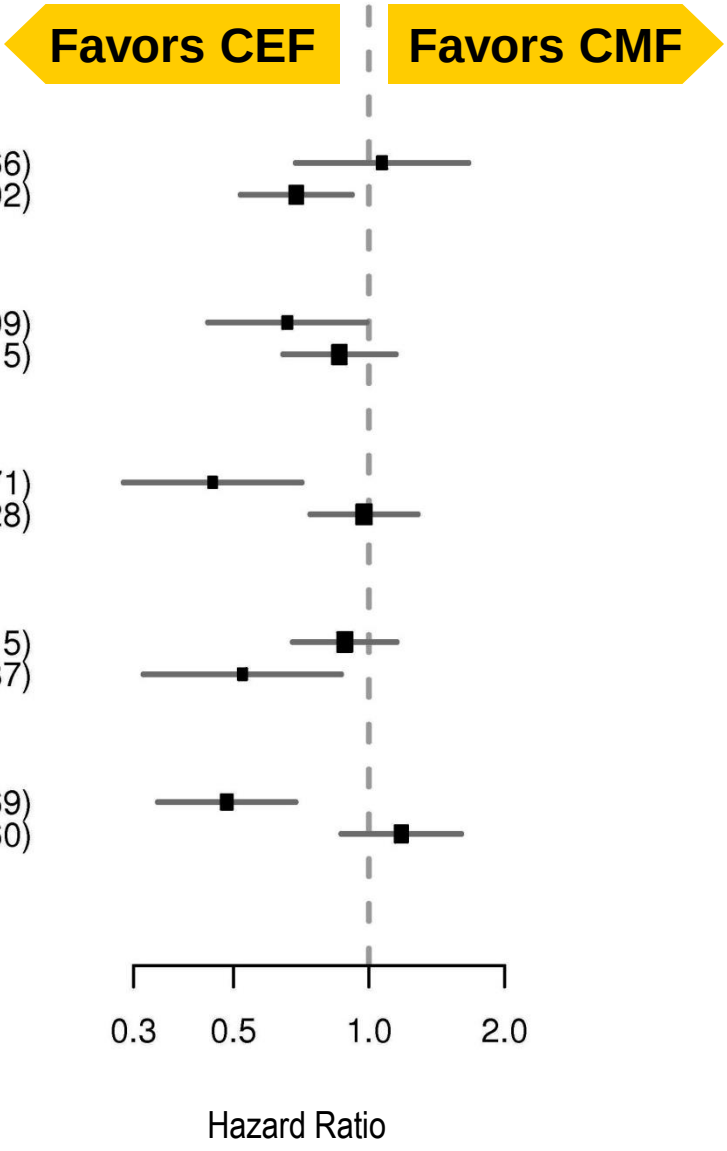
Overall Survival (%)



Ejlertsen B et al, EJC 2007;43:877

Invasive Disease-Free Survival

Group	No. of pt.s	HR	(95% CI)
ER			
Positive	197	1.07	(0.69 to 1.66)
Negative	387	0.69	(0.52 to 0.92)
P=0.10 (Test of interaction)			
HER2			
Amplified	188	0.66	(0.44 to 0.99)
Normal	435	0.86	(0.64 to 1.15)
P=0.29			
TOP2A			
Abnormal	139	0.45	(0.29 to 0.71)
Normal	484	0.98	(0.74 to 1.28)
P=0.004			
TIMP−1			
Positive	469	0.88	(0.68 to 1.15)
Negative	154	0.52	(0.32 to 0.87)
P=0.07			
2T			
Responsive	269	0.48	(0.34 to 0.69)
Non−responsive	354	1.18	(0.87 to 1.60)
P<0.0001			



Knoop et al, JCO 2005;23:7483
Nielsen et al, Acta Oncol 2008;46:725
Willemoe et al, EJC 2009;45:2528
Ejlertsen et al, JCO 2010; 28: 984

VOLUME 35 · NUMBER 23 · AUGUST 10, 2017

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

READ

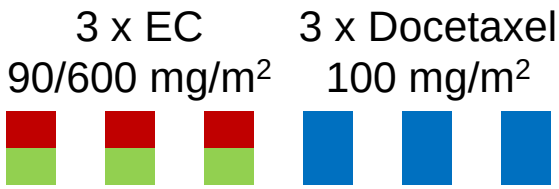
Adjuvant Cyclophosphamide and Docetaxel With or Without Epirubicin for Early *TOP2A*-Normal Breast Cancer: DBCG 07-READ, an Open-Label, Phase III, Randomized Trial

Selection Criteria

Invasive breast cancer
Comorbidity index < 3
High risk

1. Node positive
2. High risk node neg.
   - Age < 39
   - ER < 10% positive
   - HER2+
   - T size > 2 cm
   - Grade 2 or 3 IDC

→ *Altered TOP2A*
Ratio < 0.8 or ≥ 2.0 →



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Design

Adjuvant Cyclophosphamide and Docetaxel With or Without Epirubicin for Early *TOP2A*-Normal Breast Cancer: DBCG 07-READ, an Open-Label, Phase III, Randomized Trial

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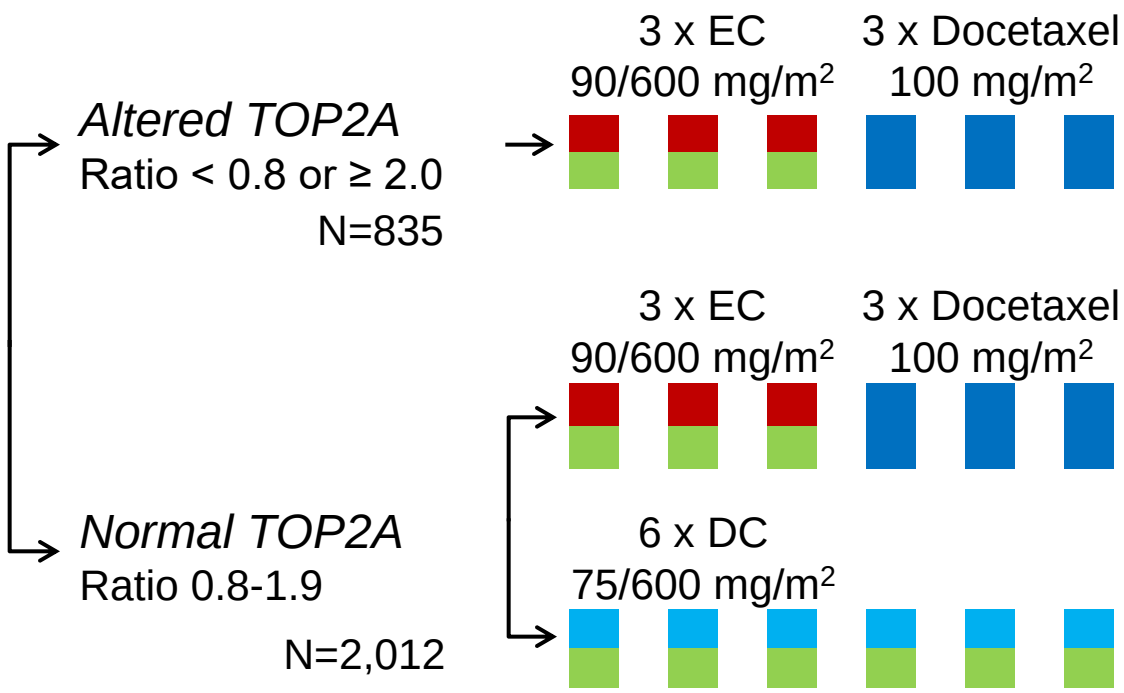

7,086 were eligible and 5,153 were screened for *TOP2A*

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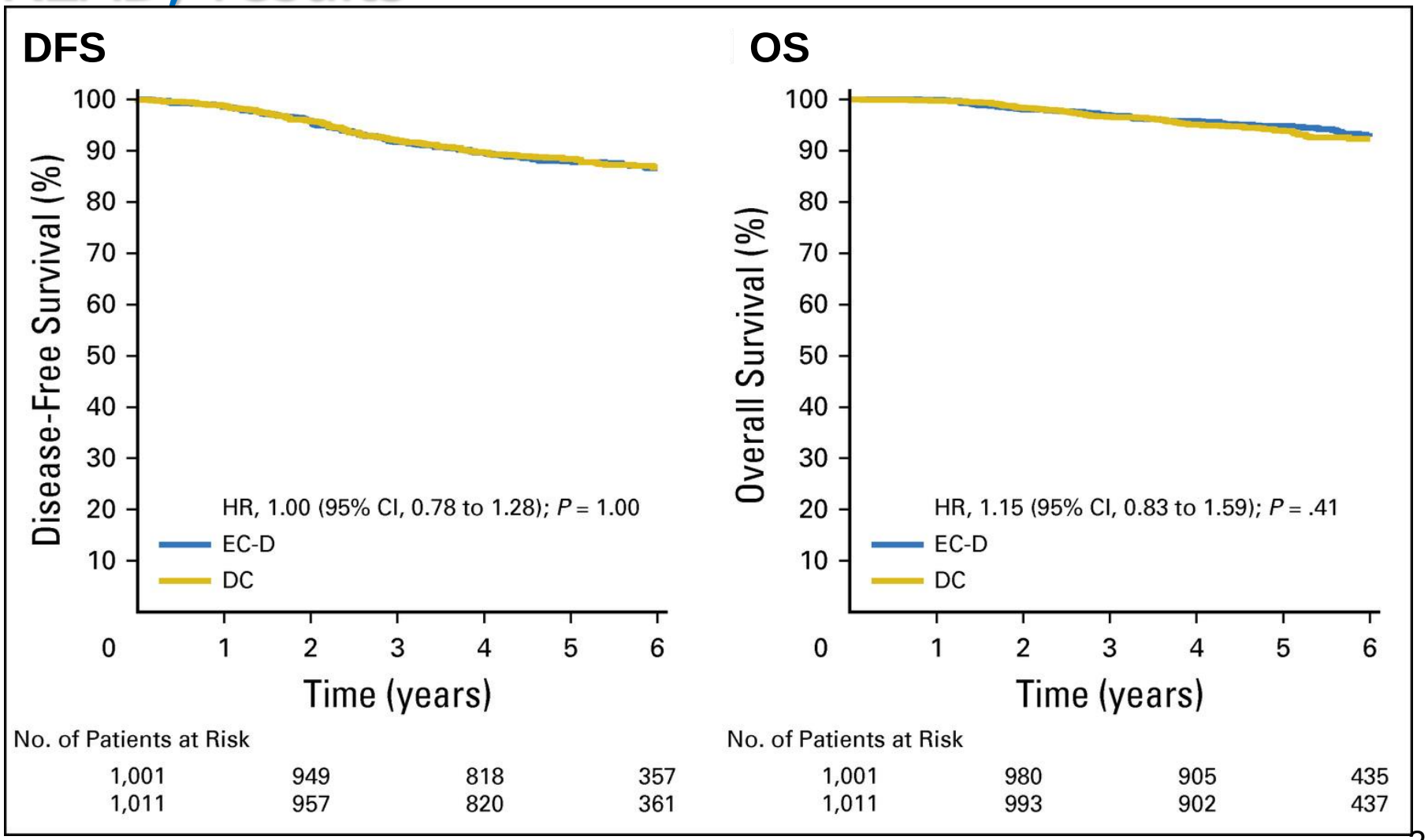
READ; results



EBCTCG meta-analyser

Cycle	Included	Comparisons	Women	Publications
1st	Trials before 1985 Follow-up to 1985	Tamoxifen Chemotherapy	16,500 13,000	NEJM 1988;319:1681
2nd	Trials before 1985 Follow-up to 1990	Tamoxifen Chemotherapy Ovarian ablation Immunotherapy Local therapy	30,000 11,000 3,000 6,300 28,500	Lancet 1992;339:71
3rd	Trials before 1990 Follow-up to 1995	Endocrine Radiotherapy	67,000 20,000	Lancet 1998;352:930
4th	Trials before 1995 Follow-up to 2000	Tam 1-2 vs 5 yr Locoregional	18,000 42,000	Lancet 2005;365:1687 Lancet 2005;366:2087

DBCG

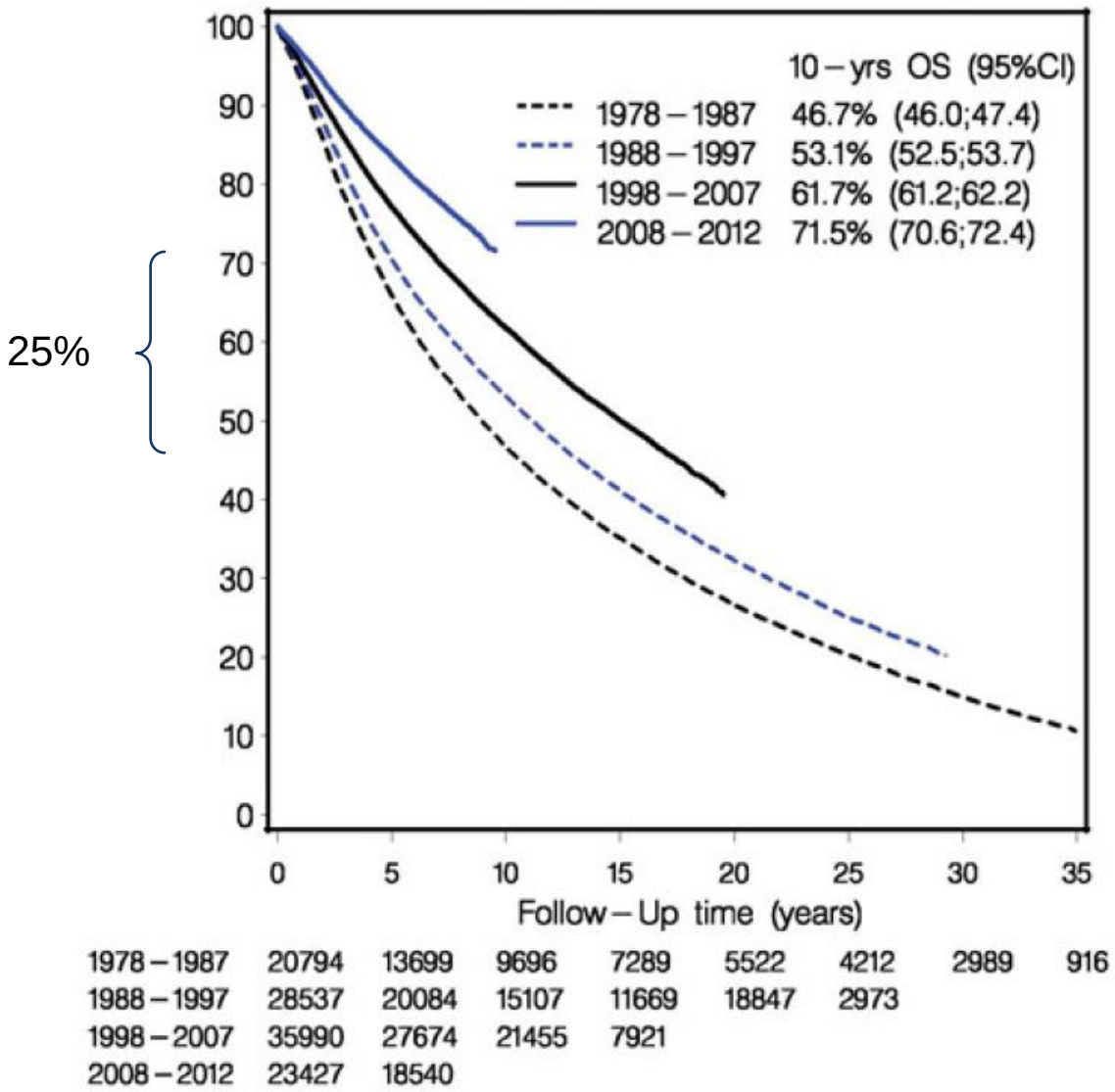
1977
40
2017
DBCG

Period	1978 – 1987	1988 – 1997	1998 – 2007	2008 – 2015
Endocrine therapy				
Premenopausal	None		Tamoxifen 5-yr	Tamoxifen 10-yr
Postmenopausal	Trial only	Tamoxifen 1-yr	Tamoxifen 5-yr	AI or AI->TAM 5-yr
Anti-HER2 therapy	None	None	Trial only	Trastuzumab 1-yr
Chemotherapy				
Premenopausal	Trial only	CMF or CEF	CEF	EC->taxane
Postmenopausal	None	CMF in ER negative	CEF in ER negative	EC->taxane

AI: aromatase inhibitor; C: cyclophosphamide; M: methotrexate; E: epirubicin; F: fluorouracil

Overall survival; all patients

1977 40 2017 DBCG



N= 108.748

1977
40
2017

DBCG

16th ACTA ONCOLOGICA SYMPOSIUM